mgr Justyna Jurczewska

Sposób żywienia, aktywność fizyczna i skład ciała a wybrane parametry metabolizmu u pacjentek z zespołem policystycznych jajników

Diet, physical activity and body composition in relation to selected metabolic parameters in patients with polycystic ovary syndrome

Rozprawa doktorska na stopień doktora
w dziedzinie nauk medycznych i nauk o zdrowiu
w dyscyplinie nauki o zdrowiu
przedkładana Radzie Dyscypliny Nauk o Zdrowiu
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Promotor: prof. dr hab. n. med. i n. o zdr. Dorota Szostak-Węgierek
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Słowa kluczowe: zespół policystycznych jajników, insulinooporność, adiponektyna, leptyna, rezystyna, otyłość brzuszna, wisceralna tkanka tłuszczowa, podskórna tkanka tłuszczowa, stres oksydacyjny, zaburzenia owulacji, dieta, aktywność fizyczna

Keywords: polycystic ovary syndrome, insulin resistance, adiponectin, leptin, resistin, abdominal obesity, visceral adipose tissue, subcutaneous adipose tissue, oxidative stress, ovulatory disorders, diet, physical activity

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Wykaz publikacji będących przedmiotem rozprawy doktorskiej

Cele pracy zostały zrealizowane w cyklu spójnych tematycznie sześciu pełnotekstowych artykułów, w tym wstępu do badania właściwego składającego się z trzech prac poglądowych oraz trzech prac oryginalnych, stanowiących badanie właściwe.

1. Wstęp do badania właściwego

Publikacja 1: Milk and Dairy Products and Their Impact on Carbohydrate Metabolism and Fertility—A Potential Role in the Diet of Women with Polycystic Ovary Syndrome

Justyna Janiszewska, Joanna Ostrowska, Dorota Szostak-Węgierek

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Publikacja 2: The Influence of Nutrition on Adiponectin—A Narrative Review

Justyna Janiszewska, Joanna Ostrowska, Dorota Szostak-Węgierek

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Publikacja 3: The Influence of Diet on Ovulation Disorders in Women —A Narrative Review

Justyna Jurczewska, Dorota Szostak-Węgierek

Nutrients 2022, 14(8): 1556-1575. DOI: 10.3390/nu14081556.

Impact Factor: 5,900 Punkty ministerialne: 140

2. Badanie właściwe

Publikacja 4: Physical Activity, Rather Than Diet, Is Linked to Lower Insulin Resistance in PCOS Women—A Case-Control Study

Justyna Jurczewska, Joanna Ostrowska, Magdalena Chełchowska, Mariusz Panczyk, Ewa Rudnicka, Marek Kucharski, Roman Smolarczyk, Dorota Szostak-Węgierek

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Publikacja 5: Abdominal Obesity in Women with Polycystic Ovary Syndrome and Its Relationship with Diet, Physical Activity and Insulin Resistance: A Pilot Study

Justyna Jurczewska, Joanna Ostrowska, Magdalena Chełchowska, Mariusz Panczyk, Ewa Rudnicka, Marek Kucharski, Roman Smolarczyk, Dorota Szostak-Węgierek

Nutrients 2023, 15(16), 3652-3669. DOI: 10.3390/nu15163652

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Publikacja 6: Antioxidant Defense Expressed as Glutathione Status and Keap1-Nrf2 System Action in Relation to Anthropometric Parameters and Body Composition in Young Women with Polycystic Ovary Syndrome

Magdalena Chełchowska, Justyna Jurczewska, Joanna Gajewska, Joanna Mazur, Dorota Szostak-Węgierek, Ewa Rudnicka, Jadwiga Ambroszkiewicz

Antioxidants 2023, 12(3): 730-744. DOI: 10.3390/antiox12030730.

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Łączna liczba punktów ministerialnych: 840

Spis treści

Wykaz skrótów

BCM	*ang. Body Cell Mass* – masa komórkowa
BIA	*ang. Bioelectrical Impedance Analysis* – analiza impedancji bioelektrycznej
BMI	*ang. Body Mass Index* – wskaźnik masy ciała
CI	*ang. Confidence Interval* – przedział ufności
CMIA	*ang. Chemiluminescent Microparticle Immunoassay* – metoda immunochemilumiscencji
DASH	*ang. Dietary Approaches to Stop Hypertention* – dietetyczne metody powstrzymania nadciśnienia
ECM	*ang. Extracellular Matrix* – macierz pozakomórkowa
ECW	*ang. Extracellular Water* – woda zewnątrzkomórkowa
ECW/ICW	*ang. Extracellular Water to Intercellular Water Ratio* – stosunek wody zewnątrzkomórkowej do wody wewnątrzkomórkowej
ELISA	*ang.* E*nzyme-linked Immunosorbent Assay* – test immunoenzymatyczny
ESPEN	*ang. European Society for Clinical Nutrition and Metabolism* – Europejskie Towarzystwo Żywienia Klinicznego i Metabolizmu
FFM	*ang. Fat Free Mass* – beztłuszczowa masa ciała
FFQ	*ang. Food Frequency Questionnaire* – kwestionariusz częstotliwości spożycia
FM	*ang. Fat Mass* – masa tkanki tłuszczowej
GnRH	*ang. Gonadotropin-releasing Hormone* - hormon uwalniający gonadotropiny
GPx	*ang. Glutathione Peroxidase* – peroksydaza glutationowa
GR	*ang.* G*lutathione Reductase* – reduktaza glutationowa
GSH	*ang. Reduced Glutathione* – glutation zredukowany
GSSG	*ang. Oxidized Glutathione* – glutation utleniony
HC	*ang. Hip Circumference* - obwód bioder
HOMA-AD	*ang. The Homeostatic Model Assessment – Adiponectin* - ocena modelu homeostazy – adiponektyna

HOMA-IR	*ang. The Homeostatic Model Assessment of Insulin Resistance* - ocena modelu homeostazy oporności na insulinę
ICW	*ang. Intercellular Water* - woda wewnątrzkomórkowa
IGF-1	*ang. Insulin-like Growth Factor I* – insulinopodobny czynnik wzrostu I
IQR	*ang. Interquartile Ranges* – rozstępy międzykwartylowe
IR	*ang. Insulin Resistance* – insulinooporność
Keap1	*ang. Kelch-like ECH-associated Protein 1* - Kelch-podobne białko 1 związane z ECH
L/A	*ang. Leptin to Adiponectin Ratio* – stosunek leptyny do adiponektyny
LH	*ang. Lutenizing Hormone* – hormon lutenizujący
MM	*ang. Muscle Mass* – masa mięśniowa
MPA	*ang. Moderate Physical Activity* – umiarkowana aktywność fizyczna
MVPA	*ang. Moderate to Vigorous Physical Activity* – umiarkowana do intensywnej aktywność fizyczna
Nrf2	*ang. Nuclear Factor Erythroid-derived 2-like Protein 2* - jądrowy czynnik transkrypcyjny pochodzenia erytroidalnego typu 2
NS	*ang. Not Statistically Significant* – nieistotne statystycznie
OR	*ang. Odds Ratio* – iloraz szans
PCOS	*ang. Polycystic Ovary Syndrome* – zespół policystycznych jajników
R (GSH/GSSG)	*ang. Index of Cellular Redox* (*reduced glutathione to oxidized glutathione ratio)* - wskaźnik redoks komórki (stosunek glutationu zredukowanego do glutationu utlenionego)
SAT	*ang. Subcutaneous Adipose Tissue* – powierzchnia tkanki tłuszczowej podskórnej
SD	*ang. Standard Deviation* - odchylenie standardowe
TBW	*ang. Total Body Water* – całkowita ilość wody w organizmie
T2DM	*ang. Type 2 Diabetes Mellitus* – cukrzyca typu 2
VAT	*ang. Visceral Adipose Tissue* – powierzchnia tkanki tłuszczowej wisceralnej
VAT/SAT	*ang. Visceral to* S*ubcutaneous Fat Ratio* – stosunek powierzchni tkanki tłuszczowej wisceralnej do tkanki tłuszczowej podskórnej

VPA	*ang. Vigorous Physical Activity* – intensywna aktywność fizyczna
WC	*ang. Waist Circumference* – obwód talii
WHR	*ang. Waist-to-Hip Ratio* – stosunek obwodu talii do obwodu bioder

Streszczenie

Wstęp

Zespół policystycznych jajników (PCOS, *ang. polycystic ovary syndrome*) jest jednym z najczęstszych zaburzeń endokrynologicznych dotykających kobiety w wieku rozrodczym. Sugeruje się, że insulinooporność (IR, *ang. insulin resistance*) odgrywa ważną rolę w patogenezie PCOS i wiąże się z ryzykiem wystąpienia zaburzeń owulacji. Można przypuszczać, że istnieje złożona zależność pomiędzy nieprawidłowym metabolizmem tkanki tłuszczowej, otyłością brzuszną, zaburzeniami owulacji, stresem oksydacyjnym oraz hiperandrogenizmem a insulinoopornością w przebiegu PCOS.

Rekomendacje dotyczące postępowania terapeutycznego w PCOS podkreślają duże znaczenie odpowiedniej diety i aktywności fizycznej w leczeniu tej jednostki chorobowej. Niniejsza praca doktorska, składająca się z trzech prac przeglądowych będących niesystematycznym przeglądem piśmiennictwa oraz trzech prac oryginalnych, analizuje znaczenie wpływu diety, aktywności fizycznej oraz stanu odżywienia na zaburzenia metaboliczne towarzyszące PCOS, ze szczególnym uwzględnieniem insulinooporności.

Cel pracy

Nadrzędnym celem pracy była analiza wpływu diety, aktywności fizycznej oraz stanu odżywienia na zaburzenia metaboliczne towarzyszące zespołowi policystycznych jajników, ze szczególnym uwzględnieniem insulinooporności.

Do celów szczegółowych należała: ocena związku pomiędzy spożyciem mleka i produktów mlecznych a ryzykiem zaburzeń gospodarki węglowodanowej oraz zaburzeń owulacji, ocena wpływu czynników żywieniowych na stężenie adiponektyny oraz na ryzyko zaburzeń owulacji, u pacjentek z PCOS ocena zależności pomiędzy dietą i aktywnością fizyczną a insulinoopornością oraz stężeniem adipokin (adiponektyna, leptyna i rezystyna) wydzielanych przez tkankę tłuszczową, określenie potencjalnego wykorzystania HOMA-AD *(ang. the homeostatic model assessment – adiponectin)* jako zastępczego markera dla HOMA-IR *(ang. the homeostatic model assessment of insulin resistance)* do oceny insulinooporności, ocena zależności pomiędzy otyłością brzuszną oraz typem dystrybucji tkanki tłuszczowej w okolicy brzusznej a występowaniem i nasileniem insulinooporności, ocena zależności pomiędzy otyłością brzuszną a dietą i aktywnością fizyczną oraz ocena związku pomiędzy parametrami

antropometrycznymi oraz składu ciała, ze szczególnym uwzględnieniem otyłości brzusznej, a parametrami obrony antyoksydacyjnej.

Materiał i metody

Grupę badaną stanowiło 56 kobiet z PCOS w wieku 18-40 lat. Grupę kontrolną stanowiło 33 zdrowych kobiet w tym samym wieku.

W badaniu dokonano pomiarów antropometrycznych oraz wykonano analizę składu ciała z uwzględnieniem tkanki tłuszczowej brzusznej (wisceralnej i podskórnej) metodą impedancji bioelektycznej. Ponadto, u każdej uczestniczki badania we krwi pobranej na czczo oznaczono stężenia glukozy i insuliny, adipokin, hormonów oraz wskaźników obrony oksydacyjnej. Insulinooporność oceniano na podstawie: HOMA-IR, HOMA-AD oraz wskaźnika L/A *(ang. leptin to adiponectin ratio)* z uwzględnieniem odpowiednio następujących punktów odcięcia: HOMA-IR ≥2,5; HOMA-AD ≥6,26 oraz L/A >2,2.

Do oceny sposobu odżywiania wykorzystano autorski kwestionariusz częstotliwości spożycia produktów, który uwzględniał produkty mające negatywny lub pozytywny związek z wrażliwością tkanek na insulinę. Metodą punktową określono stopień przestrzegania diety zalecanej w insulinooporności. Aktywność fizyczną mierzono za pomocą monitora aktywności Actigraph GT3X-BT.

Wyniki

W przeglądzie piśmiennictwa stanowiącym wstęp do badania właściwego stwierdzono, że związek pomiędzy spożyciem mleka i produktów mlecznych a ryzykiem zaburzeń gospodarki węglowodanowej jest niejasny i zależy przede wszystkim od ilości produktów mlecznych w diecie oraz ich rodzaju. Produkty te wydają się nie mieć negatywnego wpływu na płodność kobiet, jednakże obserwuje się niekorzystny wpływ odtłuszczonych produktów mlecznych na ryzyko zaburzeń owulacji. Stwierdzono również, że czynniki żywieniowe są znaczącymi czynnikami wpływającymi na stężenie adiponektyny oraz na ryzyko wystąpienia zaburzeń owulacji.

W badaniu właściwym zaobserwowano, że w grupie PCOS wyższy poziom aktywności fizycznej (wyrażony jako MVPA, *ang. moderate-to-vigorous physical activity*) był związany z niższym HOMA-IR (t=-2,109; p=0,038). Ponadto, w grupie PCOS wyższy poziom aktywności fizycznej (wyrażony jako MVPA) przekładał się na większą szansę na prawidłową wartość HOMA-IR (OR 1,012 95% CI 1,003-1,021;

p=0,01). Takich zależności nie zaobserwowano pomiędzy aktywnością fizyczną a pozostałymi wskaźnikami IR oraz adipokinami, jak również pomiędzy dietą a wszystkimi wskaźnikami IR oraz adipokinami. Zaobserwowano też silną korelację pomiędzy wartościami HOMA-IR a HOMA-AD u kobiet z PCOS, a przy wykorzystaniu HOMA-AD częściej rozpoznawano u nich IR.

Kobiety z PCOS z otyłością brzuszną charakteryzowały się istotnie statystycznie wyższymi stężeniami insuliny na czczo (odpowiednio p<0,001; p=0,007; p<0,001 i p=0,005) oraz istotnie wyższymi wartościami wskaźników HOMA-IR, HOMA-AD oraz L/A w porównaniu do kobiet z PCOS bez otyłości brzusznej. Zaobserwowano istotnie statystycznie większą częstość występowania IR mierzonej za pomocą HOMA-IR, HOMA-AD i stosunku L/A u kobiet z PCOS ze zwiększoną zawartością tkanki tłuszczowej wisceralnej, zwiększonym wskaźnikiem VAT/SAT (ang. *visceral to subcutaneous fat ratio)* oraz WHR *(ang. waist-to-hip ratio)* w porównaniu z kobietami z prawidłowymi wartościami tych parametrów. Ponadto kobiety z IR zdiagnozowaną za pomocą wszystkich wskaźników charakteryzowały się istotnie wyższą zawartością VAT (ang. *visceral adipose tissue*) i SAT (ang. *subcutaneous adipose tissue*) oraz wyższymi wskaźnikami VAT/SAT oraz WHR niż kobiety bez insulinooporności. Stwierdzono też, że stosunek VAT/SAT był najlepszym predyktorem IR diagnozowanej za pomocą HOMA-IR i HOMA-AD. Z kolei VAT >120 cm^2 okazał się najlepszym i najsilniejszym predyktorem IR mierzonej wskaźnikiem L/A, podczas gdy VAT/SAT najsilniej zwiększał prawdopodobieństwo nieprawidłowych wartości HOMA-AD.

Zaobserwowano, że lepsze przestrzeganie diety zalecanej w IR było związane z istotnie statystycznie niższą zawartością VAT (t=-2,635; p=0,011), zawartością SAT (t=-2,905; p=0,005) i wartością WHR (t=-2,631; p=0,011). Dodatkowo zauważono, że większa intensywna aktywność fizyczna była związana z istotnie statystycznie niższą zawartością VAT (t=-2,277; p=0,027), zawartością SAT (t=-2,028; p=0,048), wskaźnikiem VAT/SAT (t=-2,280; p=0,027) i WHR (t=-2,421; p=0,019). Ponadto lepsze przestrzeganie zalecanej diety w IR przekładało się na większe o 43% szanse na prawidłową zawartość VAT (OR 1,427 95% Cl 1,091–1,868; p=0,009) i o 33% na większe szanse na prawidłową wartość WHR (OR 1,325 95% 1,023–1,716; p=0,033). Dodatkowo, wyższa intensywna aktywność fizyczna wiązała się z większym prawdopodobieństwem wystąpienia prawidłowych wartości VAT (OR 1,063 95% CI 1,007-1,122; p=0,028) i VAT/SAT (OR 1,057 95% CI 1,006-1,110; p=0,028). Ponadto, analiza wieloczynnikowa wykazała, że dieta była czynnikiem niezależnym od

aktywności fizycznej, który zwiększał prawdopodobieństwo wystąpienia prawidłowej zawartości VAT (OR 1,430 95% CI 1,097–1,864; p=0,008), VAT/SAT (OR 1,273 95 % Cl 1,003-1,615; p=0,047) i WHR (OR 1,322 95% Cl 1,025-1,704; p=0,031).

Stwierdzono, że stężenie GSSG *(ang. oxidized glutathione)* i Keap1 *(ang. Kelch-like ECH-associated protein 1)* były istotnie statystycznie wyższe, natomiast wartość wskaźnika R (stosunek glutationu zredukowanego do glutationu utlenionego) była istotnie statystycznie niższa w surowicy kobiet z VAT/SAT >0,9 w porównaniu z grupą z prawidłowymi wartościami tego wskaźnika. Podobne różnice wykazano dla GSSG i wskaźnika R pomiędzy grupami WHR ≥0,85 i WHR <0,85 (odpowiednio p<0,05 i p<0,01). Co więcej, wszystkie parametry obrony antyoksydacyjnej były skorelowane z parametrami antropometrycznymi oraz składu ciała. Stwierdzono ujemne korelacje pomiędzy wskaźnikiem R a masą ciała, BMI *(ang. body mass index)*, WHR, VAT, SAT oraz wskaźnikiem VAT/SAT i całkowitą tkanką tłuszczową oraz stwierdzono dodatnie powiązania z masą beztłuszczową i całkowitą zawartością wody w organizmie. Natomiast odwrotne zależności stwierdzono pomiędzy poziomem GSSG a wymienionymi powyżej parametrami składu ciała.

Wnioski

Przegląd piśmiennictwa wykazał, że pomimo niespójnych wyników badań, mleko i produkty mleczne są istotnym elementem diety kobiet z PCOS. Ponadto sposób odżywania jest znaczącym modulatorem stężenia adiponektyny oraz czynnikiem wpływającym na ryzyko zaburzeń owulacji.

W badaniu właściwym wykazano, że aktywność fizyczna wiąże się z mniejszym nasileniem insulinooporności u kobiet z PCOS oraz mniejszym ryzykiem wystąpienia otyłości brzusznej. Natomiast dieta wydaje się być kluczowym elementem w postępowaniu terapeutycznym u kobiet z centralną kumulacją tkanki tłuszczowej. Co więcej, nieprawidłowości w składzie ciała, w szczególności otyłość brzuszna, zwiększają ryzyko oporności na insulinę oraz wiążą się z dysfunkcją parametrów obrony antyoksydacyjnej. Dlatego też dieta i aktywność fizyczna są istotnymi elementami w postępowaniu terapeutycznym kobiet z PCOS i każda kobieta z tą jednostką chorobową powinna otrzymać poradę dotyczącą modyfikacji stylu życia w zapobieganiu powikłaniom metabolicznym.

Abstract

Dissertation title: Diet, physical activity and body composition in relation to selected metabolic parameters in patients with polycystic ovary syndrome.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age. Insulin resistance (IR) is suggested to play a crucial role in the pathogenesis of PCOS and is associated with the risk of ovulatory disorders. It can be presumed that there is a complex relationship between abnormal adipose tissue metabolism, abdominal obesity, ovulatory disturbances, oxidative stress, hyperandrogenism and insulin resistance in the course of PCOS.

Recommendations regarding the treatment of PCOS have emphasized the great importance of lifestyle interventions in the management of this disease. This doctoral thesis, consisting of three literature review papers and three original research papers, analyzes the importance of diet, physical activity and nutritional status in relation to metabolic disturbances accompanying PCOS, with a particular emphasis on insulin resistance.

Aim

The primary aim of the study was to analyze the impact of diet, physical activity and nutritional status on metabolic disturbances accompanying polycystic ovary syndrome with a particular emphasis on insulin resistance.

Specific objectives of the study were to: assess the association between milk and dairy product consumption and the risk of carbohydrate metabolism disorders and ovulatory disorders, evaluate the influence of dietary factors on adiponectin levels and the risk of ovulatory disorders, in PCOS patients to investigate the relationship between diet, physical activity and insulin resistance and the concentrations of adipokines (adiponectin, leptin, and resistin) secreted by adipose tissue, determine the potential use of HOMA-AD *(the homeostatic model assessment - adiponectin)* as a substitute marker for HOMA-IR *(the homeostatic model assessment of insulin resistance)* in assessing insulin resistance, assess the relationship between abdominal obesity and the type of abdominal fat distribution and the occurrence and severity of insulin resistance, evaluate the relationship between abdominal obesity and diet and

physical activity, and assess the association between anthropometric and body composition parameters, with a particular emphasis on abdominal obesity and antioxidant defense parameters.

Materials and Methods

The study group consisted of 56 women aged 18-40 diagnosed with PCOS. A control group of 33 healthy women of the same age was also included.

Anthropometric measurements were conducted and body composition analysis, including abdominal adipose tissue (visceral and subcutaneous), was assessed using bioelectrical impedance. Additionally, fasting blood samples were collected from each participant to measure glucose and insulin levels, adipokines, hormones and oxidative defense markers. Insulin resistance was evaluated based on the following parameters: HOMA-IR, HOMA-AD, and the L/A ratio *(leptin to adiponectin ratio)*, with the following cut-off points: HOMA-IR ≥2.5; HOMA-AD ≥6.26; and L/A >2.2.

To assess dietary habits, an original food frequency questionnaire was used, considering products with either a positive or negative association with tissue insulin sensitivity. A point-based method was used to determine the adherence level to the recommended diet for insulin resistance. Physical activity was measured using the Actigraph GT3X-BT activity monitor.

Results

In the literature review constituting the introduction to the study, it was observed that the relationship between milk and dairy product consumption and the risk of carbohydrate metabolism disorders is unclear. This relationship appears to primarily depend on the quantity and type of dairy products in the diet. While these products do not seem to have a negative impact on women's fertility, there is an adverse effect noted regarding the consumption of low-fat dairy products on the risk of ovulatory disorders. Furthermore, it was found that diet is a significant factor affecting both adiponectin levels and the risk of ovulatory disorders.

In the study, it was observed that in the PCOS group a higher level of physical activity (expressed as MVPA, *moderate-to-vigorous physical activity*) was associated with lower HOMA-IR ($t=-2.109$; $p=0.038$). Furthermore, in the PCOS group, a higher level of physical activity (expressed as MVPA) translated into a greater odd of a normal

HOMA-IR level (OR 1.012, 95% CI 1.003-1.021; p=0.01). Such associations were not observed between physical activity and other IR parameters or adipokines, nor between diet and all IR parameters and adipokines. Moreover, a strong correlation was noted between HOMA-IR and HOMA-AD values in women with PCOS, with IR being more frequently identified when using HOMA-AD.

Women with PCOS and abdominal obesity exhibited statistically significantly higher fasting insulin levels (p<0.001; p=0.007; p<0.001 and p=0.005, respectively) and significantly higher values of the HOMA-IR, HOMA-AD and L/A ratio compared to non-centrally obese PCSO women. There was a statistically significantly higher frequency of insulin resistance, measured by HOMA-IR, HOMA-AD and the L/A ratio, in PCOS women with increased content of visceral adipose tissue, an elevated VAT/SAT ratio *(visceral to subcutaneous fat ratio),* and a higher WHR *(waist-to-hip ratio)* compared to women with normal values of these parameters. Furthermore, women with insulin resistance diagnosed using all indicators had significantly higher VAT *(visceral adipose tissue)* and SAT *(subcutaneous adipose tissue)* content, as well as higher VAT/SAT and WHR ratios than women without insulin resistance. It was also observed that the VAT/SAT ratio was the best predictor of insulin resistance diagnosed with HOMA-IR and HOMA-AD. On the other hand, VAT >120 cm^2 proved to be the best and strongest predictor of insulin resistance measured by the L/A ratio, while VAT/SAT most significantly increased the odds of abnormal HOMA-AD values.

It was observed that higher adherence to the diet recommended in IR was significantly associated with lower VAT content (t=-2.635; p=0.011), SAT content (t=-2.905; p=0.005), and WHR values (t=-2.631; p= 0.011). Additionally, a higher level of vigorous physical activity was significantly associated with lower VAT content (t=-2.277; p=0.027), SAT content (t=-2.028; p=0.048), the VAT/SAT ratio (t=-2.280; p=0.027) and WHR (t=-2.421; p=0.019). Furthermore, higher adherence to the recommended diet in IR translated into 43% higher odds of having normal VAT content (OR 1.427, 95% CI 1.091–1.868; p=0.009) and 33% higher odds of having a normal WHR value (OR 1.325, 95% CI 1.023–1.716; p=0.033). Additionally, higher levels of vigorous physical activity were associated with an increased odd of having normal VAT (OR 1.063, 95% CI 1.007-1.122; p=0.028) and VAT/SAT (OR 1.057, 95% CI 1.006-1.110; p=0.028) values. Moreover, multivariate analysis indicated that diet was a factor independent of physical activity, that increased odds of normal VAT content (OR 1.430,

95% CI 1.097-1.864; p=0.008), VAT/SAT (OR 1.273, 95% CI 1.003-1.615; p=0.047) and WHR (OR 1.322, 95% CI 1.025-1.704; p=0.031).

It was observed that the concentrations of GSSG *(oxidized glutathione)* and Keap1 *(Kelch-like ECH-associated protein 1)* were significantly higher, while the R ratio *(reduced glutathione to oxidized glutathione ratio)* was significantly lower in the serum of women with VAT/SAT >0.9 compared to the group with normal values of this indicator. Similar differences were found for GSSG and the R ratio between the WHR ≥0.85 and WHR <0.85 groups (respectively, $p<0.05$ and $p<0.01$). Furthermore, all antioxidant defense parameters were correlated with anthropometric and body composition parameters. Negative correlations were observed between the R ratio and body weight, BMI *(body mass index)*, WHR, VAT, SAT, VAT/SAT ratio and total body fat, while positive associations were found with lean body mass and total body water content. Conversely, inverse relationships were noted between the level of GSSG and the aforementioned body composition parameters.

Conclusions

The literature review revealed that despite inconsistent research results, milk and dairy products are significant components of the PCOS women diet. Furthermore, dietary habits play a substantial role in modulating adiponectin levels and influence the risk of ovulatory disorders.

In the study, it was demonstrated that physical activity is associated with reduced insulin resistance in women with PCOS and a lower risk of abdominal obesity. On the other hand, diet appears to be a key factor in the therapeutic management of women with central fat accumulation. Moreover, abnormalities in body composition, especially abdominal obesity, increase the risk of insulin resistance and are linked to the dysfunction of antioxidant defense parameters. Therefore, diet and physical activity are essential components of the therapeutic approach for women with PCOS and every woman with this condition should receive counsel regarding lifestyle modifications to prevent metabolic complications.

1. Wstęp

Zespół policystycznych jajników (PCOS, *ang. polycystic ovary syndrome*) jest jednym z najczęstszych zaburzeń endokrynologicznych dotykających kobiety w wieku rozrodczym, a jego częstość występowania waha się od 8-13% w zależności od zastosowanych kryteriów diagnostycznych [1]. Jest to złożona jednostka chorobowa, związana z zaburzeniami owulacji, hiperandrogenizmem (klinicznym lub biochemicznym) i/lub morfologią policystycznych jajników w badaniu ultrasonograficznym [2].

Do niedawna PCOS uważano jedynie za przyczynę trudności z zajściem w ciążę, jednakże obecnie powszechnie wiadomo, że kobiety z PCOS są szczególnie podatne na rozwój wielu zaburzeń kardiometabolicznych, do których można zaliczyć np. cukrzycę typu 2 (T2DM, *ang. type 2 diabetes mellitus*), dyslipidemię, czy insulinooporność (IR, *ang. insulin resistance*) występującą nawet u 80% przypadków kobiet z tą endokrynopatią [3,4]. IR definiowana jest jako zmniejszona wrażliwość tkanek na insulinę i odnosi się do zwiększonej ilości insuliny potrzebnej do wykonania jej funkcji metabolicznych [5]. Uważa się, że IR jest również jednym z ważniejszych elementów patogenetycznych w PCOS, ponieważ insulina działając na swój receptor w komórkach tekalnych stymuluje nadmierną produkcję androgenów oraz hamuje wątrobową produkcję globuliny wiążącej hormony płciowe, co skutkuje zwiększeniem stężenia wolnego testosteronu we krwi. Co więcej, insulina działając na receptor GnRH *(ang. gonadotropin-releasing hormone)* w podwzgórzu, zwiększa działanie LH *(ang. lutenizing hormone)* na jajnik, co również nasila nadmierną produkcję androgenów [6,7]. Należy również podkreślić, że IR zwiększa ryzyko wystąpienia zaburzeń owulacji oraz przewlekłego stanu zapalnego o niskim nasileniu, ze względu na towarzyszącą jej zwiększoną produkcję reaktywnych form tlenu oraz zmniejszone stężenie antyoksydantów [8-11]. Dlatego też, mając na uwadze fakt, że IR nie tylko nasila zaburzenia hormonalne, ale również zwiększa ryzyko powikłań metabolicznych, jej wczesna diagnoza i leczenie jest kluczowe w zapobieganiu wystąpieniu powikłań metabolicznych i hormonalnych towarzyszących PCOS.

PCOS jak również IR są ściśle powiązane z otyłością, w szczególności brzuszną. Centralne gromadzenie tkanki tłuszczowej jest charakterystyczne zarówno dla szczupłych jak i otyłych kobiet z tą jednostką chorobową [12-16]. Nadmierna centralna kumulacja wisceralnej tkanki tłuszczowej (VAT, *ang. visceral adipose tissue*) oraz

podskórnej tkanki tłuszczowej (SAT, *ang. subcutaneous adipose tissue*), jak również podwyższony stosunek VAT/SAT *(ang. visceral to subcutaneous fat ratio)* oraz WHR *(ang. waist-to-hip ratio)* nasilają kliniczne i metaboliczne cechy tej choroby, co sugeruje, że istnieje złożona zależność pomiędzy stanem odżywienia a przebiegiem PCOS [15,17,18].

Otyłość brzuszna, a w szczególności tkanka tłuszczowa wisceralna, jest ściśle powiązana ze stresem oksydacyjnym, co dodatkowo nasila zaburzenia towarzyszące PCOS [19]. Powszechnie znaną miarą stresu oksydacyjnego jest stosunek glutationu zredukowanego (GSH, *ang. reduced glutathione)* do utlenionego (GSSG, *ang. oxidized glutathione*). Układ GSH/GSSG jest głównym „buforem redoks" chroniącym struktury komórkowe przed działaniem wolnych rodników tlenowych [20,21]. W badaniach wykazano, że kobiety z PCOS charakteryzują się istotnie niższymi stężeniami GSH w porównaniu do zdrowych kobiet [22-24]. Ponadto zaobserwowano istotne statystycznie różnice w stężeniach GSH pomiędzy otyłymi kobietami z PCOS a tymi o prawidłowej masie ciała [24]. Jednakże wyniki badań dotyczących różnic pomiędzy innymi parametrami zaangażowanymi w regulację równowagi oksydacyjnej, takimi jak peroksydaza glutationowa (GPx, *ang. glutathione peroxidase*), reduktaza glutationowa (GR, ang. *glutathione reductase*), jak również białka układu Nrf2 *(ang. nuclear factor erythroid-derived 2-like protein 2)* i Keap1 *(ang. Kelch-like ECH-associated protein 1)* wśród kobiet z PCOS były przedmiotem tylko niewielu badań, w szczególności w kontekście stanu odżywienia [9,11,25].

Ponadto, należy również podkreślić, że tkanka tłuszczowa kobiet z PCOS wykazuje wiele nieprawidłowości w ilości wydzielanych adipokin, takich jak adiponektyna, leptyna oraz rezystyna, co stanowi dodatkowy czynnik ryzyka zaburzeń owulacji oraz IR w otyłości, ponieważ adipokiny te zaangażowane są w regulację owulacji oraz wrażliwości tkanek na insulinę [26-28]. Istnieje wiele danych, które pokazują, że kobiety z PCOS charakteryzują się istotnie niższym stężeniem adiponektyny oraz istotnie wyższymi stężeniami leptyny i rezystyny w porównaniu do zdrowych kobiet [29-35]. Mając na uwadze te zaburzenia obiecujące jest wykorzystanie do oceny IR w PCOS wskaźników HOMA-AD *(ang. the homeostatic model assessment – adiponectin)* i L/A *(ang. leptin to adiponectin ratio),* które w porównaniu do HOMA-IR *(ang. the homeostatic model assessment of insulin resistance)* uwzględniają dysfunkcję metabolizmu tkanki tłuszczowej. Wciąż jednak nie wiadomo, czy wspomniane nieprawidłowości są wtórne do otyłości, insulinooporności i zaburzeń

hormonalnych, czy też są niezależnym zjawiskiem w przebiegu PCOS. Natomiast wydaje się, że istnieje złożony związek pomiędzy nieprawidłowym metabolizmem tkanki tłuszczowej, otyłością brzuszną, zaburzeniami owulacji, stresem oksydacyjnym oraz hiperandrogenizmem a insulinoopornością w przebiegu PCOS [29].

Rekomendacje dotyczące postępowania terapeutycznego w PCOS podkreślają duże znaczenie modyfikacji stylu życia w leczeniu tej jednostki chorobowej [36,37]. Pomimo tego, styl życia kobiet z PCOS wykazuje wiele nieprawidłowości [38-40]. Wykazano, że redukcja masy ciała o 5% w opisywanej grupie pacjentek jest istotnie związana z poprawą gospodarki hormonalnej oraz zmniejszeniem ryzyka powikłań metabolicznych, jak również z większą szansą na pojawienie się spontanicznej owulacji [36]. Uważa się, że dieta i aktywność fizyczna są czynnikami korzystnie wpływającymi na insulinowrażliwość tkanek, stężenie adiponektyny oraz przebieg owulacji [41-48]. Co więcej, nieprawidłowa dieta oraz niska aktywność fizyczna stanowią dodatkowe czynniki ryzyka otyłości brzusznej poza czynnikami związanymi z patogenezą PCOS [49,50]. Należy podkreślić, że rola czynników dietetycznych w odniesieniu do IR, otyłości brzusznej oraz stężenia adipokin jest dość dobrze udowodniona, jednakże niewiele jest badań poświęconych temu zagadnieniu u kobiet z PCOS. Wzór żywieniowy korzystnie wpływający na insulinowrażliwość tkanek powinien być oparty na zasadach diety śródziemnomorskiej [51]. Dodatkowo wyniki badań wskazały na rolę poszczególnych produktów spożywczych i składników odżywczych w profilaktyce i leczeniu IR. Korzystny wpływ na insulinowrażliwość tkanek wydaje się mieć wzór żywieniowy bogaty w pełnoziarniste produkty zbożowe o niskim indeksie glikemicznym, warzywa, owoce, nasiona roślin strączkowych, orzechy, jogurt naturalny, oleje roślinne oraz tłuste ryby morskie. Jednocześnie mięso czerwone, zwłaszcza przetworzone oraz produkty będące źródłem cukrów prostych, disacharydów i kwasów tłuszczowych trans powinny być znacznie ograniczone ze względu na ich negatywny wpływ na wrażliwość tkanek na insulinę [52-58]. Jednakże, szczególnie dyskusyjne w kontekście wypływu na gospodarkę węglowodanową oraz owulację wydaje się być spożycie mleka i produktów mlecznych [56,59-61].

Mając na uwadze fakt, jak ważna jest rola diety, aktywności fizycznej i prawidłowego stanu odżywienia w leczeniu PCOS, jak również niewielką ilość badań łączących czynniki związane ze stylem życia a insulinoopornością, otyłością brzuszną oraz stężeniem adipokin w tej grupie pacjentek, niniejsza praca doktorska, składająca się z trzech prac przeglądowych będących niesystematycznym przeglądem

piśmiennictwa oraz trzech prac oryginalnych, analizuje znaczenie wpływu diety, aktywności fizycznej oraz stanu odżywienia na zaburzenia metaboliczne towarzyszące zespołowi policystycznych jajników, ze szczególnym uwzględnieniem insulinooporności.

2. Cel pracy

Nadrzędnym celem pracy była analiza wpływu diety, aktywności fizycznej oraz stanu odżywienia na zaburzenia metaboliczne towarzyszące zespołowi policystycznych jajników, ze szczególnym uwzględnieniem insulinooporności.

Do celów szczegółowych należało:

2.1. Wstęp do badania właściwego

- Ocena związku spożycia mleka i produktów mlecznych z ryzykiem insulinooporności, cukrzycy typu 2 oraz zaburzeń płodności u kobiet oraz ich potencjalnego wpływu na przebieg zespołu policystycznych jajników (Publikacja 1).
- Ocena wpływu czynników żywieniowych na stężenie adiponektyny (Publikacja 2).
- Ocena wpływu czynników żywieniowych na ryzyko zaburzeń owulacji u kobiet z uwzględnieniem kobiet z zespołem policystycznych jajników (Publikacja 3).

2.2. Badanie właściwe

- Ocena zależności pomiędzy dietą i aktywnością fizyczną a insulinoopornością (mierzoną za pomocą HOMA-IR, HOMA-AD i L/A ratio) oraz stężeniem adipokin wydzielanych przez tkankę tłuszczową (adiponektyna, leptyna i rezystyna) u kobiet z zespołem policystycznych jajników w porównaniu z kobietami zdrowymi (Publikacja 4).
- Określenie potencjalnego wykorzystania HOMA-AD jako zastępczego markera dla HOMA-IR do oceny insulinooporności u kobiet z zespołem policystycznych jajników (Publikacja 4).
- Ocena zależności pomiędzy otyłością brzuszną oraz typem dystrybucji tkanki tłuszczowej w okolicy brzusznej (mierzonej za pomocą wskaźników: VAT, SAT, VAT/SAT oraz WHR) a występowaniem i nasileniem insulinooporności (mierzonej za pomocą HOMA-IR, HOMA-AD i L/A ratio) u kobiet z zespołem policystycznych jajników (Publikacja 5).
- Ocena zależności pomiędzy otyłością brzuszną a dietą i aktywnością fizyczną u kobiet z zespołem policystycznych jajników (Publikacja 5).

- Ocena związku pomiędzy parametrami antropometrycznymi oraz składu ciała, ze szczególnym uwzględnieniem otyłości brzusznej, a parametrami obrony antyoksydacyjnej takimi jak GSH, GSSG, stosunek GSH/GSSG, GPx, GR oraz białka układu Nrf2 i Keap1 wśród kobiet z zespołem policystycznych jajników (Publikacja 6).

3. Materiał i metody

3.1. Wstęp do badania właściwego

Wstęp do badania właściwego stanowią trzy publikacje poglądowe będące niesystematycznym przeglądem piśmiennictwa obejmującego wyniki badań dotyczących związku pomiędzy spożyciem mleka i produktów mlecznych a ryzykiem zaburzeń gospodarki węglowodanowej oraz zaburzeń owulacji, jak również wpływu czynników żywieniowych na stężenie adiponektyny oraz ryzyko zaburzeń owulacji.

3.2. Badanie właściwe

3.2.1. Grupa badana

Grupę badaną stanowiło 56 kobiet z zespołem policystycznych jajników zakwalifikowanych do badania w Klinice Endokrynologii Ginekologicznej Warszawskiego Uniwersytetu Medycznego w latach 2021-2022. Kryterium włączenia do badania stanowił wiek 18-40 lat oraz rozpoznanie PCOS na podstawie kryteriów rotterdamskich, które obejmowały obecność co najmniej dwóch z następujących trzech kryteriów: oligoowulacja i/lub brak owulacji, kliniczny i/lub biochemiczny hiperandrogenizm oraz obraz policystycznych jajników w badaniu ultrasonograficznym [2]. Kryteriami wyłączenia z badania były: cukrzyca, dysfunkcja tarczycy, endometrioza, zespół Cushinga, guz uwalniający androgeny, wrodzony przerost nadnerczy, przewlekłe nadciśnienie tętnicze, choroby sercowo-naczyniowe, stosowanie leków hipolipemizujących, hormonalnych lub uwrażliwiających na insulinę, ciąża i laktacja. Ze względu na metodę pomiaru składu ciała BIA *(ang. bioelectrical impedance analysis)* uwzględniono dodatkowe kryteria wykluczenia, takie jak rozpoznana padaczka, wszczepiony rozrusznik serca lub defibrylator oraz metalowe endoprotezy. Do porównania badanych paramentów wykorzystano grupę kontrolną składającą się z 33 zdrowych kobiet w wieku 18-40 lat, mających prawidłowe i regularne cykle miesiączkowe, prawidłowy obraz jajników w badaniu ultrasonograficznym oraz brak cech hiperandrogenizmu (Publikacja 4). W celu dalszej analizy kobiety z PCOS podzielono na cztery grupy w zależności od zawartości VAT, SAT, wartości stosunku VAT/SAT oraz WHR (Publikacja 5) oraz na dwie grupy w zależności od wartości VAT/SAT oraz WHR (Publikacja 6).

Wszystkie uczestniczące kobiety wyraziły pisemną i świadomą zgodę na udział w badaniu. Badanie zostało zatwierdzone przez Komisję Bioetyczną Warszawskiego Uniwersytetu Medycznego (zgoda nr KB/170/2019).

3.2.2. Pomiary antropometryczne oraz analiza składu ciała metodą BIA

U pacjentek zakwalifikowanych do badania dokonano pomiarów antropometrycznych masy ciała, wzrostu, obwodu talii oraz bioder zgodnie z obowiązującymi procedurami [62,63]. BMI *(ang. body mass index)* obliczono na podstawie wzoru: masa ciała/wzrost^2 (kg/m^2), zaś wskaźnik WHR obliczono dzieląc obwód talii (cm) przez obwód bioder (cm). Otyłość brzuszną zdefiniowano jako WHR ≥0,85 (Publikacja 5 i 6) [63,64].

Badanie składu ciała z uwzględnieniem tkanki tłuszczowej brzusznej (wisceralnej i podskórnej) dokonano metodą impedancji bioelektycznej z wykorzystaniem analizatora Maltron BioScan 920-II (Maltron International Ltd., Rayleigh, UK) z przestrzeganiem procedur określonych przez producenta oraz zaleceń ESPEN *(ang. European Society of Parenteral and Enteral Nutrition)* [65,66]. Na podstawie obwodu talii oraz impedancji brzusznej tkanki wisceralnej i podskórnej za pomocą oprogramowania Maltron BioScan 920 v. 1.1.135 określono następujące parametry: powierzchnię tłuszczu podskórnego (SAT w cm^2), powierzchnię tłuszczu wisceralnego (VAT w cm^2) oraz stosunek powierzchni tłuszczu wisceralnego do podskórnego (stosunek VAT/SAT). Otyłość brzuszną określono na podstawie punktów odcięcia: VAT >120 cm^2, SAT >225 cm^2, VAT/SAT >0,9 (Publikacja 5 i 6) [66].

3.3.3. Analiza biochemiczna oraz ocena insulinooporności

U każdej uczestniczki badania pobrano na czczo krew żylną w godzinach porannych (pomiędzy 7:00 a 9:00) w fazie folikularnej (pomiędzy 2 a 6 dniem cyklu) w celu oznaczenia stężenia glukozy i insuliny na czczo (Publikacja 4, 5 i 6), stężenia adipokin takich jak adiponektyna, leptyna i rezystyna (Publikacja 4 i 5), testosteronu, androstendionu, hormonu luteinizującego, hormonu folikulotropowego, hormonu tyreotropowego, estradiolu, globuliny wiążącej hormony płciowe, 17-hydroksyprogesteronu, siarczanu dehydroepiandrosteronu, GSH, GSSG, GPx, GR, Nrf2 oraz Keap1. Na podstawie stosunku GSH do GSSH wyznaczono wskaźnik redoks komórki (R) (Publikacja 6).

Oznaczenie stężenia glukozy w surowicy przeprowadzono metodą enzymatyczną z użyciem heksokinazy (Integra 400 plus, Roche Diagnostics, Bazylea, Szwajcaria), zaś stężenie insuliny oraz innych hormonów za pomocą dwuetapowego testu immunologicznego chemiluminescencji (CMIA; Alinity I, Abbott Diagnostics GmbH, Wiesbaden, Niemcy). Z kolei stężenie adipokin w surowicy oznaczono za pomocą testu immunoenzymatycznego ELISA (*ang. enzyme-linked immunosorbent assay)* zgodnie z instrukcjami otrzymanymi od producenta. Leptynę oceniano przy użyciu zestawu firmy DRG Instruments GmbH (Marburg, Niemcy), adiponektynę za pomocą zestawu firmy TECOmedical AG (Sissach, Switzerland), a rezystynę za pomocą zestawu wyprodukowanego przez firmę Mediagnost (Reutlingen, Niemcy). Stężenia parametrów obrony antyoksydacyjnej również zmierzono za pomocą testu ELISA. Do oceny stężeń GSH i GSSG wykorzystano zestawy SunRed Bio-technology Company (Human GSH ELISA Kit Cat. No.: 201-12-5407; Human GSSG ELISA Kit Cat. No.: 201-12-5444, Szanghaj, Chiny). Stężenia Nrft2 oznaczono za pomocą zestawu NFE2L2 ELISA (cat. No. EH3417, Fine Biotech Co., Ltd., Wuhan, Chiny), stężenie Keap1 za pomocą zestawu KEAP1 (No. EH4240, Fine Biotech Co., Ltd., Wuhan, Chiny) a stężenia GR i GPx z wykorzystaniem zestawów firmy MyBioSource Inc (cat. No. MBS2703164 oraz cat. No. MBS167041, San Diego, USA).

Do oceny insulinooporności wykorzystano następujące modele matematyczne: HOMA-IR (obliczony jako: [insulina na czczo (μU/ml) × glukoza na czczo (mg/dl)]/405) (Publikacja 4, 5 i 6); HOMA-AD (obliczony jako: [insulina w osoczu na czczo (μU/ml) × glukoza na czczo (mmol/l)]/adiponektyna (μg/ml) (Publikacja 4 i 5) i L/A (obliczony jako: leptyna (ng/ml)/adiponektyna μg/ml) (Publikacja 4 i 5). Insulinooporność zdefiniowano na podstawie punktów odcięcia: HOMA-IR ≥2,5 [67], HOMA-AD ≥6,26 [68] oraz L/A >2,2 [69] (Publikacja 4 i 5).

3.3.4. Ocena zgodności diety z dietą obniżającą insulinooporność

Do oceny sposobu odżywiania wykorzystano autorski kwestionariusz częstotliwości spożycia produktów FFQ *(ang. food frequency questionnaire*), który został przeprowadzony przez dietetyka podczas bezpośredniego wywiadu z uczestniczkami badania. Kwestionariusz FFQ składał między innymi z pytań o produkty, które mają negatywny lub pozytywny związek z wrażliwością tkanek na insulinę. W punktacji oceniającej dietę uwzględniono produkty takie jak: pełnoziarniste produkty zbożowe, rafinowane produkty zbożowe, jogurt naturalny, owoce, warzywa,

oleje roślinne (w tym awokado i margaryny miękkie), tłuszcze twarde (w tym masło, margaryny twarde, olej palmowy i kokosowy), orzechy, nasiona roślin strączkowych, czerwone mięso, przetworzone czerwone mięso, tłuste ryby morskie, słodkie napoje, słodycze (w tym cukier) i fast foody. Uczestniczki zostały poproszone o podanie średniej częstotliwości spożycia i ilości porcji każdego produktu spożywczego (brak, ilość porcji w ciągu dnia, ilość porcji w tygodniu lub ilość porcji w miesiącu). Wielkość deklarowanych porcji żywności została zweryfikowana za pomocą *„Albumu Fotografii Produktów Spożywczych i Dań”* Instytutu Żywności i Żywienia [70]. Na podstawie przyznanych punktów (0, 0,5 lub 1) obliczano stopień przestrzegania diety zalecanej w insulinooporności. Maksymalna liczba punktów, które można było uzyskać wynosiła 15. Większa liczba punktów uzyskanych przez badaną pacjentkę przekładała się na większą zgodność z dietą obniżającą insulinooporność (Publikacje 4 i 5). Szczegółowy sposób przyznawania punktów przedstawiono w Tabeli 1.

Tabela 1. Sposób przyznawania punktów za poszczególne elementy diety.

Grupa produktów spożywczych	**Punktacja diety**
Pełnoziarniste produkty zbożowe	4-5 porcji dziennie -1 pkt 2-3 porcje dziennie - 0,5 pkt <2 porcji dziennie - 0 pkt
Rafinowane produkty zbożowe	0 porcji dziennie - 1 pkt 1-2 porcji dziennie - 0,5 pkt >3 porcji dziennie - 0 pkt
Jogurt naturalny	6-7 porcji tygodniowo - 1 pkt 3-5 porcji tygodniowo - 0,5 pkt <3 porcji tygodniowo - 0 pkt
Owoce	2 porcje dziennie - 1 pkt 1 porcja dziennie - 0,5 pkt 0 porcji dziennie - 0 pkt
Warzywa	≥ 5 porcji dziennie - 1 pkt 2-4 porcje dziennie - 0,5 pkt ≤ 2 porcji dziennie - 0 pkt
Oleje roślinne (w tym awokado i margaryny miękkie)	2 porcje dziennie - 1 pkt 1 porcja dziennie - 0,5 pkt 0 porcji dziennie - 0 pkt
Tłuszcze twarde (w tym masło, margaryny twarde, olej palmowy i kokosowy)	0 porcji dziennie - 1 pkt 1 porcja dziennie - 0,5 pkt >2 porcji dziennie - 0 pkt
Orzechy	6-7 porcji tygodniowo - 1 pkt 3-5 porcji tygodniowo - 0,5 pkt <3 porcji tygodniowo - 0 pkt
Nasiona roślin strączkowych	3-4 porcje tygodniowo - 1 pkt 1-2 porcje tygodniowo - 0,5 pkt 0 porcji tygodniowo - 0 pkt
Mięso czerwone	0 porcji tygodniowo - 1 pkt do 500 g tygodniowo - 0,5 pkt >500 g tygodniowo - 0 pkt

Mięso czerwone przetworzone	0 porcji miesięcznie - 1 pkt do 90 g miesięcznie - 0,5 pkt >90 g miesięcznie - 0 pkt
Tłuste ryby morskie	2 porcje tygodniowo - 1 pkt 1 porcja tygodniowo - 0,5 pkt 0 porcji tygodniowo - 0 pkt
Słodkie napoje	0 porcji dziennie - 1 pkt ≤ 250 ml dziennie - 0,5 pkt >250 ml dziennie - 0 pkt
Słodycze (w tym cukier)	≤ 2 porcji tygodniowo - 1 pkt 3-7 porcji tygodniowo - 0,5 pkt >7 porcji tygodniowo - 0 pkt
Fast foody	≤ 1 porcji miesięcznie - 1 pkt 2-3 porcje miesięcznie - 0,5 pkt >3 porcji miesięcznie - 0 pkt

3.3.5. Ocena aktywności fizycznej

Aktywność fizyczną mierzono za pomocą monitora aktywności Actigraph GT3X-BT (Actigraph Corp, Pensacola, USA), który był noszony przez 7 kolejnych dni na elastycznym pasku wokół talii nad prawym kolanem. Surowe dane z akcelerometru pobrano za pomocą oprogramowania ActiLife (wersja 6.13.0, ActiGraph Corporation).

Czas spędzony na aktywności fizycznej o umiarkowanej intensywności (MPA, *ang. moderate physical activity*), intensywnej intensywności (VPA, *ang. vigorous physical activity*) oraz łącznie umiarkowanej i intensywnej intensywności (MVPA, *ang. moderate-to-vigorous physical activity*) mierzono na podstawie progów zliczania ustalonych przez Freedsona i wsp. [71]: MPA: 1952–5724 zliczeń/min, VPA: ≥5725 zliczeń/min oraz MVPA ≥1952 zliczeń/min. Czas spędzony na aktywności o określonej intensywności określono sumując minuty w tygodniu, w którym liczba spełniała kryterium dla tej intensywności (Publikacja 4 i 5).

3.3.6. Analiza statystyczna

Analizy statystyczne wykonano za pomocą programu STATISTICA™ 13.3 (TIBCO Software, Palo Alto, CA, USA) (Publikacja 4 i 5) oraz IBM SPSS (IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY, USA: IBM Corp) (Publikacja 6). Wartość $p<0,05$ uznano za istotną statystycznie. Wykorzystano elementy statystyki opisowej takie jak średnie, odchylenia standardowe, mediany i rozstępy międzykwartylowe. Rozkłady zmiennych oceniono za pomocą testu K-kwadrat D'Agostino (Publikacja 4), testu Andersona-Darlinga (Publikacja 5) oraz testu Kołmogorowa-Smirnowa (Publikacja 6). Do porównania kobiet z PCOS do grupy kontrolnej

wykorzystano test Manna–Whitneya–Wilcoxona (Publikacja 4), zaś do porównana kobiet z PCOS podzielonych na podgrupy ze względu na miary otyłości brzusznej test Manna–Whitneya–Wilcoxona lub test t-Studenta (Publikacja 5 i 6).

Tabele kontyngencji z dokładnym testem Fishera lub testem chi-kwadrat wykorzystano do oceny zależności między częstością występowania insulinooporności według różnych wskaźników (Publikacja 4) oraz do oceny zależności między częstością i prawdopodobieństwem wystąpienia insulinooporności a różnymi wskaźnikami otyłości brzusznej (Publikacja 5).

Analizę regresji liniowej wykorzystano do oceny zależności między badanymi parametrami a aktywnością fizyczną oraz stopniem przestrzegania diety obniżającej insulinooporność. Do oszacowania parametrów regresji liniowej zastosowano estymację metodą najmniejszych kwadratów. Dla każdej zmiennej niezależnej uwzględnionej w modelu oszacowano standaryzowany współczynnik regresji (β) z 95% przedziałem ufności (95% CI, *ang. confidence interval*). Z kolei analizę regresji logistycznej przeprowadzono w celu zbadania prawdopodobieństwa normalizacji wartości badanych parametrów w zależności od punktacji diety lub ilości aktywności fizycznej. Do oszacowania parametrów regresji logistycznej zastosowano metodę estymacji największej wiarygodności. Dla każdej zmiennej niezależnej uwzględnionej w modelu oszacowano iloraz szans (OR, *ang. odds ratio*) z 95% przedziałem ufności (95% CI) (Publikacja 4 i 5).

Korelacje pomiędzy HOMA-IR oraz HOMA-AD, jak również korelacje pomiędzy adipokinami, stężeniem insuliny i glukozy na czczo oraz HOMA-IR, HOMA-AD i L/A ratio a parametrami antropometrycznymi oraz składu ciała zbadano za pomocą współczynnika korelacji Pearsona (Publikacja 4). Do obliczenia korelacji pomiędzy GSH, GSSG oraz wskaźnikiem R a parametrami antropometrycznymi oraz składu ciała, jak również zależność między Keap1 a trzema wyżej wymienionymi parametrami obrony antyoksydacyjnej wykorzystano współczynnik korelacji rho Spearmana (Publikacja 6).

