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Ocena związku markerów aktywności immunologicznej z wybranymi parametrami układu sercowo-naczyniowego u kobiet z cukrzycą typu 1 i chorobą Hashimoto - wnioski z cyklu publikacji.

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu

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Streszczenie w języku angielskim:

Title: ***Assessment of the association of markers of immune activity with selected cardiovascular parameters in women with type 1 diabetes mellitus and Hashimoto's disease: findings from the publication series.***

Type 1 diabetes mellitus (T1DM) is an autoimmune disease associated with multiple complications, of which cardiovascular complications are considered to be the most challenging in clinical practice. The coexistence of autoimmune disorders, of which Hashimoto's disease (HT) is the most common, is thought to increase cardiovascular risk. Despite many studies proving the negative effects of already subclinical hypothyroidism on the cardiovascular system, data on euthyroid patients are limited. Considering the particularly high cardiovascular risk observed in women with T1DM and the suspected involvement of immunological factors in its pathogenesis, a series of studies were conducted within this dissertation. The aim of the project was to analyze the relationship between thyroid autoimmunity in the course of HT and new markers of immune activity such as sirtuin 1, interleukin 27 (IL-27) and wisfatin and the presence of subclinical atherosclerosis or cardiac dysfunction in young, asymptomatic, euthyroid women with T1DM.

Articles 1 and 2 are reviews and they provide an introduction and rationale for the research presented in the original papers. The first discussed the molecular mechanisms involved in the development of heart failure differing according to the type of diabetes and the new therapeutic implications arising from them. The second review organized research reports suggesting a significant role of autoimmunity in the development of diabetic complications. Based on the literature review, it can be concluded that the pathogenesis of diabetic cardiac dysfunction, especially in patients with T1DM, is still not sufficiently understood and the postulated involvement of immune factors needs to be confirmed.

In study 3, we present a detailed analysis between thyroid autoimmunity in the course of HT and the intima-media thickness (cIMT) in young, asymptomatic T1DM women. The study population consisted of 102 women, including 72 with T1DM (mean age ± standard deviation, 26.26 ± 4.86) and 30 age-matched healthy controls. We found that despite euthyroidism, cIMT thickness was significantly greater in patients with T1DM and positive aTPO antibody titers (T1DM aTPO+) (0.66±0.10 mm) than in patients with T1DM without HT (T1DM aTPO-) (0.59±0.11 mm) or healthy controls (0.58±0.10 mm) ($p=0.007$, $p=0.001$, respectively). Statistical analysis showed that not only the presence of aTPO ($p=0.005$,

r=0.273), but also: HT duration (p=0.00015, r=0.367), severity of HT expressed by levothyroxine dose (p=0.006, r=0.269), ultrasound features of HT (p=0. 004, r=0.281), fT3 concentration (p=0.014, r=-0.243), fT3/fT4 ratio (p=0.042, r=-0.201) and a positive family history for HT (OR: 3.909, 95%CI: 1.014 -15.071, p=0.045) are associated with subclinical atherosclerosis.

The aim of study 4 was to investigate whether thyroid autoimmunity in course of HT is associated with decreased regional and/or global longitudinal strain (GLS) of the left ventricle in young, asymptomatic women with T1DM. A total of 88 young women (59 with T1DM and 29 controls) were included in the study and each underwent standard echocardiography and assessment using two-dimensional speckle tracking echocardiography (2D STE). GLS was shown to be slightly lower in the T1DM aTPO+ group (median and interquartile range (IQR) of GLS were: -17.1 (-16.20 - -18.15)) compared to the T1DM aTPO- group (median and IQR of GLS were: -18.3 (-17.4 - -19.6)) and significantly lower compared to the control group (median and IQR GLS were: -18.5 (-17.1 - -20.0)) (p=0.051, p=0.015, respectively). Although lower values of left ventricular longitudinal strain were found in most segments in the T1DM aTPO+ group compared with the T1DM aTPO- and control groups, statistically significant differences were found only in the two-chamber view (especially in the anterior segments) between the T1DM aTPO+ and T1DM aTPO- groups (p=0.030) and in the four-chamber view (especially in the anterolateral segments) between the T1DM aTPO+ and control groups (p=0.021). Logistic regression analyses showed that HT duration (OR: 0.997, 95%CI: 0.995-0.999, p=0.008), levothyroxine substitution (OR: 0.814, 95%CI: 0.689-0.960, p=0.013), and decreased echogenicity on thyroid ultrasound (OR: 0.309, 95%CI: 0.120-0.793, p=0.013) were significantly associated with GLS reduction.

Article 5 presents the results of a pilot study that aimed to evaluate serum levels of sirtuin 1, visfatin, and interleukin 27 (IL-27) in young, asymptomatic women with T1DM in relation to selected cardiovascular parameters and HT comorbidity. The study was based on the hypothesis that the loss of cardioprotection observed in premenopausal women with diabetes may be due to interactions between epigenetic, metabolic, and immunological factors. Fifty euthyroid women with T1DM (28 with HT and 22 without comorbidities) and 30 control women were included in the study. Serum levels of sirtuin 1, visfatin and IL-27 were assessed by ELISA. Although there were no significant differences in serum sirtuin 1, IL-27 and visfatin levels between groups, the results showed that in women with T1DM and HT, sirtuin 1 and IL-27 levels were significantly positively correlated with each other (r = 0.445, p = 0. 018), with thyroid volume (r = 0.511, p = 0.005; r = 0.482, p = 0.009, respectively) and with relative wall

thickness (RWT) ($r = -0.451$, $p = 0.016$; $r = -0.387$, $p = 0.041$, respectively), which may suggest their involvement in cardiac and thyroid remodeling in women with T1DM and HT. These relationships were not observed in the control group or for visfatin.

The results of our studies, which were presented in original papers, showed that thyroid autoimmunity in the course of HT in young, asymptomatic women with T1DM, despite euthyroidism, may be associated with subclinical atherosclerosis and regional myocardial contractile dysfunction, whereby the duration of HT and the stage of HT seem to be more important than the mere occurrence of antithyroid antibodies. The presence of lower myocardial contractility, particularly in the anterior and anterolateral segments demonstrated in women with T1DM and HT compared with women with T1DM without HT, or a control group indicate that functional impairments of these segments occur early in the development of diabetic cardiac dysfunction. Thus, it appears that noninvasive assessment of both cIMT and left ventricular longitudinal strain using the 2D-STE technique may provide valuable information about the presence of early cardiovascular changes in asymptomatic women with T1DM, which may be important for primary prevention in this group of patients. In addition, our results suggest that the mere presence of aTPO antibodies in women with T1DM is not an independent risk factor for increased cIMT or decreased GLS, but probably is only a marker of immune imbalance, which in turn plays a significant role in the pathogenesis of atherosclerosis or cardiac dysfunction in this group of patients. Cardiac and thyroid remodeling in women with T1DM and HT has been shown to be significantly associated with sirtuin 1 and IL-27 serum levels. Such relationships were not found for visfatin, nor was there a relationship between the markers studied and cIMT thickness in women with T1DM. Further studies are needed to better understand the interaction between epigenetic and immunological factors in the pathogenetic background of cardiac dysfunction in women with T1DM.