

Summary

INFLUENCE OF INTRAVENOUS METHYLPREDNISOLONE THERAPY ON DENSITOMETRIC PARAMETERS, BONE MICROARCHITECTURE AND BONE METABOLISM AMONG PATIENTS WITH GRAVES' ORBITOPATHY

Glucocorticosteroids (GCS) are commonly used drugs with potent anti-inflammatory and immunosuppressive effects. Depending on the indication, they can be administered orally, intravenously, intramuscularly, inhaled or intraarticularly and externally. Intravenous methylprednisolone (iv MP) pulse therapy is considered to be the first-line treatment in patients with active, moderate-to-severe Graves' orbitopathy (GO) according to the European Group on Graves' orbitopathy (EUGOGO) guidelines. The most common treatment protocol is twelve once-weekly iv MP pulses with a cumulative dose of 4.5 g: 6 x 0.5 g, followed by 6 x 0.25 g. Therapy with iv MP is highly effective, but is also associated with side effects. One of the less known and often overlooked aspects of the effects of intravenous GCS is their effect on bone tissue. It is well-established that oral GCS exert adverse effects on bones and are the most common cause of secondary osteoporosis and fractures. In literature, the prospective studies assessing the effect of intravenous GCS therapy on bone tissue are scarce and inconclusive. The Multidisciplinary Osteoporotic Forum, the International Osteoporosis Foundation as well as the American College of Rheumatology guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis do not provide recommendations for the management of patients treated with intravenous GCS. The aim of this study is to evaluate the effect on bone tissue of iv MP therapy given in a twelve once-weekly pulses with a total dose of 4.5 g in patients treated for active, moderate to severe GO. The densitometric parameters, microarchitecture, biochemical indices of bone metabolism and parameters of calcium-phosphate were assessed. The study included 65 patients with active, moderate to severe GO who were about to receive iv MP treatment. Therapy with twelve iv MP pulses was completed by 58 patients. In a group of 35 patients treated between 2011 and 2017, the impact of iv MP therapy on bone mineral density in the lumbar spine (LS BMD) and the femoral neck (FN BMD) was assessed (Project 1). The change in mean BMD in the group was evaluated. For each patient, it was individually determined whether the observed change between BMD measurement before and

after iv MP therapy was significant by relating the difference to the least significant change (LSC). Supplementation with 1.0 g of calcium and 800 IU of vitamin D daily was routinely provided. In a group of 15 patients treated between 2018 and 2021, the impact of iv MP therapy on the trabecular bone score (TBS) as well as LS BMD and FN BMD was evaluated (Project 2). The changes in mean TBS and BMD values were assessed. For each patient, it was individually determined whether the observed change between the measurement of TBS and BMD before and after iv MP therapy was significant, relating the difference to the LSC. In a group of 16 patients treated between 2019 and 2021, the impact of iv MP therapy on bone turnover markers (BTM) was determined: on N-terminal type I procollagen telopeptide (P1NP) and C-terminal type I collagen telopeptide (CTX) (Project 3). In the group of 16 patients treated in 2019-2021, the influence of a single pulse of 0.5 g iv MP on BTM and the parameters of calcium-phosphate metabolism was evaluated: on calcium (Ca), phosphate (P), parathyroid hormone (PTH), 25-hydroxycholecalciferol [25(OH)D] and 1,25-dihydroxycholecalciferol [1,25(OH)2D] (Project 3). In the years 2018-2021, supplementation with 1.0 g of calcium and 2000 IU of vitamin D daily was routinely provided. In the whole study group, the effect of iv MP therapy on Ca, P, PTH and 25(OH)D was measured among patients who completed the treatment with 12 pulses. Assessment

after 3-month therapy with iv MP pulses showed an increase in mean LS BMD by 1.7% in Project 1 and by 1.6% in Project 2. According to the LSC criteria, an increase in BMD was observed in 15 out of 35 patients (43%) in Project 1 and in 7 out of 15 (47%) patients in Project 2 (mainly in the LS BMD) and a decrease in BMD was noted in 2 out of 15 people in Project 2 (13%). In Project 2, the mean TBS value decreased by 2.4% in the posttreatment assessment. According to LSC criteria, TBS decreased in 5 out of 15 patients (33%). In Project 3, there was a decrease in P1NP and CTX after the iv MP therapy. After administration of a single pulse of 0.5 g iv MP, there was a transient decrease in P1NP, followed by a decrease in CTX. On the first day after the start of the single pulse of 0.5 g iv MP infusion, a transient decrease in the concentration of Ca and P in the blood was observed, accompanied by increased Ca and P excretion in the urine. On the following day, there was an increase in serum Ca and P, a decrease in urinary excretion, and finally, before the administration of the second iv MP pulse, concentrations of Ca and P normalized. The changes were independent of PTH. There was a transient increase in the level of 1,25(OH)₂D with a peak 24 hours after the administration of the first iv MP pulse. In all patients who completed iv MP therapy, there was no significant change of Ca, P and PTH levels after 3 months of treatment. No significant risk factors for the deterioration of bone microarchitecture were found.

In summary, therapy with twelve iv MP pulses given once weekly with a total dose of 4.5 g may exert a negative effect on bone tissue, manifested as deterioration of bone microarchitecture. The adverse effect of iv MP is not fully captured with BMD evaluation, and TBS adds value to the BMD assessment. Therapy with iv MP is associated with rapid changes in Ca, P, and 1,25(OH)₂D which were transient and independent of PTH. The reduction of BTM following iv MP therapy, considering the decrease in TBS despite the increase of BMD, might be a marker for dysfunctional bone remodeling. In all patients, before the beginning of treatment with iv MP, it seems necessary to start vitamin D and calcium supplementation and perform an evaluation of BMD and, if available, TBS. It is recommended to assess risk factors of fractures using FRAX, and possibly FRAX-TBS algorithms. Patients treated with iv MP should be carefully monitored for the development of skeletal complications, especially in the presence of multiple risk factors.