4. Wyniki

4.1. Wstęp do badania właściwego

4.1.1. Mleko i produkty mleczne oraz ich wpływ na gospodarkę węglowodanową i płodność — potencjalna rola w diecie kobiet z zespołem policystycznych jajników (Publikacja 1).

Związek pomiędzy spożyciem mleka i produktów mlecznych a ryzykiem zaburzeń gospodarki węglowodanowej jest przedmiotem wielu badań, a wyniki pozostają wciąż niejednoznaczne. Wiele badań wskazuje, że spożywanie mleka i produktów mlecznych dodatnio wiąże się ryzykiem insulinooporności u kobiet, jak również z wyższymi stężeniami insuliny i glukozy na czczo oraz wartościami HOMA-IR [60,61,72,73]. Związek ten obserwuje się w szczególności przy wysokim spożyciu tej grupy produktów, które ze względu na obecność aminokwasów rozgałęzionych (leucyny, izoleucyny i waliny) wykazują silne działanie stymulujące wydzielanie insuliny [74]. Sugeruje się więc, że niekorzystny wpływ spożycia produktów mlecznych na gospodarkę węglowodanową prawdopodobnie nie jest związany z osłabieniem wrażliwości tkanek na insulinę, a z tym, że białka mleka krowiego mogą wydłużać poposiłkowe wydzielanie insuliny [75]. Należy jednocześnie zauważyć, że istnieją badania, w których nie zaobserwowano związku pomiędzy obecnością produktów mlecznych w diecie a ryzykiem zaburzeń gospodarki węglowodanowej [76-78]. Ponadto istnieje wiele danych przemawiających za ich działaniem zwiększającym insulinowrażliwość tkanek oraz zmniejszającym ryzyko T2DM [56,59,79-81]. Warto podkreślić, że korzystne działanie produktów mlecznych w kontekście insulinowrażliwości tkanek obserwuje się przy dłuższym i regularnym ich spożywaniu [82,83]. Dodatkowo, wyniki badań sugerują, że znaczenie ma również rodzaj produktów mlecznych w diecie. Szczególnym produktem mlecznym wydaje się być jogurt naturalny oraz inne produkty fermentowane, które ze względu na zawarte w nich bakterie probiotyczne wykazują silne działanie uwrażliwiające tkanki na działanie insuliny [75,84,85]. Ponadto więcej danych przemawia na korzyść nabiału niskotłuszczowego nad wysokotłuszczowym, zarówno w kontekście ryzyka insulinooporności, jak i cukrzycy typu 2 [84,86,87].

Wyniki wielu badań sugerują ważną rolę produktów mlecznych we wspieraniu kobiecej płodności oraz zwiększeniu szans na urodzenie dziecka przez kobiety, które poddały się procedurze rozrodu wspomaganego [88-90]. Natomiast wyniki badań na szczurach, jak również nieliczne na kobietach, wskazują na ich niekorzystny wpływ na gospodarkę hormonalną oraz zaburzenia cyklu miesiączkowego, głównie ze względu na obecność laktozy [91-93]. Dodatkowo zwiększone spożycie produktów mlecznych może być związane z wyższymi stężeniami IGF-I *(ang. insulin-like growth factor I)* we krwi, co również ma niekorzystny wpływ na czynność jajników i liczbę pęcherzyków antralnych [94]. Ponadto, istnieją przesłanki podkreślające niekorzystny wpływ odtłuszczonych produktów mlecznych na ryzyko zaburzeń owulacji, głównie ze względu na fakt, że produkty mleczne charakteryzujące się niższą zawartością tłuszczu prowadzą do większego wydzielania IGF-1 w porównaniu do ich wysokotłuszczowych odpowiedników [95]. Co więcej, zaobserwowano dodatnią korelację pomiędzy wysokim spożyciem produktów mlecznych a ryzykiem wystąpienia PCOS [96]. Jednak wyniki badań pozostają sprzeczne, a kwestia ewentualnej przewagi nabiału niskotłuszczowego nad wysokotłuszczowym wymaga dalszych badań, w szczególności w grupie kobiet z PCOS.

4.1.2. Wpływ sposobu odżywiania na stężenie adiponektyny (Publikacja 2).

Tkanka tłuszczowa, będąca rezerwuarem energii, jest także aktywnym narządem wydzielania wewnętrznego syntetyzującym i wydzielającym różnorodne adipokiny wpływające na regulację metabolizmu człowieka. Adiponektyna jest jedną z najważniejszych adipokin. Wykazuje silne działanie kardioprotekcyjne, przeciwnowotworowe, przeciwzapalne, hipoglikemizujące oraz uwrażliwiające tkanki na działanie insuliny [97]. Wiele badań wykazało, że jej stężenie w surowicy u kobiet z PCOS jest istotnie obniżone w porównaniu do grupy kontrolnej [29-32]. Istnieje wiele czynników, które mają wpływ na ekspresję adiponektyny, ale to stan odżywienia, dieta i aktywność fizyczna wydają się być najważniejszymi modyfikowalnymi jej determinantami [97-99].

Przestrzeganie założeń diety śródziemnomorskiej jest jednym z najsilniejszych modulatorów stężenia adiponektyny. Obecność jednonienasyconych kwasów tłuszczowych, wielonienasyconych kwasów tłuszczowych omega-3, błonnika i polifenoli sprawia, że dieta śródziemnomorska jest szczególnie korzystna. Ponadto

wydaje się prawdopodobne, że związek między tą dietą a profilaktyką chorób cywilizacyjnych, takich jak nowotwory, choroby układu krążenia i zaburzenia metaboliczne, może wynikać z jej korzystnego wpływu na stężenie tej adipokiny [100,101]. Ponadto, wydaje się, że dieta DASH *(ang. Dietary Approaches to Stop Hypertention),* dieta oparta na produktach roślinnych oraz dieta o obniżonej wartości energetycznej również są wzorami żywieniowymi mogącymi powodować wzrost stężenia adiponektyny [102-104]. Także umiarkowane spożycie alkoholu, w szczególności czerwonego wina oraz produktów mlecznych wydają się wywierać korzystny wpływ na regulację jej stężenia [105-107]. Z kolei wysoki indeks glikemiczny i ładunek glikemiczny diety, wysokie spożycie rafinowanych produktów zbożowych, mięsa czerwonego, zwłaszcza przetworzonego oraz produktów bogatych w nasycone kwasy tłuszczowe, kwasy tłuszczowe trans oraz fruktozę i sacharozę to czynniki, które niekorzystnie wpływają na stężenie adiponektyny. Wydaje się zatem, że hipoadiponektynemia jest szczególnie związana ze wzorami żywieniowymi typowymi dla diety zachodniej oraz diety niskotłuszczowej i wysokowęglowodanowej [108-113].

4.1.3. Wpływ sposobu odżywiania na zaburzenia owulacji (Publikacja 3).

Niepłodność kobieca może być spowodowana różnymi mechanizmami, jednakże wśród najczęstszych jej przyczyn wymienia się zaburzenia owulacji, u których podłoża leży przede wszystkim PCOS. Nawet 80% kobiet z PCOS charakteryzuje się zaburzeniami owulacji co przyczynia się do problemów z poczęciem dziecka. Patomechanizm zaburzeń owulacji u kobiet z PCOS jest złożony, a u ich podstawy leżą przede wszystkim zaburzenia hormonalne [8]. W patogenezie niepłodności owulacyjnej dużą rolę odgrywają również: otyłość, w szczególności brzuszna, insulinooporność, stres oksydacyjny oraz nieprawidłowości w ilości wydzielanych adipokin przez tkankę tłuszczową [8,10,11,26-28].

Należy zaznaczyć, że na płodność kobiet związaną z owulacją wpływa wiele czynników, do których można zaliczyć: wiek, palenie papierosów, stres, stosowanie substancji psychoaktywnych, stan odżywienia oraz aktywność fizyczną. Ponadto także czynniki związane z dietą odgrywają ważną rolę w regulacji owulacji [48,114,115]. Sposób żywienia może wpływać na płodność i owulację u kobiet poprzez wpływ na szlaki metaboliczne, profil hormonalny i metabolizm węglowodanów [116]. Do czynników dietetycznych wpływających pozytywnie na owulację należą: produkty

zbożowe o niskim indeksie glikemicznym, białko roślinne, wysokotłuszczowe produkty mleczne, jednonienasycone i wielonienasycone kwasy tłuszczowe, kwas foliowy, witamina D, antyoksydanty oraz żelazo. Dlatego też dieta oparta na strukturze diety śródziemnomorskiej wydaje się być szczególnie korzystna, również ze względu na jej przeciwzapalne właściwości [48,117,118]. Z kolei do czynników żywieniowych, które mają negatywny wpływ można zaliczyć przede wszystkim produkty o wysokim indeksie glikemicznym, duże ilości białka zwierzęcego, nasycone kwasy tłuszczowe i kwasy tłuszczowe trans, napoje energetyzujące będące źródłem dużej ilości kofeiny oraz alkohol, które są typowo spotykane w prozapalnym zachodnim modelu żywienia [119-122].

Wymienione produkty oraz składniki odżywcze charakteryzują wzór żywieniowy znany jako dieta płodności (ang. *fertility diet*). W prospektywnym badaniu kohortowym The Nurses' Health Study II [48] wykazano, że większa zgodność z jej zasadami wiązała się z lepszą płodnością kobiet ogółem, jak również ze zmniejszeniem ryzyka niepłodności owulacyjnej. Ten sposób żywienia charakteryzował się mniejszym spożyciem kwasów tłuszczowych trans przy jednoczesnej zwiększonej podaży kwasów tłuszczowych jednonienasyconych, wyższą zawartością raczej roślinnego niż zwierzęcego białka, obecnością wysokotłuszczowych produktów mlecznych, produktów węglowodanowych o niskim ładunku glikemicznym, wysokiej zawartości żelaza niehemowego oraz wyższym spożyciem preparatów wielowitaminowych zawierających kwas foliowy. Co więcej, sugeruje się, że w grupie kobiet z PCOS przestrzeganie tego modelu żywieniowego jest szczególnie zalecane i wiąże się z pojawieniem się spontanicznych owulacji oraz ogólną poprawą płodności, co dodatkowo podkreśla rolę diety w postępowaniu terapeutycznym w tej jednostce chorobowej.

4.2. Badanie właściwe

4.2.1. Raczej aktywność fizyczna niż dieta jest związana z niższą insulinoopornością u kobiet z PCOS — badanie kliniczno-kontrolne (Publikacja 4).

Kobiety z PCOS charakteryzowały się istotnie statystycznie wyższą masą ciała (p=0,008), BMI (p=0,004), obwodem talii (p=0,003), całkowitą zawartością tkanki tłuszczowej (p=0,008), zawartością tkanki tłuszczowej wisceralnej (p=0,018)

i zawartością tkanki tłuszczowej podskórnej (p=0,003) w porównaniu ze zdrowymi kobietami z grupy kontrolnej. Ponadto w tej grupie kobiet również wskaźnik VAT/SAT był wyższy, ale różnica nie była istotna statystycznie. Kobiety z PCOS miały istotnie statystycznie niższe stężenie adiponektyny w porównaniu z kobietami z grupy kontrolnej (7,57 ± 2,44 vs. 14,15 ± 3,98 μg/ml; p<0,001). Nie zaobserwowano jednak istotnych statystycznie różnic w stężeniach leptyny i rezystyny. Kobiety z PCOS miały istotnie statystycznie wyższe wskaźniki L/A (p<0,001) oraz HOMA-AD (p=0,029) porównaniu ze zdrowymi kobietami, podczas gdy HOMA-IR nie różniło się istotnie statystycznie pomiędzy grupami.

Grupa kobiet z PCOS charakteryzowała się statystycznie istotnie niższym MVPA w porównaniu z grupą kontrolną (301,92 ± 107,67 vs. 376,60 ± 43,72 min/tydzień; p=0,003). Podobnie, MPA i VPA był również istotnie statystycznie niższe (odpowiednio p=0,012; p=0,016). Jednakże nie zaobserwowano istotnych statystycznie różnic między liczbą punktów za dietę w grupie badanej i kontrolnej (p=0,280). Szczegółowe porównanie grupy kobiet z PCOS z grupą kontrolną przedstawiono w Tabeli 2.

Tabela 2. Porównanie badanych parametrów pomiędzy grupą PCOS a grupą kontrolną.

Parametry	PCOS (n = 56)	KONTROLA (n = 33)	p-value*
WIEK I POMIARY ANTROPOMETRYCZNE			
Wiek (lata)	25,96 ± 4,10 25,00 (19 - 38)	29,12 ± 6,85 31,00 (19 - 38)	NS
Masa ciała (kg)	75,99 ± 21,46 70,00 (45,0 - 126,4)	63,09 ± 10,44 60,00 (47,0 - 93,0)	0,008
Wzrost (cm)	166,70 ± 5,12 165,00 (158 - 180)	167,42 ± 5,85 167,00 (154 - 178)	NS
BMI (kg/m^2)	27,25 ± 7,40 24,65 (17,2 - 42,9)	22,43 ± 3,17 21,90 (17,9 - 32,9)	0,004
WC (cm)	86,84 ± 18,34 84,50 (58 - 126)	75,20 ± 8,12 73,50 (63 - 91)	0,003
SKŁAD CIAŁA			
FM (kg)	27,93 ± 15,81 23,24 (7,45 - 64,37)	18,34 ± 7,44 16,75 (8,94 - 40,55)	0,008
FM (%)	34,08 ± 10,62 33,16 (15,84 - 51,96)	28,04 ± 6,66 27,92 (16,25 - 43,60)	0,010
VAT (cm^2)	154,32 ± 124,21 112,50 (21 - 350)	72,52 ± 42,24 57,00 (22 - 174)	0,018
SAT (cm^2)	149,68 ± 87,86 126,00 (37 - 380)	94,39 ± 39,99 88,00 (28 - 212)	0,003
VAT/SAT	1,03 ± 0,58 0,87 (0,38 - 2,41)	0,77 ± 0,30 0,74 (0,33 - 1,45)	NS
FFM (kg)	48,06 ± 6,14 46,76 (37,40 - 64,07)	44,91 ± 3,93 44,77 (37,25 - 53,79)	0,021
FFM (%)	65,99 ± 10,51 66,84 (48,05 - 84,16)	71,96 ± 6,66 72,08 (56,40 - 83,75)	0,010
MM (kg)	21,07 ± 2,92 20,46 (14,76 - 28,34)	19,51 ± 1,76 19,52 (16,22 - 23,71)	0,012

BCM (kg)	25,24 ± 4,41 24,2 (15,96 - 35,13)	22,87 ± 2,35 22,9 (18,79 - 28,36)	0,015
ECM (kg)	22,78 ± 2,10 22,7 (19,00 - 28,94)	22,05 ± 1,92 21,8 (18,45 - 25,92)	NS
TBW (%)	46,50 ± 5,20 46,37 (37,50 - 55,88)	49,75 ± 3,99 49,65 (41,3 - 57,61)	0,004
ECW (%)	47,15 ± 3,74 46,70 (44,32 - 67,97)	48,29 ± 3,36 47,53 (45,63 - 61,95)	0,002
ICW (%)	52,86 ± 3,75 53,30 (32,02 - 56,67)	51,70 ± 3,36 52,46 (38,04 - 54,36)	0,002
ECW/ICW	0,91 ± 0,20 0,88 (0,80 - 2,12)	0,94 ± 0,16 0,91 (0,84 - 1,63)	0,002
PARAMETRY BIOCHEMICZNE			
Glukoza na czczo (mg/dl)	91,63 ± 6,98 90,50 (77,4 - 122,0)	96,45 ± 6,26 96,00 (82,0 - 113,0)	<0,001
Insulina na czczo (μU/ml)	7,71 ± 4,39 6,50 (2,50 - 24,07)	8,24 ± 3,73 7,50 (3,40 - 18,00)	NS
Adiponektyna (μg/ml)	8,13 ± 3,51 7,57 (2,20 - 16,40)	14,70 ± 5,92 14,15 (5,02 - 27,50)	<0,001
Leptyna (ng/ml)	14,42 ± (10,77) 10,31 (1,40 - 48,20)	10,46 ± 9,25 6,60 (2,01 - 43,58)	NS
Rezystyna (ng/ml)	7,29 ± 2,50 6,72 (4,10 - 15,70)	7,41 ± 1,75 6,93 (4,73 - 12,14)	NS
HOMA-IR	1,77 ± 1,08 1,38 (0,54 - 5,59)	1,97 ± 0,92 1,70 (0,80 - 4,43)	NS
HOMA-AD	6,70 ± 5,97 4,11 (1,17 - 23,98)	3,58 ± 2,35 3,29 (0,99 - 11,63)	0,029
L/A	2,60 ± 2,74 1,40 (0,12 - 12,06)	0,93 ± 1,25 0,56 (0,13 - 6,55)	<0,001
PUNKTY ZA DIETĘ ORAZ AKTYWNOŚĆ FIZYCZNA			
Punkty za dietę	7,56 ± 2,46 7,50 (1,5 - 13,0)	8,15 ± 2,10 8,50 (3,5 - 12,0)	NS
MPA [min/tydzień]	296,06 ± 137,94 264,33 (71,50 - 611)	372,41 ± 139,28 359,10 (158,17 - 821,50)	0,012
VPA [min/tydzień]	20,24 ± 36,31 8,50 (0,00 - 223,67)	35,34 ± 45,72 16,80 (2,80 - 203,83)	0,009
MVPA [min/tydzień]	316,30 ± 141,42 301,92 (72,17 - 627,33)	407,67 ± 135,78 376,60 (186,80 - 835,33)	0,003

Dane to: średnia ± odchylenie standardowe, mediana i rozstępy międzykwartylowe. *Test Manna- Whitneya; p<0,05. Skróty: PCOS – zespół policystycznych jajników; BMI – wskaźnik masy ciała; WC – obwód talii; FM – masa tkanki tłuszczowej; VAT – powierzchnia tkanki tłuszczowej wisceralnej; SAT – powierzchnia tkanki tłuszczowej podskórnej; VAT/SAT – stosunek powierzchni tkanki tłuszczowej wisceralnej do tkanki tłuszczowej podskórnej; FFM – beztłuszczowa masa ciała; MM – masa mięśniowa; BCM – masa komórkowa; ECM – macierz pozakomórkowa; TBW – całkowita ilość wody w organizmie; ECW – woda zewnątrzkomórkowa; ICW – woda wewnątrzkomórkowa, ECW/ICW – stosunek wody zewnątrzkomórkowej do wody wewnątrzkomórkowej; HOMA-IR – ocena modelu homeostazy oporności na insulinę; HOMA-AD – ocena modelu homeostazy – adiponektyna; L/A – stosunek leptyny do adiponektyny; MPA – umiarkowana aktywność fizyczna; VPA – intensywna aktywność fizyczna; MVPA – umiarkowana do intensywnej aktywność fizyczna; NS- nieistotne statystycznie.

Współczynnik korelacji Pearsona wykazał silną dodatnią korelację między wartościami HOMA-IR i HOMA-AD w grupie badanej i kontrolnej (odpowiednio r=0,8248, p<0,001; r=0,6662, p=0,00002). Co więcej, korelacja była znacznie silniejsza w grupie kobiet z PCOS. Ponadto zaobserwowano związek między insulinoopornością rozpoznaną za pomocą HOMA-IR i HOMA-AD zarówno w grupie PCOS (χ^2=10,76; p=0,00104), jak i kontrolnej (χ^2=15,04; p=0,00011). Spośród pacjentek z PCOS 11

miało rozpoznaną IR przy użyciu obu wskaźników, przy czym tylko 2 takie kobiety były w grupie kontrolnej. Zaobserwowano istotnie statystycznie wyższą częstość występowania IR wśród kobiet z PCOS określoną na podstawie HOMA-AD niż HOMA-IR. Według wskaźnika HOMA-IR 11 kobiet z PCOS i 10 kobiet z grupy kontrolnej charakteryzowało się nieprawidłową wrażliwością tkanek na insulinę. W przypadku zastosowania wskaźnika HOMA-AD aż 22 kobiety z PCOS miały IR, podczas gdy w grupie kontrolnej tylko 3 kobiety uzyskały wynik ≥6,26. Ponadto zauważono, że prawdopodobieństwo nieprawidłowego wyniku HOMA-AD było istotnie statystycznie zwiększone w grupie PCOS w porównaniu z grupą kontrolną (OR 6,47 95% CI 1,76-23,80; p=0,0029). Z kolei wskaźnik L/A wykazał, że 25 kobiet z PCOS i tylko 2 kobiety z grupy kontrolnej miały wyniki odbiegające od normy.

Wszystkie wskaźniki IR korelowały istotnie statystycznie z parametrami antropometrycznymi oraz składu ciała wśród kobiet z PCOS. W większości korelacje te były silniejsze w grupie PCOS niż w grupie kontrolnej. HOMA-IR i wskaźnik A/L były najsilniej skorelowane z VAT (odpowiednio r=0,6061; p<0,001 i r=0,7305; p<0,001), podczas gdy, HOMA-IR był skorelowany tylko z SAT (r=0,5239; p=0,002) w grupie kontrolnej. W grupie PCOS najsilniejszą dodatnią korelację odnotowano między HOMA-AD a masą ciała (r=0,7197; p<0,001), BMI (r=0,7012; p<0,001) oraz VAT (r=0,7185; p<0,001). Dodatkowo u kobiet z PCOS HOMA-AD korelował ze wskaźnikiem VAT/SAT (r=0,6307; p<0,001), podczas gdy u kobiet bez PCOS takiego związku nie stwierdzono. Podobną zależność odnotowano w przypadku wskaźnika A/L.

Analiza regresji liniowej wykazała zróżnicowany wpływ aktywności fizycznej na wartość HOMA-IR w zależności od grupy. Zaobserwowano, że wyższy poziom aktywności fizycznej (wyrażony jako MVPA) był związany z niższym HOMA-IR w grupie PCOS (t=-2,109; p=0,038). Jednakże w grupie kontrolnej nie stwierdzono istotnej statystycznie zależności między tymi parametrami. Co więcej, nie stwierdzono związku między HOMA-IR a liczbą punktów za dietę zarówno w grupie PCOS, jak i w grupie kontrolnej. Ponadto nie zaobserwowano takiego związku między aktywnością fizyczną oraz liczbą punktów za dietę a stężeniami adipokin w surowicy (adiponektyny, leptyny i rezystyny), HOMA-AD i stosunkiem L/A w obu grupach kobiet. Uwzględnienie w analizie wartości BMI i MVPA nie wpłynęło na wyniki.

Ponadto regresja logistyczna wykazała zróżnicowany wpływ aktywności fizycznej na prawdopodobieństwo wystąpienia prawidłowej wartości HOMA-IR w zależności od grupy. W grupie PCOS wyższy poziom aktywności fizycznej

(wyrażony jako MVPA) przekładał się na większą szansę na prawidłową wartość HOMA-IR (OR 1,012 95% CI 1,003-1,021; p=0,01). Jednak w grupie kontrolnej takiej zależności nie zaobserwowano. Również wyższa punktacja za dietę nie miała wpływu na prawdopodobieństwo wystąpienia prawidłowej wartości HOMA-IR u kobiet z PCOS i kobiet z grupy kontrolnej. Podobnie nie zaobserwowano takiego związku między aktywnością fizyczną i oceną diety a stężeniami adipokin w surowicy oraz wartościami HOMA-AD i stosunku L/A w obu grupach kobiet. Podobnie jak w poprzedniej analizie, uwzględnienie wartości BMI i MVPA nie zmieniło wyników.

4.2.2. Otyłość brzuszna u kobiet z zespołem policystycznych jajników i jej związek z dietą, aktywnością fizyczną i insulinoopornością: badanie pilotażowe (Publikacja 5).

Grupa PCOS z podwyższonym VAT (>120 cm^2), SAT (>225 cm^2), wskaźnikiem VAT/SAT (>0,9) i WHR (≥0,85) charakteryzowała się istotnie statystycznie wyższymi stężeniami insuliny na czczo (odpowiednio p<0,001; p=0,007; p<0,001 i p=0,005) w porównaniu z kobietami z prawidłową wartością wskaźników otyłości brzusznej. Jednak nie wykazano istotnych statystycznie różnic w stężeniu glukozy na czczo pomiędzy tymi grupami. Dodatkowo w grupie kobiet z otyłością brzuszną stwierdzono istotnie statystycznie niższe stężenie adiponektyny oraz istotnie statystycznie wyższe stężenie leptyny i rezystyny w porównaniu z kobietami z prawidłowymi wartościami tych parametrów. Ponadto, kobiety z otyłością brzuszną miały istotnie statystycznie wyższe wartości HOMA-IR i HOMA-AD w porównaniu z kobietami bez otyłości brzusznej. Podobną zależność zaobserwowano w przypadku wskaźnika L/A.

Kobiety z PCOS z nieprawidłowymi wartościami VAT, VAT/SAT i WHR charakteryzowały się istotnie statystycznie niższym poziomem przestrzegania diety zalecanej w IR (mierzonej za pomocą punktacji diety) (odpowiednio p=0,002; p=0,023 i p=0,026) oraz istotnie statystycznie niższym poziomem intensywnej aktywności fizycznej (odpowiednio p=0,005; p=0,026 i p=0,027) w porównaniu z uczestniczkami z prawidłowymi wartościami tych wskaźników. Nie zaobserwowano takich różnic w przypadku grup różniących się zawartością tłuszczu podskórnego. Ponadto nie zaobserwowano różnic w ilości umiarkowanej aktywności fizycznej i wskaźnika MVPA między kobietami z otyłością brzuszną i bez niej. Szczegółowe porównanie

kobiet z PCOS podzielonych na podstawie wskaźników otyłości brzusznej przedstawiono w Tabeli 3 i 4.

Tabela 3. Porównanie badanych parametrów w grupie PCOS podzielonej na podstawie zawartości VAT i SAT.

Parametery	**VAT ≤120 cm n=31**	**VAT >120 cm² n=25**	**p-value***	**SAT ≤225 cm² n=47**	**SAT >225 cm² n=9**	**p-value***
WIEK I PARAMETRY ANTROPOMETRYCZNE						
Wiek (lata)	25,65 ± 4,46 25 19–38	26,36 ± 3,65 26 21–36	NS	26,28 ± 4,26 25 19–38	24,33 ± 2,78 24 21–29	NS
Masa ciała (kg)	60,01 ± 7,96 58 45–75	95,82 ± 15,41 94 70–126,4	<0,001	70,51 ± 17,86 66,7 45–119	104,64 ± 15,23 111 83,7–126,4	<0,001
Wzrost (cm)	166,26 ± 4,27 165 158–174	167,24 ± 6,07 165 158–180	NS	166,83 ± 5,1 165 158–180	166 ± 5,48 165 159–174	NS
BMI (kg/m²)	21,65 ± 2,69 21,2 17,2–27,8	34,2 ± 5,03 35,5 24,8–42,9	<0,001	25,21 ± 5,88 23,5 17,2–36,7	37,92 ± 4,97 39,3 28,7–42,9	<0,001
WC (cm)	72,77 ± 7,96 73 58–92	104,28 ± 10,94 103 86–126	<0,001	81,94 ± 15,24 76 58–118	112,44 ± 9,96 113 96–126	<0,001
HC (cm)	92,03 ± 7,37 92 72–104	117,84 ± 10,09 120 100–140	<0,001	99,62 ± 13,15 97 72–128	124,11 ± 9,99 124 113–140	<0,001
WHR	0,79 ± 0,05 0,79 0,7–0,9	0,88 ± 0,06 0,87 0,8–1	<0,001	0,82 ± 0,06 0,82 0,7–1	0,9 ± 0,07 0,9 0,81-1	0,002
SKŁAD CIAŁA						
FFM (kg)	44,08 ± 3,06 44,14 37,4–49,1	53,01 ± 5,35 52,03 43,5–64,1	<0,001	46,99 ± 5,7 46,03 37,4–64,1	53,65 ± 5,49 56,1 43,5–62	0,002
FFM (%)	74,1 ± 5,63 73,71 62,5–84,2	55,94 ± 4,84 55,35 48,1–66,3	<0,001	68,75 ± 9,07 70,79 53,7–84,2	51,6 ± 3,09 50,95 48,1–57,9	<0,001
FM (kg)	15,94 ± 5,39 15,25 7,5–28,2	42,81 ± 10,96 42,74 23,6–64,4	<0,001	23,52 ± 12,53 19,86 7,5–54,9	50,99 ± 10,13 54,45 36,6–64,4	<0,001
FM (%)	25,9 ± 5,63 26,29 15,8–37,5	44,22 ± 5,03 44,65 33,7–52	<0,001	31,25 ± 9,07 29,21 15,8–46,3	48,84 ± 3,3 49,46 42,1–52	<0,001
MM (kg)	19,13 ± 1,51 19,41 14,8–21,4	23,46 ± 2,42 22,9 19,3–28,3	<0,001	20,54 ± 2,73 20,18 14,18–28,3	23,78 ± 2,45 24,91 19,3–27,6	0,002
VAT (cm²)	55,87 ± 29,58 51 21–116	276,4 ± 78,87 296 131–350	<0,001	116,98 ± 97,89 66 21–350	349,33 ± 2 350 344–350	<0,001
SAT (cm²)	89,45 ± 34,97 78 37–194	224,36 ± 75,28 202 123–380	<0,001	118,94 ± 53,71 119 37–222	310,22 ± 43,99 285 266–380	<0,001
VAT/SAT	0,64 ± 0,36 0,55 0,4–2,4	1,51 ± 0,39 1,5 0,9–2,4	<0,001	0,89 ± 0,5 0,65 0,4–2,4	1,75 ± 0,36 1,89 1,2–2,4	<0,001
PARAMETRY BIOCHEMICZNE						
Glukoza na czczo (mg/dl)	89,94 ± 5,69 90 77,4–100,8	93,74 ± 7,93 93 81–122	NS	92,05 ± 7,38 91,8 77,4–122	89,44 ± 3,88 90 81–94	NS
Insulina na czczo (µU/ml)	5,25 ± 1,95 5 2,5–11,2	10,76 ± 4,67 9,4 4,8–24,1	<0,001	7,04 ± 3,84 6,1 2,5–20,1	11,2 ± 5,61 10,6 4,8–24,1	0,007

Adiponektyna (µg/ml)	10,13 ± 2,77 10 5,6–16,2	5,64 ± 2,68 5,3 2,2–16,4	<0,001	8,61 ± 3,57 8,3 3,2–16,4	5,6 ± 1,78 5,9 2,2–7,9	0,013
Leptyna (ng/ml)	7,97 ± 6,62 6,3 1,4–32,4	22,41 ± 9,52 20,6 8,3–48,2	<0,001	12,7 ± 10,67 9,2 1,4–48,2	23,37 ± 5,9 22,5 13,4–33,2	0,001
Rezystyna (ng/ml)	6,16 ± 1,67 5,7 4,1–13,2	8,7 ± 2,66 8,1 5,3–15,7	<0,001	7,01 ± 2,45 6,2 4,1–15,7	8,77 ± 2,37 8,3 5,7–11,8	0,027
HOMA-IR	1,17 ± 0,46 1,1 0,5–2,5	2,52 ± 1,17 2,3 1,1–5,6	<0,001	1,63 ± 0,98 1,3 0,5–4,8	2,5 ± 1,33 2,4 1,1–5,6	0,014
HOMA-AD	2,84 ± 1,57 2,3 1,2–8,3	11,5 ± 5,94 11,4 2,2–24	<0,001	5,87 ± 5,68 3,4 1,2–24	11,07 ± 5,79 11,6 3,4–20	0,005
L/A	0,93 ± 1,13 0,7 0,1–5,8	4,68 ± 2,74 4,3 0,6–12,1	<0,001	2,21 ± 2,68 0,9 0,1–12,1	4,69 ± 2,12 4,3 2–9,3	0,002
PUNKTY ZA DIETĘ I AKTYWNOŚĆ FIZYCZNA						
Punkty za dietę	8,39 ± 2,54 9 1,5–13	6,54 ± 1,95 6 4–12	0,002	7,8 ± 2,52 7,5 1,5–13	6,33 ± 1,71 6 4,5–9	NS
MPA [min/tydzień]	295,59 ± 143,76 256,8 73,7–222,2	296,64 ± 133,32 217,8 71,5–602,7	NS	301,84 ± 144,1 256,8 73,7–611	265,86 ± 101,03 291 71,5–379,7	NS
VPA [min/tydzień]	30,35 ± 46,18 11,2 0,2–223,7	7,71 ± 7,75 5,7 0–38,2	0,005	22,98 ± 39,05 9 0,2–223,7	5,96 ± 4,67 5,7 0–13,2	NS
MVPA [min/tydzień]	325,94 ± 146,42 304 82,2–627,3	304,36 ± 136,98 273,5 72,2–609	NS	234,82 ± 146,78 302,3 82,2–627,3	271,83 ± 104,69 269,7 72,2–385,3	NS

Dane to średnia ± odchylenie standardowe, mediana i rozstępy międzykwartylowe. *Test Manna–Whitneya; p<0,05. Skróty: PCOS – zespół policystycznych jajników; VAT – powierzchnia tkanki tłuszczowej wisceralnej; SAT – powierzchnia tkanki tłuszczowej podskórnej; VAT/SAT – stosunek powierzchni tkanki tłuszczowej wisceralnej do tkanki tłuszczowej podskórnej ; WHR – stosunek obwodu talii do obwodu bioder; BMI – wskaźnik masy ciała; WC – obwód talii; HC – obwód bioder; FFM –beztłuszczowa masa ciała; FM – masa tkanki tłuszczowej; MM – masa mięśniowa; HOMA-IR – ocena modelu homeostazy oporności na insulinę; HOMA-AD – ocena modelu homeostazy – adiponektyna; L/A – stosunek leptyny do adiponektyny; MPA – umiarkowana aktywność fizyczna; VPA – intensywna aktywność fizyczna; MVPA – umiarkowana do intensywnej aktywność fizyczna; NS- nieistotne statystycznie.

Tabela 4. Porównanie badanych parametrów w grupie PCOS podzielonej na podstawie wartości wskaźnika VAT/SAT i WHR.

Parametery	**VAT/SAT ≤0,9 n=29**	**VAT/SAT >0,9 n=27**	**p-value***	**WHR <0,85 n=35**	**WHR ≥0,85 n=21**	**p-value***
WIEK I PARAMETRY ANTROPOMETRYCZNE						
Wiek (lata)	25,66 ± 4,55 25 19–38	26,3 ± 3,61 26 21–36	NS	25,6 ± 3,85 25 19–35	26,57 ± 4,51 26 21–38	NS
Masa ciała (kg)	60,39 ± 8,39 58,9 45–75	92,76 ± 18,32 93 56–126,4	<0,001	66,55 ± 17,66 59 45–117	91,73 ± 17,91 91 166,33 ± 5,38	<0,001
Wzrost (cm)	166,45 ± 4,35 166 158–174	166,96 ± 5,92 165 158–180	NS	166,91 ± 5,03 166 158–178	166,33 ± 5,38 165 159–180	NS
BMI (kg/m^2)	21,73 ± 2,82 21,5 17,2–27,8	33,18 ± 6,05 34,5 21–42,9	<0,001	23,77 ± 5,91 22,3 17,2–42,9	33,06 ± 5,86 34,50 23,4–41,7	<0,001
WC (cm)	73,07 ± 8,58 72 58-92	101,63 ± 13,93 103 73-126	<0,001	77,11 ± 13,23 74 58-113	103,05 ± 13,65 103 73-126	<0,001

HC (cm)	92,76 ± 7,71 93 72-104	115,15 ± 13,32 114 84-140	<0,001	97,63 ± 14,13 94 72-140	113,43 ± 12,7 114 84-137	<0,001
WHR	0,79 ± 0,05 0,78 0,7–0,9	0,88 ± 0,06 0,87 0,8–1	<0,001	0,79 ± 0,04 0,8 0,7–0,8	0,9 ± 0,05 0,88 0,9–1	<0,001
SKŁAD CIAŁA						
FFM (kg)	44,25 ± 3,11 48,88 37,4–49,1	52,16 ± 5,97 51,3 40,4–64,1	<0,001	45,91 ± 5,49 45,54 37,4–62,6	51,65 ± 5,55 50,4 42,5–64,1	<0,001
FFM (%)	74,01 ± 5,98 73,75 62,5–84,2	57,38 ± 6,83 55,91 48,1–73,6	<0,001	71,16 ± 8,97 72,9 48,8–84,2	57,38 ± 6,53 55,35 48,1–71,6	<0,001
FM (kg)	16,15 ± 5,75 15,03 7,5–28,2	40,59 ± 13,1 41,97 15,7–64,4	<0,001	20,64 ± 12,57 15,86 7,5–59,9	40,08 ± 13,06 40,21 17,9–64,4	<0,001
FM (%)	25,99 ± 5,98 26,28 15,8–37,5	42,76 ± 6,99 44,09 26,4–52	<0,001	28,84 ± 8,97 27,1 15,8–51,2	42,81 ± 6,75 44,65 28,4–52	<0,001
MM (kg)	19,19 ± 1,56 19,41 14,8–21,4	23,08 ± 2,7 22,79 17,8–28,3	<0,001	20,06 ± 2,62 19,98 14,8–27,6	22,74 ± 2,65 22,5 18,6–28,3	<0,001
VAT (cm^2)	53,69 ± 29,98 51 21–134	262,41 ± 90,79 291 88–350	<0,001	86,37 ± 79,78 51 21–350	267,57 ± 100,31 301 66–350	<0,001
SAT (cm^2)	91,76 ± 36,05 78 45–194	211,89 ± 84,67 200 37–380	<0,001	105,46 ± 50,07 100 45–267	223,38 ± 88,55 219 37–380	<0,001
VAT/SAT	0,56 ± 0,13 0,53 0,4–0,9	1,53 ± 0,42 1,5 0,9–2,4	<0,001	0,72 ± 0,33 0,57 0,4–1,6	1,55 ± 0,52 1,59 0,5–2,4	<0,001
PARAMETRY BIOCHEMICZNE						
Glukoza na czczo (mg/dl)	89,66 ± 5,66 90 77,4–100,8	93,75 ± 7,72 93 81–122	NS	90,55 ± 5,86 90 77,4–101	93,43 ± 8,38 93 81-122	NS
Insulina na czczo (µU/ml)	4,97 ± 1,4 5 2,5–7,4	10,66 ± 4,6 9,6 4,5–24,1	<0,001	6,59 ± 3,72 5,8 2,5–20,1	9,58 ± 4,85 8,1 4,5–24,1	0,005
Adiponektyna (µg/ml)	10,4 ± 2,95 10,3 5,6–16,4	6,68 ± 2,18 5,6 2,2–13,2	<0,001	9,28 ± 3,56 8,8 2,2–16,4	6,2 ± 2,48 5,7 3,2–13,2	<0,001
Leptyna (ng/ml)	7,8 ± 6,81 6,1 1,4–32,4	21,52 ± 9,69 20,4 8,3–48,2	<0,001	8,53 ± 5,83 7,7 1,4–21,5	24,22 ± 9,97 22,5 7,8–48,2	<0,001
Rezystyna (ng/ml)	6,10 ± 1,71 5,7 4,1–13,2	8,57 ± 2,61 8 5,3–15,7	<0,001	6,8 ± 2,68 5,9 4,1–15,7	8,1 ± 1,97 7,9 5,5–11,9	0,002
HOMA-IR	1,10 ± 0,32 1,1 0,5–1,7	2,49 ± 1,15 2,3 1–5,6	<0,001	1,49 ± 0,89 1,3 0,5–4,8	2,24 ± 1,22 1,9 1–5,6	0,007
HOMA-AD	2,54 ± 0,98 2,3 1,2–4,6	11,18 ± 5,84 10,9 1,7–24	<0,001	5,02 ± 5,45 2,8 1,2–24	9,51 ± 5,84 8,3 1,7–23,2	<0,001
L/A	0,9 ± 1,16 0,6 0,1-5,8	4,44 ± 2,77 4,1 0,7-12,1	<0,001	1,37 ± 1,84 0,8 0,1-9,3	4,66 ± 2,78 4,6 0,7-12,1	<0,001
PUNKTY ZA DIETĘ I AKTYWNOŚĆ FIZYCZNA						
Punkty za dietę	8,21 ± 2,58 8,5 1,5–13	6,87 ± 2,16 6,5 4–12	0,023	8,13 ± 1,19 8 4–13	6,62 ± 2,64 6 1,5–12	0,026

MPA [min/tydzień]	307,57 ± 145,05 256,8 102,2–611	283,7 ± 131,49 271,8 71,5–602,7	NS	292,47 ± 136,01 256,8 73,7–611	302,04 ± 144,3 293 71,5–602,7	NS
VPA [min/tydzień]	31,3 ± 47,67 11,2 0,2–223,7	8,37 ± 7,66 8 0–38,2	0,026	27,8 ± 44,16 10,7 0,2–223,7	7,64 ± 6,62 6,3 0–29,2	0,027
MVPA [min/tydzień]	338,87 ± 145,6 239,5 106–627,3	292,07 ± 135,27 273,5 72,2–609	NS	320,27 ± 139,1 302,3 82,2–627,3	309,69 ± 148,42 301,5 72,2–609	NS

Dane to średnia ± odchylenie standardowe, mediana i rozstępy międzykwartylowe, *Test Manna–Whitneya; p<0,05. Skróty: PCOS – zespół policystycznych jajników; VAT – powierzchnia tkanki tłuszczowej wisceralnej; SAT – powierzchnia tkanki tłuszczowej podskórnej; VAT/SAT – stosunek powierzchni tkanki tłuszczowej wisceralnej do tkanki tłuszczowej podskórnej ; WHR – stosunek obwodu talii do obwodu bioder; BMI – wskaźnik masy ciała; WC – obwód talii; HC – obwód bioder; FFM –beztłuszczowa masa ciała; FM – masa tkanki tłuszczowej; MM – masa mięśniowa; HOMA-IR – ocena modelu homeostazy oporności na insulinę; HOMA-AD – ocena modelu homeostazy – adiponektyna; L/A – stosunek leptyny do adiponektyny; MPA – umiarkowana aktywność fizyczna; VPA – intensywna aktywność fizyczna; MVPA – umiarkowana do intensywnej aktywność fizyczna; NS- nieistotne statystycznie.

Zaobserwowano istotnie statystycznie większą częstość występowania IR mierzonej za pomocą HOMA-IR, HOMA-AD i stosunku L/A u kobiet z PCOS ze zwiększoną zawartością tkanki tłuszczowej wisceralnej, zwiększonym wskaźnikiem VAT/SAT oraz WHR w porównaniu z kobietami z prawidłowymi wartościami tych parametrów. Z kolei istotnie statycznie wyższą częstość występowania IR (mierzoną za pomocą HOMA-AD i stosunku L/A) zaobserwowano u kobiet z prawidłową zawartością tłuszczu podskórnego w porównaniu z kobietami z SAT >225 cm^2, natomiast różnice w występowaniu IR mierzonej za pomocą HOMA-IR nie były istotne statystycznie. Dodatkowo odnotowano najwyższą częstość IR u kobiet z PCOS z otyłością brzuszną ocenianą stosunkiem L/A w porównaniu z HOMA-IR i HOMA-AD. Ponadto stwierdzono, że kobiety z HOMA-IR ≥2,5 miały istotnie statystycznie wyższe wartości VAT, SAT, VAT/SAT i WHR (odpowiednio z=−3,589, p<0,001; z=-3,393, p<0,001; z=-3,714, p<0,001 i z=-3,294, p=0,001). Wykazano podobną zależność dla HOMA-AD ≥6,26 (odpowiednio z=-5,116, p<0,00; z=-4,564, p<0,001; z=-5,002, p<0,001 i z=-3,637; p<0,001) oraz stosunku L/A >2,2 (odpowiednio z=-5,795, p<0,001; z=-5,654, p<0,001; z=-5,236, p<0,001 i z=-4,844, p <0,001). Szczegółowe dane dotyczące częstości IR u kobiet z PCOS i otyłością brzuszną przedstawiono w Tabeli 5 i 6.

Tabela 5. Różnice w częstości występowania insulinooporności mierzonej za pomocą HOMA-IR, HOMA-AD i L/A w zależności od zawartości VAT i SAT.

	VAT ≤120 cm² n=31	**VAT >120 cm² n=25**	**p-value***	**SAT ≤225 cm² n=47**	**SAT >225 cm² n=9**	**p-value***
HOMA-IR ≥2,5	1,79%	17,86%	0,002	12,50%	7,14%	NS
HOMA-AD ≥6,26	3,57%	35,71%	<0,001	26,79%	12,50%	0,021
L/A >2,2	5,36%	39,29%	<0,001	30,36%	14,29%	0,007

*Różnice analizowano dokładnym testem Fishera; p<0,05. Skróty: VAT – powierzchnia tkanki tłuszczowej wisceralnej; SAT – powierzchnia tkanki tłuszczowej podskórnej; HOMA-IR – ocena modelu homeostazy oporności na insulinę; HOMA-AD – ocena modelu homeostazy – adiponektyna; L/A – stosunek leptyny do adiponektyny; NS – nieistotne statystycznie.

Tabela 6. Różnice w częstości występowania insulinooporności mierzonej za pomocą HOMA-IR, HOMA-AD i L/A w zależności od wartości wskaźnika VAT/SAT i WHR.

	VAT/SAT ≤0,9 n=29	**VAT/SAT >0,9 n=27**	**p-value***	**WHR <0,85 n=35**	**WHR ≥0,85 n=21**	**p-value***
HOMA-IR ≥2,5	0%	19,64%	<0,001	5,36%	14,29%	0,013
HOMA-AD ≥6,26	0%	39,29%	<0,001	16,07%	23,21%	0,013
L/A >2,2	5,36%	39,29%	<0,001	12,5%	32,14%	<0.001

*Różnice analizowano dokładnym testem Fishera; p<0,05. Skróty: VAT/SAT – stosunek powierzchni tkanki tłuszczowej wisceralnej do tkanki tłuszczowej podskórnej; WHR – stosunek odwodu talii do obwodu bioder; HOMA-IR – ocena modelu homeostazy oporności na insulinę; HOMA-AD – ocena modelu homeostazy – adiponektyna; L/A – stosunek leptyny do adiponektyny.

Stwierdzono, że stosunek VAT/SAT był najlepszym predyktorem IR mierzonej za pomocą HOMA-IR i HOMA-AD. Zaobserwowano, że VAT/SAT >0,9 istotnie zwiększał prawdopodobieństwo wystąpienia IR zmierzonej za pomocą HOMA-IR 41,12 razy (OR 41,12 95% CI 2,27–743,52; p<0,001), a za pomocą HOMA-AD 241,36 razy (OR 241,36 95% CI 12,67–459,97; p<0,001). Z kolei VAT >120 cm^2 okazał się najlepszym i najsilniejszym predyktorem IR mierzonej wskaźnikiem L/A (OR 68,44, 95% CI 12,57–372,76; p<0,001), a następnie WHR ≥0,85 (OR 24,00 95% CI 5,48–105,05; p< 0,001) i SAT >225 cm^2 (OR 14,11 95% Cl 1,62–122,70; p=0,007), podczas gdy VAT/SAT najsilniej zwiększał prawdopodobieństwo nieprawidłowych wyników HOMA-AD. Warto podkreślić, że zwiększona zawartość podskórnej tkanki tłuszczowej wydawała się nie zwiększać prawdopodobieństwa HOMA-IR ≥2,5. Szczegółowe ilorazy szans dla wystąpienia IR w odniesieniu do różnych wskaźników otyłości brzusznej przedstawiono w Tabeli 7.

Tabela 7. Predyktory insulinooporności u kobiet z PCOS na podstawie VAT, SAT, VAT/SAT i WHR.

Parametry	HOMA-IR	HOMA-AD	L/A
VAT			
OR	20,00	58,00	68,44
95% Cl	2,33–171,18	10,22–329,11	12,57–372,76
p-value*	0,002	<0,001	<0,001
SAT			
OR	4,57	7,47	14,11
95% Cl	0,98–21,34	1,38–40,34	1,62–122,70
p-value*	NS	0,021	0,007
VAT/SAT			
OR	41,12	241,36	38,13
95% Cl	2,27–743,52	12,67–459,97	8,17–177,85
p-value*	<0,001	<0,001	<0,001
WHR			
OR	6,56	4,69	24,00
95% Cl	1,50–28,70	1,47–15,00	5,48–105,05
p-value*	0,013	0,011	<0,001

*Iloraz szans (OR) analizowano za pomocą dokładnego testu Fishera; p<0,05. Skróty: PCOS – zespół policystycznych jajników; VAT – powierzchnia tkanki tłuszczowej wisceralnej; SAT – powierzchnia tkanki tłuszczowej podskórnej; VAT/SAT – stosunek powierzchni tkanki tłuszczowej wisceralnej do tkanki tłuszczowej podskórnej; WHR – stosunek obwodu talii do obwodu bioder; HOMA-IR – ocena modelu homeostazy oporności na insulinę; HOMA-AD – ocena modelu homeostazy – adiponektyna; L/A – stosunek leptyny do adiponektyny; CI – przedział ufności; NS – nieistotne statystycznie.

Analiza regresji liniowej wykazała zróżnicowaną zależność między punktacją diety a otyłością brzuszną mierzoną za pomocą VAT, SAT, VAT/SAT i WHR. Zaobserwowano, że lepsze przestrzeganie diety zalecanej w IR (większa liczba punktów za dietę) było związane z istotnie statystycznie niższą zawartością VAT (t=-2,635; p=0,011), zawartością SAT (t=-2,905; p=0,005) i wartością WHR (t=−2,631; p= 0,011). Nie stwierdzono jednak istotnej statystycznie zależności pomiędzy oceną diety a wskaźnikiem VAT/SAT. Dodatkowo zauważono, że większa intensywna aktywność fizyczna była związana z istotnie statystycznie niższą zawartością VAT (t=-2,277; p=0,027), zawartością SAT (t=-2,028; p=0,048), wskaźnikiem VAT/SAT (t=-2,280; p=0,027) i WHR (t=-2,421; p=0,019). Nie zaobserwowano związku między umiarkowaną aktywnością fizyczną oraz MVPA a żadnym ze wskaźników otyłości brzusznej. Uwzględnienie w analizie wartości BMI nie wpłynęło na wyniki.

Ponadto regresja logistyczna wykazała zróżnicowany wpływ punktacji diety na prawdopodobieństwo wystąpienia prawidłowej zawartości VAT i wartości WHR. Zaobserwowano, że lepsze przestrzeganie zalecanej diety w IR przekładało się na większe o 43% szanse na prawidłową zawartość VAT (OR 1,427 95% Cl 1,091–1,868; p=0,009) i o 33% na większe szanse na prawidłową wartość WHR (OR 1,325 95% 1,023–1,716; p=0,033). Natomiast nie zaobserwowano takiego związku w przypadku zawartości SAT oraz stosunku VAT/SAT. Dodatkowo, wyższa intensywna aktywność fizyczna wiązała się z większym prawdopodobieństwem wystąpienia prawidłowych

wartości VAT (OR 1,063 95% CI 1,007-1,122; p=0,028) i VAT/SAT (OR 1,057 95% CI 1,006-1,110; p=0,028). Jednakże takiego związku nie zaobserwowano w przypadku intensywnej aktywności fizycznej, zawartości SAT i WHR ani pomiędzy MVPA a którymkolwiek ze wskaźników otyłości brzusznej. Podobnie jak w poprzedniej analizie, uwzględnienie wartości BMI nie zmieniło wyników. Ponadto analiza wieloczynnikowa wykazała, że dieta była czynnikiem niezależnym od aktywności fizycznej, który zwiększał prawdopodobieństwo wystąpienia prawidłowej zawartości VAT (OR 1,430 95% CI 1,097–1,864; p=0,008), VAT/SAT (OR 1,273 95 % Cl 1,003-1,615; p=0,047) i WHR (OR 1,322 95% Cl 1,025-1,704; p=0,031).

4.2.3. Obrona antyoksydacyjna wyrażona jako status glutationu i działanie układu Keap1-Nrf2 w odniesieniu do parametrów antropometrycznych i składu ciała u młodych kobiet z zespołem policystycznych jajników (Publikacja 6).

Wartości parametrów antyoksydacyjnych w surowicy kobiet z PCOS podzielonych na grupy ze względu na wartości wskaźników otyłości brzusznej VAT/SAT oraz WHR wykazały istotne statystycznie różnice. Stwierdzono, że stężenie GSSG i Keap1 były istotnie statystycznie wyższe, natomiast wartość wskaźnika R była istotnie statystycznie niższa w surowicy kobiet z VAT/SAT >0,9 w porównaniu z grupą z prawidłowymi wartościami tego wskaźnika. Podobne różnice wykazano dla GSSG i wskaźnika R pomiędzy grupami WHR ≥0,85 i WHR <0,85 (odpowiednio $p<0,05$ i $p<0,01$). Wraz ze wzrostem wskaźnika VAT/SAT i WHR zaobserwowano niższe stężenia GSH, jednakże różnice te nie były istotne statystycznie (choć w przypadku wskaźnika WHR były na granicy istotności (p=0,053)). Inne parametry obrony antyoksydacyjnej nie różniły się istotnie statystycznie pomiędzy badanymi grupami. Szczegółowe porównanie parametrów obrony antyoksydacyjnej w zależności od wskaźników otyłości brzusznej przedstawiono w Tabeli 8 i 9.

Tabela 8. Parametry obrony antyoksydacyjnej u kobiet z PCOS podzielonych na grupy ze względu na wartości wskaźnika VAT/SAT.

Parametry	VAT/SAT ≤0,9 n=29	VAT/SAT >0,9 n=27	p-value*
[a]GSH (µmol/l)	12,25 ± 3,64	10,74 ± 3,09	0,140
[a]GSSG (µmol/l)	3,68 ± 1,31	6,04 ± 1,75	0,000
[b]R (GSH/GSSG)	3,29 2,05–5,13	1,68 1,48–2,38	0,000
[a]GPx (ng/ml)	17,66 ± 4,99	18,38 ± 4,42	0,512
[b]GR (pg/ml)	261,00 199,85–331,67	245,56 185,80–301,23	0,181
[a]Nrf2(ng/ml)	1,42 ± 0,24	1,56 ± 0,33	0,147
[a]Keap1(pg/ml)	158,78 ± 32,26	176,94 ± 28,13	0,042

[a]Dane analizowano za pomocą testu t-Studenta i przedstawiono jako średnią i odchylenie standardowe (SD). [b]Dane analizowano za pomocą testu Manna-Whitneya-Wilcoxona i przedstawiono jako mediany i rozstępy międzykwartylowe (1-3 IQR). Skróty: VAT/SAT - stosunek powierzchni tkanki tłuszczowej wisceralnej do tkanki tłuszczowej podskórnej; GSH – glutation zredukowany; GSSG – glutation utleniony; GPx - peroksydaza glutationowa; GR - reduktaza glutationowa; R (stosunek GSH/GSSG) - wskaźnik redoks komórki; Nrf2 – jądrowy czynnik transkryptyczny pochodzenia erytroidalnego 2; Keap1 – Kelch-podobne białko 1 związane z ECH.

Tabela 9. Parametry obrony antyoksydacyjnej u kobiet z PCOS podzielonych na grupy ze względu na wartości wskaźnika WHR.

Parametry	WHR <0,85 n = 35	WHR ≥0,85 n = 21	p-value*
[a]GSH (µmol/l)	12,30 ± 3,77	10,23 ± 2,37	0,053
[a]GSSG (µmol/l)	4,02 2,99–5,26	6,42 3,61–7,42	0,016
[b]R (GSH/GSSG)	2,95 1,86–4,40	1,81 1,46–2,41	0,010
[a]GPx (ng/ml)	18,89 13,44–22,18	15,83 14,09–20,74	0,537
[b]GR (pg/ml)	268,61 ± 87,68	248,82 ± 69,74	0,412
[a]Nrf2 (ng/ml)	1,44 ± 0,21	1,52 ± 0,33	0,393
[a]Keap1 (pg/ml)	168,38 ± 32,78	166,12 ± 29,76	0,800

[a]Dane analizowano za pomocą testu t-Studenta i przedstawiono jako średnią i odchylenie standardowe (SD). [b]Dane analizowano za pomocą testu Manna-Whitneya-Wilcoxona i przedstawiono jako mediany i rozstępy międzykwartylowe (1-3 IQR). Skróty: WHR - stosunek obwodu talii do obwodu bioder; GSH – glutation zredukowany; GSSG – glutation utleniony; GPx - peroksydaza glutationowa; GR - reduktaza glutationowa; R (stosunek GSH/GSSG) - wskaźnik redoks komórki; Nrf2 – jądrowy czynnik transkryptyczny pochodzenia erytroidalnego 2; Keap1 – Kelch-podobne białko 1 związane z ECH.

Stężenia GSH w surowicy były ujemnie skorelowane z obwodem bioder (p=0,012), WHR (p=0,012) i wartościami wskaźnika VAT/SAT (p=0,039). Stężenia GSSG w surowicy były dodatnio skorelowane z masą ciała (p=0,007), BMI (p=0,005), WHR (p=0,026), zawartością VAT (p=0,001) i SAT (p=0,009), stosunkiem VAT/SAT (p<0,001), całkowitą zawartością tkanki tłuszczowej (p=0,001) i masą komórek (p=0,021) oraz odwrotnie skorelowane z beztłuszczową masą ciała (p=0,001) i całkowitą zawartością wody w organizmie (p<0,001). Ponadto stwierdzono ujemne korelacje wartości indeksu R z masą ciała (p=0,002), BMI (p=0,013), WHR (p=0,007), zawartością VAT (p=0,001) i SAT (p=0,013), stosunkiem VAT/SAT (p<0,001)

i całkowitą masą tkanki tłuszczowej (p=0,02), natomiast dodatnią korelację wartości wskaźnika R z beztłuszczową masą ciała (p=0,003) i całkowitą zawartością wody w organizmie (p=0,022). Zaobserwowano również pozytywne zależności między Keap1 a wartościami wskaźnika VAT/SAT (r=0,263; p=0,05). Stężenie insuliny na czczo i HOMA-IR były dodatnio skorelowane ze stężeniami GSSG (odpowiednio r=0,418; p=0,001; r=0,405; p=0,002) i ujemnie z wartościami wskaźnika R (odpowiednio r=−0,304; p=0,003; r=−0,380; p=0,004). Z kolei związki pomiędzy stężeniami Nrf2 a insuliną na czczo (r=0,256; p=0,057) i wartościami HOMA-IR (r=0,260; p=0,053) były na granicy istotności statystycznej. W badaniu stwierdzono również dodatnią korelację pomiędzy GSSG a białkiem Keap1 (r=0,294; p=0,028) oraz ujemną pomiędzy wskaźnikiem R a Keap1 (r=-0,357; p=0,007) wśród kobiet z PCOS. Podwyższone wartości stosunku glutationu zredukowanego do glutationu utlenionego były istotnie związane ze zwiększonym poziomem reduktazy glutationowej w surowicy pacjentek z PCOS (r=0,384; p=0,009). Szczegółowe korelacje przedstawiono w Tabeli 10.

Tabela 10. Współczynniki korelacji rang Spearmana między GSH, GSSG oraz wskaźnikiem R a parametrami antropometrycznymi u kobiet z PCOS.

Parametry	**GSH**		**GSSG**		**R (GSH/GSSG)**	
	rho	p-value	rho	p-value	rho	p-value
Masa ciała (kg)	-0,135	0,357	0,323	0,007	-0,305	0,002
Wzrost (cm)	0,077	0,573	-0,089	0,516	0,066	0,629
BMI (kg/m^2)	-0,179	0,188	0,371	0,005	-0,331	0,013
WC (cm)	-0,220	0,103	0,350	0,008	-0,332	0,013
HC (cm)	-0,109	0,012	0,335	0,012	-0,274	0,041
WHR	-0,333	0,012	0,298	0,026	-0,357	0,007
VAT (cm^2)	-0,239	0,076	0,416	0,001	-0,416	0,001
SAT (cm^2)	-0,207	0,127	0,348	0,009	-0,329	0,013
VAT/SAT	-0,277	0,039	0,471	0,000	-0,504	0,000
FM (kg)	-0,164	0,227	0,396	0,003	-0,351	0,008
FM (%)	-0,172	0,205	0,448	0,001	-0,399	0,002
FFM (kg)	-0,096	0,481	0,238	0,077	0,192	0,156
FFM (%)	0,170	0,209	-0,443	0,001	0,393	0,003
MM (kg)	-0,085	0,532	0,255	0,057	-0,213	0,116
BCM (kg)	-0,092	0,499	0,308	0,021	-0,251	0,062
ECM (kg)	-0,017	0,903	0,081	0,555	-0,050	0,714
TBW (%)	0,176	0,196	-0,451	0,000	0,408	0,022
ECW (%)	0,052	0,704	-0,383	0,004	0,307	0,021
ICW (%)	-0,051	0,711	0,383	0,004	-0,306	0,022
ECW/ICW	0,051	0,711	-0,380	0,004	0,304	0,023

Skróty: GSH – glutation zredukowany; GSSG – glutation utleniony; R (stosunek GSH/GSSG) - wskaźnik redoks komórki; BMI - wskaźnik masy ciała; WC - obwód talii; HC - obwód bioder; WHR - stosunek obwodu talii do obwodu bioder; VAT – powierzchnia tkanki tłuszczowej wisceralnej; SAT – powierzchnia tkanki tłuszczowej podskórnej; VAT/SAT –stosunek powierzchni tkanki tłuszczowej wisceralnej do tkanki tłuszczowej podskórnej; FM - masa tkanki tłuszczowej; FFM – beztłuszczowa masa ciała; MM - masa mięśniowa; BCM - masa komórkowa; ECM - macierz pozakomórkowa; TBW - całkowita ilość wody w organizmie; ECW - woda zewnątrzkomórkowa; ICW - woda wewnątrzkomórkowa; ECW/ICW – stosunek wody zewnątrzkomórkowej do wody wewnątrzkomórkowej.

5. Podsumowanie wyników i wnioski

5.1. Wstęp do badania właściwego

5.1.1. Mleko i produkty mleczne oraz ich wpływ na gospodarkę węglowodanową i płodność — potencjalna rola w diecie kobiet z zespołem policystycznych jajników (Publikacja 1).

1. Nie można jednoznacznie stwierdzić, że spożycie mleka i produktów mlecznych wiąże się z ryzykiem IR u kobiet, jednakże wydaje się, że ich duży udział w diecie może być predyktorem hiperinsulinemii oraz IR.
2. Włączenie mleka i produktów mlecznych do diety kobiet wydaje się zasadne ze względu na potencjalnie korzystny wpływ tych produktów na zmniejszenie ryzyka rozwoju T2DM.
3. Zasadne jest przede wszystkim włączenie do diety kobiet jogurtu naturalnego ze względu silne dowody przemawiające za jego działaniem zwiększającym insulinowrażliwość tkanek oraz zmniejszającym ryzyko T2DM.
4. Spożywanie mleka i produktów mlecznych ogółem wydaje się nie mieć negatywnego wpływu na płodność u kobiet. Natomiast spożywanie nabiału niskotłuszczowego może się wiązać z wyższym ryzykiem zaburzeń owulacji.
5. Ze względu na brak jednoznacznych dowodów nie można stwierdzić przewagi pełnotłustych produktów mlecznych nad niskotłuszczowymi, pomimo że spożycie wysokotłuszczowego nabiału wydaje się być bardziej korzystne w PCOS.

5.1.2. Wpływ sposobu odżywiania na stężenie adiponektyny (Publikacja 2).

1. Sposób odżywiania jest znaczącym modulatorem stężenia adiponektyny.
2. Do wzorów żywieniowych korzystnie wpływających na stężenie adiponektyny można zaliczyć dietę śródziemnomorską, dietę DASH, dietę opartą na produktach roślinnych oraz dietę hipokaloryczną. Z kolei zachodni model żywienia, dieta niskotłuszczowa i wysokowęglowodanowa oraz dieta o wysokim indeksie i ładunku glikemicznym są wzorami żywieniowymi zmniejszającymi stężenie adiponektyny.

3. Do produktów oraz składników odżywczych zwiększających stężenie adiponektyny można zaliczyć: jednonienasycone kwasy tłuszczowe, wielonienasycone kwasy tłuszczowe omega-3, błonnik pokarmowy, polifenole, alkohol (w szczególności czerwone wino) oraz produkty mleczne. Z kolei do negatywnie wpływających można zaliczyć: nasycone kwasy tłuszczowe, kwasy tłuszczowe trans, monosacharydy i disacharydy, rafinowane produkty zbożowe oraz czerwone mięso, w tym przetworzone.

5.1.3. Wpływ sposobu odżywiania na zaburzenia owulacji (Publikacja 3).

1. Sposób odżywania jest znaczącym czynnikiem wpływającym na ryzyko zaburzeń owulacji.
2. Do wzorów żywieniowych korzystnie wpływających na owulację można zaliczyć dietę śródziemnomorską, natomiast zachodni model żywienia jest wzorem żywieniowym zwiększającym ryzyko zaburzeń owulacji.
3. Do produktów oraz składników odżywczych wpływających pozytywnie na owulację należą: produkty zbożowe o niskim indeksie glikemicznym, białko roślinne, jednonienasycone i wielonienasycone kwasy tłuszczowe, wysokotłuszczowe produkty mleczne, kwas foliowy, witamina D, antyoksydanty oraz żelazo niehemowe. Z kolei produkty o wysokim indeksie glikemicznym, duże ilości białka zwierzęcego, nasycone kwasy tłuszczowe i kwasy tłuszczowe trans są czynnikami istotnie zwiększającymi ryzyko zaburzeń owulacji.

5.2. Badanie właściwe

5.2.1. Raczej aktywność fizyczna niż dieta jest związana z niższą insulinoopornością u kobiet z PCOS — badanie kliniczno-kontrolne (Publikacja 4).

1. Zespół policystycznych jajników wiąże się z wieloma nieprawidłowościami w składzie ciała. Przede wszystkim kobiety z PCOS charakteryzują się wyższą zawartością tkanki tłuszczowej ogółem oraz tkanki tłuszczowej zlokalizowanej w okolicy brzusznej (VAT oraz SAT) w porównaniu do zdrowych kobiet.

2. Zespół policystycznych jajników wiąże się również z nieprawidłowościami w metabolizmie tkanki tłuszczowej oraz wrażliwości tkanek na insulinę. Kobiety z PCOS charakteryzują się niższym stężeniem adiponektyny w porównaniu do zdrowych kobiet oraz wyższymi wartościami wskaźników HOMA-AD i L/A.
3. HOMA-AD wydaje się być obiecującym markerem zastępczym do oceny IR u kobiet z PCOS, ze względu na fakt, że uwzględnia on adiponektynę, która bierze udział w regulacji insulinowrażliwości tkanek. Jego wykorzystanie do oceny IR wiązało się z częstszym wykrywaniem przypadków IR w PCOS w porównaniu do wskaźnika HOMA-IR.
4. Kobiety z PCOS cechowały się niższą aktywnością fizyczną w porównaniu do zdrowych kobiet.
5. Aktywność fizyczna wiązała się z mniejszym nasileniem insulinooporności u kobiet z zespołem policystycznych jajników. Dlatego też każdej kobiecie z PCOS należy w postępowaniu terapeutycznym udzielić porady dotyczącej zwiększenia aktywności fizycznej.
6. Ze względu na małą liczebność grupy badanej nie można jednoznacznie ocenić zależności między dietą a insulinoopornością oraz stylem życia a stężeniem adiponektyny, leptyny oraz rezystyny w surowicy w tej jednostce chorobowej.

5.2.2. Otyłość brzuszna u kobiet z zespołem policystycznych jajników i jej związek z dietą, aktywnością fizyczną i insulinoopornością: badanie pilotażowe (Publikacja 5).

1. Otyłość brzuszna u kobiet z PCOS wiąże się z nieprawidłowym metabolizmem tkanki tłuszczowej skutkującym niższym stężeniem adiponektyny oraz wyższymi stężeniami leptyny i rezystyny w surowicy, co dodatkowo może nasilać zaburzenia metaboliczne towarzyszące tej jednostce chorobowej.
2. Otyłość brzuszna u kobiet z PCOS wiąże się z zaburzeniami gospodarki węglowodanowej oraz nieprawidłową wrażliwością tkanek na insulinę. Kobiety z otyłością brzuszną charakteryzowały się wyższym stężeniem insuliny na czczo i wyższymi wartościami HOMA-IR, HOMA-AD oraz stosunkiem L/A w porównaniu do kobiet bez otyłości centralnej.

3. Kobiety z PCOS z otyłością brzuszną mają zwiększone prawdopodobieństwo wystąpienia insulinooporności (mierzonej za pomocą HOMA-IR, HOMA-AD i L/A) w porównaniu do kobiet bez otyłości centralnej.
4. Ilość wisceralnej tkanki tłuszczowej oraz wartość wskaźnika VAT/SAT są lepszymi predykatorami IR wśród kobiet z PCOS niż ilość podskórnej tkanki tłuszczowej czy wartość wskaźnika WHR.
5. Kobiety z PCOS z centralnym nagromadzeniem tkanki tłuszczowej wykazują niższy stopień przestrzegania diety obniżającej insulinooporność oraz charakteryzują się niższą intensywną aktywnością fizyczną.
6. Modyfikacja diety oraz zwiększenie aktywności fizycznej wydają się być obiecującymi metodami leczenia insulinooporności w PCOS, w szczególności u pacjentek z otyłością brzuszną, ze względu na ich korzystny wpływ na dystrybucję tkanki tłuszczowej brzusznej.

5.2.3. Obrona antyoksydacyjna wyrażona jako status glutationu i działanie układu Keap1-Nrf2 w odniesieniu do parametrów antropometrycznych i składu ciała u młodych kobiet z zespołem policystycznych jajników (Publikacja 6).

1. Otyłość brzuszna wyrażona wskaźnikiem VAT/SAT i/lub WHR wydaje się mieć negatywny wpływ na status glutationu, co może prowadzić do zakłócenia wielu biologicznych procesów komórkowych.
2. Kobiety z VAT/SAT >0,9 charakteryzowały się wyższym stężeniem GSSG i Keap1 oraz niższą wartością wskaźnika GSH/GSSG w porównaniu do kobiet z prawidłowymi wartościami wskaźnika VAT/SAT. Z kolei kobiety z WHR ≥0,85 miały wyższe stężenia GSH, GSSG i wartości wskaźnika GSH/GSSG w porównaniu do kobiet z WHR <0,85.
3. Parametry obrony antyoksydacyjnej są powiązane z parametrami antropometrycznymi oraz składem ciała u kobiet z PCOS, w tym ze wskaźnikami otyłości brzusznej.
4. Obserwowany negatywny związek Keap1 z indeksem R sugeruje, że podwyższony stres oksydacyjny zależny od stosunku VAT/SAT może prowadzić do aktywacji Nrf2 promującej ekspresję enzymów przeciwutleniających.

5. Wskaźnik GSH/GSSG oraz wskaźnik VAT/SAT wydają się być dobrymi wskaźnikami statusu oksydacyjnego kobiet z PCOS.

Wnioski

Podsumowując, modyfikacje stylu życia wydają się być obiecującą metodą wspomagającą leczenie PCOS. Dieta i aktywność fizyczna poprzez wpływ na dystrybucję tkanki tłuszczowej i jej metabolizm, wrażliwość tkanek na insulinę oraz płodność owulacyjną mogą korzystnie wpływać na przebieg PCOS. Co więcej, ocena centralnego gromadzenia tkanki tłuszczowej powinna być przeprowadzona u każdej kobiety z PCOS, aby lepiej przewidzieć insulinooporność oraz dysfunkcje parametrów obrony antyoksydacyjnej. Z tego też względu, każda kobieta z tą jednostką chorobową powinna otrzymać poradę dotyczącą modyfikacji stylu życia w zapobieganiu powikłaniom metabolicznym. Jednakże, ze względu na niewielką liczebność grupy, zależność pomiędzy dietą i aktywnością fizyczną a badanymi parametrami metabolicznymi nie może zostać jednoznacznie stwierdzona. Dlatego też, w przyszłości dobrze zaplanowane badanie interwencyjne na większej grupie pacjentek z PCOS pomogłoby lepiej ustalić rolę dobrze zbilansowanej diety oraz aktywności fizycznej w leczeniu powikłań metabolicznych i klinicznych towarzyszących PCOS.

nutrients

MDPI

Review

Milk and Dairy Products and Their Impact on Carbohydrate Metabolism and Fertility—A Potential Role in the Diet of Women with Polycystic Ovary Syndrome

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Abstract: Milk and dairy products are considered an important component of healthy and balanced diet and are deemed to exert a positive effect on human health. They appear to play a role in the prevention and treatment of carbohydrate balance disturbances. The products include numerous valuable components with a potential hypoglycemic activity, such as calcium, vitamin D, magnesium and probiotics. Multiple authors suggested that the consumption of dairy products was negatively associated with the risk of type 2 diabetes mellitus, insulin resistance and ovulation disorders. However, there are still numerous ambiguities concerning both the presumed protective role of dairy products in carbohydrate metabolism disorders, and the advantage of consuming low-fat dairy products over high-fat ones, especially in women with the risk of ovulation disorders. Therefore, this literature review aims at the presentation of the current state of knowledge concerning the relationship between dairy product consumption and the risk of insulin resistance, type 2 diabetes mellitus in women, and the potential effect on the course of polycystic ovary syndrome.

Keywords: milk; dairy products; type 2 diabetes mellitus; insulin resistance; polycystic ovary syndrome; fertility; ovulation

1. Introduction

Milk and dairy products have been considered as an important component of healthy and balanced diet for many years. According to Polish recommendations of the Food and Nutrition Institute [1], they should be included in everyday diet regardless of age. It is recommended that adults consume at least two glasses of milk daily. They may be replaced with yoghurt, kefir and, partially, cheese.

Cow milk contains 87% of water, 3–4% of lipids, 3.5% of protein, 5% of lactose and 1.2% of vitamins (B2, B12, A, D) and minerals (calcium, phosphorus, potassium, magnesium, zinc and selenium). Cow milk fat consists of 60% of saturated fatty acids, including mainly palmitic acid. The milk of ruminants also contains conjugated dienes of linoleic acids (CLAs) which present numerous health-promoting properties. However, the particularly nutritious value of milk is mostly due to high-quality protein which includes the whole set of exogenous amino acids necessary for the synthesis of body protein. Milk protein consists of 80% of casein, 20% of whey, which plays a role in short- and long-lasting regulation of food consumption via the induction of satiety signals, thereby promoting the maintenance of appropriate body weight. Bioactive milk peptides may exert a positive influence on human health through the regulation of physiological functions, a direct effect on metabolism and on some receptors. It was suggested that they presented antineoplastic, antihypertensive, antithrombotic and immunomodulatory properties. Milk and dairy products were also attributed favorable properties

in the prevention and treatment of carbohydrate metabolism disorders [2–4]. Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age. It is accompanied by oligoovulation and/or the lack of ovulation, clinical and/or biochemical hyperandrogenism and the presence of polycystic ovaries in ultrasound examination [5]. It is estimated that even 90–95% of ovulatory infertility cases are caused by this medical condition. Due to the presence of endocrine and metabolic disorders, women with PCOS are a group that is particularly susceptible to the development of insulin resistance, secondary disorders of glucose tolerance and type 2 diabetes mellitus (T2DM), cardiovascular diseases and dyslipidemia [6]. Increasing attention has recently been paid to the significance of dairy products in the diet of women with PCOS, particularly comprising their influence on ovulation and fertility and the associated risk of carbohydrate metabolism disorders, such as insulin resistance or T2DM. The obtained results are frequently contradictory. Therefore, it is necessary to conduct a comprehensive overview of the most recent studies in this area.

2. Dairy Products and Insulin Resistance

The effect of milk and dairy products on carbohydrate metabolism is the subject of numerous studies. However, the results are still contradictory. It is known that protein consumption has the same capacity to stimulate insulin secretion as carbohydrate consumption. However, it was demonstrated that not all protein-containing products exerted the same effect on insulin secretion and modulated insulin sensitivity in tissues in various ways. Milk proteins exerted the strongest influence on the secretion of insulin and incretins compared to other animal proteins [7]. It is mostly attributed to the high content of branched-chain amino acids (leucines, isoleucines, valines) which activate various pathways associated with insulin resistance [8]. However, apart from protein components, such as insulinogenic amino acids and bioactive peptides, dairy products also contain calcium, magnesium, potassium and carbohydrates with low glycemic index, which all seem to have a favorable effect on the control of glycemia, insulin secretion, insulin sensitivity of tissues and the reduction in the risk of T2DM. Moreover, unsaturated trans fatty acids which naturally occur in milk fat modulate the expression of PPAR-γ (peroxisome proliferator-activated receptor γ) and PPAR-α (peroxisome proliferator-activated receptor α), which is also beneficial in glucose homeostasis. Furthermore, fermentation and enhancing dairy products with probiotics and vitamin D may improve their glucoregulatory activity [7,9].

According to some studies conducted in women and men, the consumption of milk and dairy products might be associated with higher tissue sensitivity to the activity of insulin and lower fasting insulin levels [10,11]. The observation was confirmed by a meta-analysis of 30 randomized clinical trials. It demonstrated that the consumption of dairy products, especially low-fat ones, was beneficial in terms of tissue insulin sensitivity [12]. However, the results of some studies suggested that only long-lasting consumption of dairy products might have a beneficial effect on insulin sensitivity in tissues. A systematic review of 10 interventional studies [13] was conducted to analyze the effect of dairy products consumption on insulin sensitivity in individuals without T2DM. It was demonstrated that improved sensitivity to insulin occurred only after 12 weeks of a diet higher in dairy content, while studies lasting below 8 weeks did not show any significant changes concerning insulin sensitivity in tissues. Similar results were obtained by Rideout et al. [14], who noticed that the values of HOMA-IR (Homeostatic Model Assessment-Insulin Resistance) markedly improved over 6 months in individuals who consumed higher amounts of low-fat dairy products (four servings of milk of yoghurt daily) compared to those who consumed less (less than two servings of milk or yoghurt daily). However, not all studies confirmed those observations. A systematic review and a meta-analysis of 44 randomized studies revealed that the increased supply of dairy products exerted no effect on fasting insulin concentrations and HOMA-IR index values in healthy diabetes-free individuals [15]. A randomized clinical trial conducted by O'Connor et al. [16] also showed no significant changes in insulin secretion and insulin sensitivity in adults with hyperinsulinemia who were characterized by high dairy consumption (>4 servings/day) compared to those who consumed small amounts of dairy (≤2 servings/day). Interesting results were obtained by Eelderink et al. [17] who demonstrated that

postprandial insulin concentrations in persons consuming a diet with low dairy content (≤1 serving of dairy per day) were not significantly different compared to participants who consumed high amounts of dairy products (five servings/day in women and six servings/day in men). However, significantly higher fasting insulin and HOMA-IR values were associated with a diet high in dairy products compared to low-dairy diet (2.21 ± 0.91 versus 1.99 ± 0.72; $p = 0.027$).

There is paucity of data regarding the correlation between the consumption of milk products and the risk of insulin resistance in women. However, it may be presumed that such products may increase the risk of insulin resistance in women at various ages. Lawlor et al. [18], who investigated the association between milk consumption, insulin resistance and metabolic syndrome in 4024 British women, observed that women who had never drunk milk had lower HOMA-IR values and developed metabolic syndrome less frequently than women who regularly drank milk. Similarly, a study conducted by Tucker et al. [19] showed that the values of HOMA-IR went up with increased milk consumption in the studied women. Factors such as age, body weight, adipose tissue amount or physical activity had no significant influence on the relationship between milk consumption and HOMA-IR values. The results underlay the conclusion that long-lasting hyperinsulinemia which occurred due to high dairy consumption may be a significant predictor of insulin resistance in women. Moreover, an 8-week interventional study by Phy et al. [20] demonstrated that diet low in starch and milk products resulted in an increased sensitivity to insulin (HOMA-IR reduction by 1.9 ± 1.2, $p < 0.001$), lowered fasting insulin level (−17.0 ± 13.6 μg/mL, $p < 0.001$) and a 75 g 2 h oral glucose tolerance test (−82.8 ± 177.7 μg/mL, $p = 0.03$) in women with PCOS. An unfavorable influence of milk products in women was also confirmed in a study by von Post-Skagegård et al. [21], who demonstrated that the 120 min ratios of insulin to glucose and insulin to peptide C were significantly higher after a meal containing milk proteins compared to a meal containing fish or soy protein. Furthermore, Turner et al. [22] noted that HOMA-IR was markedly lower in women who had consumed a diet including red meat compared to diet containing milk products. Moreover, women who consumed <1 portion of milk products daily were characterized by significantly lower fasting insulin levels and HOMA-IR compared to women whose diet included from four to six portions of low-fat milk products daily.

However, not all studies indicated a negative impact of dairy product consumption on the risk of insulin resistance in women. According to some authors, the influence of dairy products was neutral or even favorable in terms of sensitivity to insulin in women. A study by Drouin-Chartier et al. [23] revealed that a diet including milk had no effect on HOMA-IR and fasting insulin levels in postmenopausal women. The Coronary Artery Risk Development in Young Adults Study (The CARDIA Study) [24] showed that a daily increase in the consumption of milk products translated into the reduction in the risk of developing insulin resistance by 30% in Black women (Odds Ratio (OR) 0.70, 95% Confidence Interval (CI), 0.54–0.91, $p < 0.05$) and by 38% in White women (OR 0.62, 95% CI, 0.46–0.84, $p < 0.05$). Yoghurt appears to be particularly beneficial in the prophylaxis of insulin resistance in women. A study by Chen et al. [25] revealed that full-fat yoghurt significantly reduced HOMA-IR, fasting insulin levels and a 75 g 2 h oral glucose tolerance test compared to full-fat milk in women with metabolic syndrome and nonalcoholic fatty liver disease. However, the study showed significantly reduced HOMA-IR, fasting glucose and insulin levels in a group of women consuming milk, while the level of insulin in a 75 g 2 h oral glucose tolerance test significantly increased. Based on the results, the authors suggested that the unfavorable influence of milk consumption on carbohydrate metabolism was not associated with weakened insulin sensitivity, but only with the fact that milk might prolong postprandial insulin secretion.

Some authors pointed out particularly beneficial properties of probiotics. A randomized clinical trial conducted in a group of women with PCOS showed that supplementation with probiotics contributed to a considerable reduction in fasting glucose levels [26]. Other studies conducted in women showed that the consumption of yoghurts fortified both with vitamin D and probiotic bacteria was associated with a significantly higher reduction in HOMA-IR and fasting insulin compared to

women consuming traditional low-fat yoghurt [27,28], so the favorable properties of yoghurt may be enhanced with the addition of probiotic bacteria and vitamin D. Therefore, the consumption of yoghurt (especially the fortified types) by women seems to have a beneficial effect on tissue insulin sensitivity. However, their positive properties may not be fully confirmed due to the paucity of studies in women with PCOS. Detailed results of studies on the effects of dairy consumption on insulin resistance in women are described in Table 1.

Basing on the observations described above, it cannot be clearly determined whether the consumption of milk and dairy products has a beneficial effect on insulin sensitivity in tissues in women, and due to the lack of studies conducted in women with PCOS, it is even more difficult to draw conclusions concerning their beneficial effect in this condition. It may even be assumed that the consumption of diet with a high dairy content may be a predictor of hyperinsulinemia and insulin resistance in women. However, it is worth emphasizing that the results of some studies suggested that only long-lasting consumption of dairy products might have a beneficial effect on reducing insulin resistance in tissues. Therefore, it is necessary to conduct more well-planned randomized clinical trials in women with PCOS to provide a clear answer concerning the significance of dairy product consumption in the prevention and treatment of insulin resistance in this condition.

Table 1. The influence of dairy product consumption on insulin resistance in women.

Author/Reference Number	Year	Study Design	Sample (*n*)	Outcome Measures	Result
Intake of Total Dairy Products					
Pereira et al. [24]	2002	Population-based prospective study Intake of total dairy products	3157 Black and White adults aged 18 to 30 years	Fasting plasma insulin and glucose	An increase in the daily intake of milk products reduced the risk of insulin resistance by 30% in black women (OR 0.70, 95% CI, 0.54–0.91, $p < 0.05$) and by 38% in white women (OR 0.62, 95% CI, 0.46–0.84, $p < 0.05$).
Tucker et al. [19]	2015	Cross-sectional study Intake of total dairy products; low intake—0 to 0.5 servings of dairy per day, moderate intake—0.6 to 1.5 servings of dairy per day, high intake—1.6 to 6 servings of dairy per day	272 middle-aged, nondiabetic and apparently healthy women	HOMA-IR score	Women who consumed diet high in dairy products had markedly higher HOMA-IR values (0.41 ± 0.53) compared to those who consumed moderate (0.22 ± 0.55) and low amounts of dairy (0.19 ± 0.58).
Intake of Low-Fat Dairy Products					
Turner et al. [22]	2015	Randomized crossover study Intake of low-fat dairy products or red meat	47 overweight and obese men and women > 20 years old	Fasting insulin, HOMA-IR score, Matsuda Index	Fasting insulin was significantly higher after a diet including milk products compared to diet including red meat (7.38 versus 5.62, $p = 0.02$). HOMA-IR was significantly higher after a diet including low-fat milk products compared to diet including red meat (1.71 versus 1.31 $p = 0.01$). Insulin sensitivity calculated with the Matsuda method was lower by 14.7% in women who had a diet including milk products compared to diet including red meat (6.81 versus 8.14, $p = 0.01$). Women who consumed <1 portion of milk products daily were characterized by significantly lower fasting insulin levels and HOMA-IR, and a significantly higher Matsuda index compared to women whose diet included from 4 to 6 portions of low-fat milk products daily (fasting insulin—6.16 versus 7.38, $p = 0.05$, HOMA-IR—1.42 versus 1.71, $p = 0.05$ and Matsuda Index 8.61 versus 6.81, $p = 0.05$).
Intake of Milk and Milk Protein					
Lawlor et al. [18]	2005	Prospective cohort study Intake of milk versus no intake of milk	4024 British women aged 60–79 years	HOMA-IR score	Women who did not drink milk had their HOMA-IR lower by 13% compared to women who drank milk (1.49 versus 1.72).

Table 1. *Cont.*

Author/Reference Number	Year	Study Design	Sample (*n*)	Outcome Measures	Result
Intake of Total Dairy Products					
von Post-Skagegård et al. [21]	2006	A randomized study Intake of three meals with different types of protein (either cod protein, milk protein or soy protein)	17 healthy women, 30–65 years old	Blood glucose, serum insulin, C-peptide	The 120 min insulin to glucose ratio was higher after a meal including milk protein compared to meals including cod or soy protein (milk protein—4.36, cod protein—2.03, soy protein—2.78, $p = 0.0002$). The 120 min insulin to peptide C ratio was significantly higher in case of a meal including milk protein compared to meals including cod or soy protein (milk protein—0.008, cod protein—0.003, soy protein—0.005, $p = 0.001$).
Drouin-Chartier et al. [23]	2015	Randomized, crossover study, diet for 6 weeks, one with 3.2 servings/d of 2% fat milk per 2000 kcal and another without milk	27 postmenopausal women in good health with abdominal obesity, less than 70 years of age	Fasting glucose, fasting insulin, Matsuda Index	No effect of milk on fasting insulin levels and insulin sensitivity index. Both diets, with and without milk, significantly reduced fasting glucose levels (diet including milk—6.08 versus 5.77, $p < 0.001$, diet not including milk—5.98 versus 5.80, $p < 0.009$).
Intake of Yoghurt					
Madjd et al. [28]	2016	Randomized single-blind controlled trial Intake of low-fat yoghurt versus probiotic yoghurt	Overweight and obese women	Fasting plasma glucose, 2 h glucose, fasting plasma insulin, HOMA-IR score, HbA1c	A significantly higher reduction was observed as regards HOMA-IR, 2 h postprandial glucose and fasting insulin in a group of women consuming probiotic yoghurt. Fasting glucose levels, 2 h glucose level, HbA1c, fasting insulin and HOMA-IR significantly decreased in both groups.
Jafari et al. [27]	2016	Randomized, placebo-controlled, double-blind parallel-group clinical trial Intake of vitamin D fortified yoghurt versus plain low-fat yoghurt for 12 weeks	59 post-menopausal women with type 2 diabetes	HOMA-IR, QUICKI	Insulin sensitivity of tissues was increased in a group of women who consumed yoghurt fortified with vitamin D—HOMA-IR (3.32 versus 2.13, $p = 0.02$), QUICKI (0.331 versus 0.348, $p = 0.001$) and fasting insulin was reduced (7.71 versus 5.17, $p = 0.03$). The markers of carbohydrate metabolism deteriorated in a group of women consuming low-fat yoghurt.
No Dairy Products in the Diet					
Phy et al. [20]	2015	Intervention study 8-week diet without starch and dairy products	24 overweight and obese women (BMI ≥ 25 kg/m^2 and ≤ 45 kg/m^2) with PCOS	Fasting and 2 h glucose and insulin, HOMA-IR score	Diet without starch and milk products reduced fasting insulin by 52% (-17.0 ± 13.6 µg/mL, $p < 0.001$), 2 h insulin in the load test of 75 g glucose by 37% (-82.8 ± 177.7 µg/mL, $p = 0.03$) and HOMA-IR by 51% (-1.9 ± 1.2, $p < 0.001$).

HOMA-IR, Homeostatic Model Assessment—Insulin Resistance; QUICKI, Quantitative Insulin Sensitivity Check Index; BMI, body mass index; HbA1c, glycated hemoglobin; PCOS, polycystic ovary syndrome; OR, odds ratio; CI, confidence interval.

3. Dairy Products and Type 2 Diabetes Mellitus

As mentioned above, dairy products, due to their high content of whey proteins which are rich in branched-chain amino acids (leucine, isoleucine, valine) and lysine, may stimulate insulin secretion and reduce postprandial glycemia, which is particularly favorable in the prophylaxis of T2DM [8]. Conversely, the excessive amount of branched-chain amino acids in the diet is considered to lead to insulin resistance in tissues via the activation of mTOR (mammalian target of rapamycin) kinase, thereby increasing the risk of T2DM [29]. It was corroborated by a prospective study conducted in a cohort of Chinese women. The study showed that higher branched-chain amino acid content consumed with meat and dairy products in the second part of pregnancy was associated with the increase in the risk of gestational diabetes mellitus by approximately 95% [30]. According to some authors, whey proteins, by modifying gene expression, may affect glucose metabolism, also by its increased use in the liver. Moreover, the influence of dairy products on glucose metabolism and the risk of T2DM may depend on glucokinase genetic polymorphism which is specific for a particular person. Therefore, it is suggested that some individuals may find high dairy intake more beneficial than others [31]. Furthermore, it seems that hyperinsulinemia due to dairy intake may be favorable in glucose homeostasis regulation in patients with hyperglycemia and T2DM [32]. Systematic reviews and meta-analyses of observational and cohort studies in women and men [32–36] indicated that dairy product consumption was negatively associated with the risk of T2DM. Moreover, such a relationship was particularly intensified in cases of low-fat and fermented dairy products. A randomized study by Díaz-López et al. [37] also revealed a negative relationship between total dairy intake and the risk of T2DM. It was particularly visible in the case of low-fat dairy products. It is consistent with the results of a meta-analysis of 13 cohort studies. The meta-analysis revealed that increasing the consumption of low-fat dairy products by 200 g daily was linked to T2DM risk reduction by 4% (Relative Risk (RR) 0.96; 95% CI 0.92, 1.00; $p = 0.072$). In the case of full-fat dairy products no such correlation was observed (RR 0.98; 95% CI 0.93, 1.04; $p = 0.52$) [32]. Similar outcomes were obtained in the Lifelines Cohort Study [38], in which a 2% reduction in the risk of prediabetes was achieved with the intake of skimmed dairy products (RR 0.98; 95% CI 0.97, 1.00; $p = 0.02$) and fermented dairy products (RR 0.98; 95% CI 0.97, 0.99; $p = 0.004$) increased by 100 g daily. Conversely, the consumption of full-fat dairy products was associated with the increased risk (RR 1.03; 95% CI 1.01, 1.06; $p = 0.004$). A systematic review of meta-analyses by Drouin-Chartier et al. [39] revealed that current evidence obtained from scientific research indicated favorable or neutral interrelations between the consumption of dairy products and T2DM occurrence. However, recommendations concerning the advantage of low-fat product consumption over full-fat ones were confirmed by a low number of reliable scientific papers. Similar conclusions were reached by Yakoob et al. [40] and Guo et al. [41] indicating no convincing evidence to confirm the hypothesis stating that low-fat dairy intake was more effective in reducing the risk of type 2 diabetes compared to full-fat dairy products. Moreover, a systematic review of studies concerning the relationship between dairy product intake and the risk of cardiovascular disease showed that the consumption of full-fat, semi-skimmed and fermented dairy products was neutrally associated with the risk of T2DM, while the consumption of low-fat dairy was positively associated with the risk [36]. According to some authors, full-fat dairy products, despite the high content of saturated fatty acids, had a positive effect on human health. It was also stated that there was insufficient evidence to confirm that those fatty acids increased the risk of cardiometabolic pathologies, such as T2DM, and they might even present some protective properties [42–44]. It is consistent with the results of a cohort study by Korat et al. [45] who demonstrated no relationship between milk fat and the risk of T2DM both in the population of men and women.

It is considered that sex is one of the biological factors modulating the course and incidence of cardiometabolic diseases, including T2DM. An increasing amount of evidence confirmed the role of sex in the course and treatment of T2DM and its influence on the increased risk of the disease [46]. Research conducted in the populations of women indicated that a diet rich in milk products was associated with a lower risk of developing T2DM [47,48]. The observations were confirmed by

systematic reviews and meta-analyses of observational and cohort studies [32,34,35], which indicated that milk product consumption was inversely correlated with the risk of T2DM in women. Moreover, Kirri et al. [49] observed that the beneficial correlation between milk product consumption and the risk of T2DM was statistically significant only in women. A prospective study by Liu et al. [50] showed that the risk of T2DM in women from the highest quintile of milk product consumption (>2.9 servings/day) was lower by 20% compared to women from the lowest quintile (<0.85 servings/day). Furthermore, each increment of the daily consumption by one serving was associated with T2DM risk reduction by 4% (RR 0.96, 95% CI, 0.93–1.0, $p < 0.05$). The beneficial effect of milk product consumption on the risk of T2DM in women is mainly attributed to low-fat milk products, while their high-fat equivalents may even increase the risk. It was confirmed by the results of a study by Margolis et al. [51] who demonstrated that the risk of T2DM in women from the highest quintile of low-fat milk product consumption was lower by 30% compared to women from the lowest quintile (RR 0.70, 95% CI, 0.64–0.77, $p < 0.0001$). However, no such correlation was demonstrated for high-fat milk products. A prospective cohort The Black Women's Health Study [52] also showed that the consumption of low-fat milk products was associated with the risk of T2DM lower by 13% in Black women. At the same time, no such correlation was observed for high-fat milk products. Another prospective The Nurses' Health Study [53] revealed a 25% lower risk of T2DM (RR 0.75; 95% CI 0.55, 1.02, $p = 0.03$) in women from the highest quintile of total milk product consumption compared to women from the lowest quintile. The beneficial influence of milk product consumption was observed both in the cases of low-fat and high-fat products. Moreover, constant high consumption of milk products continued in adulthood was also associated with a lower risk of T2DM, which might suggest that long-lasting milk product consumption might be beneficial in the context of the prophylaxis of T2DM in women.

Yoghurt appears to be a particularly important dairy product. It should be introduced into the diet of women with PCOS because of strong scientific evidence suggestive of the relationship between its consumption and lowering the risk of developing type 2 diabetes. Yoghurt consumption increases the concentrations of circulating anorexic peptides—glucagon-like peptide 1 (GLP-1) and peptide YY (PYY), whose activity is associated with the improvement of glucose homeostasis via the modulation of hepatic gluconeogenesis [54]. Fermented dairy product intake was associated with a lower risk of developing diabetes by the influence on intestinal microbiota and, thereby, on the insulin sensitivity of tissues and glucose tolerance [55]. Probiotics contained in such products may determine their favorable influence on T2DM risk [56]. A study by Liu et al. [50] revealed that the risk of T2DM was lower by 18% in women who consumed at least two servings of yoghurt weekly compared to women who consumed yoghurt less frequently than once a month (RR 0.82, 95% CI: 0.70–0.97, $p = 0.03$). Similar results were obtained in a study by Buziau et al. [57], in which the risk of developing T2DM was 19% lower in women from the highest tertile of yoghurt consumption than in women from the lowest tertile (OR 0.81; 95% CI: 0.67; 0.99; $p = 0.041$). It is consistent with the results obtained by Rosenberg et al. [58] and Margolis et al. [51] who confirmed a lower risk of developing T2DM in women consuming yoghurt. Detailed results of studies on the effects of dairy consumption on the risk of T2DM in women are described in Table 2.

Therefore, high dairy intake seems to reduce the risk of developing prediabetes and type 2 diabetes in women. It appears particularly beneficial to introduce yoghurt, fermented and low-fat dairy products into the diet. However, based on previous study results it may not be clearly confirmed whether the consumption of high-fat dairy products by women increased the risk of T2DM and had a negative impact on glycemia. Furthermore, due to the paucity of studies concerning the relationship between the consumption of milk products and the risk of T2DM in women with PCOS it seems justified to conduct a randomized clinical study in such a group of women in order to provide an explicit answer concerning the question of the influence of milk products on the course and treatment of PCOS.

Table 2. The influence of dairy product intake on the risk of type 2 diabetes mellitus (T2DM) in women.

Author/Reference Number	Year	Study Design	Sample (*n*)	Outcome Measures	Results
Pittas et al. [48]	2006	Prospective cohort study Intake of total dairy products	83,779 apparently healthy women, aged 30–55 years	T2DM	The risk of T2DM lower by 13% in women consuming higher amounts (>3 servings/day) of dairy products compared to women consuming small amounts (<1 serving/day).
Liu et al. [50]	2006	Prospective cohort study Intake of total dairy products, low-fat, full-fat and yoghurt	37,183 healthy, middle-aged and older women	T2DM	The risk of T2DM lower by 20% in women consuming higher amounts (>2.9 servings/day) of dairy products compared to women consuming small amounts (<0.85 serving/day). The risk of T2DM lower by 18% in women consuming higher amounts (>2 servings/day) of low-fat dairy products compared to women consuming small amounts (≤0.27 serving/day). The risk of T2DM lower by 18% in women consuming higher amounts (>2 servings/week) of yoghurt compared to women consuming small amounts (<1 serving/month).
van Dam et al. [52]	2006	Prospective cohort study Intake of total, low-fat and full-fat dairy products	41,186 women, aged 21–69	T2DM	The risk of T2DM lower by 25% in women consuming higher amounts (>2 servings/day) of total dairy products compared to women consuming small amounts (<1 serving/week). The risk of T2DM lower by 13% in women consuming higher amounts (>1 servings/day) of low-fat dairy products compared to women consuming small amounts (<1 serving/week). No significant correlation between the risk of T2DM and the consumption of full-fat dairy products in women.
Kirri et al. [49]	2009	Prospective cohort study Intake of total dairy products, milk, cheese and yoghurt	33,919 middle-aged and older women	T2DM	The risk of T2DM lower by 29% in women consuming higher amounts (≥300 g/day) of dairy products compared to women consuming small amounts (<50 g/day). No correlation between the consumption of milk, cheese and yoghurt and the risk of T2DM in women.

Table 2. *Cont.*

Author/Reference Number	Year	Study Design	Sample (*n*)	Outcome Measures	Results
Malik et al. [53]	2011	Prospective cohort study	116,671 female registered nurses aged 24–42	T2DM	The risk of T2DM lower by 25% in women from the highest quintile of total milk product consumption compared to women from the lowest quintile. The risk of T2DM lower by 26% in women from the highest quintile of low-fat milk product consumption compared to women from the lowest quintile. The risk of T2DM lower by 28% in women from the highest quintile of high-fat milk product consumption compared to women from the lowest quintile.
Margolis et al. [51]	2011	Prospective cohort study Intake of total, low-fat, full-fat dairy products and yoghurt	82,076 women, aged 50–79	T2DM	The risk of T2DM lower by 21% in women consuming higher amounts (>2.6 servings/day) of total dairy products compared to women consuming small amounts (<0.7 serving/day). The risk of T2DM lower by 30% in women consuming higher amounts (>1.9 servings/day) of low-fat dairy products compared to women consuming small amounts (<0.2 serving/day). The risk of T2DM lower by 54% in women consuming higher amounts (≥2 servings/week) of yoghurt compared to women consuming small amounts (<1 serving/month).
Aune et al. [34]	2013	Systematic review and dose-response meta-analysis of cohort studies Intake of total, low-fat, full-fat dairy products, milk and yoghurt	526,482 healthy men and women ≥ 20 years	T2DM	The risk of T2DM in women reduced by 34% with the increase in milk consumption by 200 g daily. The risk of T2DM in women reduced by 33% with the increase in yoghurt consumption by 200 g daily. No significant correlation with the total, full-fat, low-fat milk product consumption and cheese consumption in women.
Gijsbers et al. [32]	2016	A dose–response meta-analysis of observational studies Intake of total dairy products	579,832 healthy men and women, aged ≥ 20 years	T2DM	The risk of T2DM decreased by 3% with the increase in total dairy intake by 200 g daily. The risk of T2DM in women decreased by 8% with the increase in low-fat dairy intake by 200 g daily. The risk of T2DM in women increased by 2% with the increase in low-fat milk consumption by 200 g daily. The risk of T2DM in women reduced by 5% with the increase in high-fat milk consumption by 200 g daily. The risk of T2DM in women reduced by 11% with the increase in yoghurt consumption by 50 g daily. No correlation between the risk of T2DM and the total, high-fat milk product consumption and cheese consumption in women.

Table 2. *Cont.*

Author/Reference Number	Year	Study Design	Sample (*n*)	Outcome Measures	Results
Mishali et al. [35]	2019	Systematic review and meta-analysis of prospective cohort studies with subgroup analysis of men versus women Intake of total dairy products	545,677 men and women aged ≥ 18 years	T2DM	The risk of T2DM lower by 13% in women consuming higher amounts of dairy products compared to women consuming small amounts.
Buziau et al. [57]	2019	Prospective cohort study Intake of yoghurt	8748 Australian women, aged 45–50	T2DM	The risk of T2DM lower by 19% in women from the highest tertile of yoghurt consumption compared to women from the lowest tertile.
Rosenberg et al. [58]	2020	Prospective cohort studyT otal intake of yoghurt	59,000 U.S. Black women, aged 21–69	T2DM	The risk of T2DM lower by 18% in women consuming higher amounts (≥1 serving/day) of yoghurt compared to women consuming small amounts (<1 serving/month).

4. Dairy Products versus Ovulation and Fertility in Women

Research on the influence of dairy products on female fertility and ovulation has been conducted for many years. The results of animal studies suggested a potentially unfavorable influence of dairy products on reproductive functions due to high lactose content, which reduced ovulation in rats and led to premature ovarian insufficiency. Moreover, it was demonstrated that rats fed with high amounts of galactose were characterized by markedly lower concentrations of estradiol and elevated levels of FSH (follicle stimulating hormone) and LH (luteinizing hormone). Rats fed with lactose had considerably reduced progesterone concentrations, while no differences were confirmed in serum estradiol concentrations [59,60].

Changes in hormone levels resulting from dairy product intake were also observed in studies conducted in people. According to Kim et al. [61] each increase in the consumption of dairy products by one serving per day was associated with the reduction in serum estradiol concentrations by 4.6% and free estradiol by 4.0%. Conversely, the highest total dairy intake was linked to an increase in LH concentrations by 2.9% over the whole cycle compared to the lowest intake. However, a study by Greenlee et al. [62] revealed that dairy products supported female fertility, because the participants drinking over three glasses of milk daily were characterized by a 70% drop in the risk of infertility compared to women who did not drink milk at all. Wise et al. [63] compared the cohorts of women from Denmark and North America. In both groups they observed a positive association between milk consumption and fertility. Moreover, the authors found no significant differences between low- and full-fat milk consumption as regards the influence on fertility in either of the cohorts. Furthermore, higher lactose intake was associated with higher fertility in the study cohorts, which is inconsistent with the previous accepted view stating that lactose impaired fertility. Additionally, Afeiche et al. [64] conducted a study on women undergoing assisted reproductive technology procedures. It was demonstrated that the group of women aged ≥35 who were in the highest quartile of dairy product intake prior to the treatment was characterized by a considerably higher probability of delivering a live neonate than women in the lowest quartile. Notably, the fat content of dairy products consumed by the participants had no influence on the strength of such a relationship. Contradictory results were arrived at by Souter et al. [65], who assessed the relationship between milk protein intake and antral follicle count (AFC) in a prospective group of women of reproductive age. They concluded that higher total milk protein intake (≥5.24% of energy value or ≥2.3 glasses of milk daily) was associated with lower AFC. The authors deduced that the factors influencing the reduction in antral follicle count in women consuming dairy products might include: high amounts of steroid hormones and growth factors present in dairy products, contamination of dairy products with pesticides and chemical substances, which might markedly affect endocrine function and folliculogenesis. Furthermore, an increased dairy intake may be associated with higher concentrations of IGF-I (insulin-like growth factor I) in the blood, which also produces a negative effect on ovarian function and antral follicle count.

A prospective cohort Nurses' Health Study II (NHS II) did not reveal an association between total dairy intake and ovulatory infertility. However, increasing the consumption of low-fat milk products by one serving daily was linked to an increase in the risk of ovulatory infertility by 11%, while adding one serving of whole milk without increasing energy content was associated with reducing the risk by over 50%. According to the authors, it was due to the fact that high-fat dairy products included more estrogens and contributed to a lower-grade increase in IGF-I concentration in the serum compared to low-fat products. Moreover, based on the results, the authors hypothesized that the relationship between low-fat and full-fat dairy intake and infertility due to anovulation was stronger in women without certain clinical signs of PCOS than in women with those signs [66]. Notably, Adebamowo et al. [67] demonstrated that the consumption of skimmed milk was associated with a more common occurrence of acne, one of the clinical signs of PCOS, which may be explained by the presence of androgen precursors in milk. Rajaeieh et al. [68] studied the relationship between dairy products intake and the risk of developing polycystic ovary syndrome. They observed that each increase in milk consumption by one serving daily resulted in an increase in PCOS risk. Furthermore,

women with this medical condition were characterized by a markedly higher consumption of low-fat or skimmed milk compared to healthy women. The authors noted a possible role in the pathogenesis of PCOS, because low-fat dairy products are characterized by a considerably higher strength of stimulating IGF-I secretion compared to full-fat products. Considering the low quality of evidence, it may not be explicitly concluded that the influence of dairy products on the risk of infertility and PCOS is unfavorable. Therefore, further research is necessary in this area [69].

5. Conclusions

It seems justified to include milk and dairy products into the diet of women with polycystic ovary syndrome because of the beneficial effect of those products on the risk of developing type 2 diabetes mellitus in women. Moreover, the products appear not to have a negative effect on ovulation and fertility in women. However, due to the lack of unambiguous evidence, the advantage of full-fat over low-fat dairy products may not be confirmed despite the fact that high-fat dairy intake seems to be more beneficial in polycystic ovary syndrome. Notably, studies concerning the influence of milk consumption in women with PCOS are scarce, so its beneficial effect may not be explicitly confirmed in this group of patients. Therefore, it is necessary to conduct well-designed extensive research in women with PCOS to lead to the final conclusion as to whether milk product consumption is beneficial in their case and which products should be selected: full-fat or skimmed ones.

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Review

The Influence of Nutrition on Adiponectin—A Narrative Review

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Abstract: The adipose tissue is an active endocrine organ which synthesizes and secretes a variety of adipokines, including adiponectin with its anti-inflammatory properties. Its expression is influenced by numerous factors such as age, sex, body weight and adipose tissue content. However, dietary factors, i.e., diet structure and the percentage of individual nutrients and products, are very important modulators. Beneficial dietary habits are the Mediterranean diet, DASH diet, diet based on plant products and diet with reduced energy value. Moreover, the share of individual products and nutrients which increase the concentration of adiponectin is worth noting. This group may include monounsaturated fatty acids, polyunsaturated omega-3 fatty acids, dietary fiber, polyphenols, alcohol and milk products. Conversely, dietary ingredients which have a negative effect on the concentration of adiponectin are typical components of the Western diet: saturated fatty acids, trans fatty acids, monosaccharides and disaccharides, and red meat. Furthermore, a diet characterized by a high glycemic index such as a high-carbohydrate low-fat diet also seems to be unfavorable. Due to the fact that available knowledge should be systematized, this study aimed to summarize the most recent research on the influence of dietary factors on the concentration of adiponectin.

Keywords: adiponectin; high-molecular-weight adiponectin; diet; Mediterranean diet; Western diet; eating pattern

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1. Introduction

The adipose tissue, being the reservoir of energy, is also an active endocrine organ which synthesizes and secretes a variety of adipokines influencing the regulation of human metabolism. Adiponectin is one of the most important adipokines. It is a bioactive peptide composed of 244 amino acids constituting approximately 0.01% of plasma proteins. Plasma adipokine occurs in three types of complexes: (i) low-, (ii) medium-, and (iii) high-molecular-weight. High-molecular-weight (HMW) adiponectin is considered to be the most common and active form of adiponectin [1]. Furthermore, the activity of this adipokine also depends on the appropriate ratio between low- and high-molecular-weight adiponectin [2]. Currently, two isoforms of the adiponectin receptor are known: AdipoR1 and AdipoR2, which are located mainly in the skeletal muscles and the liver [1].

Adiponectin presents antineoplastic, cardioprotective and anti-inflammatory properties [3]. Additionally, it sensitizes tissues to insulin activity which contributes to its hypoglycemic properties [1]. Its hypolipidemic properties involve increasing the oxidation of fatty acids, reducing the storage of triglycerides in the skeletal muscles and increasing high density lipoprotein in the plasma via the activation of PPARα (Peroxisome Proliferator-Activated Receptor α). Its hypoglycemic effect is mostly due to the activation of PPARα, AMPK (AMP-Activated Protein Kinase), glucose transporters in the cell membrane such as GLUT4 (Glucose Transporter Type 4) and the reduction of gluconeogenesis in the liver [4,5].

Adiponectin expression is influenced by numerous factors including age, physical activity and ethnicity. Factors related to sex are also important determinants of its concentration. Women are characterized by a higher concentration of adiponectin compared

to men, which is mainly due to the presence of different sex hormones [6]. Genetic factors also seem to be particularly important, because the concentration of adiponectin can be inherited by up to 55% [7]. Moreover, body weight and BMI (Body Mass Index) are also strongly correlated with adiponectin concentrations. Cruz-Mejía et al. [8] observed that adiponectin concentrations were markedly lower in obese individuals compared to participants with normal body weight (16.03 ± 2.53 μg/mL vs. 28.18 ± 1.97 μg/mL; $p = 0.01$). In addition, adiponectin concentrations were negatively correlated with the degree of obesity in obese patients ($r = -0.477$; $p = 0.001$). Interesting results were obtained in the POUNDS Lost Trial [9] which revealed statistically significant correlations between adiponectin concentrations, body composition and adipose tissue distribution. Increased adiponectin concentrations were significantly correlated with the reduction in the total adipose tissue ($\beta = -0.68$; $p = 0.005$), adipose tissue located within the trunk ($\beta = -0.57$; $p = 0.005$), subcutaneous adipose tissue ($\beta = -0.42$; $p = 0.002$) and visceral adipose tissue ($\beta = -0.22$; $p = 0.02$). Similar results were obtained by Gariballa et al. [10]. They demonstrated that the increased amount of visceral adipose tissue was related to the reduction in total adiponectin concentration. Furthermore, Meshkini et al. [11] noted that the adipose tissue content within the trunk was negatively correlated with adiponectin values ($r = -0.44$; $p < 0.001$). A high amount of adipose tissue in the area was also a strong prognostic factor of adiponectin concentration ($\beta = -0.487$; $p < 0.001$).

Apart from the above mentioned factors, adiponectin concentration is also influenced by dietary patterns and the share of individual products and nutrients in the diet. An appropriate dietary structure seems to be one of the most important factors increasing adiponectin concentrations. Beneficial dietary habits are the Mediterranean diet (MD), DASH diet (Dietary Approach to Stop Hypertension), diet based on plant products and diet with a reduced energy value. The products and nutrients which increase adiponectin concentrations include monounsaturated fatty acids, polyunsaturated omega-3 fatty acids, dietary fiber, polyphenols, alcohol and milk products. Conversely, dietary ingredients which have a negative effect on the concentration of adiponectin are saturated fatty acids, trans fatty acids, monosaccharides and disaccharides, and red meat, which are typical components of the Western diet. Furthermore, a diet characterized by a high glycemic index and a high-carbohydrate low-fat diet also seem to be unfavorable [1,2,12].

Due to the fact that available knowledge should be systematized, this study aimed to summarize the most recent research on the influence of dietary factors on the concentration of adiponectin.

2. Diet-Related Factors with a Positive Influence on Adiponectin Concentrations

2.1. Dietary Structure

As regards factors which influence adiponectin expression, a key role is attributed to those which are associated with dietary habits and adhering to a healthy dietary pattern. The prospective Nurses' Health Study [13] including 1922 women revealed that total adiponectin concentrations were 24% higher and HMW adiponectin concentrations were 32% higher in women from the highest quartile of adherence to the Alternate Healthy Eating Index (AHEI) compared to the women from the lowest quartile. Similar results were obtained by Volp et al. [14] who demonstrated a direct significant correlation between Healthy Eating Index and adiponectin concentrations.

2.1.1. The Mediterranean Diet

The Mediterranean diet is one of the healthiest dietary patterns. Numerous observational and interventional studies have shown its correlation with increased adiponectin concentrations [5,15–19]. A traditional Mediterranean diet is characterized by a plentiful supply of vegetables, fruit, olive oil, fatty saltwater fish, whole-grain cereal products, moderate alcohol consumption and low red meat consumption [16]. It is suggested that the favorable activity of the MD on adiponectin expression may be due to the structure of the diet and the synergistic activity of its bioactive components, such as omega-3 fatty

acids, fiber, vitamins and polyphenols which have a positive influence on adiponectin concentrations [20].

The ATTICA epidemiological study [4] demonstrated that adiponectin concentrations were 41% higher in persons from the highest tertile of adherence to the MD diet compared to those from the lowest tertile. Moreover, the score obtained for the diet was significantly correlated with adiponectin concentrations, both in women and in men. The described correlation was confirmed with a systematic review and a meta-analysis of 20 interventional studies in which adherence to the MD was associated with a significantly higher increase in adiponectin concentration compared to the control diet [21]. Comparable outcomes were also obtained by Sureda et al. [16] in a group of 598 inhabitants of the Balearic Islands. Significantly higher adiponectin concentrations were observed in adult men who adhered to the MD compared to non-adherent men. However, such a correlation was not observed in women and adolescents of both sexes.

Mantzoros et al. [17] conducted a study in a group of women with diabetes. They demonstrated that serum adiponectin concentrations significantly improved as a result of the MD in these women. Interesting results were also obtained by Spadafranca et al. [20] who studied the changes in serum adiponectin concentrations in 99 pregnant women in terms of the degree of adherence of the dietary pattern to the MD. Women from the highest tertile of adhering to MD were characterized by a significantly lower decrease in the percentage of adiponectin concentrations during pregnancy compared to women from the lowest tertile.

The Mediterranean diet is associated with numerous benefits in both sexes, including those related to adiponectin concentrations, despite substantial differences between sex and the response to the MD [22]. This was corroborated by a prospective cohort study conducted by Kouvari et al. [18] in a group of 1514 men and 1528 women. Serum adiponectin was markedly improved in both sexes after the introduction of the MD. Additionally, participants with a higher degree of adherence to the MD were at a lower risk of developing liver steatosis, which was strongly correlated with adiponectin levels. The MÉDITA randomized trial [15] was conducted in 215 T2DM (Type 2 Diabetes Mellitus) patients whose adiponectin concentrations increased by 43% after a year of following the MD. A similar correlation was observed for HMW adiponectin. Furthermore, a study by Luisi et al. [19] confirmed that the beneficial effect of the MD, additionally enhanced with 40 g of extra virgin olive oil daily, on adiponectin concentrations was independent of body weight, because a significant increase in adiponectin concentrations was observed both in participants with normal body weight and with excessive body weight. The authors suggested that olive oil contributed to the strong anti-inflammatory effect of DM.

2.1.2. The DASH Diet

The DASH diet is another healthy dietary pattern which, if adhered to, is associated with less severe systemic inflammation [23,24]. The DASH diet is based on vegetables, fruit, nuts, seeds of pulses, whole-grain cereal products and low-fat milk products. It is also characterized by a low content of red processed meat, sweetened beverages and products with high sodium content [25]. The mechanism through which the diet may be associated with an increased adiponectin concentration may, similarly to the Mediterranean diet, result from the presence of bioactive components with strong anti-inflammatory properties, such as polyphenols and omega-3 fatty acids. Nilsson et al. [25] conducted a study in 122 elderly women. Serum adiponectin concentrations were 20% higher in women from the highest tertile of the adherence to the DASH diet compared to women from the lowest tertile. AlEssa et al. [26] demonstrated an increasing tendency of adiponectin concentrations together with increased adherence to the DASH diet. However, the correlations were on the border of statistical significance. A beneficial effect of the diet on adiponectin concentrations may also be related to low sodium supply. According to Prates et al. [27] the dietary content of sodium was negatively correlated with adiponectin concentrations ($r = -0.19$, $p = 0.03$). Despite the paucity of studies linking this dietary pattern with adiponectin concentrations,

it may be speculated that the diet may have a positive influence on the concentrations of this adipokine.

2.1.3. Plant-Based Diet

A plant-based diet is another dietary pattern which may exert a beneficial effect on serum adiponectin concentrations. It may be presumed that plant-based diets have a positive effect on adiponectin concentrations, but this is not as explicit as in the case of the MD. Adiponectin may also be influenced by bioactive components. Low animal protein and total protein content seem to be beneficial in terms of adipocyte function [28,29]. Kahleova et al. [30] noted that the concentrations of total adiponectin and HMW adiponectin increased by 19% and 15%, respectively, compared to baseline in the study group which followed a vegetarian diet for 24 weeks. Furthermore, a case-control study conducted in healthy non-obese adults revealed adiponectin concentrations to be significantly higher in women following a vegetarian diet than in those following a traditional diet. However, such a correlation was not observed in men [31]. The influence of reproductive hormones on the regulation of adiponectin concentrations may be a possible mechanism explaining why the described correlation was observed only in women [11]. A cross-sectional study conducted in a group of women showed that adiponectin concentrations were strongly correlated with FSH and SHGB concentrations [32]. Besides, sex-related differences in the expression of adiponectin may depend on differences in the distribution of the adipose tissue in men and women [11].

However, according to some authors, plant-based diets did not influence adiponectin concentrations [29,33,34] or might be associated with its lower expression [35]. Conversely, the authors explained the described correlation by the fact that the study was conducted in India in a group of 464 women (261 vegetarians and 203 non-vegetarians), where traditional vegetarian diet was characterized by a very high consumption of carbohydrates and a low consumption of fats (including omega-3 fatty acids). It was stated that various proportions between those macronutrients contributed to the difference between the studied groups of women. In addition, systematic reviews and meta-analyses of cross-sectional [36], interventional [37] and observational studies [38] demonstrated that vegetarian and vegan diets were associated with total lower inflammation compared to the traditional diet. However, no statistically significant relationship was found between this dietary pattern and adiponectin concentrations. Ambroszkiewicz et al. [29] revealed that children following a vegetarian diet were characterized by a significantly higher ratio of anti-inflammatory adiponectin and proinflammatory leptin compared to children consuming products of animal origin, which also indicated the anti-inflammatory properties of the diet.

2.1.4. Low-Energy Diet

It was also demonstrated that low-energy diets had a beneficial effect on adiponectin concentrations. It seems particularly beneficial to follow the negative energy balance pattern for a prolonged time, which resulted in effective reduction in body weight [2]. Monda et al. [39] conducted a study in 20 obese men and women. They observed that an eight-week balanced low-calorie ketogenic diet contributed to a significant increase in adiponectin concentrations both in women and in men. Furthermore, an increase was observed for all types of adiponectin of various molecular weights.

A randomized case-control study including 107 obese adults also showed that the reduction in calorie content by 500–700 kcal contributed to a significant increase in adiponectin concentrations. A similar correlation was observed in a group of individuals using diet combined with physical activity [40]. Similar results were also obtained by Christiansen et al. [41] and Abbenhardt et al. [42]. The observed correlations were confirmed by a systematic review and meta-analysis of 13 interventional studies which demonstrated that a low-calorie diet might considerably increase adiponectin concentrations. Particularly beneficial effects were observed if the diet was followed for at least 16 weeks. The authors

suggested that the beneficial effect of the reduced-calorie diet on adiponectin concentrations depended predominantly on its duration and the degree of body weight reduction [43].

Song et al. [44] demonstrated that adiponectin concentrations significantly increased with the degree of body weight loss. Moreover, the activation of the PPARαreceptor and the reduction of inflammation resulting from the low-calorie diet seem to underlie this correlation. Alternatively, it is believed that body weight reduction may strengthen the expression of adiponectin receptors in the liver and skeletal muscles [43].

2.2. Nutrients and Products Included in the Diet

Apart from healthy dietary patterns the regulation of serum adiponectin concentrations also depends on individual nutrients, i.e., monounsaturated fatty acids, polyunsaturated omega-3 fatty acids, fiber, polyphenols and products included in the diet, i.e., dairy or alcohol. Seemingly, both physical activity and the use of low-energy diets influence adiponectin concentrations, mostly via the influence on body weight. However, the influence on adiponectin concentrations seems to be direct in case of some the nutrients such as monounsaturated fatty acids or polyunsaturated omega-3 fatty acids [11].

2.2.1. Monounsaturated Fatty Acids and Polyunsaturated Omega-3 Fatty Acids

Omega-3 acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), seem to be of particular importance in the context of adiponectin concentrations. Their main dietary sources are fatty saltwater fish and seafood [45]. The mechanism through which omega-3 acids induce adiponectin expression is mostly associated with PPARγ activation, the increased expression of adiponectin genes and the inhibition of the receptors of calcium ion channels [46,47]. Moreover, omega-3 acids reduce the concentrations of TNFα (Tumor Necrosis Factor α) and IL-6 (Interleukin 6), which inhibit the activity of the gene of this adipokine [48].

A randomized case-control study by Mazaherioun et al. [49] revealed that adiponectin concentrations significantly increased compared to baseline values in a group of individuals supplementing omega-3 fatty acids at a dose of 2.7 g/day. Furthermore, the study showed that PUFA (Polyunsaturated Fatty Acids) supplementation increased the expression of AdipoR1 and AdipoR2, adiponectin receptor genes, in persons with T2DM. Similar results were obtained by Barbosa et al. [48] who demonstrated that omega-3 supplementation at a dose of 3 g/day was also associated with significantly increased adiponectin concentrations. A study by Khorrami et al. [50] conducted in patients with atrial fibrillation showed that adiponectin concentrations significantly increased as a result of eight weeks of daily supplementation with 2 g of fish oil compared to the placebo arm. Similarly, Balfegó et al. [51] conducted a study in individuals who enhanced their diet with 100 g of sardines for 6 months. Adiponectin concentrations significantly increased from 2.1 ± 0.3 µg/mL at baseline to 3.0 ± 0.3 µg/mL after six months ($p = 0.04$). Interesting results were obtained by Song et al. [52] who demonstrated that adiponectin concentrations increased in each of the three groups over the period of 12 weeks. The groups differed in terms of the dose of EPA and DHA (gr. 1–3.1 g/d; gr. 2–6.2 g/d; gr. 3–12.4 g/d). However, the highest increase in adiponectin concentrations was observed in the group in which the dose of PUFA was the highest. This suggests that the amount of consumed omega-3 acids might also be of importance as regards the influence on adiponectin concentrations.

Similar correlations were also observed in women with PCOS [53,54]. Furthermore, the beneficial effect of omega-3 acids on adiponectin was observed in women with insulin resistance and with normal sensitivity to insulin [53]. The described correlations between omega-3 acids and adiponectin concentrations were confirmed by systematic reviews and meta-analyses of randomized case-control studies [45,46].

Linseed is another source of omega-3 acids. Linseed exerts a positive effect on adiponectin expression because it contains alpha-linolenic acid (ALA), which may also act as a ligand for the PPARγ receptor. Haidari et al. [55] conducted a randomized study in a group of women with PCOS. They demonstrated that linseed might significantly

increase adiponectin concentrations. A significant increase in adiponectin concentrations was observed in comparison with baseline values in a study group which enhancing their diet with 30 g of ground linseed for 12 weeks. Gomes et al. [56] also demonstrated that the supplementation with 3 g of ALA significantly increased serum adiponectin concentrations after 60 days. However, a systematic review and a meta-analysis of seven randomized case-control studies revealed no statistically significant correlation between adiponectin concentrations and linseed consumption [57].

Notably, other studies revealed an important role of polyunsaturated omega-6 fatty acids and monounsaturated fatty acids on the regulation of adiponectin concentrations. A study by Kalgaonkar et al. [58] conducted in a group of women with PCOS showed that both walnuts and almonds significantly increased adiponectin concentrations. The results suggested that both linoleic acid found in walnuts and oleic acid found in almonds had a positive effect on adipokine concentrations. The described correlation was confirmed by a systematic review and meta-analysis of three randomized case-control studies which showed that walnuts were a dietary component with the potential of increasing adiponectin concentrations [59]. It is worth noting the results of a study by Kabiri et al. [60] conducted in obese women, which revealed that a diet rich in olive oil had a tendency to increase adiponectin concentrations (correlation on the border of statistical significance ($p = 0.06$)).

Furthermore, suitable ratios of dietary omega-3 and omega-6 acids [61] and polyunsaturated and saturated fatty acids [13] seem to be important factors. Fargnoli et al. [13] demonstrated significantly higher total adiponectin and HMW concentrations in women with the lowest ratio of polyunsaturated to saturated fatty acids compared to women with the highest ratio.

2.2.2. Dietary Fiber

Dietary fiber is another component of food which has a positive effect on adiponectin concentrations. A review of 52 studies conducted by Silva et al. [2] showed that the presence of fiber in the diet contributed to an increase in adiponectin concentrations, even up to 60–115%. The prospective Nurses' Health Study [13] demonstrated that women from the highest quartile of cereal fiber consumption had significantly higher total adiponectin and HMW adiponectin concentrations compared to women from the lowest quartile. A cross-sectional observational study by Pereira et al. [62] showed that a higher consumption of fiber included in vegetables and fruit was associated with higher adiponectin concentrations. The concentrations of adiponectin were 4.7 μg/mL ($p = 0.03$) higher in individuals from the highest quartile of cereal fiber consumption compared to participants from the lowest quartile.

The cross-sectional Health Professionals Follow-up Study [63], which included 780 men with T2DM, revealed that adiponectin concentrations were significantly higher in men from the highest quartile of cereal fiber consumption compared to men from the lowest quartile. Notably, the correlations between total fiber and vegetable fiber consumption and adiponectin concentrations were not statistically significant. Similar results were obtained by AlEssa et al. [64], who demonstrated that the consumption of both total fiber and fiber from cereals, vegetables and fruit was positively associated with adiponectin concentrations. Similar results were also obtained by Mantzoros et al. [17]. They observed that the consumption of whole-grain cereal products which were the source of dietary fiber was associated with significantly higher adiponectin concentration. Such an explicit correlation was also observed in the case of the consumption of fruit and nuts which also constitute an important source of dietary fiber. The seeds of pulses, including lentils, chickpeas, beans, broad beans and soy, are also excellent sources of both soluble and insoluble dietary fiber [65]. A study by Mirmiran et al. [65] conducted in a group of T2DM patients demonstrated that a diet in which two servings of red meat were replaced with pulse seeds effectively increased adiponectin concentrations.

2.2.3. Polyphenols

Adiponectin concentrations and the expression of its receptors seem to be influenced by polyphenols which are secondary plant metabolites characterized by strong anti-inflammatory properties [66]. Coffee and green tea are rich sources of polyphenols. Caffeine and the catechin it includes have a beneficial effect on adiponectin mainly through the stimulation of the PPARγ receptor expression [67]. Some studies have revealed a correlation between the consumption of coffee and adiponectin concentrations [68–70]. A cross-sectional study conducted in Japan included 665 men. It revealed that higher coffee consumption was associated with higher adiponectin concentrations [71]. Similar results were also observed in relation to green tea [72–74]. Moreover, a study by Fragopoulou et al. [5] demonstrated that adiponectin concentrations were positively correlated with green tea consumption. However, a systematic review and a meta-analysis of 14 randomized case-control studies revealed no statistically significant correlation between serum adiponectin concentrations and green tea consumption. Nevertheless, the authors suggested that this might be due to the high heterogeneity of the analyzed studies (I2 D 91.7%; $p < 0.0001$) [75].

Curcumin is another polyphenol which has a beneficial effect on the expression of adiponectin [76,77]. Mirhafez et al. [78] conducted a study in a group of patients with nonalcoholic fatty liver disease and found that supplementation with curcumin for eight weeks contributed to a significant increase in adiponectin concentrations. Comparable results were also obtained by Adibian et al. [79] whose 10-week study included 44 patients with T2DM. The described correlations were confirmed by systematic reviews and meta-analyses of randomized case-control studies which showed a significant increase in adiponectin concentrations resulting from curcumin supplementation [80,81]. Furthermore, the highest increase was observed in case of interventions of at least 10-week duration [81].

It may be presumed that other polyphenols also increase the expression of adiponectin, but the data are too scarce to confirm correlations between such substances as anthocyanins, lignans, resveratrol or quercetin and the concentration of adiponectin [82–88]. A study by Tucakovic et al. [82] revealed that a four-week diet enhanced with the Queen Garnet plum, which is rich in anthocyanins, increased adiponectin concentrations by an average of 3.83 μg/mL ($p = 0.048$). Yang et al. [83] also demonstrated a correlation between anthocyanin supplementation for 12 weeks and adiponectin concentrations compared to placebo. Comparable results were also obtained by Jeong et al. [84], who demonstrated that the daily consumption of black raspberry for 12 weeks was associated with a considerable increase in adiponectin concentrations.

Resveratrol is another polyphenol influencing adiponectin. A randomized case-control study by Tomé-Carneiro et al. [85] revealed that a six-month dietary supplementation with grape extract increased adiponectin concentrations by 9.6% ($p = 0.01$) compared to placebo. The correlation was confirmed by a systematic review and a meta-analysis of 10 randomized case-control studies which showed that resveratrol supplementation contributed to a marked increase in adiponectin concentrations [89].

A study by Shahi et al. [86] revealed that lignans present in sesame seeds also had strong anti-inflammatory properties, and a diet enriched with sesame seeds significantly increased adiponectin concentrations in T2DM patients.

In addition, quercetin, mainly found in onion skin, also presented a beneficial effect in terms of adiponectin concentrations. Kim et al. [87] conducted a study in a group of women with excessive body weight. Quercetin supplementation for 12 weeks resulted in a significant increase in adiponectin concentration by 3.3 μg/mL compared to baseline. Additionally, a study by Rezvan et al. [88] including women with PCOS showed that oral quercetin supplementation increased the expression of the AdipoR1 and AdipoR2 adiponectin receptors.

2.2.4. Dairy Products

Dairy products also seem to exert positive effects on adiponectin concentrations. However, there is a paucity of studies to confirm such a relationship. Nevertheless, due to the anti-inflammatory properties of such products, especially natural yoghurt, we may presume their positive effect on adiponectin concentrations [90]. A positive correlation between adiponectin concentrations and dairy products may be related to the content of milk fat, whey protein, vitamin D, calcium, potassium, magnesium and the reciprocal relations between those components [91]. A cross-sectional study including 612 Japanese individuals revealed that a diet characterized by the consumption of milk products was associated with higher adiponectin concentrations [91]. Yannakoulia et al. [92] also demonstrated a correlation between adiponectin concentrations and a dietary pattern characterized by a high intake of whole-grain cereal products and low-fat milk products. Similar results were obtained by Niu et al. [93], but a correlation was only observed for low-fat milk products. The correlation with high-fat milk products remained statistically insignificant. Fragopoulou et al. [5] also confirmed that the intake of low-fat milk products was positively correlated with adiponectin concentrations.

2.2.5. Alcohol

Moderate alcohol consumption also proved to be beneficial in relation to adiponectin concentrations. The prospective Nurses' Health Study [13] revealed that the respective total adiponectin and HMW adiponectin levels were 28% and 45% higher in women from the highest quintile of alcohol intake (0.62–7.19 servings/d) compared to women who consumed no alcohol. Pischon et al. [12] and Bell et al. [94] also showed a significant positive correlation between moderate alcohol consumption and serum adiponectin concentrations. A similar correlation was reported in a study by Beulens et al. [95]. They noted that moderate alcohol intake for four weeks contributed to an increase in total adiponectin concentrations of 12.5% ($p < 0.001$). Furthermore, a cross-sectional study by Nova et al. [96] revealed that the relationship between adiponectin concentrations and moderate alcohol consumption was particularly visible in the case of wine ($p = 0.017$). The possible beneficial effect of this type of alcohol on adiponectin concentrations may be due to the content of polyphenols which are characterized by strong anti-inflammatory properties. However, some studies revealed no effect of alcohol consumption on the concentration of this adipokine [14,97,98]. Additionally, completely different results were observed as regards excessive alcohol consumption which was distinctly associated with low adiponectin concentrations [97,99]. The mechanism through which chronic heavy alcohol consumption is associated with reduced adiponectin concentrations is related to increased oxidative stress, the intensified expression of CYP2E1 (Cytochrome P450 2E1) and the reduced expression of PPARγ [100]. Detailed results of studies on the positive effects of dietary patterns on the concentration of adiponectin are described in Table 1.

To conclude, adherence to the Mediterranean diet is related to particularly significant beneficial effect on serum adiponectin concentrations. The reciprocal relations between the components of this diet (i.e., monounsaturated fatty acids, polyunsaturated omega-3 fatty acids, fiber and polyphenols) and their individual properties contribute to such a positive effect. Moreover, the advantages of the Mediterranean diet are visible regardless of body weight, health status and sex. The properties of the DASH diet also seem promising. However, more research is necessary to provide an explicit confirmation of its positive effect on adiponectin concentrations. Furthermore, the plant-based diet and low-calorie diet seem to be beneficial in the context of adiponectin concentrations. Additionally, moderate alcohol consumption and dairy product intake seem to be of importance in terms of the regulation of adiponectin concentrations. However, more research is needed to determine the influence of such products on the expression of adiponectin.

Table 1. Dietary patterns and the concentration of adiponectin (AD)—A positive effect.

Author/Reference	Year	Study Design	Sample	Results
			HEALTHY DIET	
Fargnoli et al. [13]	2008	Prospective cohort study	1922 women free of CVD, diabetes and cancer, aged 30–55 y	Total AD concentration was 24% higher (15.68 ± 1.03 μg/mL vs. 12.61 ± 1.03 μg/mL; $p < 0.0001$) and HMW AD was 32% higher (5.71 ± 1.04 μg/mL vs. 4.34 ± 1.04 μg/mL; $p < 0.0001$) in women from the highest quartile of adherence to AHEI compared to women from the lowest quartile.
Volp et al. [14]	2016	Cross-sectional study	157 apparently healthy men and women, aged 18–35 y	A correlation between the Healthy Eating Index and AD concentrations ($r = 0.20074$; $p = 0.02$).
			THE MEDITERRANEAN DIET	
Mantzoros et al. [17]	2006	Cross-sectional study	987 diabetic women, aged 30–55 y	Higher adherence to the MD was associated with markedly higher AD concentrations compared to the lowest adherence (6.91 ± 1.06 μg/mL vs. 5.49 ± 1.04 μg/mL; $p < 0.01$).
Fragopoulou et al. [5]	2010	Cross-sectional study	532 men and women free of CVD, aged > 18 y	Higher adherence to the MD was associated with markedly higher AD concentrations compared to the lowest adherence (4.8 ± 2.0 μg/mL vs. 3.4 ± 1.9 μg/mL; $p < 0.001$). A correlation between scores obtained for the MD and AD concentrations (women: rho = 0.156; $p = 0.02$), (men: rho = 0.130; $p = 0.02$).
Schwingshackl et al. [21]	2014	A systematic review and meta-analysis of 17 interventional studies	2300 men and women, aged 25–77 y	Adherence to the rules of the MD was related to significantly higher AD concentrations compared to the control diet (WMD: 1.69 mg/mL, 95% CI 0.27, 3.11; $p = 0.02$).
Maiorino et al. [15]	2016	Randomized control study	215 men and women with newly diagnosed T2DM, aged > 18 y	Following the MD for a year was associated with an increase in total AD concentrations by 43% (6.12 vs. 8.80 μg/mL; $p < 0.001$) and HMV AD by 54% (2.41 vs. 3.72 μg/mL; $p < 0.01$).
Sureda et al. [16]	2018	Cross-sectional study	598 men and women, aged 12–65 y	Adherence to the rules of the MD was related to significantly higher AD concentrations compared to non-adherence 13.1 ± 6.7 μg/mL vs. 9.5 ± 2.4 μg/mL; $p < 0.05$). No correlation found in women and adolescents of both sexes.
Spadafranca et al. [20]	2018	Cohort study	99 normal weight, pregnant women, aged 25–43 y	Women from the highest tertile of adhering to the MD were characterized by a lower decrease in the percentage of AD concentrations compared to women from the lowest tertile (10% ± 11% vs. −34% ± 3%; $p = 0.01$).

Table 1. *Cont.*

Author/Reference	Year	Study Design	Sample	Results
Luisi et al. [19]	2019	Interventional study	36 men and women, aged > 18 y	Following the MD enhanced with 40 g/d of extra virgin olive oil was associated with increased AD concentrations (increase by 0.6 ± 0.26 μg/mL; $p < 0.01$ in a group with normal body weight and an increase by 1.6 ± 0.2 μg/mL; $p < 0.01$ in a group with excessive body weight).
Kouvari et al. [18]	2020	Prospective cohort study	3042 apparently healthy men and women, aged > 18 y	Higher adherence to the MD was associated with markedly higher AD concentrations compared to the lowest adherence 4.8 ± 2.0 μg/mL vs. 3.4 ± 1.9 μg/mL; $p < 0.001$)
			THE DASH DIET	
Nilsson et al. [25]	2019	Cross-sectional study	112 women, aged 65–70 y	The highest tertile of adherence to the DASH diet was associated with markedly higher AD concentrations compared to the lowest tertile (12.9 ± 3.3 μg/mL vs. 11.5 ± 3.4 μg/mL; $p = 0.008$).
			PLANT-BASED DIET	
Kahleova et al. [30]	2011	Randomized control study	74 men and women with T2DM, aged 30–70 y	An increase in total AD by 19% (95% CI 7.5–25.4; $p < 0.05$) and HMV AD by 15% (95% CI 3.6–23.6; $p < 0.05$) after 24 weeks of following a vegetarian diet.
Ambroszkiewicz et al. [29]	2018	Cross-sectional study	117 prepubertal children, aged 5–10 y	Following a vegetarian diet was associated with a significantly higher adiponectin to leptin ratio (0.70 (0.37–0.93) vs. 0.39 (0.28–0.74); $p = 0.005$) compared to the traditional diet.
Mirmiran et al. [65]	2019	Randomized cross-over clinical trial	31 men and women with T2DM, aged 50–75 y	The consumption of two servings of pulses instead of red meat for eight weeks was associated with an increase in AD concentrations (10.5 ± 3.0 μg/mL vs. 13.1 ± 3.0 μg/mL; $p < 0.05$).
Lovrenčić et al. [31]	2020	Case-control study	76 non-obese men and women, aged 19–59	Following a vegetarian diet was associated with significantly higher AD concentrations compared to the traditional diet ($p = 0.03$). No correlation in men.
			LOW-CALORIE DIET	
Christiansen et al. [41]	2010	Randomized controlled trial	79 obese men and women, aged 18–45 y	VLCD diet (800 kcal/d) was associated with a 19% increase in AD concentrations after 12 weeks ($p < 0.01$).
Abbenhardt et al. [42]	2013	Randomized controlled trial	439 overweight or obese postmenopausal women, aged 50–75 y	AD concentrations increased by 9.5% after 12 months of following LCD (12.4 μg/mL (11.3–13.5) vs. 13.5 μg/mL (12.5–14.6); $p < 0.0001$) and by 6.6% (12.8 μg/mL (11.7–13.9) vs. 13.6 μg/mL (12.5–14.8); $p = 0.0001$) as a result of combining LCD with physical activity.

Table 1. *Cont.*

Author/Reference	Year	Study Design	Sample	Results
Bouchonville et al. [40]	2014	Randomized controlled trial	107 obese men and women, aged ≥ 65 y	Calorie reduction of the diet by 500–700 kcal contributed to an increase in AD concentration by 8.9 μg/mL (3.5–14.8); $p < 0.01$), while the combination of reduction diet and physical activity contributed to an AD increase by 6.5 μg/mL (0.8–12.3; $p = 0.02$).
Salehi-Abargouei et al. [43]	2015	Systematic review and meta-analysis of interventional trials (13 interventional studies)	937 men and women, aged 20–75 y	The use of LCD was associated with an increase in AD concentration (Hedges' g = 0.34, 95 % CI 0.17–0.50; $p < 0.001$), especially if the diet was followed for at least 16 weeks (Hedges' g for ≤ 16 weeks = 0.48, 95% CI: 0.12–0.83; $p = 0.01$, (Hedges' g for > 6 weeks = 0.30, 95 % CI: 0.11–0.48; $p = 0.002$).
Monda et al. [39]	2020	Interventional study	20 obese men and women, aged 20–60 y	The use of ketogenic VLCD for 8 weeks was associated with a significant increase in AD concentrations both in women (12.44 ± 1.07 μg/mL vs. 27.3 ± 1.33 μg/mL; $p < 0.05$), and in men (9.23 ± 0.7 μg/mL vs. 32.67 ± 1.6 μg/mL; $p < 0.05$).
POLYUNSATURATED FATTY ACIDS				
Fargnoli et al. [13]	2008	Prospective cohort study	1922 women, free of CVD, diabetes and cancer, aged 30–55 y	Women from the group characterized by the lowest ratio of PUFA to SFA consumption had significantly higher total AD (12.66 ± 1.03 μg/mL vs. 11.47 ± 1.03 μg/mL; $p = 0.01$) and HMW (4.19 ± 1.04 μg/mL vs. 3.60 ± 1.03 μg/mL; $p = 0.005$) compared to women with the highest ratio.
Kalgaonkar et al. [58]	2011	Randomized, prospective study	36 women with PCOS, aged 20–45 y	The consumption of walnuts and almonds significantly increased AD concentrations (walnuts: 9.5 ± 1.6 μg/mL vs. 11.3 ± 1.8 μg/mL; $p = 0.0241$; almonds: 10.1 ± 1.5 μg/mL vs. 12.2 ± 1.4 μg/mL; $p = 0.0262$).
Nadjarzadeh et al. [53]	2015	Randomized double-blind placebo-controlled clinical trial.	84 women with polycystic ovary syndrome, aged > 18 y	Omega-3 supplementation (180 mg EPA and 120 mg DHA) for eight weeks significantly increased AD concentrations (4.44 ± 1.92 μg/mL vs. 5.62 ± 2.68 μg/mL; $p < 0.005$).
Gomes et al. [56]	2015	Randomized double-blind, placebo-controlled trail	20 men and women with T2DM, aged 30–65 y	Supplementation with 3 g of ALA increased AD concentrations after 60 days (10.61 ± 6.53 μg/mL vs. 15.01 ± 11.68 μg/mL; $p = 0.01$).
Balfegó et al. [51]	2016	Pilot randomized trial	35 men and women with T2DM, aged 40–70 y	Introducing 10 g of sardines into the diet (five times a week for six months) was associated with a significant increase in AD concentrations (2.1 ± 0.3 μg/mL vs. 3.0 ± 0.3 μg/mL; $p = 0.04$)
Barbosa et al. [48]	2017	Randomized, double-blind placebo-controlled clinical trial	80 men and women with at least one cardiovascular risk factor, aged 30–74 y	Omega-3 supplementation (3 g/d) for two months significantly increased AD concentrations (14.8 ± 10.0 μg/mL vs. 18.2 ± 12.1 μg/mL; $p = 0.021$).

Table 1. *Cont.*

Author/Reference	Year	Study Design	Sample	Results
Mazaherioun et al. [49]	2017	Randomized, placebo-controlled, double-blind clinical trial	88 men and women with T2DM, aged 30–65 y	Omega-3 supplementation (2.7 g/d) significantly increased AD concentrations (5.09 ± 2.79 μg/mL vs. 5.58 ± 3.13 μg/mL; $p < 0.001$).
Mejia-Montilla et al. [54]	2018	Prospective study	195 women with PCOS, aged > 18 y	N-3 supplementation (180 mg EPA and 120 mg DHA) significantly increased AD concentrations (3.9 ± 1.1 μg/mL vs. 5.3 ± 1.4 μg/mL; $p = 0.001$), both in women with HOMA-IR <3.5 (3.9 ± 1.1 μg/mL vs. 5.3 ± 1.4 μg/mL; $p < 0.0001$), and in those with HOMA-IR >3.5 (4.1 ± 1.1 μg/mL vs. 5.6 ± 1.3 μg/mL; $p = 0.005$).
Song et al. [52]	2018	Double-blind randomized controlled trial	201 healthy men and women, aged > 40 y	An increase in AD concentrations over 12 weeks as a result of omega-3 supplementation at a dose of: 3.1 g/d (5.79 ± 2.68 μg/mL vs. 6.36 ± 2.64 μg/mL; $p < 0.05$), 6.2 g/d (5.72 ± 2.07 μg/mL vs. 6.87 ± 2.58 μg/mL; $p < 0.01$) and 12.4 g/d (5.81 ± 2.13 μg/mL vs. 7.43 ± 2.63 μg/mL; $p < 0.01$).
Bahreini et al. [47]	2018	A systematic review and meta-analysis of interventional trials (10 randomized controlled trails)	177 men and women with T2DM, aged > 18 y	An increase in AD concentrations by 0.57 μg/mL as a result of omega-3 supplementation (95% CI 0.15–1.31; $p = 0.01$).
Becic et al. [45]	2018	A systematic review and meta-analysis of interventional trials (10 randomized controlled trails)	460 men and women with prediabetes and T2DM, aged > 18 y	An increase in AD concentrations by 0.48 μg/mL as a result of omega-3 supplementation (95% Cl 0.27–0.68; $p < 0.00001$).
Haidari et al. [55]	2020	Randomized open-labeled controlled clinical trial	41 women with PCOS, aged 18–45 y	An increase in AD concentrations over 12 weeks as a result of supplementation with 30 g of ground linseed (13.04 ± 3.36 μg/mL vs. 17.36 ± 4.1 μg/mL; $p = 0.002$).
Khorrami et al. [50]	2020	Randomized double-blind, placebo-controlled study	80 overweight or obese men and women with atrial fibrillation, aged > 50 y	An increase in AD concentrations over eight weeks as a result of supplementation with 2 g/d of fish oil (11.88 ± 6.94 μg/mL vs. 13.15 ± 7.33 μg/mL; $p = 0.026$).
Yang et al. [59]	2020	A systematic review and meta-analysis of randomized clinical trials (3 randomized controlled trails)	823 men and women, aged > 18 y	The consumption of walnuts significantly increased AD concentrations (WMD: 0.440 μg/mL; 95% CI: 0.323 to 0.557; $p < 0.001$).

Table 1. *Cont.*

Author/Reference	Year	Study Design	Sample	Results
			DIETARY FIBER	
Qi et al. [63]	2005	Cross-sectional study	780 men with T2DM, aged 40–75 y	Men from the highest quartile of dietary fiber consumption had significantly higher AD concentrations compared to men from the lowest quartile (17.3 μg/mL vs. 14.2 μg/mL; $p = 0.006$).
Mantzoros et al. [17]	2006	Cross-sectional study	987 diabetic women, aged 30–55 y	The consumption of whole-grain cereal products was associated with significantly higher AD concentrations (6.11 ± 1.06 μg/mL vs. 4.92 ± 1.05 μg/mL; $p < 0.01$).
Fargnoli et al. [13]	2008	Prospective cohort study	1922 women free of CVD, diabetes and cancer, aged 30–55 y	Women from the highest quartile of cereal fiber consumption were characterized by significantly higher total AD concentrations (14.73 ± 1.03 μg/mL vs. 13.36 ± 1.04 μg/mL; $p < 0.04$) and AD HMW (5.32 ± 1.04 μg/mL vs. 4.56 ± 1.04 μg/mL; $p < 0.02$) compared to women from the lowest quartile.
Pereira et al. [62]	2016	Observational, cross-sectional study	43 men and women, 18–60 y	A higher consumption of fiber included in vegetables and fruit was associated with higher AD concentrations (r = 0.50; $p = 0.0007$). The concentrations of adiponectin were 4.7 μg/mL ($p = 0.03$) higher in individuals from the highest quartile of cereal fiber consumption compared to participants from the lowest quartile.
AlEssa et al. [64]	2016	Cross-sectional study	2458 women, free of diabetes, aged 43–70 y	Women from the highest quintile of total fiber ($p < 0.001$), cereal fiber ($p < 0.001$), fruit fiber ($p = 0.014$) and vegetable fiber ($p = 0.011$) consumption had significantly higher AD concentrations compared to women from the lowest quintile.
			CURCUMIN	
Campos-Cervantes et al. [77]	2011	Randomized, single blind, placebo-controlled trial	50 obese men, aged 25–30 y	An increase in AD concentrations after six and 12 weeks of supplementation with 500 mg of curcumin (after six weeks: 16.0 μg/mL vs. 18.5 μg/mL; $p < 0.01$ and after 12 weeks: 16.0 μg/mL vs. 18. μg/mL; $p < 0.02$).
Panahi et al. [76]	2016	Randomized controlled trial	117 men and women, aged > 18 y	An increase in AD concentrations after eight weeks of supplementation with 1000 mg of curcumin (12.67 ± 2.13 μg/mL vs. 21.28 ± 4.40 μg/mL; $p < 0.001$).
Mirhafez et al. [78]	2019	Randomized, double blind, placebo-controlled, cross-over trial	65 men and women with nonalcoholic fatty liver disease, aged > 18 y	Supplementation with 250 mg/d of curcumin for wight weeks caused a significant increase in AD concentrations (14.35 ± 7.72 μg/mL vs. 18.23 ± 9.75 μg/mL; $p < 0.001$).
Adibian et al. [79]	2019	Randomized, double blind, placebo-controlled trial	44 men and women with T2DM, aged 40–70 y	Supplementation with 1500 mg/d of curcumin for 10 weeks caused a significant increase in AD concentrations (52.0 ± 8.0 μg/mL vs. 64.0 ± 3.0 μg/mL; $p < 0.0001$).

Table 1. *Cont.*

Author/Reference	Year	Study Design	Sample	Results
Clark et al. [81]	2019	A systematic review and meta-analysis of interventional trials (10 randomized controlled trails)	652 men and women with type 2 diabetes, prediabetes subjects, obese men or with metabolic syndrome, aged 18–84 y	Supplementation with curcumin caused a significant increase in AD concentrations compared to placebo (WMD: 0.82 Hedges' g; 95% CI 0.33–1.30; p<0.001). A particularly beneficial effect of at least 10 weeks of supplementation (WMD: 1.05 Hedges' g; 95% CI: 0.64 to 1.45; $p < 0.001$).
Akbari et al. [80]	2019	Systematic review and meta-analysis of randomized controlled trials (21 randomized controlled trails)	1646 men and women with metabolic syndrome	An increase in AD concentrations after supplementation with curcumin (SMD 1.05; 95% CI 0.23–1.87; $p = 0.01$).
			ANTHOCYANINS	
Jeong et al. [84]	2014	Prospective randomized double-blind study	77 men and women with metabolic syndrome, aged 18–75 y	Daily black raspberry consumption for 12 weeks was associated with an increase in AD concentrations (5.7 ± 5.1 μg/mL vs. 7.7 ± 5.0 μg/mL; $p < 0.05$).
Tucakovic et al. [82]	2018	Randomized, double-blind, placebo-controlled, cross-over trial	20 apparently healthy men and women, aged 18–65 y	Supplementation with the Queen Garnet plum for four weeks increased AD concentrations by the average of 3.83 μg/mL ($p = 0.048$).
Yang et al. [83]	2020	Randomized controlled trial	160 men and women with T2DM or prediabetes	Anthocyanin supplementation for 12 weeks was associated with an increase in AD concentrations compared to placebo (increase by 0.46 μg/mL; $p = 0.038$).
			RESVERATROL	
Tomé-Carneiro et al. [85]	2013	Triple-blind, placebo-controlled clinical trial	75 men and women, aged > 18 y	Supplementation with grape extract for six months increased AD concentrations by 9.6% ($p = 0.01$).
Mohammadi-Sartang et al. [89]	2017	Systematic review and meta-analysis of randomized controlled trials (9 randomized controlled trails)	590 men and women, aged > 18 y	Resveratrol supplementation significantly increased AD concentrations (WMD: 1.10 μg/mL, 95% CI 0.88, 1.33; $p < 0.001$)
			QUERCETIN	
Kim et al. [87]	2016	Randomized double-blind, placebo-controlled study	37 healthy overweight and obese women	AD increase after 12 weeks of quercetin supplementation (3.6 ± 2.0 μg/mL vs. 6.9 ± 2.3 μg/mL; $p < 0.05$).
Rezvan et al. [88]	2018	Randomized double-blind, placebo-controlled study	81 women with PCOS, aged 20–40 y	An increased expression of the AD receptors (AdipoR1 and AdipoR2) after 12 weeks of supplementation with 1 g/d of quercetin ($p < 0.01$).

Table 1. *Cont.*

Author/Reference	Year	Study Design	Sample	Results
			LIGNANS	
Shahi et al. [86]	2017	Randomized double-blind, placebo-controlled study	48 men and women with T2DM, aged 30–60 y	AD increase after eight weeks of supplementation with 200 mg/d of sesamin (6.21 ± 1.33 μg/mL vs. 7.34 ± 2.88 μg/mL; $p = 0.024$).
			COFFEE	
Williams et al. [70]	2008	Prospective cohort study	982 women with T2DM and 1058 nondiabetic women	The consumption of ≥4 cups of coffee daily was associated with significantly higher AD compared to the consumption of <1 cup a week (women with T2DM: 7.7 vs. 6.1 μg/mL; $p = 0.002$, nondiabetic women: 15.0 vs. 13.2 μg/mL; $p = 0.04$).
Kempf et al. [68]	2010	Single-blind clinical trial	47 men and women, free of T2DM, aged 18–65 y	The consumption of eight cups of coffee daily was associated with significantly higher AD concentrations compared to consuming no coffee (8421 (6634–11256) ng/mL vs. 7957 (6317, 10901) ng/mL; $p < 0.05$).
Imatoh et al. [71]	2011	Cross-sectional study	665 men, aged > 18 y	The consumption of ≥3 cups of coffee daily was associated with significantly higher AD compared to consuming no coffee (6.9 ± 3.3 μg/mL vs. 6.0 ± 2.6 μg/mL; $p < 0.01$).
Yamashita et al. [69]	2012	Cross-sectional study	3317 men and women, aged 35–69 y	The consumption of ≥4 cups of coffee daily was associated with significantly higher AD compared to the consumption of <1 cup a week (7.23 (6.84–7.65) μg/mL vs. 6.58 (6.40–6.76) μg/mL; $p = 0.005$).
			GREEN TEA	
Hsu et al. [73]	2008	Randomized, double-blind, placebo-controlled clinical trial	78 obese women, aged 16–60 y	An increase in AD concentrations after 12 weeks of supplementation with 400 mg of green tea extract (18.9 ± 6.7 μg/mL vs. 21.4 ± 8.7 μg/mL; $p < 0.01$).
Fragopoulou et al. [5]	2010	Cross-sectional study	532 men and women free of CVD, aged > 18 y	A correlation was found between green tea consumption and AD concentrations (rho = 0.108; $p = 0.04$).
Liu et al. [74]	2014	Randomized, double-blind, and placebo-controlled trial	102 men and women with T2DM, aged 20–65 y	An increase in AD concentrations after 16 weeks of supplementation with 500 mg of green tea extract (20.2 ± 5.1 μg/mL vs. 21.7 ± 5.1 μg/mL; $p < 0.046$).
Chen et al. [72]	2016	Randomized, double-blind trial	92 obese women, aged 20–60 y	An increase in AD concentrations after 12 weeks of supplementation with 856.8 mg of green tea extract (20.9 ± 11.0 μg/mL vs. 24.0 ± 10.7 μg/mL; $p = 0.009$).
			DAIRY PRODUCTS	
Yannakoulia et al. [92]	2008	Cross-sectional study	196 apparently healthy women, aged 18–84 y	A correlation occurred between AD and a dietary pattern rich in low-fat dairy and whole-grain cereal products ($r = 0.15$; $p = 0.04$).

Table 1. *Cont.*

Author/Reference	Year	Study Design	Sample	Results
Niu et al. [93]	2013	Cross-sectional one-year longitudinal study	938 apparently healthy men and women, aged > 18 y	The consumption of low-fat milk products (58.9–375 g/d) was associated with significantly higher AD concentrations compared to no consumption of such products (8.3 (7.8, 8.9) μg/mL vs. 7.3 (6.9, 7.6) μg/mL; $p < 0.01$).
Fragopoulou et al. [5]	2010	Cross-sectional study	532 man and women free of CVD, aged > 18 y	A correlation occurred between the consumption of low-fat milk products and AD concentrations (rho = 0.119, $p = 0.04$).
Bahari et al. [91]	2018	Cross-sectional study	612 men and women, 35–69 y	A diet characterized by the higher consumption of milk products was associated with higher AD concentrations (4.78 (3.24, 7.38) μg/mL vs. 3.68 (2.42, 6.12) μg/mL; $p = 0.004$).
			ALCOHOL	
Pischon et al. [12]	2005	Prospective cohort study	532 men, aged 40–75 y	Men from the highest quintile of AD concentrations (>24.9 μg/mL) consumed significantly more alcohol (16.2 ± 1.06 g/d vs. 13.05 ± 0.7 g/d) compared to men from the lowest quintile of AD concentrations (<10.6 μg/mL); $p = 0.006$). A correlation occurred between AD concentrations and alcohol consumption ($r = 0.14$; $p = 0.002$).
Fargnoli et al. [13]	2008	Prospective cohort study	1922 women free of CVD, diabetes and cancer, aged 30–55 y	Total AD concentrations were 28% higher (16.01 ± 1.03 vs. 12.50 ± 1.03; $p < 0.0001$) and HMW AD concentrations were 45% higher (6.10 ± 1.04 vs. 4.21 ± 1.03; $p < 0.0001$) in women from the highest quintile of alcohol consumption compared to those who consumed no alcohol.
Beulens et al. [95]	2007	Randomized, controlled, cross-over trial	17 apparently healthy men, aged 18–40 y	Moderate alcohol consumption (32 g/d) for four weeks caused an increase in total AD concentrations by 12.5% ($p < 0.001$).
Bell et al. [94]	2015	Prospective cohort study	2855 men and women, aged 40–63 y	Alcohol consumption was cross-sectionally associated with AD concentrations ($\beta = 0.003$; $p < 0.001$).
Nova et al. [96]	2019	Observational cross-sectional study	240 men and women, aged 55–85 y	Wine consumption was associated with higher AD ($\beta = 204$, 95% CI: 37–370; $p = 0.017$).

Abbreviations: CVD, Cardiovascular disease; y, years; AHEI, Alternate Healthy Eating Index; AD, adiponectin; AD HMW, high-molecular-weight adiponectin; MD, Mediterranean diet; WMD, Weighted Mean Difference, T2DM, Type 2 Diabetes Mellitus; DASH, Dietary Approach to Stop Hypertension; VLCD, very low calorie diet; LCD, low calorie diet; PUFA, Polyunsaturated Fatty Acids; SFA, Saturated Fatty Acids; PCOS, polycystic ovary syndrome; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; ALA, α-linolenic acid; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance.

3. Diet-Related Factors with a Negative Influence on Adiponectin Concentrations

3.1. Dietary Structure

Incorrect dietary patterns, mainly including the Western diet, are also highly correlated with adiponectin concentrations. The Western diet is mostly characterized by the high content of highly processed food, red meat and refined cereal products [101]. A systematic review and meta-analysis of 12 observational studies revealed an association of the diet with a chronic inflammation [102]. Likewise, a cross-sectional study by Jafari-Vayghan et al. [101] demonstrated that the Western diet was negatively correlated with adiponectin concentrations. Comparable results were also obtained by Alves-Santos et al. [103] in a group of pregnant women. Adherence to the Western dietary pattern was negatively related to intra-gestational adiponectin concentrations.

3.1.1. High-Carbohydrate and Low-Fat Diet

The proportions between individual macronutrients also seem to be significant in relation to adiponectin concentrations. The results were particularly unfavorable in the case of a diet containing high amounts of carbohydrates and low amounts of lipids. A randomized case-control study by Song et al. [44] showed a significant reduction in adiponectin concentrations by 9.4% in a group of persons following a low-fat high-carbohydrate diet compared to those whose diets included the standard content of those macronutrients. Ruth et al. [104] also demonstrated that a high-carbohydrate low-fat diet was associated with a lower mean increase in adiponectin concentrations compared to a high-fat low-carbohydrate diet. Comparable results were obtained by Rajaie et al. [105] who noted that following a high-carbohydrate diet was linked to a significant reduction in the blood content of adiponectin. The authors suggested that the excessive consumption of carbohydrates activated proinflammatory factors by contributing to hyperglycemia and hypertriglyceridemia resulting in reducing adiponectin concentrations. The analysis of correlation in a study by Meshkini et al. [11] revealed that adiponectin concentrations in the circulation were negatively related to the amount of carbohydrates in the diet. A study by Pischon et al. [12] also showed that a 5% increase in energy obtained from carbohydrates instead of lipids was associated with a significant reduction in adiponectin concentrations by 0.59 mg/L. Kasim-Karakas et al. [106] also demonstrated that following a low-fat diet contributed to a reduction in adiponectin concentrations. The change from eucaloric diet providing 35% of energy from lipids into eucaloric diet providing 15% of energy from lipids was associated with a 14% reduction in adiponectin concentrations in healthy postmenopausal women. Similar results were obtained in a study by Murillo-Ortiz et al. [107], who found that women who consumed a diet with a reduced lipid content (12% of energy) for six months were characterized by significantly lower adiponectin concentrations compared to women whose diets included the standard amount of lipids (30% of energy).

3.1.2. High Glycemic Index of the Diet

A high dietary glycemic index also had a negative influence on adiponectin concentrations. The mechanisms of such a correlation have not been precisely described. However, such a dietary pattern may exert a negative effect on adiponectin concentrations by increased glycemia which may contribute to the reduction in the expression of adiponectin in the adipose tissue and activate mTORC1 (mammalian target of rapamycin complex). It is also possible that a high glycemic index reduces adiponectin concentrations by increasing the amount of the adipose tissue [11]. Cerman et al. [108] found a negative correlation between the glycemic index of a diet and serum adiponectin concentrations. A study by Meshkini et al. [11] also revealed that adiponectin concentrations were negatively correlated with the glycemic index and glycemic load of a diet. Furthermore, a high glycemic index was one of stronger negative predictors of the concentration of this adipokine. AlEssa et al. [61] demonstrated that adiponectin concentrations decreased along with increase in the glycemic index. Similar results were obtained by Pischon et al. [12] who observed

that each increase of the glycemic index by 1 unit was related to a significant decrease in adiponectin concentration by 1.32 mg/L. The correlations between adiponectin concentrations and dietary glycemic index were also demonstrated in studies by Pereira et al. [62], Qi et al. [63] and Loh et al. [109] in patients with T2DM.

3.2. Nutrients and Products Included in the Diet

Saturated fatty acids, trans fatty acids, monosaccharides and disaccharides are the components of the Western diet which are responsible for its proinflammatory properties. Moreover, a high red meat content, particularly processed meat, is a factor which negatively affects adiponectin concentrations. The influence of these dietary components on this adipokine seems to be direct, similarly to those of the remaining dietary components [110].

3.2.1. Saturated Fatty Acids and Trans Fatty Acids

Negative influence on adiponectin concentrations was predominantly observed in case of saturated fatty acids which may affect adiponectin expression in adipocytes via interaction with transcription factors [111]. According to Prates et al. [27], the consumption of large amounts of SFA (Saturated Fatty Acids) was negatively correlated with adiponectin concentrations. A high consumption of total lipids and cholesterol was also negatively interrelated with adiponectin concentrations. A study by Lepsch et al. [110] revealed a correlation between SFA consumption during pregnancy and reduced adiponectin concentrations. Furthermore, Haidari et al. [111] reported that a negative correlation between SFA and adiponectin concentrations was statistically significant both in patients with asthma and in the healthy controls. A negative influence on adiponectin expression was also observed in case of trans fatty acids which were significantly linked to reduced adiponectin as reported in the Nurses' Health Study [13]. Women from the highest quartile of the consumption of trans fatty acids had significantly lower adiponectin concentrations compared to women from the lowest quartile. A similar correlation was also observed in relation to HMW adiponectin. Additionally, a study by Pereira et al. [62] revealed that a lower consumption of trans fatty acids was associated with significantly higher adiponectin concentrations.

3.2.2. Monosaccharides and Disaccharides

There is a paucity of research on correlations between a diet rich in monosaccharides and disaccharides and adiponectin concentrations. However, as fructose largely contributes to the accumulation of visceral adipose tissue, it may be presumed that individuals whose diets are characterized by high fructose content may present a higher tendency towards reduced adiponectin concentrations [112]. The assumption was confirmed by a study conducted by Rezvani et al. [112]. They reported that participants who consumed large amounts of fructose were characterized by significantly reduced adiponectin concentrations. Moreover, a similar correlation was also observed in relation to glucose. A negative influence of these monosaccharides on adiponectin concentrations was observed only after 10 weeks of the intervention. Therefore, it may be assumed that only the long-term use of a diet including high monosaccharide content exerts a negative effect on this adipokine. Similar results were obtained by Pollock et al. [113], who studied a group of 559 adolescents. They reported that a diet rich in fructose was associated with significantly lower adiponectin concentrations. Besides, Magalhaes et al. [114] demonstrated that adiponectin was also influenced by the consumption of sucrose which is a disaccharide. Participants whose diets were rich in sucrose were characterized by significantly reduced adiponectin concentrations (<0.35 μg/mL). The correlation occurred both in individuals with nonalcoholic fatty liver disease and in healthy participants. Furthermore, hypoadiponectinemia was associated with the consumption of sweets and sweetened beverages by healthy individuals.

3.2.3. Red Meat

Similar to monosaccharides and disaccharides, a paucity of research has been performed to investigate correlations between red meat consumption and adiponectin concentrations. However, because of the proinflammatory properties of red meat, particularly processed meat, it may be assumed that its high dietary content adversely affects adiponectin concentrations [115]. A study by Fargnoli et al. [13] revealed that adiponectin concentrations decreased with an increasing red meat to poultry ratio in the diet. Ley et al. [116] also demonstrated the presence of a correlation between the consumption of red meat and adiponectin concentrations. Women from the highest quartile of the total consumption of unprocessed and processed red meat had significantly lower adiponectin concentrations compared to women from the lowest quartile. Interestingly, Chai et al. [115] found that the consumption of processed red meat was significantly related to reduced adiponectin concentrations in women. Surprisingly, such a correlation was not observed in men. Additionally, the authors noted that BMI might be an intermediate factor between red meat consumption and adiponectin concentrations. A diet rich in red meat may contribute to body weight increase and promote adipose tissue deposition, which may induce obesity-related inflammation. Detailed results of studies on the negative effects of dietary patterns on the concentration of adiponectin are described in Table 2.

To conclude, a negative influence on adiponectin concentrations seems to be exerted mainly by a high glycemic index diet and by the Western diet, characterized by the consumption of red meat, particularly processed meat, and products which provide high amounts of saturated fatty acids, trans fatty acids, fructose and sucrose. All components of this diet seem to have a direct negative effect on adiponectin concentrations. However, more research is necessary to confirm whether the high dietary content of red meat, monosaccharides and disaccharides is directly linked to the expression of adiponectin. Moreover, proportions between proteins, lipids and carbohydrates in the diet are of enormous importance, as high-carbohydrate and low-fat diets are significantly related to hypoadiponectinemia.

Table 2. Dietary patterns and the concentration of adiponectin (AD)—A negative effect.

Author/Reference	Year	Study Design	Sample	Results
			THE WESTERN DIET	
Jafari-Vayghan et al. [101]	2015	Cross-sectional study	150 apparently healthy men and women, aged 25–50 y	Adherence to the Western dietary pattern was negatively correlated with AD concentrations ($r = -0.19$; $p = 0.02$).
Alves-Santos et al. [103]	2018	Prospective cohort study	173 pregnant women free of infectious and chronic diseases, aged 20–40 y	Adherence to the Western dietary pattern was negatively correlated with AD concentrations during pregnancy (high vs. low tertile of adherence: $\beta = -1.11$; 95% CI −2.00, −0.22; $p < 0.05$).
			HIGH-CARBOHYDRATE LOW-FAT DIET	
Pischon et al. [12]	2005	Prospective cohort study	532 men, aged 40–75 y	A 5% increase in energy obtained from carbohydrates instead of lipids was associated with reduction in AD concentrations by 0.59 μg/mL ($p = 0.05$).
Kasim-Karakas et al. [106]	2006	Interventional study	22 healthy postmenopausal women, aged > 50 y	Following the eucaloric LFHC diet was linked to a reduction in AD concentrations (16.3 ± 2.1 μg/mL to 14.2 ± 2.0 μg/mL; $p < 0.05$).
Rajaie et al. [105]	2013	Randomized cross-over clinical trial	30 overweight or obese women with metabol ic syndrome, aged 20–65 y	Following HCD for 6 weeks was linked to AD concentration reduction by 1.68 ± 2.30 μg/mL (10.6 ± 0.3 μg/mL vs. 8.9 ± 0.3 μg/mL; $p < 0.001$).
Ruth et al. [104]	2013	Randomized clinical trial	55 obese men and women, aged 21–62 y	Following an HFLC diet for 12 weeks was related to a significant increase in AD concentrations (+0.40 ± 0.66 μg/mL, $p = 0.045$).
Song et al. [43]	2016	Randomized controlled interventional study	93 women and men aged 21–76 years	AD decreased by 9.4% ($p = 0.008$) in individuals following an LFHC diet compared to those following a diet with a moderate fat content.
Murillo-Ortiz et al. [107]	2017	Randomized controlled clinical trial	100 postmenopausal women with breast cancer, aged >48 y	Following a diet with the reduced fat content (12% of energy) for 6 months was associated with reduced AD concentrations (21.23 ± 14.32 μg/mL vs. 16.05 ± 10.25 μg/mL; $p < 0.001$).
Meshkini et al. [11]	2018	Cross-sectional study	89 apparently healthy men and women, aged 18–75 y	AD concentrations were negatively correlated with the amount of carbohydrates in the diet ($r = -0.24$, $p = 0.02$).
			GLYCEMIC INDEX AND GLYCEMIC LOAD OF THE DIET	
Qi et al. [63]	2005	Cross-sectional study	780 men with T2DM, aged 40–75 y	AD concentrations significantly lower in the highest quintile of the GI of the diet compared to the lowest GI (14.3 μg/mL vs. 16.4 μg/mL; $p = 0.005$). AD concentrations significantly lower in the highest quintile of the GL of the diet compared to the lowest GL (14.1 μg/mL vs. 17.2 μg/mL; $p = 0.004$).

Table 2. *Cont.*

Author/Reference	Year	Study Design	Sample	Results
Pischon et al. [12]	2005	Prospective cohort study	532 men, aged 40–75 y	Men from the highest quintile of AD concentrations (>24.9 μg/mL) were characterized by a significantly higher GL of the diet (124.7 ± 2.1 vs. 128.5 ± 1.0; $p = 0.04$) compared to men from the lowest quintile of AD concentrations (<10.6 μg/mL); $p = 0.006$). Each GL increment by 1 unit was associated with AD reduction by 1.32 μg/mL ($p = 0.02$).
Loh et al. [109]	2013	Cross-sectional study	305 T2DM men and women, aged 19–75 y	A negative correlation between the GI of the diet and AD concentrations ($\beta = -0.272$, 95% CI −0.262–0.094; $p < 0.001$).
Cerman at tal. [108]	2016	Cross-sectional study	86 men and women apparently healthy or with acne vulgaris, aged > 18 y	A negative correlation between the GI of the diet and AD concentrations ($r = -0.212$; $p = 0.049$).
Pereira et al. [62]	2016	Observational, cross-sectional study	43 men and women, aged 18–60 y	A high GI of the diet was negatively correlated with AD concentrations ($r = -0.47$; $p = 0.0017$).
AlEssa et al. [64]	2016	Cross-sectional study	2458 women, free of diabetes, aged 43–70 y	Women from the highest quintile of diet GI had significantly lower AD concentrations compared to women from the lowest quintile (11.7 (11.2, 12.3) μg/mL vs. 12.9 (12.4, 13.4) μg/mL; $p < 0.001$).
Meshkini et al. [11]	2018	Cross-sectional study	89 apparently healthy women and men, aged 18–75 y	AD concentrations were negatively correlated with diet GI ($r = -0.43$; $p < 0.001$) and GL ($r = -0.29$; $p = 0.007$). A high GI diet was one of stronger negative predictors of AD concentrations ($\beta = -0.176$, $p = 0.04$).
SATURATED FATTY ACIDS AND TRANS FATTY ACIDS				
Fargnoli et al. [13]	2008	Prospective cohort study	1922 women free of CVD, diabetes and cancer, aged 30–55 y	Women from the highest quartile of trans fatty acid consumption had significantly lower total AD concentrations (13.5 ± 1.03 μg/mL vs. 14.96 ± 1.03 μg/mL, $p = 0.0002$) and AD HMW concentrations (4.49 ± 1.04 μg/mL vs. 5.20 ± 1.04 μg/mL; $p = 0.0008$) compared to women from the lowest quartile.
Haidari et al. [111]	2014	Case-control study	94 men and women apparently healthy or with asthma	AD concentrations were negatively correlated with SFA consumption in persons with asthma ($r = -0.319$; $p = 0.033$) and in healthy individuals ($r = -0.356$; $p = 0.016$).
Pereira et al. [62]	2016	Observational, cross-sectional study	43 men and women, aged 18–60 y	AD concentrations were negatively related to the consumption of trans fatty acids ($r = -0.4$, $p = 0.008$).

Table 2. *Cont.*

Author/Reference	Year	Study Design	Sample	Results
Prates et al. [27]	2016	Cross-sectional study	122 men and women with T1DM, aged > 18 y	AD concentrations were negatively correlated with SFA consumption ($r = -0.25$, $p = 0.004$), total fat consumption ($r = -0.20$, $p = 0.02$), and cholesterol consumption ($r = -0.20$, $p = 0.021$).
Lepsch et al. [110]	2016	Prospective cohort study	201 pregnant women, aged 22–31 y	A negative correlation between SFA consumption and AD concentrations ($\beta = -41.039$; $p = 0.008$).
MONOSACCHARIDES AND DISACCHARIDES				
Pollock et al. [113]	2012	Cross-sectional study	559 adolescents, aged 14–18 y	A diet with high fructose content was associated with significantly lower AD concentrations (8.4 ± 0.4 µg/mL vs. 9.1 ± 0.4 µg/mL; $p = 0.033$).
Rezvani et al. [112]	2013	Double-blind parallel arm study	32 overweight or obese men and women, aged 40–72 years	Participants who consumed high quantities of glucose ($p = 0.028$) and fructose ($p = 0.0011$) had significantly decreased AD concentrations after 10 weeks.
Magalhaes et al. [114]	2014	Cross-sectional study	60 obese women with nonalcoholic fatty liver disease or apparently healthy, aged >20 y	Diet rich in sucrose was significantly related to low AD concentrations (<0.35 µg/mL) in healthy women ($p = 0.054$) and in women with NAFLD ($p = 0.045$). Diet rich in sweets ($p = 0.046$) and sweetened beverages ($p = 0.054$) was significantly correlated with low AD concentrations in healthy women (<0.35 µg/mL).
RED MEAT				
Fargnoli et al. [13]	2008	Prospective cohort study	1922 women free of CVD, diabetes and cancer, aged 30–55 y	Women from the highest quartile of the red meat to poultry consumption ratio had significantly lower total AD concentrations (13.24 ± 1.03 µg/mL vs. 14.52 ± 1.03 µg/mL, $p = 0.02$) compared to women from the lowest quartile.
Ley et al. [116]	2014	Prospective cohort study	21700 women, aged 30–55 y	Women from the highest quartile of the consumption of red meat (13.7 (13.1, 14.3) µg/mL vs. 15.0 (14.4, 15.6) µg/mL, $p = 0.003$), unprocessed red meat (14.0 (13.4, 14.5) µg/mL vs. 15.0 (14.4, 15.6) µg/mL; $p = 0.01$) and processed red meat (13.9 (13.3, 14.5) µg/mL vs. 15.0 (14.4, 15.6) µg/mL; $p = 0.007$) had significantly lower AD concentrations compared to women from the lowest quartile.
Chai et al. [115]	2017	Case-control study	1223 men and women free of cancer, aged 45–75 y	The consumption of red processed meat was associated with reduced AD concentrations in women ($\beta = -0.082$; $p = 0.005$).

Abbreviations: AD, adiponectin; AD HMW, high-molecular-weight adiponectin; y, years; LFHC, low-fat high-carbohydrate diet, HFLC, high-fat low-carbohydrate diet, HCD, high calorie diet, IG, glycemic index, GL, glycemic load, SFA, Saturated Fatty Acids; CVD, cardiovascular disease, NAFLD, nonalcoholic fatty liver disease.

4. Conclusions

Dietary factors play an extremely important role in the regulation of adiponectin concentrations. Adherence to the Mediterranean dietary pattern is one of the strongest modulators of its concentration. The presence of monounsaturated fatty acids, polyunsaturated omega-3 fatty acids, fiber and polyphenols make the Mediterranean diet particularly beneficial. Moreover, it seems likely that the relationship between MD and the prevention of civilization diseases, such as cancer, cardiovascular disease and metabolic disorders, may result from its influence on the concentration of this adipokine. It seems that the DASH diet, diet based on plant products and diet with reduced energy value also contain dietary patterns responsible for the increase in adiponectin concentrations. Additionally, the moderate consumption of alcohol and milk products appear to be significant in terms of exerting a beneficial influence on the regulation of its concentrations. Conversely, high glycemic index and glycemic load, a high consumption of red meat, particularly processed meat, and products rich in saturated fatty acids, trans fatty acids, and fructose and sucrose are factors which adversely affect adiponectin concentrations (the summary of the influence of dietary factors on the concentration of adiponectin constitutes Figure 1). Therefore, it seems that hypoadiponectinemia is particularly associated with dietary patterns typical of the Western diet and high-carbohydrate low-fat diet. Due to the paucity of data to confirm the correlation between individual dietary components, it is necessary to conduct more research to determine which dietary components are directly related to the expression of adiponectin.

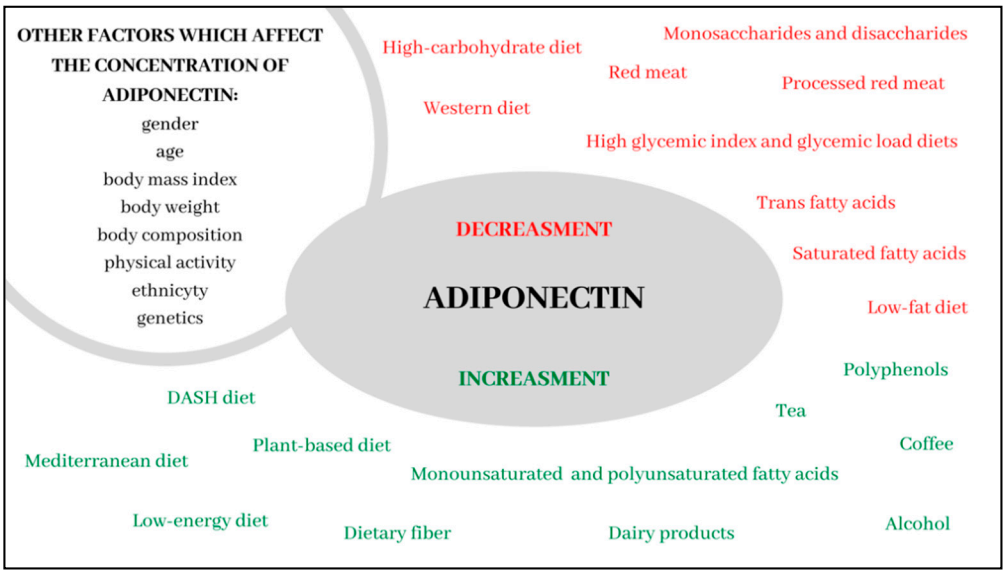

Figure 1. Summary of the influence of dietary factors on the concentration of adiponectin.

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Review

The Influence of Diet on Ovulation Disorders in Women—A Narrative Review

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Abstract: Female infertility is commonly due to ovulation disorders. They are mostly related to polycystic ovary syndrome, which is currently viewed as one of the most common endocrine disorders in women of reproductive age. Ovulation-related female fertility is influenced by multiple factors which may include: age, smoking cigarettes, stress, use of psychoactive substances, and physical activity. Moreover, diet-related factors play an important role in the regulation of ovulation. Dietary components that exert a positive influence on ovulation include: carbohydrate products with low glycemic index, plant protein, monounsaturated and polyunsaturated fatty acids, folic acid, vitamin D, antioxidants, and iron. A diet based on the structure of the Mediterranean diet also seems beneficial. Components that have a negative influence mostly include high glycemic index carbohydrates, large amounts of animal protein, saturated fatty acids, and trans fatty acids, which are typically found in the Western model of nutrition. Due to the paucity of studies that presented a direct link between nutrition and the risk of anovulatory infertility, this study aimed to summarize the most recent research on the influence of dietary factors on ovulation disorders and indicate the possibilities of future research.

Keywords: female fertility; ovulation disorders; diet; nutrition; insulin sensitivity

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1. Introduction

According to the World Health Organization (WHO), infertility is defined as the inability to conceive despite at least 12 months of regular unprotected intercourse. It is estimated that the problem of infertility may be experienced by even 48 million couples worldwide. The etiology of this disorder may be related to male, female, combined, or idiopathic factors [1]. However, it is believed that female factors are responsible for 35–40% of infertility cases. Female infertility may be due to endocrine disorders, endometriosis, fallopian tube injury, infection, or environmental factors. However, female infertility is commonly associated with ovulation disorders. They are mostly due to polycystic ovary syndrome (PCOS), which is currently viewed as one of the most common endocrine disorders in women of reproductive age [2,3]. It was estimated that 80% of women with PCOS experience ovulation disorders that contribute to problems with conception [4].

The pathomechanism of anovulation in women with PCOS seems to be very complex and may be associated with abnormalities in the secreted gonadotropins and their impaired functioning, which leads to the inhibition of antral follicle development. Common endocrine abnormalities in non-ovulating women with PCOS include elevated serum levels of androgens and luteinizing hormone (LH) with normal or slightly decreased serum follicle stimulating hormone (FSH) levels, which is essential for the proper proliferation of ovarian granulosa cells. Therefore, the role of LH seems to be significant in the pathomechanism of ovulation disorders [5]. It was observed that the follicles of women with PCOS are prematurely sensitive to the action of LH, which results in the suppression of FSH and the impaired development of the dominant follicle. In addition, a high frequency

of pulsatile gonadotropin releasing hormone (GnRH) secretion was observed in the group of women with PCOS, resulting in a disturbed LH to FSH ratio. However, it was also observed that antral follicles, which are unable to pass to the pre-ovulatory phase in this group of women, are sensitive to the action of follicle-stimulating hormone. The adjustment of its levels usually restores ovulation and fertility [5,6]. Moreover, the results of a study by Teede et al. [7] additionally indicated the key role of anti-Mullerian hormone (AMH), produced by pre-antral and antral follicles, in the genesis of abnormal GnRH activity and the resulting increase in LH and androgens. Conversely, it is believed that, in addition to neuroendocrine factors, local intraovarian factors also contribute to the arrest of antral follicle development. First of all, elevated blood androgens, affecting numerous metabolic pathways, may lead to the premature arrest of granular cell proliferation, which results in the lack of dominant follicle formation. Another mechanism underlying the causes of ovulation disorders among women with PCOS is related to being overweight and obese [5,6]. Studies by Chavarro et al. [8] and Rich-Edwards et al. [9] revealed a relationship between BMI (Body Mass Index) value and a relative risk of ovulation disorders, as a correlation occurred between excess body weight and LH levels. Moreover, hormone abnormalities in individuals with excessive weight may be exacerbated by associated tissue insulin resistance and hyperinsulinemia, which may potentiate the effect of LH on granular cells in the follicle and increase the chances of premature maturation [5]. Additionally, women with PCOS are characterized by the occurrence of disturbances in adipokines secreted by the adipose tissue, leptin in particular, the concentration of which is significantly elevated in PCOS women with obesity [10]. Leptin levels vary depending on the phase of the menstrual cycle, which means that it plays a significant role in regulating hormonal balance in women and is essential for the course of ovulation [11]. This adipokine stimulates the pituitary gland to secrete LH and may also activate gonadotropin-releasing hormone receptors in the hypothalamus which, in turn, stimulate LH secretion [12]. Therefore, preconception body weight reduction in women with excessive weight is one of the key elements leading to success in conceiving by regulating hormonal balance, decreasing leptin concentration, and inducing spontaneous ovulations [13–15]. Furthermore, PCOS women typically present with decreased concentrations of adiponectin, whose action is mainly associated with increasing the sensitivity of tissues to insulin [10]. This adipokine is believed to interact with the hypothalamic–pituitary–gonadal axis and regulate the secretion of GnRH. Adiponectin may also enhance the expression of ovarian insulin receptors and decrease the synthesis of androgens in ovaries, which may lead to an improvement in ovulation, especially in PCOS women [16].

Ovulation-related female fertility is influenced by multiple factors that may include: age, smoking cigarettes, stress, the use of psychoactive substances, and physical activity [3,17]. Diet-related factors should also be taken into account, as they play an important role in the regulation of ovulation. Diet and its nutritional components may influence female fertility and ovulation via their effect on metabolic pathways, endocrine profile, and carbohydrate metabolism. Particular significance in the pathogenesis of ovulation disorders is attributed to insulin resistance, which is the most important factor linking anovulatory infertility to nutrition [18]. Another very important factor that increases the risk of ovulation disorders is oxidative stress and chronic inflammation [19]. High levels of inflammatory markers during the menstrual cycle in women are associated with a higher risk of an anovulatory cycle, mainly by increasing oxidative stress in the ovary [20].

Dietary components that have a positive influence on ovulation include: carbohydrate products with low glycemic index, plant protein, monounsaturated and polyunsaturated fatty acids, folic acid, vitamin D, antioxidants, and iron. A diet based on the structure of the Mediterranean diet also seems beneficial due to its anti-inflammatory properties. Components exerting a negative influence mostly include high glycemic index carbohydrates, large amount of animal protein, saturated fatty acids, and trans fatty acids, which are typical of the Western model of nutrition, which is closely related to increased oxidative stress.

The role of the diet and other modifiable factors associated with lifestyle in the prophylaxis of fertility disorders is still under research. However, few studies presented a direct link between nutrition and the risk of anovulatory infertility. Therefore, the aim of the present literature review was to summarize available knowledge about diet and its relation to anovulatory infertility and indicate the possibilities of future research.

2. Dietary Patterns

A prospective cohort Nurses' Health Study II (NHS II), which was conducted in 17,544 women trying to conceive, revealed that diet and nutrients included in it markedly influenced fertility and the reduction of the risk of ovulation disorders. Women from the highest quintile of adherence to diet were at a 66% lower risk of anovulatory infertility compared to women from the lowest quintile. Basing on the results, the so called "fertility diet" pattern was developed. It was characterized by the lower consumption of trans fatty acids with the simultaneous increased supply of monounsaturated fatty acids, higher plant protein content and the presence of high-fat milk products, carbohydrate products with low glycemic index, and high iron content. Moreover, adhering to this dietary pattern was associated with a lower risk of fertility disorders caused by other factors [8]. It was suggested that particular benefits related to consuming the "fertility diet" were observed in women with PCOS, as adherence to the diet was linked to the occurrence of spontaneous ovulation with the overall fertility improvement in this group [21].

The beneficial effect of the Mediterranean diet (MD) on female fertility is also an interesting issue [22,23]. Traditional Mediterranean diet is characterized by the high supply of vegetables, fruit, olive oil, fatty saltwater fish, and whole-grain cereal products. Alcohol consumption should be moderate and red meat consumption should be low [18]. MD has a great potential to reduce inflammation and concentrations of oxidative stress markers, which was linked to the risk of ovulation disorders, particularly in women with PCOS [19]. The results of a study by Fatima et al. [24] showed that patients with PCOS were characterized by low levels of glutathione, vitamins C and E, and significantly increased activity of antioxidant enzymes, such as glutathione peroxidase, glutathione reductase, and glutathione transferase compared to women without PCOS. Chronic, low-grade inflammation in women with PCOS may affect the functioning of the ovaries, interfering with the synthesis and release of sex hormones, follicular maturation, and ovulation [25].

Due to the lack of research to link this diet to the risk of anovulatory infertility, its direct influence on ovulation may not be explicitly confirmed. However, due to its beneficial effect on female fertility and the similarity to the assumptions of the "fertility diet" it may be concluded that it also has a positive influence on ovulation. Additionally, its potentially beneficial effect on ovulation is considerably enhanced by the anti-inflammatory character of the diet [26]. Linoleic acid is considered as a particularly important element of MD. It is a precursor of prostaglandins, which play a significant role in the course of ovulation and increase the response of ovaries to gonadotropin, thereby exerting a positive effect on ovulation [23,27].

The Western dietary pattern is entirely different. It is rich in simple carbohydrates, whose main sources include sugar, sweets, and sweetened beverages, and red and processed red meat. Moreover, it is characterized by the low consumption of fresh fruit and vegetables, whole grain cereals, poultry, and fish. It is a high glycemic index diet, which is additionally rich in saturated fatty acids and trans fatty acids, which increase the risk of anovulatory infertility. The Western dietary pattern is inversely correlated with female fertility through its negative influence on endocrine metabolism and ovarian reserve [17]. According to Hajishafiee et al. [28], lower consistency between nutrition and the Western diet was associated with a 35% lower probability of infertility in women with PCOS. However, due to the lack of research to assess correlations between the Western diet and anovulatory infertility, it may not be explicitly confirmed that the diet increased the risk of ovulation disorders. Nevertheless, considering the correlations between diet and reduced fertility, increased insulin resistance, and a high percentage of components increasing the risk of

infertility due to ovulation disorders and aggravating inflammation, it may be assumed that the diet exerts a negative effect on ovulation in women.

3. Carbohydrates and Low Glycemic Index Diet

Considering a fertility-promoting nutrition model, one should remember low glycemic index (GI) carbohydrates, as insulin sensitivity and glucose homeostasis are regarded to be some of the most important factors determining female fertility [23]. The mechanism through which the high glycemic index of the diet and high carbohydrate content of the diet contribute to fertility and ovulation disorders results from their influence on tissue sensitivity to insulin. Furthermore, insulin directly influences ovarian function and ovulation via its participation in the response of ovarian follicles to gonadotropin. Therefore, high insulin levels were found to be associated with abnormal ovarian steroid genesis and impaired oocyte development. Moreover, hyperinsulinemia is strongly correlated with hyperandrogenism, which also contributes to the occurrence of ovulation disorders and exacerbates endocrine disorders in women [17,29,30]. Another mechanism linking ovulation disorders to a diet with a high glycemic index and high carbohydrate content appears to be low-grade inflammation. A diet with a high glycemic index and low in dietary fiber was shown to be strongly correlated with inflammation. In particular, fructose is attributed to a strong pro-inflammatory effect. In addition, postprandial hyperglycemia caused by the supply of large amounts of high GI carbohydrates is associated with the intensification of inflammation and oxidative stress through the production of reactive oxygen species [31].

It is believed that both the quality and quantity of carbohydrates have a specific influence on the risk of developing anovulatory infertility. A cohort NHS II study [32] revealed that women in the highest quintile of the total carbohydrate consumption were at a 78% higher risk of anovulatory infertility compared to women from the lowest quintile of the consumption of this macronutrient. The results of these study were confirmed by a systematic review of seven interventional studies, which revealed that the use of a low-carbohydrate diet was associated with a higher ovulation rate [14]. Palomba et al. [33] noted that the combination of a hypocaloric diet providing 45% of energy from carbohydrates with physical activity and clomiphene citrate resulted in a considerable improvement in ovulation rates compared to pharmacotherapy and traditional diet. The results may suggest that reduced carbohydrate supply may be effective in the induction of ovulation in women via the influence on insulin sensitivity. When considering low-carbohydrate diets, it is also worth mentioning the ketogenic diet, which provides less than 20 g of carbohydrates a day, and its impact on the course of polycystic ovary syndrome. The use of this diet is primarily associated with the reduction of body weight, improvement in carbohydrate metabolism, and a significant decrease in insulin resistance and in circulating markers of inflammation [34]. A study conducted by Mavropoulos et al. [35] showed that women with PCOS who followed the ketogenic diet for 24 weeks showed an improvement in the LH/FSH ratio and a reduction of fasting insulin and percentage of free testosterone, which all have a considerable impact on ovulation. However, due to the paucity of research in this area, this diet should be recommended with caution, especially in the case of women of reproductive age.

Apart from the quantity, the quality of the carbohydrates also seems to be a very important factor. A study by Chavarro et al. [32] demonstrated that the consumption of products with low glycemic index (e.g., brown rice, whole grain pasta, and bread) was inversely correlated with the risk of anovulatory infertility, while products with high glycemic index (e.g., white rice, boiled potatoes, or breakfast cereals) had a negative effect on the course of ovulation.

Special attention is paid to dietary fiber, the source of which are products with low glycemic index. Chavarro et al. [32] demonstrated that fiber consumption increased by 10 g/day was associated with a 44% lower risk of developing ovulation disorders in women aged over 32. Such a correlation was not observed in women aged below 32 years.

However, it was found in the BioCycle cohort [36] that the consumption of dietary fiber over the recommended dose was associated with an increased risk of the lack of ovulation. The authors suggested that the observed phenomenon resulted from reduced hormone concentrations due to the high consumption of fiber, especially the water-soluble fraction.

Particular benefits of diets with low glycemic index are observed in women with PCOS. It was noted in this group of patients that the low quality of carbohydrate products and high glycemic index and load were particularly linked to ovulation disorders [37]. It is believed that insulin resistance and hyperinsulinemia are factors that lead to ovulation disorders, endocrine disorders, and abnormal endometrial structure, and, therefore, to infertility in PCOS patients. Hyperinsulinemia may also have a direct negative effect on the development of ovarian follicle in this group of women. It may even inhibit its development, leading to anovulatory cycles [4,38]. Furthermore, a meta-analysis and systematic review of 10 randomized studies revealed that the use of low glycemic index diets was associated with decreased testosterone levels in women with PCOS. It suggests that the beneficial effect of a low GI diet in this group of women was not only associated with the direct influence of carbohydrates on fertility and ovulation, but also with the influence of the diet on hormonal regulation, whose homeostasis determined the normal course of ovulation [39]. According to a randomized study by Sordia-Hernández et al. [40], which included 37 women with PCOS, ovulatory cycles occurred in 24.6% of women consuming a low glycemic index diet. Only 7.4% of women consuming a traditional diet who did not focus on glycemic index had ovulatory cycles. The observed differences in the frequency of ovulation cycles in both diets may result from reduced androgen concentrations and increased tissue sensitivity to insulin being the consequence of consuming a low glycemic index diet.

Another important factor associated with carbohydrate products is the influence of dietary Advanced Glycation End Products (AGE) on female fertility and ovulation. AGEs are formed as a result of the reaction of the amino groups of protein, lipid, amino acid, and nucleic acid with the aldehyde group of reducing carbohydrate, during frying and preparing products rich in carbohydrates and proteins at high temperatures. They are especially characteristic for the Western diet, which is rich in highly processed products, simple sugars, animal protein, and fat. It is believed that they play an essential role in the deregulation of ovarian function and ovulation, because they may accumulate in the granulosa cell layer. Diets high in AGE compounds may disrupt ovarian function, folliculogenesis, and steroidogenesis in particular, contributing to oxidative stress and disrupting hormonal balance. AGEs mainly interfere with LH and FSH action and they lead to ovulation disorders in women with PCOS [41,42].

To sum up, due to the fact that the insulin sensitivity of tissues is one of the more important determinants of the normal course of ovulation, low glycemic index diet plays a significant role in its regulation. Moreover, it seems that limiting carbohydrate supply is also of key importance in the prevention of ovulatory infertility. Therefore, the diet of a woman trying to conceive who has problems related to ovulation disorders should be balanced with regards to both the quantity and quality of carbohydrates provided.

4. Plant and Animal Protein

Wholesome protein also constitutes a very important component in the "fertility diet". However, some studies showed that protein might have a negative effect on fertility, which is mainly related to its source [43,44]. Chavarro et al. [44] demonstrated that women from the highest quintile of total protein consumption were at a 41% higher risk of anovulatory infertility compared to women from lower quintiles of the consumption of this macronutrient. Furthermore, the addition of one portion of meat daily resulted in a 32% increase in the risk of ovulatory disorders. It was shown that protein obtained from red meat and poultry considerably increased the risk of anovulatory infertility, while no negative influence on ovulation was observed in the case of egg and fish protein. A study by Zhang et al. [45], which included 2217 women with PCOS without ovulation and with normal ovulation, revealed that women with ovulation disorders were characterized by a significantly higher

share of meat in the diet compared to women with normal ovulation. Moreover, red processed meat was found to have a particularly negative effect on fertility, as its consumption was related to numerous adverse health outcomes. Therefore, its negative effect on ovulation may also be speculated [46]. However, it is worth noting that women characterized by a higher consumption of animal protein also consumed more saturated fatty acids compared to those who consumed smaller quantities of animal protein. They were also less physically active. Therefore, the potential influence of both those factors needs to be considered, as they may intensify the correlation between animal protein consumption and ovulation disorders [44].

An entirely different effect on ovulation was observed in relation to plant protein. The consumption of 5% of energy from plant protein instead of animal protein diminished the risk of anovulatory infertility by over 50%. Furthermore, changing carbohydrates into plant protein also appeared to have a positive effect on ovulation. The consumption of plant protein at the level of 5% of energy requirement instead of carbohydrates was associated with the reduction of the risk of ovulation disorders by as much as 43% [44]. A potentially beneficial effect of plant protein on fertility may be linked to improved insulin sensitivity and lower postprandial secretion of this hormone compared to animal protein [17]. Both types of protein have an entirely different effect on the concentrations of circulating IGF-1 (Insulin-like Growth Factor 1). It was observed that women consuming higher amounts of animal protein had higher IGF-1 concentrations, which was correlated with the occurrence of ovulation disorders and abnormal development of ovarian follicles [18,47].

The effect of milk products on ovulation disorders is another interesting issue, as they constitute a significant source of protein in the diet. Milk products are believed to have a toxic influence on fertility due to the high galactose content, which disturbs ovulation in mice and leads to premature ovarian insufficiency [48]. Additionally, their consumption adversely affects hormonal regulation in women [36]. A cohort BioCycle study [49] showed that a higher frequency of anovulation was noted in women consuming higher amounts of cream and yoghurt. However, some authors confirmed a positive influence of milk and milk products on female fertility, regardless of fat content [50,51]. Interesting results were obtained in a cohort NHS II study [52], which showed no correlation between the total consumption of milk products and anovulatory infertility. However, significant differences were observed as regards their influence on ovulation depending on fat content. Increasing the consumption of low-fat milk products by one portion daily was linked to an 11% increase in the risk of anovulatory infertility, while adding one portion of whole milk without increasing energy consumption decreased the risk of ovulatory infertility by over 50%. The authors suggested that differences in the influence of milk products with various fat content on ovulation resulted from the fact that milk products characterized by higher fat content had higher estrogen content and caused lower IGF-1 increase compared to their lean equivalents. Furthermore, a beneficial effect of high-fat milk products on ovulation may be associated with the presence of trans palmitic acid, which seems to increase insulin sensitivity [17]. Moreover, the relationship between the consumption of low-fat and high-fat milk products and anovulatory infertility appeared to be particularly intense in women without typical PCOS clinical manifestations compared to women with such manifestations [52].

To sum up, basing on the research, it may be speculated that a higher share of plant protein than animal protein is more beneficial in the context of anovulatory infertility. Due to the lack of research to link the consumption of red meat to anovulatory infertility, it may not be confirmed whether the product increases the risk of ovulation disorders. However, considering the fact that red meat consumption, particularly processed, increases insulin resistance, its negative effect on ovulation may be speculated. Moreover, due to the lack of explicit research results, the influence of milk products on ovulation may not be explicitly confirmed, particularly as regards high-fat products, which are the source of saturated fatty acids, thereby intensifying ovulation disorders.

5. Unsaturated and Saturated Fatty Acids

Suitable quality and quantity of consumed fatty acids is of utmost importance in the prophylaxis of fertility disorders. Both insufficient and excessive amount of fat in the diet seem to have a negative effect on fertility. Insufficient fat content in the diet may contribute to the occurrence of abnormal menstrual cycles (prolonged follicular phase, secondary amenorrhea, and longer cycles) [53]. A study by Chavarro et al. [53] revealed that total fat consumption was inversely proportional to the risk of anovulatory infertility. However, after comprising potential confounding factors, the correlations were significantly weaker and statistically insignificant. Conversely, the results obtained by Mumford et al. [54] indicated that high-fat diet triggered increased testosterone synthesis in women, which also affects ovulation. Additionally, it is assumed that high-fat diet disrupts the functioning of the hypothalamic–pituitary–ovarian axis, leading to endocrine disorders and prolonged menstrual cycles, which may also contribute to the development of ovulation disorders in women. This correlation is mostly due to insulin resistance and excessive ovarian and hypothalamic stimulation by insulin [55].

However, the quality, and not the quantity, of fat in the diet seems more important as regards ovulation disorders. It is believed that PUFA (polyunsaturated fatty acid) supplementation exerts a beneficial effect on female fertility through the influence on LH and FSH concentrations, maturation of the dominant follicle, the quality of oocytes, and ovulation induction [56]. Moreover, omega-3 fatty acids regulate the maturation and development of oocytes mostly via the regulation of the PPAR (peroxisome proliferator-activated receptor) receptor. The expression of all three of its isoforms was identified in the ovarian tissue. The expression of PPARγ increases with the growth of the follicle and is subsequently rapidly decreased in response to LH release and ovulation. Furthermore, omega-3 acids stimulate ovulation via the expression of genes and COX-2 (cyclooxygenase 2) activity [57]. It was demonstrated that omega-3 acid supply was associated with higher progesterone concentrations and a lower risk of ovulation disorders. As regards women with PCOS, PUFA acids have a positive effect on metabolic and endocrine parameters. However, their direct influence on ovulation was not observed in this group of women [54]. Mumford et al. [58] demonstrated that the consumption of docosapentaenoic acid, which is structurally similar to eicosapentaenoic acid, was linked to a reduced risk of anovulation in a cohort of healthy and regularly menstruating women. Similar inverse correlations were observed for their polyunsaturated omega-3 fatty acids. However, they were devoid of statistical significance. Furthermore, the consumption of total fat and polyunsaturated fatty acids was unrelated to higher testosterone levels, but it was associated with increased progesterone levels, which promoted the reduction of the risk of anovulation. Monounsaturated fatty acids (MUFA) are also beneficial in the context of fertility mainly by reducing inflammation [58]. Interestingly, Chavarro et al. [53] reported that the consumption of MUFA, total polyunsaturated fatty acids, n-3 PUFA, and n-6 PUFA was not associated with anovulatory infertility.

SFA (saturated fatty acids) and TFA (trans fatty acids) were found to exert a particularly negative effect on ovulation [59]. Interestingly, cohort studies by Mumford et al. [54] and Chavarro et al. [53] revealed no correlation between SFA consumption and the relative risk of anovulation. However, Chavarro et al. [53] observed a correlation between the consumption of TFA contained in sweets, hard margarines and fast food, and ovulation disorders. The replacement of unsaturated fatty acids with saturated fatty acids also has a negative impact on ovulation disorders. The change of 2% of energy obtained from polyunsaturated fatty acids or monounsaturated fatty acids into TFA was associated with a doubled risk of anovulatory infertility. Moreover, each increase of energy obtained from TFA by 2% instead of carbohydrate-derived energy was also associated with anovulatory infertility, and each increase of energy from TFA by 2% was associated with a 73% increase in the risk of ovulation disorders in women. Ghaffarzad et al. [60] conducted a study in women with PCOS and demonstrated that higher concentrations of trans fatty acids in erythrocytes were associated with an increased risk of ovulation disorders in this group of women. A potential correlation between TFA and anovulatory infertility was related

to the increased insulin resistance of tissues, inflammatory marker concentrations, and a 40% reduction in the expression of the PPARγ receptor, which were attributed a significant share in the regulation of ovulation.

To sum up, a diet rich in monounsaturated and polyunsaturated fatty acids seems to have a positive effect on ovulation. However, good quality research is necessary in this matter for the explicit identification of a correlation between unsaturated fatty acids and ovulatory fertility. Moreover, the influence of the amount of fat in the diet is dubious, so research is necessary as well. Trans fatty acids also have a negative influence on ovulation. Therefore, diet poor in processed products, sweets, and fast food seems to have a positive effect on the risk of ovulation disorders.

6. Alcohol and Caffeine

Caffeine and alcohol seem to have a negative effect on female fertility, as they may particularly increase the risk of ovulation disorders [61]. Chavarro et al. [61] demonstrated that the consumption of energy drinks containing caffeine was related to a 47% increase in the risk of anovulatory infertility in women consuming at least two or more caffeine-containing beverages compared to women who drank less than one beverage with caffeine per week. Various hypotheses have been developed as regards the possible mechanisms of the potential influence of caffeine on reproduction, but the mechanisms have not been elucidated yet. Caffeine consumption may affect ovulatory fertility via the influence on reproductive hormone concentrations (e.g., decreased levels of estradiol), changes in hormone metabolism, and the activity of ovaries. Due to its interaction with sex hormones, caffeine consumption may negatively affect the length of the cycle. High caffeine intake (>300 mg/day) may even inhibit ovulation, but the mechanism is still unclear [62].

Despite a potentially negative influence of caffeine on fertility, some research showed no correlation between drinking tea and coffee and female fertility [63,64]. Chavarro et al. [60] revealed no correlation between the consumption of caffeine from tea and coffee and the risk of anovulatory infertility. A potentially positive influence of caffeine on ovulation may result from its effect on tissue insulin sensitivity and carbohydrate metabolism, which modulates the process of ovulation to a considerable extent [65].

The effect of alcohol on ovulation is currently under research with the results being contradictory. Differences in the results may mostly be due to the type of consumed alcohol, health status, and other confounding factors [66]. The negative influence of alcohol consumption on female fertility was mainly due to its effect on hormonal regulation, menstrual cycle, ovarian reserve, oocyte maturation, and ovulation [17,67,68]. Alcohol consumption, leading to increased estrogen concentrations and decreased FSH, inhibits folliculogenesis and ovulation [69]. According to Chavarro et al. [61], women consuming about 10 g or more alcohol daily (about >1 drink a day) were at an almost 50% higher risk of anovulatory infertility compared to women who denied drinking alcohol. The correlation was particularly intense in the case of spirit drinks.

To sum up, due to the lack of unambiguous results, it may not be stated that caffeine consumption disturbs ovulation in women. Seemingly, tea and coffee consumption does not affect ovulation, while energy drinks containing caffeine may considerably disturb ovulation in women. Moreover, alcohol consumption has a particularly unfavorable effect in the context of ovulatory infertility. Due to the negative effect of alcohol on other fertility parameters, it should be eliminated from the diet of women trying to conceive.

7. Vitamins and Minerals

Appropriate supply of vitamins and minerals also has a positive influence on female ovulatory fertility. A significant role is attributed to group B vitamins (B6, B12, and folic acid in particular), antioxidant vitamins (A, C, E), vitamin D, and iron. A study by Chavarro et al. [70] demonstrated that the consumption of multivitamin supplements at least three times a week was associated with the reduced risk of anovulatory infertility. The correlation seems to be mostly related to folic acid. It was confirmed that the consumption of 700 μg of

folic acid daily reduced the risk of ovulation disorders by 40–50%. Another cohort BioCycle Study by Gaskin et al. [71] including 259 healthy women aged 18–44 showed that folic acid supplementation was inversely correlated with the risk of anovulation. Women from the highest tertile of folate consumption (270.6 µg/d) had 64% lower chances of developing anovulation compared to women from the lowest tertile (100.9 µg/d). A similar correlation was observed as regards the consumption of cereal products fortified with folic acid with the observed correlation between tertiles being non-linear. Interestingly, such a correlation was not observed with reference to the consumption of folates with food. It might have been due to the fact that synthetic folic acid is more easily absorbed in the digestive tract compared to its natural equivalents.

The mechanism through which folic acid exerts a beneficial effect on female fertility is mostly related to its influence on oxidative stress and the production of proinflammatory cytokines, which may have a significant effect on ovulation and the development of oocytes. Another possible mechanism through which folic acid influences the course of ovulation is related to the lower response of ovaries to FSH stimulation in the case of low folate concentrations in the blood serum [71]. However, its influence on homocysteine concentrations seems to be crucial. It regulates homocysteine concentrations with vitamin B6 and B12, so their supply seems to be of key importance for female fertility [17]. A cohort study including 259 regularly menstruating women who used no hormonal contraceptives or diet supplements revealed a correlation between higher homocysteine concentrations and a 33% increase in the risk of anovulation. Moreover, a higher ratio of folic acid to homocysteine reduced the risk of anovulation by 10%. The correlation was mostly due to the fact that homocysteine influenced the concentrations of reproductive hormones during individual phases of the cycle, which was important in the context of ovulation [72].

Antioxidants also seem very important for ovulation, as oxidative stress was found to increase the risk of anovulatory infertility [17]. Possible mechanisms of action of antioxidants on female fertility include improved blood flow in the endometrium, reduced reproductive hormone concentrations, increased tissue sensitivity to insulin and the influence on ovulation, prostaglandin synthesis, and steroid genesis [73]. Furthermore, vitamin C found at high concentrations in oocyte cytosol participates in collagen synthesis, which is important for the growth of the Graafian follicles, ovulation, and the luteal phase [17]. Considering the influence of vitamins on female fertility, a particular role is attributed to vitamin D. Vitamin D may take part in the modulation of female reproductive functions, as its receptors are present in numerous tissues of reproductive organs, such as the ovaries, endometrium, and placenta. Moreover, vitamin D influences a number of endocrine processes and the steroid genesis of reproductive hormones. Furthermore, it may induce oocyte maturation and ovulation. It also influences carbohydrate metabolism and insulin sensitivity of tissues, which may contribute to the modulation of ovulation [17]. A randomized placebo-controlled clinical trial included 186 women in whom ovulation was induced with clomiphene citrate and combined with vitamin D supplementation. Vitamin D supplementation significantly improved ovulation rates (92.5% of women in the treatment group vs. 78.5% in the control group had successful ovulation) [74]. Similar results were obtained in a different randomized study including women in whom ovulation was induced with clomiphene citrate and who were also administered vitamin D or coenzyme Q10. The study revealed that both supplements significantly increased the indices of ovulation in PCOS women resistant to clomiphene citrate treatment. Furthermore, a marked improved endocrine profile was noted in both groups [75].

As regards minerals, iron seems the most important. Its deficiencies are frequently observed in women of reproductive age as a consequence of menstruation-related loss. The use of non-heme iron and iron supplements was inversely correlated with the risk of ovulation disorders in women in the cohort NHS II study. The correlation was probably due to the presence of transferrin in the ovaries. It influences the development of ovarian follicles and female gametes [76]. Another cohort BioCycle Study [77] was carried out to assess the correlation between the consumption of minerals and the risk of

ovulation disorders. The correlation was only confirmed between low sodium, selenium, and manganese consumption. The consumption of sodium < 1500 mg, selenium < 55 µg, and manganese < 1.8 mg was associated with an increased risk of anovulation compared to suitably higher consumption. No influence on ovulation was observed as regards other minerals.

To sum up, a diet rich in vitamins and minerals exerts an extremely significant effect on ovulation. Particular significance is attributed to group B vitamins, which participate in the regulation of homocysteine concentrations. Moreover, the role of antioxidant vitamins and vitamin D seems very important. The effect of iron on the regulation of ovulation also seems promising, but there is a paucity of studies to link the consumption of iron to ovulation. The summary of the influence of particular dietary factors on the risk of ovulation disorders was presented in the Table 1 and Figure 1.

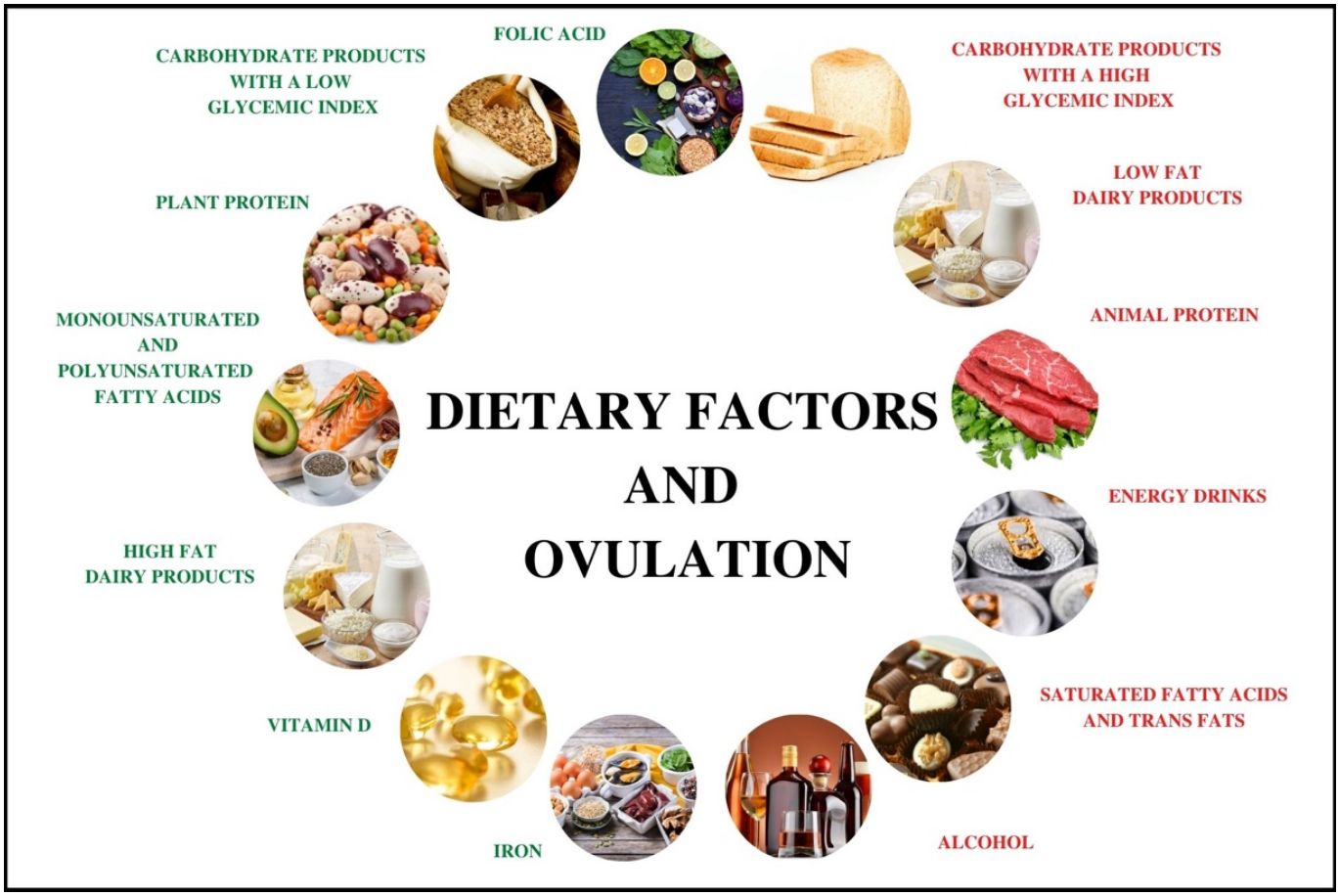

Figure 1. The influence of dietary factors on the risk of ovulation disorders. Factors with a positive influence on ovulation are presented in green, while those which increase the risk of ovulation disorders are presented in red. Ovulation is positively influenced by components typical of the Mediterranean diet (e.g., low glycemic index carbohydrates, plant protein, and unsaturated fatty acids), while components typical of the Western diet have a negative effect (e.g., animal protein, carbohydrates with a high glycemic index, and saturated fatty acids).

Table 1. Dietary patterns and the risk of anovulation.

First Author/ Reference Number	Year	Study Design	Sample	Result
Dietary pattern				
Chavarro et al. [8]	2007	A prospective cohort study (NHS II)	17,544 women, aged 25–42 years	Higher adherence to the FD was associated with a lower risk of anovulatory infertility compared to the lowest adherence (RR 0.34 (95% CI 0.23–0.48) vs. RR 0.68 (95% CI 0.52–0.89); $p < 0.001$).
Carbohydrates and low glycemic index diet				
Chavarro et al. [32]	2009	A prospective cohort study (NHS II)	18,555 women, 25–42 years	An increase in cereal fiber intake by 10 g/day was associated with a 44% lower risk of anovulatory infertility among women older than 32 (RR 0.56 (95% CI 0.34–0.93); $p = 0.02$). The risk of anovulatory infertility was 78% higher in women from the highest quintile of total carbohydrate intake (60% of calories) compared to women from the lowest quintile (42% of calories) (RR 1.78 (95% CI 1.14–2.78); $p = 0.005$). A linear trend towards a higher risk of anovulatory infertility with increasing carbohydrate intake (p trend = 0.005). The risk of anovulatory infertility was 92% higher in women from the highest quintile of glycemic load compared to women from the lowest quintile (RR 1.92 (95% CI 1.26–2.92); $p = 0.01$). The risk of anovulatory infertility was 55% higher in nulliparous women from the highest quintile of glycemic index compared to women from the lowest quintile (RR 1.55 (95% CI 1.02–2.37); $p = 0.05$). Dietary glycemic index was positively associated with the risk of anovulatory infertility among nulliparous women (p interaction = 0.02).
Gaskin et al. [36]	2009	A prospective cohort study (The BioCycle Study)	250 women, aged 18–44 years	Each 5 g/day increase in total fiber intake was associated with a 78% increased risk of an anovulatory cycle (RR 1.78 (95% CI 1.11–2.84); $p < 0.05$). Soluble fiber had a stronger, positive association with an increased risk of anovulation (OR 6.73 (95% CI 1.18–38.26) than insoluble fiber (OR 2.15 (95% CI 1.22–3.77) and fruit fiber (OR 3.05 (95% CI 1.07–8.71); $p < 0.05$). Dietary fiber consumption was positively associated with incidents of anovulation ($p = 0.004$), with an OR of 10.98 (95% CI: 1.5, 80.5) for women at or above the DRI ($\geq$22 g/day) compared to the lowest DRI ($\leq$10 g/day).

Table 1. *Cont.*

First Author/ Reference Number	Year	Study Design	Sample	Result
McGrice et al. [14]	2017	A Systematic Review of 7 intervention studies	Infertile women with obesity, aged > 18 years	The use of low-carbohydrate diet (less than 45% of total energy obtained from carbohydrates) was associated with a higher ovulation rate ($p < 0.05$) compared to the usual diet.
Palomba et al. [33]	2010	A randomized controlled trial	96 PCOS women with obesity, aged 18–35 years with anovulatory infertility and known CC resistance	The intervention (structured exercise + 35% protein, 45% carbohydrate, 20% fat diet with calorie deficit + CC) was effective in increasing probability of ovulation under CC treatment.
Sordia-Hernández et al. [40]	2015	A randomized controlled clinical trial	40 patients with the diagnosis of PCOS, infertility, and anovulation, mean age 26 years	24.6% (14/57) of the cycles were ovulatory in women who consumed a low glycemic index diet. In those who consumed a normal glycemic index diet, only 7.4% (4/54) of the cycles were ovulatory ($p = 0.014$).
Plant and animal protein products				
Chavarro et al. [52]	2007	A prospective cohort study (NHS II)	18,555 women, 25–42 years	The risk of anovulatory infertility was 27% lower in women from the highest quintile of intake of high-fat dairy products (≥1 servings/day) compared to women from the lowest quintile (≤1 servings/week) (RR 0.73 (95% CI 0.52–1.01); $p < 0.05$). Adding one daily serving of full-fat milk without increasing energy intake was associated with a reduction in the risk of anovulatory infertility by 63% (RR 0.37 (95% CI 0.19–0.70), $p = 0.002$). An inverse association between dairy fat intake and anovulatory infertility (p trend = 0.05). The risk of anovulatory infertility higher by 71% in women from the highest quintile of intake of low-fat dairy products (especially yoghurt and sherbet/frozen yoghurt) (one serving a day) compared to women from the lowest quintile (≤1 servings/week) (RR 1.71 (95% CI 1.24–2.77); $p = 0.002$).

Table 1. *Cont.*

First Author/ Reference Number	Year	Study Design	Sample	Result
Chavarro et al. [44]	2008	A prospective cohort study (NHS II)	18,555 women, 25–42 years	Consuming 5% of energy from plant protein rather than from carbohydrates was associated with a 43% lower risk of anovulatory infertility (RR 0.57 (95% CI 0.32–1.00); $p = 0.05$). Consuming 5% of energy from vegetable protein rather than from animal protein was associated with a 52% lower risk of anovulatory infertility (RR 0.48 (95% CI 0.28–0.81); $p = 0.007$). The risk of anovulatory infertility was 41% higher in women from the highest quintile of total protein intake (23.1% of calories) compared to women from the lowest quintile (15.4% of calories) (RR 1.41 (95% CI 1.04–1.91); $p = 0.02$). The risk of anovulatory infertility was 39% higher in women from the highest quintile of animal protein intake (18.5% of calories) compared to women from the lowest quintile (10.2% of calories) (RR 1.39 (95% CI 1.01–1.90); $p = 0.03$). Adding one serving of meat per day was associated with a 32% higher risk of anovulatory infertility (RR 1.32 (95% CI 1.08–1.62); $p = 0.01$). Adding one serving of chicken or turkey per day was associated with a 53% greater risk of anovulatory infertility (RR 1.53 (95% CI 1.12–2.09); $p = 0.01$). Consuming 5% of total energy intake as animal protein instead of from carbohydrates was associated with 19% greater risk of anovulatory infertility (RR 1.19 (95% CI 1.03–1.38); $p = 0.02$).
Kim et al. [49]	2017	A prospective cohort study (The BioCycle Study)	259 healthy, regularly menstruating women, aged 18–35 years	Associations between intakes of >0 servings of yoghurt (RR 2.1 (95% CI 1.2–3.7) and cream (RR 1.8 (95% CI 1.0–3.2) and a higher risk of sporadic anovulation compared to no intake.
Zhang et al. [44]	2020	A prospective cohort study	2217 infertile women with PCOS (with ovulation and without), aged > 18 years	PCOS women with anovulation had a higher rate of meat favorable diet than PCOS women with ovulation (54.60% vs. 41.30%, RR 1.69 (95%CI 1.28–2.23), $p < 0.01$).
Unsaturated and saturated fatty acids				
Chavarro et al. [53]	2007	A prospective cohort study (NHS II)	18,555 women, 25–42 years	Each 2% increase in the intake of energy from *trans* unsaturated fats, rather than from carbohydrates was associated with a 73% higher risk of anovulatory infertility (RR 1.73 (95% CI 1.09–2.73); $p = 0.02$). Obtaining 2% of energy intake from trans fats rather than from n-6 polyunsaturated fats was associated with a 79% higher risk of anovulatory infertility (RR 1.79 (95% CI 1.11–2.89); $p = 0.02$). Obtaining 2% of energy from trans fats rather than from monounsaturated fats was associated with a more than doubled risk of anovulatory infertility (RR 2.31; (95% CI 1.09–4.87), $p < 0.05$).

Table 1. *Cont.*

First Author/ Reference Number	Year	Study Design	Sample	Result
Ghaffarzad et al. [60]	2014	A case-control study	29 women with PCOS, aged 19–35 years	Higher concentrations of trans fatty acids (trans linoleate) in erythrocytes were associated with an increased incidence of ovulation disorders in this group of women (OR 1.218 (95% CI 1.016–1.46); $p = 0.033$).
Mumford et al. [54]	2016	A prospective cohort study (The BioCycle Study)	259 regularly menstruating, healthy women, aged 18–44 years	The intake of PUFA docosapentaenoic acid (22:5 n–3) was associated with a reduced risk of anovulation (highest tertile compared with the lowest tertile: (RR: 0.42 (95% CI 0.18–0.95); $p < 0.05$).
Alcohol and caffeine				
Chavarro et al. [61]	2009	A prospective cohort study (NHS II)	18,555 women, 25–42 years	Women consuming 2 or more caffeinated soft drinks per day were at a 47% greater risk of anovulatory infertility than women who consumed less than 1 caffeinated soft drink per week (RR 1.47 (95% CI 1.09–1.98); $p = 0.01$). Women consuming 10 g or more of alcohol per day (approximately > 1 drink/day) were at a 47% greater risk of anovulatory infertility than women who did not drink any alcohol (RR 1.47 (95% CI 1.02–2.10), $p = 0.03$).
Vitamins and minerals				
Chavarro et al. [76]	2006	A prospective cohort study (NHS II)	17,544 women, aged 25–42 years	Women who consumed iron supplements were at a significantly lower risk of anovulatory infertility than women who did not use iron supplements (RR 0.60 (95% CI 0.39–0.92); $p = 0.003$). The risk of anovulatory infertility was 47% lower in women from the highest quintile of iron intake (77 mg/day) compared to women from the lowest quintile (11 mg/day) (RR 0.53 (95% CI 0.35–0.82); $p = 0.003$). The risk of anovulatory infertility was 40% lower in women from the highest quintile of nonheme iron intake (76 mg/d) compared to women from the lowest quintile (9.7 mg/d) (RR 0.60 (95% CI (0.39–0.92); $p = 0.005$).
Chavarro et al. [70]	2008	A prospective cohort study (NHS II)	18,555 women, 25–42 years	The risk of anovulatory infertility was 41% lower in women who used multivitamins $\geq$ 6 times per week compared to women who did not use multivitamins (RR 0.59 (95% CI 0.46, 0.75); $p < 0.001$). The risk of anovulatory infertility was 39% lower in women from the highest quintile of intake of folic acid (1138 µg/day) compared to women from the lowest quintile (243 µg/day) (RR 0.61 (95% CI 0.37, 1.00); $p = 0.04$).
Gaskin et al. [71]	2012	A prospective cohort study (The BioCycle Study)	259 women, aged 18–44 years	Women in the highest tertile of folate consumption (270.6 g/d) had a 64% lower chance of anovulation compared to women in the lowest tertile of folate consumption (100.9 g/d) (OR 0.36 (95% CI 0.14, 0.92); $p = 0.03$).

Table 1. *Cont.*

First Author/ Reference Number	Year	Study Design	Sample	Result
Kim et al. [77]	1217	A prospective cohort study (The BioCycle Study)	259 regularly menstruating women, aged 18–44 years	Sodium intake < 1500 mg (RR 2.70 (95 % CI 1.00–7.31) and manganese intake < 1.8 mg (RR 2.00 (95% CI 1.02–3.94) were associated with an increased risk of anovulation, compared to higher intakes, $p < 0.05$.
Yahya et al. [75]	2019	A randomized- controlled, open-label study	45 PCOS women, aged 18–40 years	Both dietary supplements (vitamin D3 or CO-enzyme Q10) in combination with CC, significantly improved ovulation rates in clomiphene citrate-resistant women with PCOS.
Rasheedy et al. [74]	2019	A double blind, randomized clinical trial	186 women undergoing the induction of ovulation with CC, aged 25–35 years	Women with PCOS undergoing the induction of ovulation: vitamin D supplementation significantly improved the ovulation rate. More than 90% (92.5%) of women in the treatment group took CC (50 mg) twice daily and vitamin D3 (10,000 IU), and 78.5% in the control group (placebo) had successful ovulation ($p = 0.007$).

Abbreviations: NHS II, Nurses' Health Study II; RR, relative risk; Cl, confidence interval; FD, fertility diet; OR, odds ratio; PUFA, Polyunsaturated Fatty Acids; PCOS, polycystic ovary syndrome; DRI, dietary recommended intake; CC, clomiphene citrate, IU, international unit.

8. Conclusions

Adherence to a balanced diet with all necessary nutrients has a considerable influence on female fertility and the risk of ovulation disorders. An adequate supply of plant protein, unsaturated fats, and low glycemic index carbohydrates is of high importance. Moreover, it is crucial to provide the appropriate amount of vitamins and minerals, mostly including folic acid, vitamin D, antioxidant vitamins, and iron. Additionally, the supply of saturated fatty acids, trans fatty acids, and high glycemic index carbohydrates should be limited. However, due to the lack of randomized clinical trials in this area, especially as regards a group of women with polycystic ovary syndrome, the importance of individual components in ovulation may not be clearly confirmed. It is necessary to perform more high-quality research comprising the significance of individual nutrients, food products, and the whole structure of the diet in order to develop a model of nutrition that will be helpful in the treatment of women with ovulation disorders.

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nutrients

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Article

Physical Activity, Rather Than Diet, Is Linked to Lower Insulin Resistance in PCOS Women—A Case-Control Study

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Abstract: Insulin resistance (IR) is a prominent feature of polycystic ovary syndrome (PCOS). The importance of lifestyle interventions in the management of PCOS is strongly highlighted and it is suggested that diet and physical activity may significantly influence insulin sensitivity. Therefore, we evaluated the link between diet and physical activity and various indices of insulin resistance, including adipokines secreted by the adipose tissue in 56 PCOS and 33 healthy control women. The original food frequency questionnaire and Actigraph GT3X-BT were used to assess the adherence to the diet recommended in IR and the level of physical activity, respectively. We observed that higher levels of physical activity were associated with lower HOMA-IR and a greater chance of its normal value in PCOS group. No such relationship was observed for other IR indices and adipokines or for the diet. However, we noted a strong correlation between HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) and HOMA-AD (Homeostatic Model Assessment-Adiponectin) in PCOS women. Additionally, when we used HOMA-AD we observed a higher prevalence of IR among PCOS women. Our study supports the beneficial role of physical activity in the management of insulin resistance in PCOS women. Moreover, our findings indicate that HOMA-AD may be a promising surrogate marker for insulin resistance assessment in women with PCOS.

Keywords: polycystic ovary syndrome; insulin resistance; adipokines; HOMA-IR; HOMA-AD; L/A ratio; physical activity; diet

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1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age. It is a complex condition commonly associated with anovulation, hyperandrogenemia (clinical or biochemical) and/or polycystic ovary morphology [1]. The prevalence of PCOS varies from 8 to 13% depending on the used diagnostic criteria [2].

Until recently, PCOS had only been considered as a cause of reproductive failure; however, it is now well-acknowledged that PCOS women are particularly susceptible to the development of many cardiometabolic disorders. Additionally, PCOS is strongly associated with obesity, which has an impact on the metabolic and reproductive complications in the course of this disease. As a result of hyperandrogenism, PCOS women are more likely to have abdominal obesity with increased content of visceral or subcutaneous fat compared to healthy women. Interestingly, the excessive accumulation of the visceral adipose tissue

is also reported in PCOS women with normal body weight; thus, this parameter is not only related to BMI (body mass index). In addition, such fat distribution is strongly linked to hyperglycemia, compensatory hyperinsulinemia and insulin resistance [3,4]. Moreover, the adipose tissue is a very crucial and active endocrine organ which synthesizes and secretes a variety of adipokines influencing the regulation of metabolism related to the sensitivity of tissues to insulin [5]. The adipose tissue of women with PCOS shows many abnormalities in the secretion of adipokines which also play a significant role in the course of polycystic ovary syndrome. Some of these changes are characterized by increased serum concentrations of leptin and resistin and reduced expression of adiponectin. However, it is still unknown whether the anomalies are secondary to obesity, insulin resistance and hormonal imbalance or if they are inherent in the course of PCOS [6].

Insulin resistance (IR) is defined as reduced insulin sensitivity and refers to an increased amount of insulin needed to perform its metabolic actions [7]. It is a prominent feature of PCOS and affects approximately 80% of its cases [8]. However, the prevalence of IR in women with PCOS is highly inconsistent due to different IR measures and cutoff values [9]. IR is mainly promoted in PCOS via hyperandrogenemia, which alters insulin activity in adipocytes and the skeletal muscle. Furthermore, IR decreases adiponectin concentrations, which also increases the sensitivity of tissues to insulin [10]. Nevertheless, IR is also believed to be one of more important pathogenetic components of PCOS. Insulin, acting on its receptor in the theca cells, stimulates the excessive production of androgens and inhibits the hepatic production of sex hormone binding globulin, which results in an increase in the concentration of free testosterone in the blood. In addition, insulin, by acting on the GnRH (gonadotropin-releasing hormone) receptor in the hypothalamus, increases the effect of LH (luteinizing hormone) on the ovary, which intensifies the excessive production of androgens. These mechanisms indicate that IR and hyperandrogenism are closely related to each other and significantly affect the pathogenesis and course of PCOS [10,11].

It is suggested that diet and physical activity significantly influence insulin sensitivity. Importantly, the role of dietary patterns in relation to IR is remarkable and quite well proven [12–15]. Physical activity, being an integral part of any balanced lifestyle, is recommended for PCOS women. Particularly, vigorous aerobic physical exercise may result in an improvement in insulin sensitivity [16]. Recent recommendations regarding the treatment of PCOS have emphasized the great importance of lifestyle interventions in the management of this disease [17,18]. It is well-known that, in this group of women, reductions of 5% of body weight were associated with the improvement of hormonal and metabolic parameters and a greater chance of spontaneous ovulation [17]. Importantly, lifestyle changes appear to be as effective in treating this disease as metformin. Therefore, it was suggested that lifestyle modifications should be the first line of treatment in PCOS [15].

Bearing in mind the fact that IR that accompanies PCOS does not only aggravate the hormonal imbalance and ovulation disorders but it also increases the risk of cardiometabolic complications, it is important to establish the role of a balanced diet and physical activity in the management of IR in this disease. Therefore, in this study we aimed to evaluate the link between diet and physical activity and various indices of insulin resistance, including adipokines secreted by the adipose tissue.

2. Materials and Methods

2.1. Participants

This case-control study included 56 women with polycystic ovary syndrome and 33 healthy control women, who were enrolled in the Department of Gynecological Endocrinology of the Medical University of Warsaw in 2021–2022. The inclusion criteria for the study group were as follows: age between 18 and 40 and polycystic ovary syndrome diagnosed according to the Rotterdam diagnostic criteria. They included the presence of at least two of the following three criteria: oligo-/amenorrhea, clinical and/or biochemical hyperandrogenism and polycystic ovaries detected via ultrasound exam [19]. Exclusion criteria were as follows: diabetes; thyroid dysfunction; endometriosis; Cushing's syndrome;

androgen-releasing tumor; congenital adrenal hyperplasia; chronic hypertension, cardiovascular diseases; the use of lipid-lowering, hormonal or insulin-sensitizing drugs; pregnancy; and lactation. The additional exclusion criteria, such as diagnosed epilepsy, an implanted pacemaker or defibrillator and metal endoprostheses, were included due to the method of body composition measurement (BIA—Bioelectrical Impedance Analysis). Women in the control group aged between 18 and 40 were generally healthy with no chronic diseases. They had normal and regular menstrual cycles with no signs of hyperandrogenism and the sonographic appearance of the ovaries was normal. All participating women provided written informed consent to participate in the study. The study was approved by the Ethics Committee of the Medical University of Warsaw (no. KB/170/2019).

2.2. Anthropometric Measurements

Body weight and height measurements were performed using standard procedures [20]. Body mass index was calculated as follows: weight (kg)/height2 (m^2). The interpretation of the ratio was based on the classification specified by the World Health Organization (WHO): <18.5 kg/m^2—underweight; 18.5–24.9 kg/m^2—normal weight; 25.0–29.9 kg/m^2—overweight; and ≥30.0 kg/m^2—obese [21]. In addition, waist circumference was measured according to WHO recommendations at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest using a stretch-resistant tape [22].

2.3. Body Composition Analysis with Bioelectrical Impedance (BIA)

Whole body composition was assessed using the Maltron BioScan 920-II multi-frequency bioelectrical impedance analyzer according to the manufacturer's instructions (Maltron International Ltd., Rayleigh, UK). According to the European Society of Parenteral and Enteral Nutrition, the women were instructed to follow certain recommendations before undergoing the BIA measurement, i.e., no alcohol and no fluids containing caffeine for 24 h before the test, lack of physical activity for 12 h before the test and empty stomach and bladder before the test [23]. The subjects were measured in the supine position with the limbs separated, 30 degrees away from the body axis, after resting for about 3 min. Before placing the electrodes on the top middle part of the right hand and the top middle part of the right foot, the sites were cleaned using isopropyl alcohol to limit the possible errors and ensure adherence [24].

The quantitative analysis of abdominal adipose tissue (subcutaneous and visceral) was performed in a standing position, with the upper limbs away from the body. The configuration of the placement of the electrodes was strictly defined by the manufacturer of the device [24]. Based on the waist circumference and the impedance of the visceral and abdominal tissue, the following parameters were determined: subcutaneous fat surface (SAT in cm^2), visceral fat surface (VAT in cm^2) and visceral-to-subcutaneous fat ratio (VAT/SAT ratio).

2.4. Biochemical Analysis

After 12-h fasting, venous blood was collected from each participant during the follicular phase (2–6 days) of the menstrual cycle between 7 am and 9 am. To obtain the serum, the samples were centrifuged at 2500× *g* for 10 min at 4 °C. On the day of blood collection, serum glucose and insulin levels were determined. The rest of the serum was divided into small portions and stored for no longer than 3 months at −80 °C until the remaining biochemical tests were performed.

Serum glucose level was assayed via the enzymatic method with hexokinase (Integra 400 plus analyzer, Roche Diagnostics, Basel, Switzerland), whereas serum insulin concentrations were analyzed using two-step chemiluminescent microparticle immunoassay (CMIA; Alinity I analyzer; Abbott Diagnostics GmbH, Wiesbaden, Germany).

To assess insulin resistance, the following mathematical models were used: HOMA-IR (the homeostatic model assessment of insulin resistance calculated as: [fasting insulin (μU/mL) × fasting glucose (mg/dL)]/405); HOMA-AD (the homeostatic model

assessment-adiponectin calculated as: [fasting plasma insulin (μU/mL) × fasting glucose (mmol/L)/adiponectin (μg/mL)] and L/A (leptin-to-adiponectin ratio calculated as: leptin (ng/mL)/adiponectin μg/mL). The defined cutoff points for different insulin resistance indices used were HOMA-IR ≥ 2.5 [25], HOMA-AD ≥ 6.26 [26] and L/A > 2.2 [27].

The concentrations of serum adipokines were determined via commercial enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions. Leptin was assessed using a kit from DRG Instruments GmbH (Marburg, Germany). The analytical sensitivity of the assay was 0.7 ng/mL, while intra- and inter-assay coefficients of variation (CV) were 4.2–7.3% and 3.7–9.1%, respectively. Total adiponectin was determined using a kit manufactured by TECOmedical AG (Sissach, Switzerland) with a lower detection limit below 0.27 ng/mL, intra-assay CV of 3.14–3.67% and inter-assay CV of 6.93–8.16%. Resistin was measured using a kit manufactured by Mediagnost (Reutlingen, Germany); the analytical sensitivity of the assay was 0.012 ng/mL, while the intra- and inter-assay CV were 4.49–4.97% and 3.37–6.67%, respectively.

2.5. Nutritional Assessment

The assessment of the women's nutrition was based on the original food frequency questionnaire (FFQ), which was conducted during a face-to-face interview with a qualified nutritionist. The FFQ consisted of 15 items which have a negative or positive relationship with the sensitivity of tissues to insulin. The main food products included wholegrain cereal products, refined cereal products, natural yoghurt, fruits, vegetables, vegetable oils (including avocado and soft margarines), animal fats (including butter, solid margarines, palm oil and coconut oil), nuts, legumes, red meat, processed red meat, fatty sea fish, sweet drinks, sweets (including sugar) and fast food. The participants were asked to report their average frequency (none, daily, weekly or monthly) and portion sizes for consumption of each food item. The sizes of declared food portions were verified using the "Album of Photographs of Food Products and Dishes" from the National Food and Nutrition Institute [28].

Based on the awarded points (0, 0.5 or 1), the score of the adherence to the diet recommended in insulin resistance was calculated. A greater number of points received by a subject translated into greater compliance with the diet, lowering insulin resistance. The maximum number of points that could be obtained was 15.

2.6. Physical Activity

Physical activity was measured using an Actigraph GT3X-BT activity monitor (Actigraph Corp, Pensacola, FL, USA) worn for 7 consecutive days at an elastic belt around the waist and positioned on the right hip. Raw accelerometer data were downloaded using ActiLife software (version 6.13.0, ActiGraph Corporation). The intensity of physical activity was measured using cut points for adults established by Freedson et al. [29]. To estimate the level of physical activity, the numbers of total minutes of moderate, vigorous and moderate-to-vigorous physical activity (MVPA) per week were recorded.

2.7. Statistical Analysis

All calculations were performed with STATISTICA TM 13.3 software (TIBCO Software, Palo Alto, CA, USA). Variable distributions were evaluated with the D'Agostino's K-squared test and descriptive statistics (means, standard deviations, medians and interquartile ranges) were calculated. Due to the fact that the Study and Control Groups were not of equal sizes, the Mann–Whitney–Wilcoxon test was used to compare differences between them. The contingency tables with the Fisher's exact test or chi-square test were used to assess the relationship between the frequency of insulin resistance in various measures.

Linear regression analysis was used to assess the relationship between the examined parameters and physical activity or diet scores. The least square estimation was used to estimate parameters for linear regression. A standardized regression coefficient (β) with a 95% confidence interval (95% CI) was estimated for each independent variable included in

the model. Logistic regression analysis was performed in order to examine the chances of normal values of the examined parameters depending on the scores for diet or physical activity. The maximum likelihood method of estimation was used to estimate parameters for logistic regression. For each independent variable included in the model, an odds ratio (OR) with a 95% confidence interval (95% CI) was estimated. Correlations between variables were examined using Pearson's correlation coefficient. p-values of <0.05 were considered statistically significant.

3. Results

3.1. Characteristics of PCOS and Healthy Women

The characteristics of PCOS and control women, i.e., the age and height, were comparable and were not significantly different. As expected, the anthropometric and body composition data showed several differences between the groups. Women with PCOS had significantly higher body weight (p = 0.008), BMI (p = 0.004), waist circumference (p = 0.003), total fat mass (p = 0.008), visceral fat (p = 0.018) and subcutaneous fat (p = 0.003) compared to healthy control women. Interestingly, the VAT/SAT ratio was also higher in this group, though the difference was not statistically significant.

Biochemical blood parameters also showed differences between groups. PCOS women had a significantly lower concentration of adiponectin compared to control women (7.57 ± 2.44 vs. 14.15 ± 3.98 µg/mL; p < 0.001). However, we did not observe any significant differences in leptin and resistin levels. Women with PCOS had significantly higher L/A ratios compared to healthy women (p < 0.001). Interestingly, women from the Study Group had lower HOMA-IR values compared to the Control Group, though the difference was not statistically significant. This result was in contrast to another measure of insulin resistance, i.e., HOMA-AD, where the results clearly differed between the groups. PCOS women were characterized by significantly higher HOMA-AD compared to control women (4.11 ± 3.86 vs. 3.29 ± 1.37; p = 0.029).

PCOS Group was characterized by significantly lower MVPA compared to the Control Group (301.92 ± 107.67 vs. 376.60 ± 43.72 min/week; p = 0.003). Similarly, moderate and vigorous physical activity levels were also significantly lower (p = 0.012; p = 0.016, respectively). We did not observe significant differences between the diet scores between the Study and Control Groups (p = 0.280). The detailed comparisons of anthropometric data, body composition measures, biochemical parameters and the diet score are shown in Table 1.

Table 1. Comparison of anthropometric, body composition, biochemical parameters, physical activity and diet score between PCOS Group and Control Group.

Parameters	PCOS (n = 56)	CONTROL (n = 33)	p-Value *
Age and Anthropometric Measurements			
Age (years)	25.96 ± 4.10	29.12 ± 6.85	NS
	25.00 (19–38)	31.00 (19–38)	
Weight (kg)	75.99 ± 21.46	63.09 ± 10.44	0.008
	70.00 (45.0–126.4)	60.00 (47.0–93.0)	
Height (cm)	166.70 ± 5.12	167.42 ± 5.85	NS
	165.00 (158–180)	167.00 (154–178)	
BMI (kg/m^2)	27.25 ± 7.40	22.43 ± 3.17	0.004
	24.65 (17.2–42.9)	21.90 (17.9–32.9)	
WC (cm)	86.84 ± 18.34	75.20 ± 8.12	0.003
	84.50 (58–126)	73.50 (63–91)	

Table 1. *Cont.*

Parameters	PCOS (n = 56)	CONTROL (n = 33)	*p*-Value *
Body Composition			
FM (kg)	27.93 ± 15.81	18.34 ± 7.44	0.008
	23.24 (7.45–64.37)	16.75 (8.94–40.55)	
FM (%)	34.08 ± 10.62	28.04 ± 6.66	0.010
	33.16 (15.84–51.96)	27.92 (16.25–43.60)	
VAT (cm^2)	154.32 ± 124.21	72.52 ± 42.24	0.018
	112.50 (21–350)	57.00 (22–174)	
SAT (cm^2)	149.68 ± 87.86	94.39 ± 39.99	0.003
	126.00 (37–380)	88.00 (28–212)	
VAT/SAT	1.03 ± 0.58	0.77 ± 0.30	NS
	0.87 (0.38–2.41)	0.74 (0.33–1.45)	
FFM (kg)	48.06 ± 6.14	44.91 ± 3.93	0.021
	46.76 (37.40–64.07)	44.77 (37.25–53.79)	
FFM (%)	65.99 ± 10.51	71.96 ± 6.66	0.010
	66.84 (48.05–84.16)	72.08 (56.40–83.75)	
MM (kg)	21.07 ± 2.92	19.51 ± 1.76	0.012
	20.46 (14.76–28.34)	19.52 (16.22–23.71)	
BCM (kg)	25.24 ± 4.41	22.87 ± 2.35	0.015
	24.2 (15.96–35.13)	22.9 (18.79–28.36)	
ECM (kg)	22.78 ± 2.10	22.05 ± 1.92	NS
	22.7 (19.00–28.94)	21.8 (18.45–25.92)	
TBW (%)	46.50 ± 5.20	49.75 ± 3.99	0.004
	46.37 (37.50–55.88)	49.65 (41.3–57.61)	
ECW (%)	47.15 ± 3.74	48.29 ± 3.36	0.002
	46.70 (44.32–67.97)	47.53 (45.63–61.95)	
ICW (%)	52.86 ± 3.75	51.70 ± 3.36	0.002
	53.30 (32.02–56.67)	52.46 (38.04–54.36)	
ECW/ICW	0.91 ± 0.20	0.94 ± 0.16	0.002
	0.88 (0.80–2.12)	0.91 (0.84–1.63)	
Biochemical Parameters			
Fasting glucose (mg/dL)	91.63 ± 6.98	96.45 ± 6.26	<0.001
	90.50 (77.4–122.0)	96.00 (82.0–113.0)	
Fasting insulin (μU/mL)	7.71 ± 4.39	8.24 ± 3.73	NS
	6.50 (2.50–24.07)	7.50 (3.40–18.00)	
Adiponectin (μg/mL)	8.13 ± 3.51	14.70 ± 5.92	<0.001
	7.57 (2.20–16.40)	14.15 (5.02–27.50)	
Leptin (ng/mL)	14.42 ± (10.77)	10.46 ± 9.25	NS
	10.31 (1.40–48.20)	6.60 (2.01–43.58)	
Resistin (ng/mL)	7.29 ± 2.50	7.41 ± 1.75	NS
	6.72 (4.10–15.70)	6.93 (4.73–12.14)	

Table 1. *Cont.*

Parameters	PCOS (n = 56)	CONTROL (n = 33)	*p*-Value *
HOMA-IR	1.77 ± 1.08	1.97 ± 0.92	NS
	1.38 (0.54–5.59)	1.70 (0.80–4.43)	
HOMA-AD	6.70 ± 5.97	3.58 ± 2.35	0.029
	4.11 (1.17–23.98)	3.29 (0.99–11.63)	
L/A	2.60 ± 2.74	0.93 ± 1.25	<0.001
	1.40 (0.12–12.06)	0.56 (0.13–6.55)	
Diet Score and Physical Activity			
Diet score	7.56 ± 2.46	8.15 ± 2.10	NS
	7.50 (1.5–13.0)	8.50 (3.5–12.0)	
Moderate [min/week]	296.06 ± 137.94	372.41 ± 139.28	0.012
	264.33 (71.50–611)	359.10 (158.17–821.50)	
Vigorous [min/week]	20.24 ± 36.31	35.34 ± 45.72	0.009
	8.50 (0.00–223.67)	16.80 (2.80–203.83)	
MVPA [min/week]	316.30 ± 141.42	407.67 ± 135.78	0.003
	301.92 (72.17–627.33)	376.60 (186.80–835.33)	

Data are mean ± standard deviation, median and interquartile ranges. * Mann–Whitney test; $p < 0.05$. Abbreviations: NS—not statistically significant; BMI—body mass index; WC—waist circumference; FM—fat mass; VAT—visceral fat surface; SAT—subcutaneous fat surface; VAT/SAT—visceral to subcutaneous fat ratio; FFM—fat free mass; MM—muscle mass; BCM—body cell mass; ECM—extracellular matrix; TBW—total body water; ECW—extracellular water; ICW—intercellular water, ECW/ICW—extracellular water-to-intercellular water ratio; HOMA-IR—homeostatic model assessment of insulin resistance; HOMA-AD—homeostatic model assessment—adiponectin; L/A—leptin-to-adiponectin ratio; and MVPA—moderate-to-vigorous physical activity.

3.2. Insulin Resistance and Correlation between HOMA-IR and HOMA-AD

The Pearson's correlation coefficient revealed a strong positive correlation between HOMA-IR and HOMA-AD in the Study and Control Groups ($r = 0.8248$, $p < 0.001$; $r = 0.6662$, $p = 0.00002$, respectively). Moreover, the correlation was much stronger in the group of women with PCOS.

According to the HOMA-IR index, 11 women with PCOS and 10 women from the Control Group were characterized by abnormal tissue sensitivity to insulin. Regarding the HOMA-AD index, as many as 22 women with PCOS had insulin resistance, while only 3 women had a score ≥ 6.26 in the Control Group. In addition, we noted that the probability of an abnormal HOMA-AD result was significantly increased in PCOS Group (OR 6.47, 95% CI 1.76–23.80; $p = 0.0029$). Finally, the L/A ratio used to assess insulin resistance showed that 25 women with PCOS and only two women from the Control Group had abnormal results.

In addition, we observed a relationship between the normal result obtained in HOMA-IR and HOMA-AD in both PCOS ($\chi^2 = 10.76$; $p = 0.00104$) and Control Groups ($\chi^2 = 15.04$; $p = 0.00011$). As regards women with PCOS, 11 had insulin resistance according to both indices, with only two such patients being found in the Control Group.

3.3. Effect of Diet and Physical Activity on Adipokines and Insulin Resistance

Linear regression analysis showed a differential effect of physical activity on the HOMA-IR value depending on the group. We observed that higher levels of physical activity (expressed as MVPA) were associated with lower HOMA-IR in PCOS Group ($t = -2.109$; $p = 0.038$). However, there was no statistically significant relationship between those parameters in the Control Group. Moreover, there was no relationship between HOMA-IR and diet score both in PCOS and Control Groups. Additionally, no such relationship was observed between physical activity or the diet score and adipokines, HOMA-AD and

the L/A ratio in both groups of women. Adjustment for BMI and MVPA did not affect the results.

In addition, logistic regression showed that there was a differential effect of physical activity on the normal level of HOMA-IR depending on the group. In the PCOS Group, higher levels of physical activity (expressed as MVPA) translated into a greater chance of a normal HOMA-IR level (OR 1.012, 95% CI 1.003–1.021; $p = 0.010$). However, no such relationship was observed in the Control Group. In addition, the diet score did not have an effect on normal HOMA-IR value in PCOS and control women. Similarly, no such link was observed between physical activity or the diet score and adipokines, HOMA-AD and the L/A ratio in both groups of women. Similarly to the previous analysis, adjustment for BMI and MVPA did not change the outcomes.

3.4. Correlations between Adipokines, Insulin Resistance Markers and Anthropometric Measurements and Body Composition

The analysis of the group of PCOS women revealed negative-to-moderate correlations between serum adiponectin and weight ($r = -0.5997$; $p < 0.001$), BMI ($r = -0.6057$; $p < 0.001$), waist circumference ($r = -0.6034$; $p < 0.001$), fat mass ($r = -0.5835$; $p < 0.001$), VAT ($r = -0.6508$; $p < 0.001$), SAT ($r = -0.5232$; $p < 0.001$) and VAT/SAT ratio ($r = -0.5187$; $p < 0.001$). In this group, serum leptin and resistin were also significantly related to all the anthropometric and body composition measurements (moderate-to-strong positive correlations). As regards non-PCOS women, we noted that only leptin was significantly associated with anthropometric and body composition measurements and the correlations were mostly stronger than in PCOS Group.

Fasting insulin and fasting glucose of PCOS women correlated positively with all measurements, except for fat free mass where the correlation was inverse ($r = -0.6014$, $p > 0.001$ and $r = -0.5437$, $p < 0.001$, respectively). As for the Control Group, only the correlation between fasting insulin and SAT was statistically significant ($r = 0.5100$, $p = 0.02$). In case of fasting glucose, none of the relationships were significant.

All IR indices were correlated with anthropometric and body composition measurements in PCOS women. HOMA-IR and the A/L ratio were the most strongly correlated with VAT ($r = 0.6061$, $p < 0.001$ and $r = 0.7305$, $p < 0.001$, respectively). Interestingly, HOMA-IR was only correlated with SAT ($r = 0.5239$, $p = 0.002$) in the Control Group. In PCOS Group, we noted the strongest positive correlation between HOMA-AD and weight ($r = 0.7197$, $p < 0.001$), BMI ($r = 0.7012$, $p < 0.001$) and VAT ($r = 0.7185$, $p < 0.001$). Other HOMA-AD correlations were of moderate strength. In the Control Group, the correlations of HOMA-AD with anthropometric and body composition parameters were generally much weaker. Additionally, in PCOS women HOMA-AD was correlated with VAT/SAT ratio ($r = 0.6307$, $p < 0.001$), whereas no such link was observed in non-PCOS women. We noted a similar relationship in case of the A/L ratio. Correlations between adipokines, insulin resistance markers and anthropometric measurements and body composition in PCOS and non-PCOS women are presented in detail in Table 2.

Table 2. Correlation between adipokines, insulin resistance markers and anthropometric measurements and body composition.

Parameters	Adiponectin		Leptin		Resistin		Fasting Insulin		Fasting Glucose		HOMA-IR		HOMA-AD		A/L	
	PCOS	Control	PCOS	Control	PCOS	Control	PCOS	Control	PCOS	Control	PCOS	Control	PCOS	Control	PCOS	Control
Weight (kg)	−0.5997 *	−0.2335	0.6896 *	0.7141 *	0.6133 *	0.0802	0.6041 *	0.2121	0.5819 *	0.0998	0.5859 *	0.2177	0.7197 *	0.5340 *	0.6807 *	0.7304 *
BMI (kg/m^2)	−0.6057 *	−0.1443	0.7208 *	0.7676 *	0.6034 *	0.1274	0.6062 *	0.2520	0.5419 *	0.0784	0.5903 *	0.2516	0.7012 *	0.5169 *	0.6979 *	0.7393 *
WC (cm)	−0.6034 *	−0.2544	0.7154 *	0.6545 *	0.5639 *	0.0706	0.6147 *	0.1175	0.5715 *	0.1690	0.5984 *	0.1404	0.6983 *	0.4317 *	0.6907 *	0.5929 *
FM (%)	−0.5835 *	0.0914	0.7437 *	0.7838 *	0.5843 *	0.1219	0.6139 *	0.3266	0.5412 *	0.1059	0.5823 *	0.3240	0.6735 *	0.4727 *	0.6958 *	0.6481 *
VAT (cm^2)	−0.6508 *	0.1500	0.7396 *	0.7544 *	0.4915 *	0.0486	0.6224 *	0.2457	0.5575 *	0.1170	0.6061 *	0.2572	0.7185 *	0.4746 *	0.7305 *	0.6371 *
SAT (cm^2)	−0.5232 *	0.2665	0.6736 *	0.8015 *	0.4339 *	0.1994	0.6038 *	0.5100 *	0.4743 *	0.1871	0.5742 *	0.5239 *	0.5766 *	0.6985 *	0.5949 *	0.7710 *
VAT/SAT	−0.5187 *	0.1072	0.5978 *	0.1897	0.4688 *	−0.1556	0.5616 *	−0.2847	0.5042 *	0.0313	0.5401 *	−0.2794	0.6307 *	−0.1145	0.5890 *	0.0860
FFM (%)	0.5852 *	0.0910	−0.7451 *	−0.7844 *	−0.5933 *	−0.1212	−0.6014 *	−0.3268	−0.5437 *	−0.1060	−0.5886 *	−0.3242	−0.6805 *	−0.4729 *	−0.6992 *	−0.6486 *
MM (kg)	−0.5526 *	−0.2201	0.5457 *	0.4099 *	0.5778 *	0.0493	0.5265 *	0.0539	0.5236 *	0.0438	0.5170 *	0.0603	0.6707 *	0.4017 *	0.6598 *	0.5530 *

Data are presented as Pearson's r coefficients; * $p < 0.05$. Abbreviations: HOMA-IR—homeostatic model assessment of insulin resistance; HOMA-AD—homeostatic model assessment—adiponectin; L/A—leptin-to-adiponectin ratio; BMI—body mass index; WC—waist circumference; FM—fat mass; VAT—visceral fat surface; SAT—subcutaneous fat surface; VAT/SAT—visceral-to-subcutaneous fat ratio; FFM—fat free mass; and MM—muscle mass.

4. Discussion

It is well-proven that PCOS is strongly associated with carbohydrate metabolism disorders, especially with IR. It was observed that this group of patients was up to seven times more likely to develop type 2 diabetes mellitus and impaired glucose tolerance compared to healthy women [30]. According to numerous studies, PCOS women had higher fasting insulin and HOMA-IR compared to healthy non-PCOS women [7,31–36]. Contrary to most studies, our publication and studies by Mishra et al. [37], Seow et al. [38] and Pandit et al. [39] did not show any significant differences between those parameters in the Study and Control Groups. Notably, due to the fact that insulin and HOMA-IR are closely correlated with androgens some authors suggested that IR was only particularly intense in PCOS patients with severe hyperandrogenism [10,40]. Moghetti et al. [40] reported a higher prevalence of IR (measured by hyperinsulinemic-euglycemic glucose clamp) observed in the PCOS phenotype associated with hyperandrogenism. Barrea et al. [41] also emphasized that the exacerbation of IR measured by HOMA-IR was different due to the metabolic status of the examined PCOS women. Metabolically healthy obese PCOS women had significantly lower fasting insulin and HOMA-IR compared to metabolically unhealthy obese PCOS women. Additionally, it should be noted that HOMA-IR is not the most accurate method for assessing IR [9]. The above mentioned factors may explain why different results were obtained in our study and show that other factors influencing IR in women with PCOS should be considered, with particular emphasis on androgenization and abdominal obesity.

The early diagnosis and management of IR in women with PCOS is one of the most important aspects of treating this disease. However, there are no recommendations regarding the assessment of IR in this group of women. The hyper-insulinemic–euglycemic glucose clamp is the gold standard method for assessing insulin sensitivity. Nevertheless, due to the fact that it is very complex, invasive and impractical, the method is mainly used for research purposes [8]. Amisi et al. [8] reviewed surrogate IR assessment methods in PCOS, which would be much easier to use in clinical practice. One of the methods mentioned in this review was linked to adipokines, which are involved in the regulation of tissue insulin sensitivity and HOMA-IR.

In the present study, apart from HOMA-IR we used HOMA-AD to evaluate IR. To our knowledge, our study is the first one that uses HOMA-AD in a group of women with PCOS. HOMA-AD is a very promising marker for IR assessment because it also includes adiponectin, which is involved in the regulation of insulin sensitivity. This surrogate IR marker was first validated in Japanese adults and presented a stronger correlation with the euglycemic–hyper-insulinemic clamp technique than HOMA-IR ($r = -0.643$, $p < 0.001$; $r = -0.591$, $p < 0.001$, respectively) [42]. A study by Vilela et al. [43] conducted in adult women with metabolic syndrome also revealed a stronger correlation between HOMA-AD and euglycemic–hyper-insulinemic clamp compared to HOMA-IR, which suggests that it may be a more sensitive IR marker. Our study demonstrated a strong positive correlation between HOMA-IR and HOMA-AD in the Study and Control Groups. Moreover, the correlation was much stronger in the group of women with PCOS. In contrast to HOMA-IR, we observed significantly higher HOMA-AD values in the PCOS Group compared to non-PCOS Group. Additionally, when we used HOMA-AD we observed a higher prevalence of IR among PCOS women.

In our research, we also proposed the L/A ratio to assess IR in PCOS women. It was previously suggested by Larsen et al. [27] that, in obese adults, the L/A ratio could be a potential biomarker for IR. As regards PCOS women, it was confirmed that the L/A ratio correlated positively with HOMA-IR [44–46]. Furthermore, Golbahar et al. [47] demonstrated that the L/A ratio was independently associated with PCOS, indicating its high sensitivity and specificity for the diagnosis of PCOS. We observed that the L/A ratio was significantly higher in PCOS women compared to their healthy counterparts. Several other authors obtained similar results [45,47–49]. Moreover, Savastano et al. [48] reported that the L/A ratio was significantly higher in lean and obese PCOS women compared to lean and obese controls, which indicates the possibility of using this indicator to assess IR

independently of BMI. However, it would be worth considering the influence of abdominal obesity on this parameter.

The importance of physical activity in the prevention and treatment of many chronic diseases is well documented [50]. Studies in women with PCOS showed that physical activity had a beneficial effect on the hormonal profile, ovulation and regulation of the menstrual cycle, which translated directly into reproductive health and pregnancy rates [51,52]. Our study also showed that physical activity should be an integral part of PCOS treatment due to its beneficial effect on insulin resistance. We reported that higher physical activity was related to lower HOMA-IR in the PCOS Group. Moreover, higher levels of physical activity were associated with greater chances of attaining normal HOMA-IR values. A systematic review of 46 studies revealed that vigorous aerobic exercise improved insulin sensitivity in women with PCOS [16]. This finding was also confirmed by two recent systematic reviews and meta-analyses [53,54]. Turan et al. [55] found a significant decrease in HOMA-IR in non-overweight PCOS women after 8 weeks of structured exercise, while in the Control Group no difference was observed. Several studies using HOMA-IR revealed a correlation between exercise and insulin sensitivity, where the authors found a significant decrease in insulin resistance in the PCOS Group [56–59]. Some researchers also observed an improvement in insulin sensitivity but measured with different methods than HOMA-IR [31,60,61]. Changes were also observed independently of weight loss.

No relationship was observed between the amount of physical activity and the concentrations of all tested adipokines (adiponectin, leptin and resistin). The results obtained by Stener-Victorin et al. [62], Covington et al. [60] and Almenning et al. [57], where the concentration of adiponectin was unrelated to physical activity, were similar to our findings. Contrary to our results, Al Eisa et al. [59] noted that 12 weeks of moderate aerobic training had a significant positive effect on adiponectin levels in PCOS women. Another study in PCOS women showed that 12 weeks of HITT exercise contributed to an increase in adiponectin concentration, while the level of leptin remained unchanged [63]. Souza et al. [58] found that 8 weeks of aerobic activity resulted in an increase in adiponectin and a decrease in leptin, albeit only in lean women with PCOS. Covington et al. [60] observed that 8 weeks of aerobic exercise caused a decrease in the ratio of leptin to high-molecular-weight adiponectin, while leptin to total adiponectin ratio was unchanged. It is believed that the effects of exercise on adipokine levels may occur more quickly in non-overweight than overweight PCOS women and reduction in body weight is the most important factor influencing adipokine concentration. Furthermore, changes in the visceral adipose tissue as a result of physical activity are the most important factors reinforcing these relationships [58,63]. These mechanisms may explain the lack of the influence of physical activity on adipokines in our study, as well as HOMA-AD and the L/A ratio. Therefore, in the future interventional study should be carried out to determine whether different intensities of physical activity are associated with changes in adipokines and tissue insulin sensitivity.

The importance of diet, in addition to physical activity, was clearly emphasized in the recommendations regarding the treatment of PCOS [17,18]. Despite this fact, the eating habits of women with PCOS show many abnormalities. Several papers revealed that the diet and lifestyle of PCOS patients was poor compared to the control group [36,64,65]. However, our study revealed no statistically significant difference between dietary patterns in PCOS and non-PCOS women. A systematic review and meta-analysis of 19 studies highlighted that a balanced diet in PCOS contributed to better insulin sensitivity (measured via HOMA-IR) [15]. The Mediterranean diet, DASH diet (Dietary Approaches to Stop Hypertension) and low glycemic index diet seem to be the healthiest dietary approaches that have the strongest relationship with greater insulin sensitivity among PCOS women [12–15]. A study by Bykowska-Derda et al. [3] showed that PCOS women with low adherence to the western dietary pattern were at a lower risk of having IR. In particular, high intake of meat was associated with metabolic disorders in PCOS. Interestingly, dietary patterns rich in plant products and physical activity were related to improvement in metabolic health among PCOS women. According to a study by Nybacka et al. [66], 4 months of

dietary intervention (well-balanced diet with caloric restrictions) was associated with an improvement in HOMA-IR. In our study, we proposed assessing the diet using a diet score, which comprised the effects of dietary factors and a negative and positive impact on insulin sensitivity. However, higher adherence to the diet that increased insulin sensitivity (measured by diet score) was not found to be associated with HOMA-IR, HOMA-AD, A/L ratio and adipokine levels, even though adiponectin concentration was also influenced through dietary patterns and particular products and nutrients in the diet [5]. Our results are similar to those obtained by several other authors [1,67,68]. Wang et al. [1] reported that HOMA-IR values did not differ in PCOS women after 6 months of intervention (balanced diet with caloric restriction and moderate physical activity three times per week). Shishehgar et al. [68] observed that hypocaloric low glycemic index diet was unrelated to an improvement in insulin sensitivity (measured via HOMA-IR). Nybacka et al. [67] also did not note a change in HOMA-IR values as a result of a well-balanced diet developed individually by a dietitian. Dâmaso et al. [69] observed no influence of dietary modifications on adiponectin concentration and HOMA-AD values in overweight and obese women. However, they observed a significant improvement in leptin concentrations. When analyzing research results, it should be emphasized that lifestyle modification alone seems to be insufficient; satisfactory results are achieved only after combining diet and physical activity with pharmacological treatment in some patients with PCOS. Moreover, available evidence suggests that the adiponectin-mediated relationship between exercise, diet and insulin sensitivity is more likely at the level of receptor expression, which may explain why lifestyle modifications do not immediately translate into laboratory results [70]. Due to the unclear results of research concerning the relationship between diet and the course of PCOS, it seems reasonable to conduct an intervention study assessing the impact of this parameter on the metabolic profile of women with PCOS, with particular emphasis on IR.

The use of an accelerometer for the precise measurement of physical activity was a strength of our study. However, this study had several limitations. Firstly, the size of the Study and Control Groups was small. Secondly, the use of the original food frequency questionnaire based on declared frequency and portion sizes by the participants might lead to the under- or over-estimation of dietary intake. Finally, our population was mainly Caucasian, with the participants holding a university education and high socioeconomic status, which could significantly reduce the representativity of the study.

5. Conclusions

In conclusion, our study supports the role of physical activity in the management of insulin resistance in PCOS women. Due to the fact that physical activity promotes very important metabolic changes, all women with PCOS should be given the general advice to be physically active. However, due to the small size of the Study and Control Groups the role of diet in the treatment of insulin resistance in PCOS cannot be unequivocally stated; the same is true of the role of lifestyle intervention in modulating adiponectin, leptin and resistin concentrations. Moreover, our findings indicated that HOMA-AD might be a promising surrogate marker for insulin resistance assessment in women with PCOS. Therefore, studies in a larger group of PCOS patients are particularly needed to establish the role of HOMA-AD in the diagnosis of insulin resistance and the role of diet and physical activity in treating this metabolic disorder.

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Abdominal Obesity in Women with Polycystic Ovary Syndrome and Its Relationship with Diet, Physical Activity and Insulin Resistance: A Pilot Study

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Abstract: Abdominal obesity is a common feature of women with polycystic ovary syndrome (PCOS), and it is known to exacerbate insulin resistance (IR). Improper dietary and physical activity patterns are crucial environmental factors involved in the development of obesity, and they can significantly influence the central deposition of adipose tissue. Therefore, in this cross-sectional study, we aimed to evaluate the relationship between abdominal adiposity (measured by VAT (visceral adipose tissue), SAT (subcutaneous adipose tissue), VAT/SAT ratio (visceral to subcutaneous fat ratio), and WHR (waist-to-hip ratio)) and the prevalence and odds ratios of IR (measured by the homeostatic model assessment of insulin resistance (HOMA-IR), the homeostatic model assessment-adiponectin (HOMA-AD) and leptin to adiponectin ratio (L/A ratio)) in 56 PCOS women. Furthermore, we investigated the relationship between these abdominal obesity indices and diet and physical activity. An original food frequency questionnaire and Actigraph GT3X-BT were used to assess adherence to the diet recommended in IR and the level of physical activity, respectively. We observed a higher prevalence of IR among women with higher VAT, VAT/SAT, and WHR values compared to women with normal values of those abdominal obesity indices. Moreover, VAT/SAT seemed to be the best predictor of IR measured by HOMA-IR and HOMA-AD. However, VAT appeared to be the best and strongest predictor of IR measured by the L/A ratio. We also observed that higher adherence to the diet recommended in IR and higher levels of vigorous physical activity were associated with lower values of central fat accumulation indices and a greater chance of their normal values. Our findings indicate that central obesity increases the odds of IR and supports the beneficial role of diet and physical activity in the management of abdominal obesity in PCOS women.

Keywords: polycystic ovary syndrome; abdominal obesity; visceral adipose tissue; subcutaneous adipose tissue; insulin resistance; HOMA-IR; HOMA-AD; L/A ratio; physical activity; diet

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1. Introduction

Polycystic ovary syndrome (PCOS) is a common and heterogeneous condition among women of reproductive age. PCOS is characterized by anovulation, hyperandrogenemia (clinical or biochemical), and/or polycystic ovary morphology. In addition to these characteristics, hyperinsulinemia, insulin resistance (IR), and obesity are other important features of this syndrome. Numerous factors promote obesity in PCOS, including small or large size for gestational age, maternal PCOS, intrauterine hyperandrogenism, or menarche,

which occurs too early or too late [1]. It is estimated that obesity is present in up to 75% of women with this endocrinopathy and may exacerbate the clinical and metabolic features of the disease. Additionally, it is observed that the central distribution of adipose tissue is particularly common in this group of women. A meta-analysis of 35 studies revealed that PCOS women had an elevated prevalence of central obesity (RR (relative risk) 1.73 95% CI 1.31–2.30; $p < 0.05$) compared to women without PCOS [2]. Moreover, the central accumulation of adipose tissue was found to be characteristic of both normal weight, overweight and obese women with PCOS and was associated with the disease regardless of BMI [3–5].

IR, defined as decreased responsiveness or sensitivity to the metabolic actions of insulin, is one of the most essential features of PCOS and affects up to 80% of its cases [6]. The early diagnosis and management of IR in women with PCOS is one of the most important aspects of preventing metabolic and hormonal complications. HOMA-IR (the homeostatic model assessment of insulin resistance) is the most commonly used marker for IR diagnosis in clinical practice. However, it is very often insensitive and may cause the underdetection of IR in PCOS cases [6,7]. HOMA-AD (the homeostatic model assessment-adiponectin) and L/A ratio (leptin to adiponectin ratio) are promising markers in the evaluation of IR in PCOS women because they concentrate on adipokines which are involved in the regulation of tissue insulin sensitivity [8–10]. Notably, apart from energy storage function, the adipose tissue is also a very crucial and active endocrine organ that secretes a variety of adipokines influencing the regulation of metabolism related to the sensitivity of tissues to insulin and reproductive function [11]. There is substantial evidence confirming that women with PCOS, regardless of obesity, are characterized by significantly lower concentrations of adiponectin compared to healthy women [8,12–17]. Leptin and resistin are other adipokines whose concentrations are abnormal in PCOS women. According to numerous authors, women with PCOS were characterized by an increased concentration of those adipokines, which further exacerbated the obesity-related disorders of tissue sensitivity to insulin [9,12,14,16–18]. Interestingly, it is subject to research whether those abnormalities in secreted adipokines in PCOS women are the direct result of abdominal obesity or whether they are rather related to PCOS.

The inter-relationship between obesity, IR, and endocrine abnormalities in PCOS is of complex nature. Obesity is known to exacerbate carbohydrate metabolism disorders and is an intermediate link between PCOS and IR. According to Li et al. [7], overweight and obese women with PCOS were at higher odds for IR (OR = 4.11, 95% CI 2.38–7.11, $p < 0.001$; OR = 10.99, 95% CI 5.82–20.76, $p < 0.001$, respectively) compared to lean PCOS subjects. However, a systematic review and meta-analysis of 28 studies highlighted that the diagnosis of PCOS independently of obesity was associated with a 27% decrease in insulin sensitivity [19]. Abdominal obesity particularly promotes hyperinsulinemia and IR in PCOS women, independently of the total quantity of body fat. It is considered that visceral adipose tissue is more strongly related to metabolic and hormonal disturbances in PCOS women than the subcutaneous one [5,11]. Visceral adipose tissue is regarded to cause disturbances in insulin signaling in women with PCOS and increase lipolysis, which encourages IR [3]. Additionally, excess abdominal adipose tissue is associated with low-grade chronic inflammation, which is another important element in the pathogenesis of IR in this endocrinopathy [20–22].

Recent recommendations regarding the treatment of PCOS highlighted the great importance of lifestyle interventions in the management of this disease and for weight control practice [23,24]. It was well-proven that a 5% reduction in body weight was associated with metabolic and hormonal improvements in the course of PCOS [23]. Improper dietary and physical activity patterns are crucial environmental factors involved in the development of obesity and IR in PCOS women, and they may significantly influence body composition, including the central deposition of adipose tissue. In particular, a poor-quality diet and low physical activity constitute additional risk factors for elevated abdominal adiposity apart from those associated with the pathophysiology of the disease [21,25].

Given the role of central abdominal obesity in the pathogenesis of IR in PCOS, in the present study, we aimed to investigate the relationship between the type of accumulation of body fat tissue (measured by VAT (visceral adipose tissue), SAT (subcutaneous adipose tissue), VAT/SAT ratio (visceral to subcutaneous fat ratio) and WHR (waist-to-hip ratio)) and the prevalence and odds ratios of IR (measured by HOMA-IR, HOMA-AD, and L/A) among PCOS women. Moreover, we analyzed the association between abdominal obesity, diet, and physical activity to establish the potential role of lifestyle interventions in the prevention and treatment of abdominal obesity in patients with PCOS.

2. Materials and Methods

2.1. Participants

This study included 56 women aged 18–40 years diagnosed with polycystic ovary syndrome according to the Rotterdam diagnostic criteria [26]. The participants were admitted to the Department of Gynecological Endocrinology of the Medical University of Warsaw in the years 2021–2022. The exclusion criteria were as follows: diabetes, thyroid dysfunction, endometriosis, Cushing's syndrome, androgen-releasing tumor, congenital adrenal hyperplasia, chronic hypertension, cardiovascular diseases, the use of lipid-lowering, hormonal or insulin-sensitizing drugs, pregnancy, lactation and contraindications to body composition analysis (diagnosed epilepsy, implanted pacemaker or defibrillator and metal endoprostheses). For further analysis, the women were divided into four groups according to the visceral and subcutaneous fat content, visceral-to-subcutaneous fat ratio, and waist-to-hip ratio values. All the women provided written informed consent to participate in the study. The study was approved by the Ethics Committee of the Medical University of Warsaw (consent no. KB/170/2019).

2.2. Anthropometric Measurements

Body weight and height measurements were performed using standard procedures [27]. Body mass index (BMI) was calculated as follows: weight/height^2 [kg/m^2]. The interpretation of the values of this ratio was based on the classification published by the World Health Organization (WHO) [28]. Waist and hip circumferences were measured according to the WHO recommendations using stretch-resistant tape. Waist circumference was measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest, while hip circumference was measured around the widest part of the buttocks. The waist-to-hip ratio (WHR) was calculated by dividing the waist circumference by the hip circumference. Abdominal obesity was defined as WHR $\geq$ 0.85 [29].

2.3. Body Composition Analysis with Bioelectrical Impedance (BIA)

In order to assess whole body composition, Maltron BioScan 920-II multi-frequency bioelectrical impedance analyzer was used (Maltron International Ltd., Rayleigh, UK). Before taking the BIA measurement, the women were instructed with the following guidelines provided by the European Society of Parenteral and Enteral Nutrition (ESPEN): no alcohol or fluids containing caffeine for 24 h before the test, lack of physical activity for 12 h before the test, empty stomach and bladder before the test [30]. The subjects underwent measurements according to manufacturer's instructions in the supine position with the limbs separated 30 degrees away from the body axis after resting for about 3 min. The electrodes were placed on the top middle part of the right hand and on the top middle part of the right foot. To limit the possible errors and to ensure adherence, the sites were first cleaned with isopropyl alcohol [31].

In order to determine abdominal obesity, the quantitative analysis of subcutaneous and visceral tissue was performed in a standing position, with the upper limbs away from the body. The electrodes were placed in accordance with the manufacturer's guidelines [31]. Based on waist circumference and the impedance of visceral and abdominal tissue, the following parameters were determined using Maltron BioScan 920 v. 1.1.135 software: subcutaneous fat surface (SAT in cm^2), visceral fat surface (VAT in cm^2) and visceral to

subcutaneous fat ratio (VAT/SAT ratio). The cut-off for abdominal obesity was >120 cm^2 for VAT and >225 cm^2 for SAT. At the same time, the cut-off for VAT/SAT was defined above 0.9 [31].

2.4. Biochemical Analysis

Venous blood samples were obtained in the morning (between 7 a.m. and 9 a.m.) from each participant after 12 h fasting during the follicular phase (between days 2–6 of the menstrual cycle). In order to obtain the serum, the samples were centrifuged at 2500× *g* for 10 min at 4 °C. The serum for adipokine analyses was stored no longer than 3 months at −80 °C until being processed, while serum glucose and insulin results were determined on the day of blood collection.

Serum glucose level was assayed via the enzymatic method with hexokinase (Integra 400 plus analyzer, Roche Diagnostics, Basel, Switzerland), while serum insulin concentrations were analyzed using two-step chemiluminescent microparticle immunoassay (CMIA; Alinity I analyzer; Abbott Diagnostics GmbH, Wiesbaden, Germany). The concentrations of serum adipokines (adiponectin, leptin, and resistin) were determined by commercial enzyme-linked immunosorbent assay (ELISA), according to the manufacturer's instructions. Leptin was assessed using a kit from DRG Instruments GmbH (Marburg, Germany). The analytical sensitivity of the assay was 0.7 ng/mL; intra-assay and inter-assay coefficients of variation (CV) were 4.2–7.3% and 3.7–9.1%, respectively. Total adiponectin was determined using a kit manufactured by TECOmedical AG (Sissach, Switzerland) with a lower detection limit below 0.27 ng/mL, intra-assay CV: 3.14–3.67%, and inter-assay CV: 6.93–8.16%. Resistin was measured using a kit manufactured by Mediagnost (Reutlingen, Germany) with the analytical sensitivity of the assay 0.012 ng/mL, intra-assay CV: 4.49–4.97%, and inter-assay CV: 3.37–6.67%.

The following mathematical models were used to establish insulin resistance: HOMA-IR (calculated as [fasting insulin (μU/mL) × fasting glucose (mg/dL)]/405); HOMA-AD (calculated as [fasting plasma insulin (μU/mL) × fasting glucose (mmol/L)]/adiponectin (μg/mL)) and L/A (calculated as leptin (ng/mL)/adiponectin (μg/mL)). The defined cut-off points were ≥2.5 for HOMA-IR [32], ≥6.26 for HOMA-AD [33], and >2.2 for L/A ratio [34].

2.5. Nutritional Assessment and Physical Activity Measurement

As we have already fully reported in our previous study [8], adherence to the diet recommended for insulin resistance was assessed with the original 15 food items food frequency questionnaire (FFQ) administered by a qualified nutritionist during a face-to-face interview. The participants were asked to report their average frequency (none, daily, weekly, or monthly) and the portion size of consumption for each food item. By assigning points 0, 0.5, or 1 for each item, adherence score was calculated.

For physical activity measurement, the participants wore an Actigraph GT3X-BT activity monitor (Actigraph Corp, Pensacola, FL, USA) at a belt around their waist, positioned on their right hip, over seven consecutive days. Raw accelerometer data were downloaded using ActiLife software (version 6.13.0, ActiGraph Corp, Pensacola, FL, USA). The duration of physical activity of moderate (MPA) or vigorous intensity (VPA), separately or combined (MVPA), was measured based on count thresholds corresponding to moderate or vigorous intensity activity. Freedson's cut-off levels [35] were used to differentiate between the three intensity levels of physical activity: moderate physical activity (MPA): 1952–5724 counts/min, vigorous physical activity (VPA): ≥5725 counts/min and moderate + vigorous physical activity (MVPA) ≥ 1952 counts/min. Time spent in activity of a defined intensity (MPA, VPA, or MVPA) was determined by summing minutes in a week where the count met the criterion for the respective intensity.

2.6. Statistical Analysis

Statistical analyses were conducted using STATISTICA™ 13.3 software (TIBCO Software, Palo Alto, CA, USA). A *p*-value of less than 0.05 was considered statistically significant. The Anderson-Darling test was used to evaluate variable distributions, and descriptive statistics were calculated, including the means, standard deviations, medians, and interquartile ranges. The comparison of women divided into four groups according to VAT, SAT, VAT/SAT, and WHR were performed with the Mann–Whitney–Wilcoxon test. Contingency tables with Fisher's exact test were used to assess the relationship between the frequency and odds of insulin resistance in different abdominal obesity indices.

Linear regression analysis was employed to evaluate the relationship between abdominal obesity and physical activity or diet scores. Parameters for linear regression were estimated using the least square estimation method. A standardized regression coefficient (β) with a 95% confidence interval (95% CI) was calculated for each independent variable included in the model. Logistic regression analysis was conducted to examine the odds of normal values for the examined parameters based on diet or physical activity scores. Parameters for logistic regression were estimated using the maximum likelihood method. An odds ratio (OR) with a 95% CI was calculated for each independent variable included in the model.

3. Results

3.1. Baseline Clinical Features in Women with PCOS Divided According to the VAT, SAT, VAT/SAT Ratio and WHR

PCOS patients in each group were of similar age and height. As expected, the anthropometric and body composition data showed several differences between each group. The PCOS group with increased VAT (>120 cm^2), SAT (>225 cm^2), VAT/SAT ratio (>0.9), and WHR ($\geq$0.85) had a significantly higher body weight level ($p < 0.001$ for each group), BMI ($p < 0.001$ for each group), waist circumference ($p < 0.001$ for each group), hip circumference ($p < 0.001$ for each group), total fat mass ($p < 0.001$ for each group) and muscle mass ($p < 0.01$ for each group) compared to the women with the normal values of those parameters.

Biochemical blood parameters also showed differences between groups, except for fasting glucose levels, which were not significantly different. We observed significantly higher levels of fasting insulin in the serum of women with increased VAT, SAT, VAT/SAT, and WHR ($p < 0.001$, $p = 0.007$, $p < 0.001$, and $p = 0.005$, respectively) compared to women with normal values of abdominal obesity indices. Additionally, in those groups of PCOS women, we also found lower adiponectin and higher leptin and resistin serum levels compared to those with the normal values of those parameters. Women with abdominal obesity had higher HOMA-IR and HOMA-AD values in contrast to women without abdominal obesity. We observed a similar relationship in the case of the L/A ratio.

Comparing diet scores between those groups of PCOS women, we found that women with increased VAT, VAT/SAT, and WHR values were characterized by significantly lower levels of adherence to the diet recommended in IR (measured by diet score) ($p = 0.002$, $p = 0.023$ and $p = 0.026$, respectively) as well as significantly lower levels of vigorous physical activity ($p = 0.005$, $p = 0.026$ and $p = 0.027$, respectively). Interestingly, we did not observe such differences in the case of groups that differed in subcutaneous fat content. Moreover, we observed no differences in the amount of moderate physical activity and the MVPA index in any group. Detailed comparisons of baseline clinical features of women divided into four groups are shown in Table 1.

Table 1. Baseline clinical features in women with PCOS divided according to VAT, SAT, VAT/SAT ratio and WHR.

Parameters	VAT ≤120 cm *n* = 31	VAT >120 cm^2 *n* = 25	*p*-Value *	SAT ≤225 cm^2 *n* = 47	SAT >225 cm^2 *n* = 9	*p*-Value *	VAT/SAT ≤0.9 *n* = 29	VAT/SAT >0.9 *n* = 27	*p*-Value *	WHR <0.85 *n* = 35	WHR ≥0.85 *n* = 21	*p*-Value *
AGE AND ANTHROPOMETRIC MEASUREMENTS												
Age (years)	25.65 ± 4.46 25 19–38	26.36 ± 3.65 26 21–36	NS	26.28 ± 4.26 25 19–38	24.33 ± 2.78 24 21–29	NS	25.66 ± 4.55 25 19–38	26.3 ± 3.61 26 21–36	NS	25.6 ± 3.85 25 19–35	26.57 ± 4.51 26 21–38	NS
Weight (kg)	60.01 ± 7.96 58 45–75	95.82 ± 15.41 94 70–126.4	<0.001	70.51 ± 17.86 66.7 45–119	104.64 ± 15.23 111 83.7–126.4	<0.001	60.39 ± 8.39 58.9 45–75	92.76 ± 18.32 93 56–126.4	<0.001	66.55 ± 17.66 59 45–117	91.73 ± 17.91 91 63–126.4	<0.001
Height (cm)	166.26 ± 4.27 165 158–174	167.24 ± 6.07 165 158–180	NS	166.83 ± 5.1 165 158–180	166 ± 5.48 165 159–174	NS	166.45 ± 4.35 166 158–174	166.96 ± 5.92 165 158–180	NS	166.91 ± 5.03 166 158–178	166.33 ± 5.38 165 159–180	NS
BMI kg/m^2	21.65 ± 2.69 21.2 17.2–27.8	34.2 ± 5.03 35.5 24.8–42.9	<0.001	25.21 ± 5.88 23.5 17.2–36.7	37.92 ± 4.97 39.3 28.7–42.9	<0.001	21.73 ± 2.82 21.5 17.2–27.8	33.18 ± 6.05 34.5 21–42.9	<0.001	23.77 ± 5.91 22.3 17.2–42.9	33.06 ± 5.86 34.50 23.4–41.7	<0.001
WC (cm)	72.77 ± 7.96 73 58–92	104.28 ± 10.94 103 86–126	<0.001	81.94 ± 15.24 76 58–118	112.44 ± 9.96 113 96–126	<0.001	73.07 ± 8.58 72 58–92	101.63 ± 13.93 103 73–126	<0.001	77.11 ± 13.23 74 58–113	103.05 ± 13.65 103 73–126	<0.001
HC (cm)	92.03 ± 7.37 92 72–104	117.84 ± 10.09 120 100–140	<0.001	99.62 ± 13.15 97 72–128	124.11 ± 9.99 124 113–140	<0.001	92.76 ± 7.71 93 72–104	115.15 ± 13.32 114 84–140	<0.001	97.63 ± 14.13 94 72–140	113.43 ± 12.7 114 84–137	<0.001
WHR	0.79 ± 0.05 0.79 0.7–0.9	0.88 ± 0.06 0.87 0.8–1	<0.001	0.82 ± 0.06 0.82 0.7–1	0.9 ± 0.07 0.9 0.81–1	0.002	0.79 ± 0.05 0.78 0.7–0.9	0.88 ± 0.06 0.87 0.8–1	<0.001	0.79 ± 0.04 0.8 0.7–0.8	0.9 ± 0.05 0.88 0.9–1	<0.001
BODY COMPOSITION												
FFM (kg)	44.08 ± 3.06 44.14 37.4–49.1	53.01 ± 5.35 52.03 43.5–64.1	<0.001	46.99 ± 5.7 46.03 37.4–64.1	53.65 ± 5.49 56.1 43.5–62	0.002	44.25 ± 3.11 48.88 37.4–49.1	52.16 ± 5.97 51.3 40.4–64.1	<0.001	45.91 ± 5.49 45.54 37.4–62.6	51.65 ± 5.55 50.4 42.5–64.1	<0.001
FFM (%)	74.1 ± 5.63 73.71 62.5–84.2	55.94 ± 4.84 55.35 48.1–66.3	<0.001	68.75 ± 9.07 70.79 53.7–84.2	51.6 ± 3.09 50.95 48.1–57.9	<0.001	74.01 ± 5.98 73.75 62.5–84.2	57.38 ± 6.83 55.91 48.1–73.6	<0.001	71.16 ± 8.97 72.9 48.8–84.2	57.38 ± 6.53 55.35 48.1–71.6	<0.001
FM (kg)	15.94 ± 5.39 15.25 7.5–28.2	42.81 ± 10.96 42.74 23.6–64.4	<0.001	23.52 ± 12.53 19.86 7.5–54.9	50.99 ± 10.13 54.45 36.6–64.4	<0.001	16.15 ± 5.75 15.03 7.5–28.2	40.59 ± 13.1 41.97 15.7–64.4	<0.001	20.64 ± 12.57 15.86 7.5–59.9	40.08 ± 13.06 40.21 17.9–64.4	<0.001
FM (%)	25.9 ± 5.63 26.29 15.8–37.5	44.22 ± 5.03 44.65 33.7–52	<0.001	31.25 ± 9.07 29.21 15.8–46.3	48.84 ± 3.3 49.46 42.1–52	<0.001	25.99 ± 5.98 26.28 15.8–37.5	42.76 ± 6.99 44.09 26.4–52	<0.001	28.84 ± 8.97 27.1 15.8–51.2	42.81 ± 6.75 44.65 28.4–52	<0.001
MM (kg)	19.13 ± 1.51 19.41 14.8–21.4	23.46 ± 2.42 22.9 19.3–28.3	<0.001	20.54 ± 2.73 20.18 14.18–28.3	23.78 ± 2.45 24.91 19.3–27.6	0.002	19.19 ± 1.56 19.41 14.8–21.4	23.08 ± 2.7 22.79 17.8–28.3	<0.001	20.06 ± 2.62 19.98 14.8–27.6	22.74 ± 2.65 22.5 18.6–28.3	<0.001
VAT (cm^2)	55.87 ± 29.58 51 21–116	276.4 ± 78.87 296 131–350	<0.001	116.98 ± 97.89 66 21–350	349.33 ± 2 350 344–350	<0.001	53.69 ± 29.98 51 21–134	262.41 ± 90.79 291 88–350	<0.001	86.37 ± 79.78 51 21–350	267.57 ± 100.31 301 66–350	<0.001
SAT (cm^2)	89.45 ± 34.97 78 37–194	224.36 ± 75.28 202 123–380	<0.001	118.94 ± 53.71 119 37–222	310.22 ± 43.99 285 266–380	<0.001	91.76 ± 36.05 78 45–194	211.89 ± 84.67 200 37–380	<0.001	105.46 ± 50.07 100 45–267	223.38 ± 88.55 219 37–380	<0.001
VAT/SAT	0.64 ± 0.36 0.55 0.4–2.4	1.51 ± 0.39 1.5 0.9–2.4	<0.001	0.89 ± 0.5 0.65 0.4–2.4	1.75 ± 0.36 1.89 1.2–2.4	<0.001	0.56 ± 0.13 0.53 0.4–0.9	1.53 ± 0.42 1.5 0.9–2.4	<0.001	0.72 ± 0.33 0.57 0.4–1.6	1.55 ± 0.52 1.59 0.5–2.4	<0.001

Table 1. *Cont.*

Parameters	VAT ≤120 cm *n* = 31	VAT >120 cm^2 *n* = 25	*p*-Value *	SAT ≤225 cm^2 *n* = 47	SAT >225 cm^2 *n* = 9	*p*-Value *	VAT/SAT ≤0.9 *n* = 29	VAT/SAT >0.9 *n* = 27	*p*-Value *	WHR <0.85 *n* = 35	WHR ≥0.85 *n* = 21	*p*-Value *
BIOCHEMICAL PARAMETERS												
Fasting glucose (mg/dL)	89.94 ± 5.69 90 77.4–100.8	93.74 ± 7.93 93 81–122	NS	92.05 ± 7.38 91.8 77.4–122	89.44 ± 3.88 90 81–94	NS	89.66 ± 5.66 90 77.4–100.8	93.75 ± 7.72 93 81–122	NS	90.55 ± 5.86 90 77.4–101	93.43 ± 8.38 93 81,122	NS
Fasting insulin (µU/mL)	5.25 ± 1.95 5 2.5–11.2	10.76 ± 4.67 9.4 4.8–24.1	<0.001	7.04 ± 3.84 6.1 2.5–20.1	11.2 ± 5.61 10.6 4.8–24.1	0.007	4.97 ± 1.4 5 2.5–7.4	10.66 ± 4.6 9.6 4.5–24.1	<0.001	6.59 ± 3.72 5.8 2.5–20.1	9.58 ± 4.85 8.1 4.5–24.1	0.005
Adiponectin (µg/mL)	10.13 ± 2.77 10 5.6–16.2	5.64 ± 2.68 5.3 2.2–16.4	<0.001	8.61 ± 3.57 8.3 3.2–16.4	5.6 ± 1.78 5.9 2.2–7.9	0.013	10.4 ± 2.95 10.3 5.6–16.4	6.68 ± 2.18 5.6 2.2–13.2	<0.001	9.28 ± 3.56 8.8 2.2–16.4	6.2 ± 2.48 5.7 3.2–13.2	<0.001
Leptin (ng/mL)	7.97 ± 6.62 6.3 1.4–32.4	22.41 ± 9.52 20.6 8.3–48.2	<0.001	12.7 ± 10.67 9.2 1.4–48.2	23.37 ± 5.9 22.5 13.4–33.2	0.001	7.8 ± 6.81 6.1 1.4–32.4	21.52 ± 9.69 20.4 8.3–48.2	<0.001	8.53 ± 5.83 7.7 1.4–21.5	24.22 ± 9.97 22.5 7.8–48.2	<0.001
Resistin (ng/mL)	6.16 ± 1.67 5.7 4.1–13.2	8.7 ± 2.66 8.1 5.3–15.7	<0.001	7.01 ± 2.45 6.2 4.1–15.7	8.77 ± 2.37 8.3 5.7–11.8	0.027	6.10 ± 1.71 5.7 4.1–13.2	8.57 ± 2.61 8 5.3–15.7	<0.001	6.8 ± 2.68 5.9 4.1–15.7	8.1 ± 1.97 7.9 5.5–11.9	0.002
HOMA-IR	1.17 ± 0.46 1.1 0.5–2.5	2.52 ± 1.17 2.3 1.1–5.6	<0.001	1.63 ± 0.98 1.3 0.5–4.8	2.5 ± 1.33 2.4 1.1–5.6	0.014	1.10 ± 0.32 1.1 0.5–1.7	2.49 ± 1.15 2.3 1–5.6	<0.001	1.49 ± 0.89 1.3 0.5–4.8	2.24 ± 1.22 1.9 1–5.6	0.007
HOMA-AD	2.84 ± 1.57 2.3 1.2–8.3	11.5 ± 5.94 11.4 2.2–24	<0.001	5.87 ± 5.68 3.4 1.2–24	11.07 ± 5.79 11.6 3.4–20	0.005	2.54 ± 0.98 2.3 1.2–4.6	11.18 ± 5.84 10.9 1.7–24	<0.001	5.02 ± 5.45 2.8 1.2–24	9.51 ± 5.84 8.3 1.7–23.2	<0.001
L/A	0.93 ± 1.13 0.7 0.1–5.8	4.68 ± 2.74 4.3 0.6–12.1	<0.001	2.21 ± 2.68 0.9 0.1–12.1	4.69 ± 2.12 4.3 2–9.3	0.002	0.9 ± 1.16 0.6 0.1–5.8	4.44 ± 2.77 4.1 0.7–12.1	<0.001	1.37 ± 1.84 0.8 0.1–9.3	4.66 ± 2.78 4.6 0.7–12.1	<0.001
DIET SCORE AND PHYSICAL ACTIVITY												
Diet score	8.39 ± 2.54 9 1.5–13	6.54 ± 1.95 6 4–12	0.002	7.8 ± 2.52 7.5 1.5–13	6.33 ± 1.71 6 4.5–9	NS	8.21 ± 2.58 8.5 1.5–13	6.87 ± 2.16 6.5 4–12	0.023	8.13 ± 1.19 8 4–13	6.62 ± 2.64 6 1.5–12	0.026
Moderate [min/week]	295.59 ± 143.76 256.8 73.7–222.2	296.64 ± 133.32 217.8 71.5–602.7	NS	301.84 ± 144.1 256.8 73.7–611	265.86 ± 101.03 291 71.5–379.7	NS	307.57 ± 145.05 256.8 102.2–611	283.7 ± 131.49 271.8 71.5–602.7	NS	292.47 ± 136.01 256.8 73.7–611	302.04 ± 144.3 293 71.5–602.7	NS
Vigorous [min/week]	30.35 ± 46.18 11.2 0.2–223.7	7.71 ± 7.75 5.7 0–38.2	0.005	22.98 ± 39.05 9 0.2–223.7	5.96 ± 4.67 5.7 0–13.2	NS	31.3 ± 47.67 11.2 0.2–223.7	8.37 ± 7.66 8 0–38.2	0.026	27.8 ± 44.16 10.7 0.2–223.7	7.64 ± 6.62 6.3 0–29.2	0.027
MVPA [min/week]	325.94 ± 146.42 304 82.2–627.3	304.36 ± 136.98 273.5 72.2–609	NS	234.82 ± 146.78 302.3 82.2–627.3	271.83 ± 104.69 269.7 72.2–385.3	NS	338.87 ± 145.6 239.5 106–627.3	292.07 ± 135.27 273.5 72.2–609	NS	320.27 ± 139.1 302.3 82.2–627.3	309.69 ± 148.42 301.5 72.2–609	NS

Data are mean ± standard deviation, median and interquartile ranges. * Mann–Whitney test; $p < 0.05$. Abbreviations: VAT—visceral fat surface; SAT—subcutaneous fat surface; VAT/SAT—visceral to subcutaneous fat ratio; WHR—waist to hip ratio; BMI—body mass index; WC—waist circumference; HC—hip circumference; FFM—fat-free mass; FM—fat mass; MM—muscle mass; HOMA-IR—homeostatic model assessment of insulin resistance; HOMA-AD—homeostatic model assessment—adiponectin; L/A—leptin to adiponectin ratio; MVPA—moderate to vigorous physical activity; NS—not statistically significant.

3.2. Abdominal Obesity and Insulin Resistance

We observed a significantly higher prevalence of IR measured by HOMA-IR, HOMA-AD, and the L/A ratio in PCOS women with increased visceral fat content, VAT/SAT ratio, and WHR value compared to those with the normal values of those parameters. Interestingly, a significantly higher IR frequency (measured by HOMA-AD and the L/A ratio) was observed in women with normal subcutaneous fat content compared to women with SAT > 225 cm^2. However, those differences for IR measured by HOMA-IR were not statistically significant. Additionally, we noted the highest frequency of IR in PCOS women with abdominal obesity evaluated by the L/A ratio compared to HOMA-IR and HOMA-AD. Detailed data on the frequency of IR in women with PCOS and abdominal obesity are presented in Table 2. Moreover, we found that women with HOMA-IR $\geq$ 2.5 had higher VAT, SAT, VAT/SAT, and WHR values (z = −3.589; $p < 0.001$, z = −3.393; $p < 0.001$, z = −3.714; $p < 0.001$ and z = −3.294; $p = 0.001$, respectively). We found a comparable relationship for HOMA-AD $\geq$ 6.26 (z = −5.116; $p < 0.001$, z = −4.564; $p < 0.001$, z = −5.002; $p < 0.001$ and z = −3.637; $p < 0.001$, respectively) and the L/A ratio >2.2 (z = −5.795; $p < 0.001$, z = −5.654; $p < 0.001$, z = −5.236; $p < 0.001$ and z = −4.844; $p < 0.001$, respectively).

Table 2. Differences in the prevalence of insulin resistance measured by HOMA-IR, HOMA-AD and L/A divided according to VAT, SAT, VAT/SAT ratio and WHR.

	VAT ≤120 cm^2 n = 31	VAT >120 cm^2 n = 25	*p*-Value *	SAT ≤225 cm^2 n = 47	SAT >225 cm^2 n = 9	*p*-Value *	VAT/SAT ≤0.9 n = 9	VAT/SAT >0.9 n = 29	*p*-Value*	WHR <0.85 n = 35	WHR ≥0.85 n = 21	*p*-Value *
HOMA-IR ≥ 2.5	1.79%	17.86%	0.002	12.50%	7.14%	NS	0.0%	19.64%	<0.001	5.36%	14.29%	0.013
HOMA-AD ≥ 6.26	3.57%	35.71%	<0.001	26.79%	12.50%	0.021	0.0%	39.29%	<0.001	16.07%	23.21%	0.013
L/A > 2.2	5.36%	39.29%	<0.001	30.36%	14.29%	0.007	5.36%	39.29%	<0.001	12.50%	32.14%	<0.001

* The differences were analyzed with Fisher's exact test; $p < 0.05$. Abbreviations: VAT—visceral fat surface; SAT—subcutaneous fat surface; VAT/SAT—visceral to subcutaneous fat ratio; WHR—waist-to-hip ratio; HOMA-IR—homeostatic model assessment of insulin resistance; HOMA-AD—homeostatic model assessment—adiponectin; L/A—leptin to adiponectin ratio; NS—not statistically significant.

We found that the VAT/SAT ratio was the best predictor of IR measured by HOMA-IR and HOMA-AD. We observed that VAT/SAT > 0.9 significantly increased the odds of developing IR. When measured with HOMA-IR, they increased 41.12 times (OR 41.12, 95% Cl 2.27–743.52; $p < 0.001$), and with HOMA-AD, they increased 241.36 times (OR 241.36, 95% Cl 12.67–459.97; $p < 0.001$). VAT > 120 cm^2 appeared to be the best and strongest predictor of IR measured by the L/A ratio (OR 68.44, 95% Cl 12.57–372.76; $p < 0.001$), followed by WHR $\geq$ 0.85 (OR 24.00, 95% Cl 5.48–105.05; $p < 0.001$) and SAT > 225 cm^2 (OR 14.11, 95% Cl 1.62–122.70; $p = 0.007$), while VAT/SAT was found to be the most likely to increase the odds of abnormal HOMA-AD results. Interestingly, increased subcutaneous fat content appeared not to increase the odds of HOMA-IR $\geq$ 2.5. Detailed odds ratios for IR in relation to abdominal obesity are presented in Table 3.

3.3. Effect of Diet and Physical Activity on Abdominal Obesity

Linear regression analysis showed a differential effect of the diet score on abdominal obesity measured by VAT, SAT, VAT/SAT, and WHR. We observed that higher adherence to the diet recommended in IR (a higher diet score) was associated with lower VAT content (t = −2.635; $p = 0.011$), SAT content (t = −2.905; $p = 0.005$), and WHR value (t = −2.631; $p = 0.011$). However, no statistically significant relationship was determined between the diet score and the VAT/SAT ratio. Additionally, we noted that higher vigorous physical activity was associated with lower VAT content (t = −2.277; $p = 0.027$), SAT content (t = −2.028; $p = 0.048$), VAT/SAT ratio (t = −2.280; $p = 0.027$) and WHR (t = −2.421; $p = 0.019$). Conversely, no relationship was observed between moderate physical activity and MVPA and any of the fat distribution indices. Adjustment for BMI did not affect the results.

In addition, logistic regression showed a differential effect of the diet score on the odds of normal VAT content and WHR value. We observed that higher adherence to the

diet recommended in IR translated into 43% greater odds of normal VAT content (OR 1.427, 95% Cl 1.091–1.868; $p = 0.009$) and 33% greater odds of normal WHR value (OR 1.325, 95% 1.023–1.716; $p = 0.033$). Interestingly, the diet score did not have an effect on the odds of normal SAT content or the VAT/SAT ratio. Additionally, higher vigorous physical activity was associated with greater odds of normal VAT (OR 1.063, 95% CI 1.007–1.122; $p = 0.028$) and VAT/SAT (OR 1.057, 95% CI 1.006–1.110; $p = 0.028$) values. However, no such relationship was observed in the case of vigorous physical activity or SAT content and WHR or between MVPA and any of the abdominal obesity indices. Similarly to the previous analysis, adjustment for BMI did not change the outcomes. Additionally, multivariate analysis showed that the diet score was a factor independent of physical activity that increased the odds of normal VAT content (OR 1.430, 95% Cl 1.097–1.864; $p = 0.008$), VAT/SAT (OR 1.273, 95% Cl 1.003–1.615; $p = 0.047$) and WHR (OR 1.322, 95% Cl 1.025–1.704; $p = 0.031$) ratios.

Table 3. Predictors of insulin resistance in PCOS women based on VAT, SAT, VAT/SATand WHR.

Parameters	HOMA-IR	HOMA-AD	L/A
VAT			
OR	20.00	58.00	68.44
95% Cl	2.33–171.18	10.22–329.11	12.57–372.76
p-value *	0.002	<0.001	<0.001
SAT			
OR	4.57	7.47	14.11
95% Cl	0.98–21.34	1.38–40.34	1.62–122.70
p-value *	NS	0.021	0.007
VAT/SAT			
OR	41.12	241.36	38.13
95% Cl	2.27–743.52	12.67–459.97	8.17–177.85
p-value *	<0.001	<0.001	<0.001
WHR			
OR	6.56	4.69	24.00
95% Cl	1.50–28.70	1.47–15.00	5.48–105.05
p-value *	0.013	0.011	<0.001

* The odds ratios were analyzed with Fisher's exact test; $p < 0.05$. Abbreviations: VAT—visceral fat surface; SAT—subcutaneous fat surface; VAT/SAT—visceral to subcutaneous fat ratio; WHR—waist-to-hip ratio; HOMA-IR—homeostatic model assessment of insulin resistance; HOMA-AD—homeostatic model assessment—adiponectin; L/A—leptin to adiponectin ratio; NS—not statistically significant.

4. Discussion

It is widely acknowledged that PCOS women are more susceptible to the central accumulation of body fat compared to healthy BMI-matched counterparts. Abdominal obesity, distributed in subcutaneous areas as well as in the visceral parts of the abdomen, is present in 50–60% of cases of PCOS women [2,3,36,37]. Similarly to other papers, our previous study confirmed that PCOS women were characterized by a higher content of VAT and SAT compared to age-matched healthy women [4,5,8,37–40]. Other studies related to PCOS and based on waist circumference and WHR calculation also revealed that PCOS women had a greater tendency to accumulate body fat, predominantly in the central location [22,40,41]. Those results were confirmed by a systematic review and a meta-analysis of 47 studies. Higher accumulations of visceral fat (SMD (standardized mean difference) 0.41, 95% CI 0.23–0.59, $p < 0.001$) and abdominal subcutaneous fat (SMD 0.31, 95% CI 0.20–0.41, $p = 0.008$) were observed in PCOS women compared to BMI-matched controls [42].

BMI is the most widely accepted obesity indicator. However, it is not devoid of limitations. One of them is the inability to assess body fat distribution. Therefore, waist circumference (WC) and WHR are commonly used in clinical practice as more accurate indicators of abdominal adiposity. Nevertheless, they may be unable to reflect the volume and functions of adipocytes completely and accurately [41,43,44]. Therefore, computed

tomography or magnetic resonance imaging seems to be a better method for assessing abdominal obesity due to the fact that they provide accurate information about the type and quantity of abdominal fat deposits [42]. In our study, apart from WHR, we also used bioelectrical impedance assessment for a more precise determination of the distribution and quantity of abdominal fat deposits (visceral and subcutaneous abdominal compartments). Furthermore, to evaluate abdominal obesity, we also proposed the VAT/SAT ratio, a measure of body fat distribution between VAT and SAT compartments, which is believed to be one of the best indicators of obesity-related metabolic comorbidities in men and women [43,45–47].

According to numerous authors, PCOS women had higher fasting insulin and HOMA-IR compared to healthy non-PCOS women [7,8,13,16,39,48]. Our previous investigation did not confirm this observation. However, the present study revealed that PCOS women with increased VAT, SAT, VAT/SAT, and WHR had significantly higher levels of fasting insulin in the serum and HOMA-IR compared to women with the normal values of abdominal obesity indices [8]. We also observed that other indicators of IR (HOMA-AD and the L/A ratio) were also higher in women with PCOS and abdominal obesity. Additionally, we noted that women with IR had significantly higher abdominal fat accumulation in contrast to women without IR. Our present results regarding abdominal obesity and IR are in accordance with previous findings by Chen et al. [11] and Mu et al. [36]. Wang et al. [49] evaluated abdominal obesity with VAI (Visceral Adiposity Index). They also reported that higher insulin levels and HOMA-IR values were observed in PCOS women with increased VAI values. Moreover, women with IR had significantly higher VAI values than women with normal insulin sensitivity. In a study by Mu et al. [36], normal-weight PCOS women with central obesity were at an increased risk of IR compared to their normal-weight non-centrally obese counterparts (OR 3.83, 95% CI 2.23–6.58; $p < 0.001$). Some other authors also demonstrated that IR was a more prominent feature in overweight and obese PCOS women than in lean PCOS women; however, without distinguishing the types of body fat distribution [40,44,50,51]. Our study also revealed a higher prevalence of IR measured by all three indicators in women with abdominal obesity (evaluated by VAT, VAT/SAT, and WHR). Interestingly, no such relationship was observed in the case of subcutaneous adipose tissue. A lower prevalence of IR was observed in PCOS women with an increased SAT content.

Our previous results stayed in line with the results obtained by other authors and confirmed that all IR indices correlated positively with abdominal obesity indicators. HOMA-IR, HOMA-AD, and the L/A ratio showed the strongest correlation with VAT content (r = 0.6061, $p < 0.001$; r = 0.7185, $p < 0.001$ and r = 0.7305, $p < 0.001$, respectively) compared to SAT and the VAT/SAT ratio [7,8,44,48,52]. However, other studies emphasized that WHR was also a parameter related to IR in PCOS women, specifically those assessed with the use of HOMA-IR [44,49,53]. Our present results revealed that VAT/SAT seemed to be the best predictor of IR measured by HOMA-IR and HOMA-AD. Conversely, VAT appeared to be the best and strongest predictor of IR measured by the L/A ratio. Moreover, apart from HOMA-IR, an increased SAT content was also associated with higher odds for IR. Research by Jena et al. [5] revealed similar results, as SAT was also not associated with HOMA-IR values. In contrast to those results, Tulloch-Reid et al. [54] demonstrated that SAT correlated with IR more strongly than with VAT in women. However, this study did not concern PCOS women. Our data are consistent with the findings of the Framingham Heart Study conducted in 3223 men and women, where the VAT/SAT ratio was associated with a risk of IR to a larger extent than VAT alone [47]. Using a multivariate linear regression model, Ng et al. [38] observed that abdominal obesity measured by waist circumference was an independent predictor of IR in PCOS women. Several studies demonstrated that VAI was the best predictor of metabolic syndrome and IR in PCOS women [49,55,56], while others indicated that WHR was also a useful insulin sensitivity predictor [53]. In the Framingham Heart Study [57] concerning the association between VAT and SAT compartments and metabolic risk factors among men and women, it was

pointed out that both types of adipose tissue were associated with increased odds of metabolic syndrome. However, the relationship was stronger for VAT than SAT, even after adjustment for potential confounders. Our study also showed a weaker but still influential association between the odds of IR (measured by HOMA-AD and the L/A ratio) and SAT accumulation in PCOS women. Despite the fact that SAT seems to be less associated with metabolic alterations in PCOS women than VAT, VAT/SAT, or WHR, it is still a metabolically active compartment of abdominal adipose tissue that should not be overlooked. Therefore, all types of abdominal fat distribution must be clearly analyzed when assessing the relationship between metabolic disorders in PCOS women.

There are numerous structural, functional, and prognostic differences between VAT and SAT. Due to the fact that VAT is more metabolically active and shows a greater lipolytic activity, it is more strongly associated with the pathogenesis of IR, T2DM (type 2 diabetes mellitus), and other metabolic disorders than SAT [37,38,46]. Currently, it is considered that SAT is also linked to metabolic complications in PCOS women. Therefore, it should be pointed out that different fat compartments contribute to IR risk to varying degrees [58]. Disparate results regarding the prevalence of IR and SAT accumulation obtained in our study may be partially explained by the fact that some authors reported that SAT might exert protective effects against cardiometabolic alterations [59,60]. Interestingly, a prospective cohort study by Porter et al. [60] conducted in men and women demonstrated that a possible protective effect of SAT on cardiometabolic risk factors existed only in those in the highest tertile of VAT accumulation. The protective role of SAT may be explained by the fact that this adipose tissue contains larger adipocytes and secretes more cardioprotective adipokines and smaller quantities of pro-inflammatory markers than the visceral one. Notably, VAT and SAT compartments differ in the secretion of metabolically active adipokines. SAT secretes more leptin and adiponectin, whereas VAT secretes more resistin, visfatin, interleukin-6, interleukin-8, and plasminogen activator inhibitor-1 than SAT does [10,60]. Our previous research stayed in line with other papers, which revealed that adiponectin levels were inversely correlated with BMI, total body fat, and the markers of abdominal obesity, whereas a positive correlation was observed for leptin and resistin levels [8,12,13,18,61]. We also observed that all three adipokines showed the strongest correlation with VAT [8].

Adiponectin is one of the most crucial adipokines which regulates insulin sensitivity, and its concentration is negatively correlated with HOMA-IR. Moreover, adiponectin presents anti-inflammatory, antineoplastic, and cardioprotective properties [12]. In a study by Cardoso et al. [62], adiponectin concentration decreased with an increase in body fat percentage in PCOS women. Moreover, obesity, especially the visceral one, is known to decrease the expression level of adiponectin receptors and reduce its postreceptor signaling [21]. Leptin and resistin are other adipokines involved in insulin sensitivity management. Hyperleptinemia and an increased level of resistin are associated with obesity and result in impaired glucose metabolism and IR [12]. It is well established that women with PCOS may experience dysregulation in the synthesis of adipokines in the adipose tissue [62]. We previously reported that PCOS women were characterized by significantly lower adiponectin levels compared to non-PCOS women, while leptin and resistin did not differ between those two groups [8]. In contrast to those results, the present study showed that leptin and resistin levels differed significantly when we stratified PCOS women based on abdominal adiposity indices. PCOS women with abdominal obesity were characterized by lower adiponectin concentrations but also higher leptin and resistin levels. Our results are consistent with those of other authors, where leptin and resistin levels were increased in obese PCOS women [12,16,63]. However, it is still under investigation whether such abnormalities are the result of obesity, IR, or hormonal disorders or if they constitute independent symptoms of PCOS. The results of our study may suggest that leptin and resistin levels are strongly correlated with abdominal obesity, and their secretion is upregulated in increased abdominal adiposity among PCOS women, whereas hypoadiponectinemia

is associated with PCOS diagnosis independently of abdominal obesity. Therefore, more research is needed to determine a definite answer to this question in the future.

The importance of diet and physical activity in the management of obesity in PCOS is well documented, and lifestyle modifications are recommended as the first-line therapeutic element in weight management strategies in women with this endocrinopathy [23,24]. It is regarded that the Mediterranean diet (MD) and the Dietary Approaches to Stop Hypertension diet (DASH) are associated with a lower risk of abdominal obesity in men and women in the general population [64–68]. In particular, dietary fiber was found to be inversely correlated with abdominal adiposity, whereas simple carbohydrates, dietary trans, and saturated fats were characterized by a positive correlation [69]. The data regarding the relationship between individual products, as well as the MD and DASH diet and abdominal obesity in PCOS, are missing. However, Rodrigues et al. [25] reported that poor quality diet was related to overweight and obesity, also the abdominal one (measured by WC) in PCOS women. They also suggested that the quality, rather than the quantity, of consumed food was a more important factor affecting body composition. Our study supports those results. We observed that a dietary pattern (evaluated by the diet score), which was similar to the MD and DASH diet, rich in wholegrain cereal products with a low glycemic index, vegetables, fruits, legumes, nuts, natural yogurt, vegetable oils, and fatty sea fish, and poor in red meat, especially processed, and products that were a source of simple sugars, disaccharides, and trans fatty acids seemed to have a beneficial effect on abdominal obesity indices. Higher adherence to this dietary pattern (a higher diet score) was associated with lower VAT content, SAT content, and WHR value (no relationship with VAT/SAT). Moreover, a higher diet score was associated with greater odds of a normal VAT content and WHR value (SAT and VAT/SAT were not related). Regrettably, women with abdominal obesity were characterized by significantly lower compliance with this dietary pattern. A study by Ehsani et al. [70] revealed that a diet rich in fried vegetables, vegetable oils (except olive oil), salty snacks, legumes, eggs, fast foods, onion, and garlic, and poor in sweets, high/low-fat dairy products, cruciferous vegetables, simple sugars, and honey was positively related to VAI, another abdominal obesity indicator in PCOS women. Moreover, they noted that each one-degree increase in compliance with this diet was associated with two times greater odds of visceral tissue dysfunction (OR 2.77, 95% CI 1.15–6.66, $p < 0.05$). Interestingly, another study by Alissa et al. [71] showed that a very diverse diet (a high diet diversity index) in women with PCOS was associated with a higher risk of abdominal obesity (measured by WHR). The authors explained their observations by the fact that a large number of products in the diet could lead to the consumption of excessive amounts of energy during the day. In our research, the diet score included low glycemic index products, which seemed to have an inverse relationship with abdominal obesity. A study by Melekoglu et al. [72] partially confirmed this observation. In PCOS women, low glycemic load was inversely associated with the WHR value. Furthermore, low glycemic index was unrelated to abdominal adiposity index (such a relationship was observed in a group of healthy women). A study by Graff et al. [73] revealed that a high glycemic index was associated with higher WC in PCOS women. Conversely, a study by Goss et al. [74] revealed that a reduced-carbohydrate diet (41% of energy from carbohydrates) for eight weeks resulted in the reduction of SAT (−7.1%) and VAT compartments (−4.6%). Research by Pasquali et al. [75] demonstrated that a hypocaloric diet added to metformin treatment in PCOS women with abdominal obesity resulted in the reduction of WC and visceral depots (SAT and VAT/SAT ratio remained unchanged). Similar findings regarding the reduction of abdominal obesity were observed in a PCOS group in a study by Zhang et al. [76] (VAT) and Marzouk et al. [77] (WC). It is worth mentioning that the VAT compartment is believed to be more susceptible to reduction than SAT due to the greater metabolic and lipolytic activity. Our study supports the importance of a particular dietary pattern in the management of abdominal obesity in PCOS women. However, future studies should focus on the relationship between individual dietary factors, which can potentially modify the risk of abdominal adiposity in this group of women.

Data regarding the relationship between abdominal fat distribution and physical activity in PCOS women are scarce. Our study is one of the few that examines the relationship between physical activity and abdominal obesity in a group of women with PCOS. Several studies conducted in the general population indicated the beneficial influence of physical activity on the central accumulation of body fat [78,79]. A study by Ando et al. [79] demonstrated that a sedentary lifestyle was associated with VAT accumulation, whereas standing time was inversely related to VAT. In our research, we noted that higher vigorous physical activity levels were associated with lower VAT content, SAT content, VAT/SAT ratio, and WHR. Furthermore, higher vigorous physical activity was associated with greater odds of normal VAT and the VAT/SAT value (no relationship with SAT and WHR). Moreover, women with abdominal obesity were characterized by significantly lower vigorous physical activity than non-centrally obese women. However, MVPA was not related to abdominal obesity indices in PCOS women. Other authors supported our findings, but they evaluated abdominal obesity with WC measurements [80–82]. An interventional study by Hutchison et al. [39] demonstrated that 12 weeks of intensified aerobic exercise resulted in the reduction of visceral fat (-12.0 cm^2, $p = 0.03$), while no significant change was observed in the control group. On the contrary, SAT was significantly decreased in control women, which was not observed in women with PCOS. Our data stay in line with the results of other studies and indicate that low physical activity is an important contributor to abdominal obesity among PCOS women. Bearing in mind our previous report, in which we demonstrated that physical activity was a crucial environmental factor involved in IR management in PCOS women, we may assume that the improvement of tissue insulin sensitivity in physically active women may be significantly modulated by abdominal obesity [8].

The strength of our study was the precise assessment of abdominal fat distribution using the Maltron BioScan 920-II multi-frequency bioelectrical impedance analyzer rather than only anthropometric surrogate measures of body fat. Moreover, another strength was the use of an accelerometer for the precise measurement of physical activity. However, the study findings should be interpreted in light of some limitations, with the small sample size being the first one. Secondly, the use of an original food frequency questionnaire based on frequency and portion sizes declared by the participants might lead to the underestimation or overestimation of dietary intake. The third limitation might be linked to the use of the surrogate measures of IR measurement instead of a hyperinsulinemic euglycemic clamp—the gold standard technique. Finally, our population was only Caucasian, which could significantly reduce the representativeness of the study.

5. Conclusions

In conclusion, our study indicates that PCOS women with abdominal obesity may have increased odds of IR (evaluated by HOMA-IR, HOMA-AD, and the L/A ratio) compared to non-centrally obese PCOS women. Moreover, an increased VAT/SAT ratio and VAT seem to be better predictors of IR among PCOS women than SAT or WHR. SAT is also an important abdominal compartment associated with the risk of IR. However, much more weakly linked to impaired insulin sensitivity. Taken together, the assessment of abdominal adiposity should be performed to better predict IR in PCOS, and all abdominal indices should be considered in analyzing the relationship between abdominal fat distribution and the risk of metabolic complications. Additionally, diet and physical activity are linked to reduced IR risk, probably, among others, by modulating the abdominal obesity status in PCOS women. The modification of diet and an increase in physical activity seem to be promising methods in the treatment of insulin resistance in PCOS, especially in abdominally obese PCOS patients. However, studies in a larger group of PCOS patients are particularly needed to establish the role of abdominal fat compartments in the management of IR in PCOS and its relationship with diet and physical activity.

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antioxidants

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Article

Antioxidant Defense Expressed as Glutathione Status and Keap1-Nrf2 System Action in Relation to Anthropometric Parameters and Body Composition in Young Women with Polycystic Ovary Syndrome

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Abstract: Metabolic disorders present in women with polycystic ovary syndrome (PCOS) and the associated risk of obesity may result in increased oxidative stress and reproductive failure. Therefore, we evaluated the concentrations of reduced glutathione (GSH), oxidized glutathione (GSSG), glutathione peroxidase (GPx), and reductase (GR), as well as nuclear factor erythroid 2-related factor 2 (Nrf2) and Kelch-like ECH-associating protein1 (Keap1) in the serum of 56 women with PCOS divided according to the visceral to subcutaneous fat surface ratio (VAT/SAT) and waist-to-hip ratio (WHR) values. Antioxidant parameter levels were measured by competitive inhibition enzyme immunoassay technique. As the VAT/SAT ratio and WHR increased, we observed significantly higher concentrations of GSSG and Keap1 protein and a lower value of the GSSG/GSH ratio (R-index), which is considered an index of cellular redox ($p < 0.05$). Negative correlations were found between the R-index and body weight, BMI, WHR, subcutaneous and visceral fat surface and the VAT/SAT ratio, and total body fat; positive links were found with fat free mass and total body water. Opposite associations were noted between GSSG level and the aforementioned body composition parameters. Oxidative stress characterized by a depleted reduced-to-oxidized glutathione index is associated with anthropometric and body composition parameters in women with PCOS. In particular, abdominal obesity expressed by the VAT/SAT ratio and/or WHR seems to have a negative impact on glutathione status, which may lead to a disruption of many biological cell processes. The observed negative association of Keap1 with R-index suggests that the elevated oxidative changes dependent on the VAT/SAT ratio may lead to Nrf2 activation to promote antioxidant enzyme expression. Although the GSH/GSSG index as well as the VAT/SAT ratio appear to be good indicators of oxidative status, studies on a larger group of patients should continue to confirm these links among women with PCOS.

Keywords: polycystic ovary syndrome; glutathione; glutathione peroxidase; glutathione reductase; obesity; oxidative stress; nuclear factor erythroid 2-related factor 2

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1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies and its prevalence—depending on the adopted diagnostic criteria and the population studied—ranges from 4 to 16% of reproductive-age women [1–3]. Characteristic features of the syndrome include menstrual disorders, hyperandrogenism, and often obesity and

infertility [4–6]. In addition to primary and secondary infertility, pregnancy complications are more common in this patient group, including gestational diabetes, hypertension, preeclampsia, and a higher risk of miscarriage or low-birth-weight offspring [7–9].

It is estimated that up to 60–70% of patients with PCOS are overweight or obese, with particularly increased central distribution of adipose tissue. Central accumulation of adipose tissue is characteristic of both lean and obese women with this disease entity [1]. Visceral adipose tissue is a highly active endocrine organ secreting hormonally active proteins—adipokines, pro-inflammatory cytokines and growth factors involved in the regulation of energy homeostasis, and carbohydrate and lipid metabolism [10,11]. The adipose tissue of women with PCOS shows many abnormalities in the secretion of these compounds, which affect the clinical signs of the disease and exacerbate existing endocrine and metabolic disorders, often leading to reproductive failure [2,3,12].

Insulin resistance in PCOS resulting in hyperglycemia and higher levels of free fatty acids can lead to increased reactive oxygen species (ROS) production, especially when accompanied by overweight and obesity. Because PCOS is also associated with reduced antioxidant levels, it is considered a state of increased risk for oxidative stress. Research conducted in this area suggests that there may be a strong relationship between impaired adipose tissue metabolism, insulin resistance, hyperandrogenism, inflammation, and oxidative stress in the pathogenesis of PCOS [1–3,13–18] (Figure 1).

A commonly known measure of oxidative stress is the ratio of reduced glutathione (GSH) to oxidized glutathione (GSSG). The GSH/GSSG system is the main "redox buffer" that protects cellular structures from the damaging effects of free oxygen radicals, and the reactivity of this compound is conditioned by the presence of a thiol group. Glutathione in reduced form in the presence of glutathione peroxidase (GPx) reacts with hydrogen peroxide (H_2O_2) and lipid peroxide, oxidizing to disulfide. Regeneration of the active thiol form occurs with the participation of NADPH-dependent glutathione reductase (GR), belonging to flavoproteins. In addition to the regeneration of GSH from GSSG, the second process affecting the increase in glutathione concentration is its neosynthesis. The de novo synthesis of GSH in the cell is limited by the availability of its constituent amino acids, and in particular by the availability of the sulfur amino acid precursor, cysteine [19,20]. Modification of the oxidation state of protein cysteine residues is significantly responsible for the role of GSH in redox-dependent cell signaling. The process of protein glutathionylation is a mechanism that protects sensitive protein thiols from irreversible oxidation, and thus from irreversible loss of their biological activity [18]. One of the transcription factors involved in cell signaling and containing selected cysteine residues is nuclear factor erythroid 2-related factor 2 (Nrf2). Under physiological conditions, Nrf2 exists in the cytoplasm in the form of a complex with Keap1 protein (Kelch-like ECH-associating protein 1). Reactive oxygen and nitrogen species (RNS) formed in excess can oxidize the specific cysteine residues of Keap1, leading to a conformational change of this protein, the release of Nrf2, and its translocation to the cell nucleus. Through the activation of the antioxidant response element (ARE) in the nucleus, it participates in the transcriptional regulation of many antioxidant genes—including, i.e., glutathione S-transferase, NAPH-oxidoreductase, and glutamate-cysteine ligase, the rate-limiting enzyme in glutathione synthesis [19,21,22]. Given the important role of GSH in cellular defense mechanisms, the induction of regulatory enzymes involved in its synthesis plays a key role in protecting cells from excessive oxygen free radical activity [20].

According to the meta-analysis conducted by Murri et al. [1], patients with PCOS had approximately 50% lower glutathione levels compared with healthy women and no changes in glutathione peroxidase activity. There are no systematic data on the relationships between glutathione status and adipose tissue and the risk of metabolic disorders in women with PCOS. There are also limited reports on the Keap1-Nrf2 system action in this disease, and these mainly concern animal models [23,24].

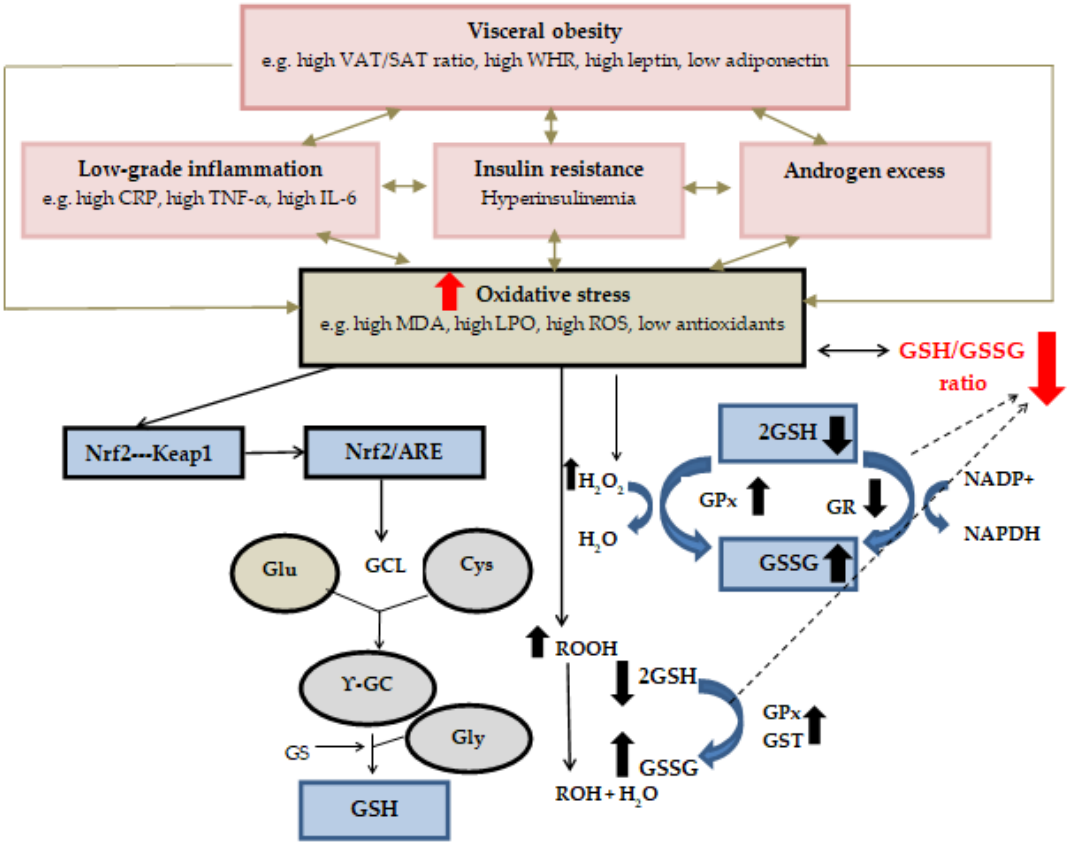

Figure 1. Possible links between oxidative stress and glutathione status and the Keap1-Nrf2 system action in women with polycystic ovary syndrome. Oxidative stress leads to the upregulation of the Keap1-Nrf2 system, resulting in the expression of, e.g., glutamate-cysteine ligase—the rate-limiting enzyme in glutathione synthesis. Oxidative stress dysregulated the glutathione regeneration enzymatic process, resulting in decreased GSH/GSSG ratio levels. Nrf2 = nuclear factor erythroid-derived 2-like protein 2; Keap1 = Kelch-like ECH-associated protein 1; ARE = antioxidant response element; GCL = glutamate-cysteine ligase; GS = glutathione synthetase; Cys = cysteine; Glu = glutamate; Gly = glycine; γGC = γglutamyl-cysteine; GSH = reduced glutathione; GSSG = oxidized glutathione; GPx = glutathione peroxidase; GR = glutathione reductase; GST = glutathione transferase; GSH/GSSG ratio = index cellular redox; CRP = C-reactive protein; TNF-α = tumor necrosis factor α; IL-6 = interleukin 6; VAT = visceral fat surface; SAT = subcutaneous fat surface; WHR = waist-to-hip ratio; MDA = malondialdehyde; LPO = lipid peroxidation; ROS = reactive oxygen species.

In this study, we aimed to evaluate glutathione status and the function of the Keap1-Nrf2 system in relation to anthropometric parameters and body composition in young women with polycystic ovary syndrome. Therefore, the serum concentrations of GSH, GSSG, GPx and GR, as well as the values of Nrf2 and Keap1 proteins in patients with PCOS, were determined. The interrelationships between the tested antioxidants and the link between antioxidants and body composition parameters were also investigated.

2. Materials and Methods

2.1. Participants

The study was conducted in accordance with the ethical standards established by the Declaration of Helsinki after obtaining approval from the Ethical Committee of the Medical University of Warsaw (consent no. KB/170/2019). All participants were acquainted with the objectives and procedures of the study. Patients gave written consent for the analysis of biological samples, anthropometric and body composition measurements, and the use of clinical information collected from their medical records.

The study included 56 Caucasian women with polycystic ovary syndrome, recruited in the Department of Gynecological Endocrinology of the Medical University in Warsaw in the years 2021–2022. The inclusion criteria for the study group were PCOS diagnosed according to the Rotterdam diagnostic criteria (presence of at least two of the following three criteria: oligo-/amenorrhea, clinical and/or biochemical hyperandrogenism, image of polycystic ovary according to ultrasound exam) [25]. Exclusion criteria included: diabetes, chronic hypertension, cardiovascular diseases, thyroid dysfunction, endometriosis, congenital adrenal hyperplasia, Cushing's syndrome, androgen releasing tumor, use of lipid-lowering or insulin-sensitizing drugs, exacerbated state of chronic and acute somatic disease and/or contagious diseases, mental disorders, genetic defects, pregnancy, and lactation. Due to the method of body composition measurement (BIA—bioelectrical impedance analysis), the additional exclusion criteria were: diagnosed epilepsy, implanted pacemaker or defibrillator, and metal endoprostheses. For further analysis, the patients were divided into two groups according to their visceral to subcutaneous fat surface ratio and the waist-to-hip ratio values.

2.2. Anthropometric Measurements

Body weight and height were measured according to the established standards [26]. Body mass index (BMI) was calculated as the ratio between body weight and height squared (kg/m^2). Interpretation of these results followed the international classification provided by the World Health Organization (WHO): <18.5kg/m^2 = underweight; 18.5–24.9 kg/m^2 = normal weight; 25.0–29.9 kg/m^2 = overweight; ≥30.0 kg/m^2 = obese [27].

In addition, waist and hip circumference were measured. According to the WHO recommendations [28], waist circumference was measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest, using a stretch-resistant tape. Hip circumference was measured around the widest part of the buttocks. The cut-off point for high values of the waist circumference was >80 cm. Additionally, to measure abdominal obesity, the waist-to-hip ratio (WHR) was calculated by dividing the waist circumference by the hip circumference. Abdominal obesity was defined as WHR $\geq$ 0.85 [28].

2.3. Body Composition Analysis with Bioelectrical Impedance

Whole body composition of the women was measured using a Maltron BioScan 920-II multi-frequency bioelectrical impedance analyzer according to the manufacturer's instructions (Maltron International Ltd., Rayleigh, UK). Body composition analysis was performed in the supine position with the limbs separated by 30° from the body. Before starting the examination, the participants were recommended to rest for about three minutes. The electrodes were placed on the top middle part of the right hand and on the top middle part of the right foot. Before placing the electrodes, the placement sites were cleaned using isopropyl alcohol to limit possible errors and ensure adherence.

Quantitative analysis of abdominal adipose tissue (subcutaneous and visceral) was performed in a standing position with the upper limbs separated from the body. The configuration of electrode placement was strictly defined by the device's manufacturer [29]. Based on the anthropometric measurements and body composition tests, the following parameters were determined: subcutaneous fat surface (SAT in cm^2), visceral fat surface (VAT in cm^2), and the ratio of visceral to subcutaneous fat (VAT/SAT ratio). The cut-off for VAT was >120 cm^2 and that for SAT was >225 cm^2. At the same time, a VAT/SAT ratio above 0.90 was adopted as a risk factor for metabolic diseases [29]. The obtained results were processed using the Maltron BioScan 920 v. 1.1.135 software. According to the guidelines of the European Society of Parenteral and Enteral Nutrition (ESPEN) for body composition tests, the subjects had to meet the following conditions: entering the test on an empty stomach, emptying the bladder 30 min before the test, lack of physical activity for 12 h before the test, no alcohol and no fluids containing caffeine for 24 h before the test [30].

2.4. Biochemical Analysis

For biochemical analysis, 5 mL of venous blood was collected in the morning from all participants after 12 h of overnight fasting during the follicular phase between days two and six of their menstrual cycle.

Blood samples were prepared in a manner appropriate for the planned biochemical analyses. The serum samples obtained after centrifugation were divided into small portions, some of which were used for testing on the day of collection, and the remaining part was frozen at −80 °C until the rest of the biochemical analyses were performed (stored no longer than three months).

Serum fasting glucose concentrations were determined by enzymatic reference method with hexokinase using commercial kits on Integra 400 plus a biochemical analyzer (Roche Diagnostics, Basel, Switzerland).

Serum insulin, testosterone (T), luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), estradiol (E2), androstenedione (A), 17-hydroxyprogesterone (17-OHP), dehydroepiandrosterone sulfate (DHEA-S), and sex hormone binding globulin (SHBG) levels were measured using one- or two-step chemiluminescent microparticle immunoassay (CMIA; Alinity I analyzer, Abbott Diagnostics GmbH, Wiesbaden, Germany).

To determine insulin resistance, the homeostasis model assessment for insulin resistance (HOMA-IR) was calculated using the following formula: HOMA-IR = [fasting insulin (μU/mL) × fasting glucose (mmol/L)]/22.5.

Serum concentrations of antioxidant defense parameters were measured using immunoenzymatic methods following the manufacturer's instructions.

GSH and GSSG levels were determined using kits based on a sandwich enzyme-linked immunosorbent assay (ELISA) with two specific and high affinity monoclonal antibodies (Human GSH ELISA Kit Cat. No.: 201-12-5407; Human GSSG ELISA Kit Cat. No.: 201-12-5444, SunRed Bio-technology Company, Shanghai, China), which we have previously described in detail [31]. To assess the cellular redox index, the GSH/GSSG ratio was calculated.

Nuclear factor (erythroid-derived 2)-like 2, also known as NFE2L2 or Nrf2 was measured using human an NFE2L2 ELISA kit (cat. No. EH3417, Fine Biotech Co., Ltd., Wuhan, China) based on the double-antibody sandwich ELISA technique. The pre-coated antibody was an anti-human NFE2L2 monoclonal antibody, while the detection antibody was a biotinylated polyclonal antibody. Samples and biotinylated antibodies were added into ELISA plate wells. Then, avidin–peroxidase conjugates (HRP-streptavidin) were added to the wells. TMB substrate was used for coloration after the enzyme conjugate had already been thoroughly washed out of the wells. TMB (3,3′,5,5′-tetramethylbenzidine) reacts to form a blue product from the peroxidase activity, and finally turns to yellow after adding the stop solution. The color intensity and quantity of target analyte in the sample were positively correlated. The levels of GR, GPx, and Keap1 proteins were determined in an analogous manner using a human glutathione reductase ELISA kit (cat. No. MBS2703164, MyBioSource Inc., San Diego, CA, USA), a human glutathione peroxidase ELISA kit (cat. No. MBS167041, MyBioSource Inc., San Diego, CA, USA), and a human KEAP1 (Kelch-like ECH-associated protein 1) ELISA kit (cat. No. EH4240, Fine Biotech Co., Ltd., Wuhan, China), respectively. The concentrations of NFE2L2, Keap1, GR, and GPx in the samples were calculated by comparing the O.D. of the samples to the standard curve. The intra- and inter-assay CVs were less than 8.0% and 10% for NFE2L2, Keap1, and GPx, whereas they were 10% and 12% for GR, respectively. Assay sensitivity was less than 0.094 ng/mL for NFE2L2, 14.063 pg/mL for Keap1, 0.260 ng/mL for GPx, and 35.000 pg/mL for GR, respectively.

2.5. Statistical Analysis

Statistical analysis included 40 parameters in four groups: baseline clinical features (13), anthropometric data and body composition (20), and antioxidant defense parameters (7). The normality of each parameter was checked using the Kolmogorov–Smirnov

test. The study group was divided into two according to the visceral to subcutaneous fat surface ratio, with a cut-off point of 0.90, and independently into two groups according to the waist-to-hip ratio values, with a cut-off point of 0.85. For each of the identified subgroups, the mean values of the respective parameters were presented with the standard deviation (SD) if the distribution did not deviate from normal, or the median along with the interquartile range (1-3IQR) if the hypothesis of normality of distribution was rejected. In the first case, the groups were compared using the parametric Student's *t*-test and in the second case using the nonparametric Mann–Whitney test. The level of correlation between GSH, GSSG, as well as the R-index and anthropometric parameters was also calculated using Spearman's rho. The relationship between Keap1 and the three aforementioned antioxidant defense parameters are presented graphically as a scatter plot.

All reported p-values were two-tailed, and values = <0.05 were considered significant. IBM SPSS v.28 statistical software was used (IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY, USA: IBM Corp).

3. Results

Table 1 shows a comparison of the clinical characteristics of the 56 participants with PCOS stratified twice: once based on the VAT/SAT ratio ($\leq$0.90; >0.90) values and a second time based on the WHR values (<0.85; $\geq$0.85). Patients in each group were of similar age (median 25 years). We observed significantly higher levels of fasting insulin and HOMA-IR values in the serum of women with increased VAT/SAT index (VAT/SAT > 0.90) and WHR ratio (WHR $\geq$ 0.85) when compared with women with normal values of these parameters ($p < 0.01$). Fasting glucose levels were also higher in these groups, but the difference was not statistically significant.

Table 1. Baseline clinical features in women with PCOS divided according to the visceral to subcutaneous fat surface ratio and the waist-to-hip ratio.

Parameters	VAT/SAT $\leq$ 0.90 *n* = 29	VAT/SAT > 0.90 *n* = 27	*p*-Value	WHR < 0.85 *n* = 35	WHR $\geq$ 0.85 *n* = 21	*p*-Value
[a] Age (years)	25.66 ± 4.55	26.30 ± 3.61	0.323	25.60 ± 3.85	26.00 ± 4.51	0.541
[a] Fasting [b] Glucose (mmol/L)	4.98 ± 0.31	5.21 ± 0.43	0.062	5.03 ± 0.33	5.19 ± 0.47	0.323
[b] Fasting Insulin (µmU/mL)	5.00 3.87–6.25	9.60 7.30–13.80	0.000	5.80 4.20–7.40	8.10 5.44–13.05	0.006
[b] HOMA-IR Index	1.13 0.83–1.36	2.34 1.62–3.16	0.000	1.29 0.93–1.68	1.87 1.25–2.92	0.008
[b] LH (mIU/mL)	5.81 4.37–68.00	6.58 3.30–9.26	0.922	5.73 3.89–8.20	8.01 3.25–10.12	0.243
[b] FSH (mIU/mL)	4.88 4.50–6.47	5.27 4.75–6.28	0.491	4.88 4.48–6.61	5.27 4.73–6.24	0.417
[a] T (ng/mL)	0.56 ± 0.13	0.53 ± 0.19	0.394	0.52 ± 0.16	0.59 ± 0.15	0.115
[b] E2 (pg/mL)	29.00 23.50–44.50	34.00 25.00–46.97	0.486	36.99 24.00–42.00	34.62 21.90–49.00	0.576
[b] DHEAS (µmol/L)	9.11 6.76–12.26	8.51 6.20–15.08	0.812	8.96 6.72–11.81	8.93 6.25–15.56	0.537
[b] A (ng/mL)	3.39 2.98–3.88	2.59 2.19–3.63	0.054	3.24 2.27–3.68	3.01 2.52–3.91	0.793
[b] 17-OHP (ng/mL)	1.53 1.24–2.07	1.20 0.83–1.49	0.006	1.47 1.01–1.77	1.23 0.84–1.55	0.170
[b] TSH (µIU/mL)	1.65 1.22–2.26	1.70 1.07–2.60	0.980	1.70 1.24–2.23	1.63 0.98–2.74	0.819
[b] SHBG (nmol/L)	62.00 46.50–71.00	28.00 20.00–39.00	0.000	52.00 39.00–67.00	30.00 20.30–46.90	0.002

[a] Data were analyzed using Student's *t*-test and presented as mean and standard deviation (SD). [b] Data were analyzed using the Mann–Whitney U test and presented as medians and interquartile ranges (1-3IQR). VAT/SAT = ratio of visceral to subcutaneous fat; WHR = waist-to-hip ratio; HOMA-IR = homeostatic model assessment for insulin resistance; LH = luteinizing hormone; FSH = follicle-stimulating hormone; T = testosterone; E2 = estradiol; DHEA-S = dehydroepiandrosterone sulfate; A = androstenedione; 17-OHP = 17-hydroxyprogesterone; TSH = thyrotropin; SHBG = sex hormone binding globulin.

We found that patients with higher VAT/SAT and WHR ratios had significantly lower levels of SHBG than patients with VAT/SAT $\leq$ 0.90 ($p < 0.001$) and WHR < 0.85 ($p < 0.01$). Additionally, lower VAT/SAT values were associated with lower levels of 17-OHP ($p < 0.01$). We did not observe significant differences in LH, FSH, T, E2, A, TSH, and DHEAS concentrations between the studied groups.

As expected, anthropometric and body composition indices differed significantly in both groups divided by VAT/SAT and WHR values. The PCOS group with increased VAT/SAT ratios had statistically higher subcutaneous and visceral adipose tissue content, BMI, total body fat, and muscle mass compared with the PCOS group with normal VAT/SAT ratio ($p < 0.001$). Additionally, this group of women was characterized by a significantly higher WHR compared with women with VAT/SAT $\leq$ 0.90 ($p < 0.001$). Similar relationships were observed in the group of women with WHR $\geq$ 0.85. The subjects' detailed anthropometric data and body composition measures are shown in Table 2.

Table 2. Characteristics of anthropometric data and body composition in women with PCOS divided according to the visceral to subcutaneous fat surface ratio and the waist-to-hip ratio values.

Parameters	VAT/SAT $\leq$ 0.90 *n* = 29	VAT/SAT > 0.90 *n* = 27	*p*-Value	WHR < 0.85 *n* = 35	WHR $\geq$ 0.85 *n* = 21	*p*-Value
[b] Body Weight (kg)	58.90 54.50–68.00	93.00 81.00–111.00	0.000	59.00 56.00–70.00	91.00 77.5–105.5	0.000
[a] Height (cm)	166.45 ± 4.35	166.96 ± 5.92	0.987	166.91 ± 5.03	166.33 ± 5.38	0.546
[a] BMI kg/m^2	21.73 ± 2.83	33.18 ± 6.05	0.000	23.78 ± 5.91	33.06 ± 5.86	0.000
[b] WC (cm)	72.00 67.50–78.50	103.00 95.00–113.00	0.000	74.00 68.00–86.00	103.00 95.50–115.00	0.000
[b] HC (cm)	93.00 88.00–98.50	114 109.00–124.00	0.000	94.00 90.00–104.00	114.00 104.00–123.00	0.000
WHR	0.78 0.76–0.83	0.87 0.84–0.91	0.000	0.80 0.76–0.82	0.88 0.87–0.95	0.000
[b] VAT (cm^2)	51.00 31.00–63.00	291.00 184.00–350.00	0.000	51.00 33.00–115.00	301.00 100.00–350.00	0.000
[b] SAT (cm^2)	78.00 74.75–198.75	200.00 59.50–110.00	0.000	100.00 68.00–127.00	219.00 150.50–284.50	0.000
[b] VAT/SAT	0.53 0.47–0.62	1.50 1.19–1.89	0.000	0.57 0.48–0.93	1.59 1.26–1.96	0.000
[b] FM (kg)	15.03 12.19–21.11	41.97 32.34–49.38	0.000	15.86 12.33–23.60	40.21 28.84–50.54	0.000
[b] FM (%)	26.28 26.09–43.84	44.09 39.29–46.95	0.000	27.10 22.12–33.71	42.81 37.77–48.00	0.000
[a] FFM (kg)	44.25 ± 3.11	52.16 ± 5.97	0.000	45.91 ± 5.49	51.65 ± 5.55	0.000
[a] FFM (%)	74.01 ± 5.98	57.38 ± 6.83	0.000	71.16 ± 8.97	57.38 ± 6.53	0.000
[a] MM (kg)	19.19 ± 1.56	23.08 ± 2.69	0.000	19.98 ± 2.63	22.74 ± 2.66	0.001
[a] BCM (kg)	22.21 ± 2.11	28.49 ± 3.88	0.000	23.56 ± 3.88	28.04 ± 3.82	0.000
[a] ECM (kg)	21.94 ± 1.61	23.68 ± 2.22	0.002	22.28 ± 1.91	23.62 ± 2.19	0.013
[a] TBW (%)	50.38 ± 3.26	42.37 ± 3.41	0.000	48.93 ± 4.45	42.45 ± 3.62	0.000
[a] ECW (%)	48.73 ± 4.61	45.45 ± 0.88	0.000	47.69 ± 3.75	46.25 ± 3.63	0.000
[a] ICW (%)	51.26 ± 4.61	54.58 ± 0.95	0.000	52.33 ± 3.78	53.74 ± 3.63	0.000
[a] ECW/ICW	0.97 ± 0.26	0.83 ± 0.03	0.000	0.93 ± 0.21	0.97 ± 0.17	0.000

[a] Data were analyzed using Student's *t*-test and presented as mean and standard deviation (SD). [b] Data were analyzed using the Mann–Whitney U test and presented as medians and interquartile ranges (1-3IQR). VAT/SAT = ratio of visceral to subcutaneous fat; WHR = waist-to-hip ratio; BMI = body mass index; WC = waist circumference; HC = hip circumference; FM = fat mass; FFM = fat-free mass; MM = muscle mass; BCM = body cell mass; ECM = extracellular matrix; TBW = total body water; ECW = extracellular water; ICW = intercellular water.

Serum antioxidant parameters in women with PCOS from each subgroup are summarized in Tables 3 and 4. We found that GSSG and Keap1 protein concentrations were statistically higher, while the R-index value was significantly lower in the serum of women with increased VAT/SAT compared with the group with normal values of this ratio ($p < 0.001$; Table 3).

Table 3. Antioxidant defense parameters in women with PCOS divided according to the visceral to subcutaneous fat surface ratio values.

Parameters	VAT/SAT ≤ 0.90 *n* = 29	VAT/SAT > 0.90 *n* = 27	*p*-Value
[a] GSH (µmol/L)	12.25 ± 3.64	10.74 ± 3.09	0.140
[a] GSSG (µmol/L)	3.68 ± 1.31	6.04 ± 1.75	0.000
[b] R (GSH/GSSG)	3.29 2.05–5.13	1.68 1.48–2.38	0.000
[a] GPx (ng/mL)	17.66 ± 4.99	18.38 ± 4.42	0.512
[b] GR (pg/mL)	261.00 199.85–331.67	245.56 185.80–301.23	0.181
[a] Nrf2 (ng/mL)	1.42 ± 0.24	1.56 ± 0.33	0.147
[a] Keap1 (pg/mL)	158.78 ± 32.26	176.94 ± 28.13	0.042

[a] Data were analyzed using Student's *t*-test and presented as mean and standard deviation (SD). [b] Data were analyzed using the Mann–Whitney U test and presented as medians and interquartile ranges (1-3IQR). VAT/SAT = ratio of visceral to subcutaneous fat; GSH = reduced glutathione; GSSG = oxidized glutathione; GPx = glutathione peroxidase; GR = glutathione reductase; R (GSH/GSSG ratio) = index of cellular redox; Nrf2 = nuclear factor erythroid-derived 2-like protein 2; Keap1 = Kelch-like ECH-associated protein 1.

Table 4. Antioxidant defense parameters in women with PCOS divided according to the waist-to-hip ratio values.

Parameters	WHR < 0.85 *n* = 35	WHR ≥ 0.85 *n* = 21	*p*-Value
[a] GSH (µmol/L)	12.30 ± 3.77	10.23 ± 2.37	0.053
[a] GSSG (µmol/L)	4.02 2.99–5.26	6.42 3.61–7.42	0.016
[b] R (GSH/GSSG)	2.95 1.86–4.40	1.81 1.46–2.41	0.010
[a] GPx (ng/mL)	18.89 13.44–22.18	15.83 14.09–20.74	0.537
[b] GR (pg/mL)	268.61 ± 87.68	248.82 ± 69.74	0.412
[a] Nrf2 (ng/mL)	1.44 ± 0.21	1.52 ± 0.33	0.393
[a] Keap1 (pg/mL)	168.38 ± 32.78	166.12 ± 29.76	0.800

[a] Data were analyzed using Student's *t*-test and presented as mean and standard deviation (SD). [b] Data were analyzed using the Mann–Whitney U test and presented as medians and interquartile ranges (1-3IQR). BMI = body mass index; WHR = waist-to-hip ratio; GSH = reduced glutathione; GSSG = oxidized glutathione; GPx = glutathione peroxidase; GR = glutathione reductase; R (GSH/GSSG ratio) = index of cellular redox; Nrf2 = nuclear factor erythroid-derived 2-like protein 2; Keap1 = Kelch-like ECH-associated protein 1.

Similar differences were shown for GSSG and R-index between the WHR ≥ 0.85 and WHR < 0.85 groups ($p < 0.05$ and $p < 0.01$, respectively; Table 4). Other antioxidant defense parameters were not significantly different between all the studied groups. As the VAT/SAT and WHR ratio increased, we observed lower concentrations of reduced glutathione; however, these differences were not statistically significant (although in the case of the WHR ratio, they were at the limit of significance $p = 0.053$; Tables 3 and 4).

The correlations of GSH, GSSG, and the R-index with anthropometric parameters and body composition in women with PCOS are shown in detail in Table 5 (whole group). Serum GSH concentrations were negatively correlated with hip circumference, WHR, and VAT/SAT ratio values. Serum GSSG levels were positively associated with weight, BMI, WHR, subcutaneous and visceral adipose tissue content, the VAT/SAT ratio, total body fat, and cell mass, and inversely correlated with fat-free mass and total body water. In contrast, we found negative correlations of R-index values with weight, BMI, WHR, subcutaneous and visceral adipose tissue content, the VAT/SAT ratio, and total body fat mass, whereas we found a positive correlation of R-index values with fat-free mass and total body water. We also observed positive relations between Keap1 and VAT/SAT ratio values (r = 0.263; $p = 0.05$).

Table 5. Spearman's rank correlation coefficients between GSH, GSSG, as well as R-index and anthropometric parameters in women with PCOS.

Parameters	GSH		GSSG		R (GSH/GSSG)	
	rho	*p*− Value	rho	*p*− Value	rho	*p*− Value
Weight (kg)	−0.135	0.357	0.323	0.007	−0.305	0.002
Height (cm)	0.077	0.573	−0.089	0.516	0.066	0.629
BMI kg/m^2	−0.179	0.188	0.371	0.005	−0.331	0.013
WC (cm)	−0.220	0.103	0.350	0.008	−0.332	0.013
HC (cm)	−0.109	0.012	0.335	0.012	−0.274	0.041
WHR	−0.333	0.012	0.298	0.026	−0.357	0.007
VAT (cm^2)	−0.239	0.076	0.416	0.001	−0.416	0.001
SAT (cm^2)	−0.207	0.127	0.348	0.009	−0.329	0.013
VAT/SAT	−0.277	0.039	0.471	0.000	−0.504	0.000
FM (kg)	−0.164	0.227	0.396	0.003	−0.351	0.008
FM (%)	−0.172	0.205	0.448	0.001	−0.399	0.002
FFM (kg)	−0.096	0.481	0.238	0.077	0.192	0.156
FFM (%)	0.170	0.209	−0.443	0.001	0.393	0.003
MM (kg)	−0.085	0.532	0.255	0.057	−0.213	0.116
BCM (kg)	−0.092	0.499	0.308	0.021	−0.251	0.062
ECM (kg)	−0.017	0.903	0.081	0.555	−0.050	0.714
TBW (%)	0.176	0.196	−0.451	0.000	0.408	0.022
ECW (%)	0.052	0.704	−0.383	0.004	0.307	0.021
ICW (%)	−0.051	0.711	0.383	0.004	−0.306	0.022
ECW/ICW	0.051	0.711	−0.380	0.004	0.304	0.023

GSH = reduced glutathione; GSSG = oxidized glutathione; R (GSH/GSSG ratio) = index of cellular redox; BMI = body mass index; WC = waist circumference; HC = hip circumference; WHR = waist-to-hip ratio; VAT = visceral fat surface; SAT = subcutaneous fat surface; VAT/SAT = ratio of visceral to subcutaneous fat; FM = fat mass; FFM = fat-free mass; MM = muscle mass; BCM = body cell mass; ECM = extracellular matrix; TBW = total body water; ECW = extracellular water; ICW = intercellular water.

Increased concentrations of insulin and HOMA-IR levels observed in women with PCOS were positively correlated with oxidized glutathione concentrations (r = 0.418, p = 0.001; r = 0.405, p = 0.002, respectively) and negatively correlated with R-index values (r = −0.304, p = 0.003; r = −0.380, p = 0.004, respectively). In addition, associations between Nrf2 concentrations and insulin (r = 0.256, p = 0.057) and HOMA-IR levels (r = 0.260, p = 0.053) were on the border of significance.

Figure 2A–C shows the relationships between glutathione status parameters and Keap1 protein in women with PCOS. There was a statistically significant positive correlation between levels of GSSG and Keap1 concentrations (A), no correlations between GSH and Keap1 levels (B), and a significant negative correlation between Keap1 levels and R-index values (C). Additionally, increased values of reduced glutathione to oxidized glutathione ratio were significantly associated with increased levels of glutathione reductase in the serum of patients with PCOS (r = 0.384, p = 0.009). Other relationships between the selected antioxidant defense parameters were not confirmed.

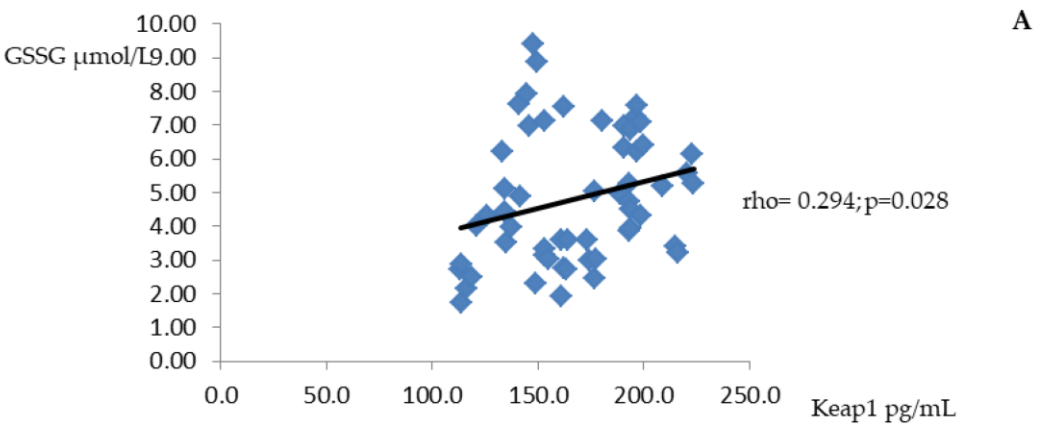

Figure 2. *Cont.*

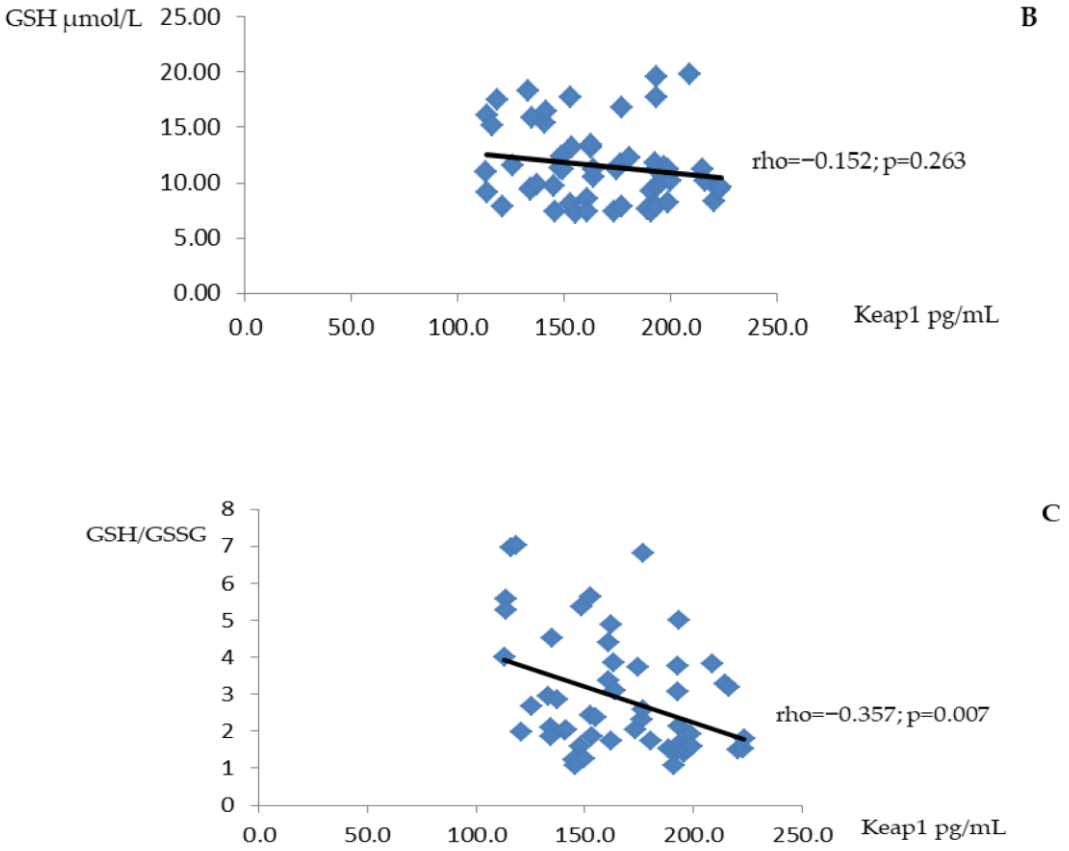

Figure 2. Scatter plot for the relationships between Keap1 and GSSG (**A**), GSH (**B**), as well as R-index (**C**) in women with PCOS.

4. Discussion

Compared with healthy counterparts, body fat distribution is different in women with PCOS due to the predominant accumulation of visceral fat and abdominal obesity [3,12,32]. Accompanying PCOS, abnormal adipose tissue metabolism and associated chronic low-grade inflammation are a significant source of reactive oxygen species [14,33]. Excess free radicals with reduced antioxidant activity—including glutathione, an important small-molecule antioxidant observed in patients with PCOS—may be responsible for exacerbating oxidative stress [18].

Studies determining glutathione status in patients with PCOS mainly concern its reduced form or the activity of glutathione peroxidase [1,17]. In the PCOS group, GSH concentrations were lower by half compared with healthy women [16,34,35]. Data on GPx activity are inconclusive and show both lower, higher, and unchanged activity of this enzyme in patients with polycystic ovary syndrome [5,15,17]. The most frequently analyzed relations were glutathione and GPx, with indicators of insulin resistance, hyperandrogenism, and infertility [3,4,18,36]. Associations between parameters of glutathione status and body composition have not been systematically studied and require attention. This is particularly important given that visceral obesity occurs in both overweight and normal-weight women [32].

In the present study, we showed differences in the levels of the tested oxidative stress markers both when dividing the groups due to WHR, determining abdominal obesity, and VAT/SAT, determining an additional increased risk of metabolic syndrome. We demonstrated that reduced glutathione was slightly higher in the group of PCOS women with low WHR and VAT/SAT ratios. This finding is consistent with the results obtained by Uckan et al. [35], who found significant differences in the level of this association between nonobese and obese patients with PCOS. Similarly to others, we revealed a close association of glutathione with WHR and the VAT/SAT ratio, while we did not confirm an association

of GSH with insulin parameters [16,18,35]. As a result of GPx catalyzing the neutralization of toxic H_2O_2, reduced glutathione is oxidized to disulfide (oxidized glutathione), which—with the participation of glutathione reductase and NADPH coenzyme—is reduced back to thiol, which is an important redox cycle in the cell [36]. The effect of obesity on GPx activity has not been clearly confirmed [3,35]. Data determining oxidized glutathione levels in patients with PCOS are also unknown. In our study, GSSG levels were significantly higher in patients with elevated WHR and VAT/SAT with unchanged GPx and slightly lower GR levels. Due to the high lipolytic activity of visceral tissue and the release of large amounts of fatty acids and pro-inflammatory cytokines, peroxidative damage and the accumulation of GSSG may be enhanced in patients with PCOS [37]. Oxidized glutathione is a potentially toxic metabolite for cells. Elevated oxidized glutathione concentrations lead to a disruption of the GSH/GSSG ratio, which is crucial for many biological cell processes, such as the regulation of gene transcription or enzyme and receptor activity [36]. In the present study, high GSSG concentrations were accompanied by low GSH/GSSG ratio levels, which may suggest a shift in the balance toward oxidative processes. The close positive associations of GSSG and negative correlations of the GSH/GSSG ratio with most anthropometric data (e.g., WHR, BMI, WC, and HC) and body composition parameters (e.g., VAT/SAT ratio and fat mass in kg and %) may suggest the severity of oxidative stress in PCOS patients with abdominal and visceral obesity. The low R-index value may indicate an impaired process of reducing excessive GSSG to the active form of GSH with the involvement of glutathione reductase.

In our study, GR levels were the lowest in patients with the highest VAT/SAT ratio, while GR correlated positively with GSSG concentration and negatively with the R-index value. This confirms the important role of this enzyme in the glutathione redox cycle.

As we noted in the introduction, in addition to the regeneration of GSH from GSSG via GR, the concentration of this compound in cells is dependent on de novo synthesis. The neosynthesis of GSH in the cells is limited by the availability of cysteine, whose oxidative modifications are largely responsible for glutathione's role in redox-dependent cell signaling. Containing cysteine residues, Nrf2 participates in the transcriptional regulation of many antioxidant genes, including enzymes that regulate the rate of glutathione synthesis. Activation of Nrf2 by pro-oxidant factors or specific Nrf2 activators (e.g., resveratrol, quercetin, and astaxanthin) is associated primarily with conformational changes in the Keap1 inhibitory protein [21,38–40]. In a rat model of PCOS, Li et al. [23] confirmed that granulosa cells (GCs) under oxidative stress show high levels of Nrf2 and heme oxygenase-1 (HO-1). Additionally, Wang et al. [24] documented that humanin, a mitochondrial-derived peptide, regulates oxidative stress in the ovaries of patients with polycystic ovary syndrome via the Keap1-Nrf2 pathway. Similarly, Gharaei et al. [21] showed that astaxanthin supplementation in women with PCOS undergoing assisted reproductive techniques positively affected antioxidant status in the blood and Keap1-Nrf2 pathway activation in GCs.

The links between oxidative stress, glutathione, and the Keap1-Nrf2 system have not yet been described. We observed slightly increased Nrf2 levels in patients with abnormal VAT/SAT and WHR ratios. In addition, in the group with VAT/SAT > 0.90, we found significantly higher Keap1 protein levels. Moreover, the negative association of Keap1 with the R-index may suggest that the elevated oxidative changes observed in this group may lead to Keap1 dissociations from Nrf2 and the activation of this factor to promote antioxidant enzyme expression. The unchanged GPx levels observed in all the groups with PCOS and only slightly reduced GR in the groups with increased risk of metabolic disorders may be the result of a compensatory antioxidant response associated with the activation of the Keap1-Nrf2 system. It is currently known that, in addition to Keap1, there are other factors that can regulate Nrf2 gene transcription. These include phosphorylation of Nrf2 by protein kinases or acetylation of Nrf2 [41,42]. For this reason, our research in this area should be considered preliminary and should be continued to confirm possible links between Nrf2 action and antioxidant response in women with PCOS.

Strengths and Limitations

A strength of the presented research was taking comprehensive measurements of glutathione status markers in the blood of women with PCOS in relation to body composition, with particular emphasis on visceral adipose tissue storage. Moreover, determining the ratio of GSH to GSSG allowed us to estimate the severity of oxidative stress in these patients. Assessment of Nrf2 and Keap1 proteins in the serum of patients with PCOS also seems to be important, although, on the other hand, it may be a certain limitation. Serum concentrations of this factor may not reflect the true cellular antioxidant response as Nrf2 functions mainly in the cell nucleus, and released forms do not always represent its free or active status. Another limitation of the study is that we did not measure serum levels of sulfur amino acids, which are important for the synthesis of this compound. However, we are planning to assess the amino acid profile—such as cysteine, cysteamine, cysteinylglycine, and homocysteine—in a future study of patients with PCOS. Finally, the lack of lipid profile and inflammatory markers may be a further limitation of our study. However, it is well known that patients with PCOS often have abnormal lipid levels, and chronic low-grade systemic inflammation is an important factor in this disease [6,14,33,43,44].

5. Conclusions

In conclusion, oxidative stress characterized by a depleted reduced-to-oxidized glutathione index is associated with anthropometric and body composition parameters in women with PCOS. In particular, abdominal obesity expressed by the VAT/SAT ratio and/or WHR seems to have a negative impact on glutathione status, which may lead to a disruption of many biological cell processes. The observed negative association of Keap1 with the R-index suggests that the elevated oxidative changes dependent on the VAT/SAT ratio may lead to Nrf2 activation to promote antioxidant enzyme expression. Although the GSH/GSSG index, as well as the VAT/SAT ratio, appear to be good indicators of oxidative status, studies on a larger group of patients should continue to confirm these links among women with PCOS.

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8. Aneks

Aneks 1. Spis tabel

Aneks 2. Kwestionariusz częstotliwości spożycia

Aneks 3. Opinia komisji bioetycznej

Aneks 4. Oświadczenia współautorów o merytorycznym i procentowym wkładzie w powstawanie publikacji

Spis tabel

KWESTIONARIUSZ CZĘSTOTLIWOŚCI SPOŻYCIA PRODUKTÓW

RODZAJ PRODUKTU	ILE PORCJI W CIĄGU DNIA?	ILE PORCJI W CIĄGU TYGODNIA?	ILE PORCJI W CIAGU MIESIĄCA?
PRODUKTY ZBOŻOWE			
Pieczywo pełnoziarniste np. chleb i bułki razowe, pieczywo z ziarnami			
Pieczywo rafinowane tzw. białe np. chleb i bułki pszenne, pszenno-żytnie, tostowe			
Kasze gruboziarniste np. gryczana, pęczak, bulgur			
Kasze drobnoziarniste np. manna, kuskus, jęczmienna łamana			
Makarony z mąki z pełnego przemiału np. gryczany, razowy, żytni, ryz brązowy			
Makarony z mąki pszennej np. makaron z pszenicy durum, jajeczny, ryż biały			
Płatki owsiane, płatki żytnie, domowe musli			
Gotowe produkty śniadaniowe np. płatki do mleko, musli, płatki kukurydziane			
PRODUKTY MLECZNE			
Mleko krowie			
Jogurt naturalny			
Maślanki, kefiry			
Sery twarogowe naturalne			
Sery podpuszczkowe tzw. żółte, mozzarella, pleśniowe			

Produkty mleczne smakowe np. jogurty owocowe, maślanki owocowe			
TŁUSZCZE			
Oleje roślinne np. oliwa z oliwek, olej rzepakowy, olej lniany			
Olej słonecznikowy, olej z pestek winogron, olej sojowy			
Olej palmowy, olej kokosowy			
Masło			
Awokado			
Margaryna twarda			
Margaryna miękka			
Śmietana oraz śmietanka			
Smalec, słonina, łój			
Majonez i inne sosy			
OWOCE I PRZETWORY OWOCOWE			
Owoce świeże			
Owoce mrożone			
Owoce suszone			
Dżemy owocowe, powidła, konfitury			

WARZYWA I ZIEMNIAKI			
Warzywa świeże			
Warzywa mrożone			
Ziemniaki			
ORZECHY I ZIARNA			
Niesolone orzechy np. włoskie, brazylijskie, nerkowca			
Pestki dyni, słonecznika, sezam			
Solone, prażone orzechy i ziarna			
MIĘSO, JAJA, NASIONA ROŚLIN STRĄCZKOWYCH			
Mięso drobiowe i jego przetwory np. kurczak, indyk, szynka i polędwica			
Mięso czerwone np. wołowe, cielęce, wieprzowe, bekon, boczek			
Czerwone mięso przetworzone np. szynka, polędwica, kiełbasy, pasztety, kabanosy			
Jaja np. jajecznica, na twardo, na miękko, omlety			
Nasiona roślin strączkowych			
RYBY I OWOCE MORZA			
Tłuste ryby morskie np. łosoś, śledź, makrela			
Ryby chude np. mintaj, dorsz, pstrąg			

Krewetki, małże, ostygi, kraby, przegrzebki, ośmiornica, kalmary			
NAPOJE			
Woda mineralna gazowana i niegazowana			
Soki owocowe			
Soki warzywne			
Kawa i herbata			
Słodzone napoje gazowane np. Fanta, Cola, Sprite, napoje energetyzujące			
Alkohol			
SŁODYCZE I SŁONE PRZEKĄSKI			
Cukierki, herbatniki, batoniki, żelki, czekolada, ciasta, pączki, drożdżówki, budyń, kisiel, lody			
Cukier do słodzenia, miód			
Słone paluszki, czipsy, paluszki,			
Fast foody np. frytki, pizza, kebab			

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KB/.170./2019

Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym
w dniu 02 grudnia 2019 r. po zapoznaniu się z wnioskiem:

Dr hab. Dorota Szostak-Węgierek
Zakład Dietetyki Klinicznej,
ul. E.Ciołka 27, 01-445 Warszawa

dotyczącym: wyrażenia opinii w sprawie badania pt.: „ Wpływ interwencji dietetycznej na skład ciała, insulinooporność, parametry stresu oksydacyjnego, profil hormonalny oraz biochemiczne markery metabolizmu tkanki tłuszczowej u pacjentek z zespołem policystycznych jajników."

wyraża następującą
o p i n i ę

- stwierdza, że jest ono dopuszczalne i zgodne z zasadami naukowo-etycznymi*.
- ~~stwierdza, że jest ono niedopuszczalne i niezgodne z zasadami naukowo-etycznymi.*~~

Uwagi Komisji – *verte*

Komisja działa na podstawie art.29 ustawy z dnia 5.12.1996r. o zawodzie lekarza /Dz.U.nr 28/97 poz.152 wraz z późn.zm./, zarządzenia MZiOS z dn.11.05.1999r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych /Dz.U.nr 47 poz.480/, Ustawy prawo farmaceutyczne z dnia 6 września 2001r. (Dz.U.Nr 126, poz. 1381 z późn. zm.) oraz Zarządzenie nr 56/2007 z dnia 15 października 2007r. w sprawie działania Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym /Regulamin Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym/.
Komisja działa zgodnie z zasadami GCP .

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma-Kozakiewicz

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KB/ 68 /A2021

Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym **w dniu 30 lipca 2021 r.** po zapoznaniu się z wnioskiem:

Dr hab. Dorota Szostak-Węgierek
Zakład Dietetyki Klinicznej,
ul. E.Ciołka 27, 01-445 Warszawa

dotyczącym: akceptacji zmian w dokumentacji obejmujących:
-program badania wersja nr 2 z dnia 14.06.2021
-informacja dla pacjenta z grupy kontrolnej wersja nr 2 z dnia 14.06.2021
do badania pt. „ Wpływ interwencji dietetycznej na skład ciała, insulinooporność, parametry stresu oksydacyjnego, profil hormonalny oraz biochemiczne markery metabolizmu tkanki tłuszczowej u pacjentek z zespołem policystycznych jajników."

wyraża następującą
o p i n i ę

- stwierdza, że są one dopuszczalne i zgodne z zasadami naukowo-etycznymi*.
- ~~stwierdza, że są one niedopuszczalne i niezgodne z zasadami naukowo-etycznymi.*~~

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Warszawa, 30.08.2023

mgr Justyna Jurczewska

OŚWIADCZENIE

Jako współautor publikacji pt. *„Milk and Dairy Products and Their Impact on Carbohydrate Metabolism and Fertility—A Potential Role in the Diet of Women with Polycystic Ovary Syndrome”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie wyżej wymienionej publikacji stanowi udział w opracowaniu koncepcji pracy, przegląd piśmiennictwa oraz przygotowanie manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 70%.

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Prof. dr hab. n. med. i n. o zdr.
Dorota Szostak-Węgierek

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mgr Justyna Jurczewska

OŚWIADCZENIE

Jako współautor publikacji pt. *„The Influence of Diet on Ovulation Disorders in Women—A Narrative Review”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie wyżej wymienionej publikacji stanowi udział w opracowaniu koncepcji pracy, przegląd piśmiennictwa oraz przygotowanie manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 70%.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Prof. dr hab. n. med. i n. o zdr.
Dorota Szostak-Węgierek

OŚWIADCZENIE

Jako współautor publikacji pt. *„The Influence of Diet on Ovulation Disorders in Women—A Narrative Review”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie wyżej wymienionej publikacji stanowi udział w opracowaniu koncepcji pracy i konsultacja merytoryczna manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 30%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

mgr Justyna Jurczewska

OŚWIADCZENIE

Jako współautor publikacji pt. *„Physical Activity, Rather Than Diet, Is Linked to Lower Insulin Resistance in PCOS Women—A Case-Control Study”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi konceptualizacja projektu badania, opracowanie metodologii, zbieranie i przygotowanie danych do analizy, przegląd literatury oraz przygotowanie manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 60%.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Dr n. o zdr. Joanna Ostrowska

OŚWIADCZENIE

Jako współautor publikacji pt. *„Physical Activity, Rather Than Diet, Is Linked to Lower Insulin Resistance in PCOS Women—A Case-Control Study”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi pomoc w opracowaniu metodologii oraz konsultacja merytoryczna manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 5%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Dr hab. n. med. Magdalena Chełchowska

OŚWIADCZENIE

Jako współautor publikacji pt. *„Physical Activity, Rather Than Diet, Is Linked to Lower Insulin Resistance in PCOS Women—A Case-Control Study”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi wykonanie oznaczeń biochemicznych oraz konsultacja merytoryczna manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 5%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Dr hab. n. o zdr. Mariusz Panczyk

OŚWIADCZENIE

Jako współautor publikacji pt. *„Physical Activity, Rather Than Diet, Is Linked to Lower Insulin Resistance in PCOS Women—A Case-Control Study”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi analiza statystyczna danych. Mój udział procentowy w przygotowanie publikacji określam jako 5%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Dr n. med. Ewa Rudnicka

OŚWIADCZENIE

Jako współautor publikacji pt. *„Physical Activity, Rather Than Diet, Is Linked to Lower Insulin Resistance in PCOS Women—A Case-Control Study”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi rekrutacja pacjentek do badania. Mój udział procentowy w przygotowanie publikacji określam jako 5%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Lek. med. Marek Kucharski

OŚWIADCZENIE

Jako współautor publikacji pt. *„Physical Activity, Rather Than Diet, Is Linked to Lower Insulin Resistance in PCOS Women—A Case-Control Study”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi rekrutacja pacjentek do badania. Mój udział procentowy w przygotowanie publikacji określam jako 5%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Prof. dr hab. n. med. Roman Smolarczyk

OŚWIADCZENIE

Jako współautor publikacji pt. *„Physical Activity, Rather Than Diet, Is Linked to Lower Insulin Resistance in PCOS Women—A Case-Control Study”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi konsultacja merytoryczna manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 5%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Prof. dr hab. n. med. i n. o zdr.
Dorota Szostak-Węgierek

OŚWIADCZENIE

Jako współautor publikacji pt. *„Physical Activity, Rather Than Diet, Is Linked to Lower Insulin Resistance in PCOS Women—A Case-Control Study”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi konceptualizacja projektu badania, nadzór nad prowadzonym badaniem i konsultacja merytoryczna manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 10%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

mgr Justyna Jurczewska

OŚWIADCZENIE

Jako współautor publikacji pt. *„Abdominal Obesity in Women with Polycystic Ovary Syndrome and Its Relationship with Diet, Physical Activity and Insulin Resistance: A Pilot Study”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi konceptualizacja projektu badania, opracowanie metodologii, zbieranie i przygotowanie danych do analizy, przegląd literatury oraz przygotowanie manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 60%.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Dr n. o zdr. Joanna Ostrowska

OŚWIADCZENIE

Jako współautor publikacji pt. *„Abdominal Obesity in Women with Polycystic Ovary Syndrome and Its Relationship with Diet, Physical Activity and Insulin Resistance: A Pilot Study”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi pomoc w opracowaniu metodologii oraz konsultacja merytoryczna manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 5%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Dr hab. n. med. Magdalena Chełchowska

OŚWIADCZENIE

Jako współautor publikacji pt. *„Abdominal Obesity in Women with Polycystic Ovary Syndrome and Its Relationship with Diet, Physical Activity and Insulin Resistance: A Pilot Study”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi wykonanie oznaczeń biochemicznych oraz konsultacja merytoryczna manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 5%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Dr hab. n. o zdr. Mariusz Panczyk

OŚWIADCZENIE

Jako współautor publikacji pt. *„Abdominal Obesity in Women with Polycystic Ovary Syndrome and Its Relationship with Diet, Physical Activity and Insulin Resistance: A Pilot Study”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi analiza statystyczna danych. Mój udział procentowy w przygotowanie publikacji określam jako 5%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Dr n. med. Ewa Rudnicka

OŚWIADCZENIE

Jako współautor publikacji pt. *„Abdominal Obesity in Women with Polycystic Ovary Syndrome and Its Relationship with Diet, Physical Activity and Insulin Resistance: A Pilot Study”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi rekrutacja pacjentek do badania. Mój udział procentowy w przygotowanie publikacji określam jako 5%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Lek. med. Marek Kucharski

OŚWIADCZENIE

Jako współautor publikacji pt. *„Abdominal Obesity in Women with Polycystic Ovary Syndrome and Its Relationship with Diet, Physical Activity and Insulin Resistance: A Pilot Study”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi rekrutacja pacjentek do badania. Mój udział procentowy w przygotowanie publikacji określam jako 5%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Prof. dr hab. n. med. Roman Smolarczyk

OŚWIADCZENIE

Jako współautor publikacji pt. *„Abdominal Obesity in Women with Polycystic Ovary Syndrome and Its Relationship with Diet, Physical Activity and Insulin Resistance: A Pilot Study”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi konsultacja merytoryczna manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 5%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Prof. dr hab. n. med. i n. o zdr.
Dorota Szostak-Węgierek

OŚWIADCZENIE

Jako współautor publikacji pt. *„Abdominal Obesity in Women with Polycystic Ovary Syndrome and Its Relationship with Diet, Physical Activity and Insulin Resistance: A Pilot Study”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi konceptualizacja projektu badania, nadzór nad prowadzonym badaniem i konsultacja merytoryczna manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 10%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Dr hab. n. med. Magdalena Chełchowska

OŚWIADCZENIE

Jako współautor publikacji pt. *„Antioxidant Defense Expressed as Glutathione Status and Keap1-Nrf2 System Action in Relation to Anthropometric Parameters and Body Composition in Young Women with Polycystic Ovary Syndrome”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi pomoc w konceptualizacji projektu badania, przeglądzie literatury oraz przygotowaniu manuskryptu, wykonanie oznaczeń biochemicznych oraz konsultacja merytoryczna manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 15%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

mgr Justyna Jurczewska

OŚWIADCZENIE

Jako współautor publikacji pt. *„Antioxidant Defense Expressed as Glutathione Status and Keap1-Nrf2 System Action in Relation to Anthropometric Parameters and Body Composition in Young Women with Polycystic Ovary Syndrome”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi konceptualizacja projektu badania, opracowanie metodologii, zbieranie i przygotowanie danych do analizy, przegląd literatury oraz przygotowanie manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 60%.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Dr n. biol. Joanna Gajewska

OŚWIADCZENIE

Jako współautor publikacji pt. *„Antioxidant Defense Expressed as Glutathione Status and Keap1-Nrf2 System Action in Relation to Anthropometric Parameters and Body Composition in Young Women with Polycystic Ovary Syndrome”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi pomoc w opracowaniu metodologii oraz konsultacja merytoryczna manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 5%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Dr hab. n. o zdr. Joanna Mazur

OŚWIADCZENIE

Jako współautor publikacji pt. *„Antioxidant Defense Expressed as Glutathione Status and Keap1-Nrf2 System Action in Relation to Anthropometric Parameters and Body Composition in Young Women with Polycystic Ovary Syndrome”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi analiza statystyczna danych oraz konsultacja merytoryczna manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 5%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Prof. dr hab. n. med. i n. o zdr.
Dorota Szostak-Węgierek

OŚWIADCZENIE

Jako współautor publikacji pt. *„Antioxidant Defense Expressed as Glutathione Status and Keap1-Nrf2 System Action in Relation to Anthropometric Parameters and Body Composition in Young Women with Polycystic Ovary Syndrome”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi konsultacja merytoryczna manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 5%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Dr n. med. Ewa Rudnicka

OŚWIADCZENIE

Jako współautor publikacji pt. *„Antioxidant Defense Expressed as Glutathione Status and Keap1-Nrf2 System Action in Relation to Anthropometric Parameters and Body Composition in Young Women with Polycystic Ovary Syndrome”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi rekrutacja pacjentek do badania. Mój udział procentowy w przygotowanie publikacji określam jako 5%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)

Warszawa, 30.08.2023

Dr n. biol. Jadwiga Ambroszkiewicz

OŚWIADCZENIE

Jako współautor publikacji pt. *„Antioxidant Defense Expressed as Glutathione Status and Keap1-Nrf2 System Action in Relation to Anthropometric Parameters and Body Composition in Young Women with Polycystic Ovary Syndrome”* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badania oraz przedstawienie pracy w formie publikacji stanowi nadzór nad wykonywaniem oznaczeń laboratoryjnych i konsultacja merytoryczna manuskryptu. Mój udział procentowy w przygotowanie publikacji określam jako 5%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej mgr Justyny Jurczewskiej.

.....
(podpis oświadczającego)