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Mini Review

Bone Effects of Glucorticoids; Complex Relationship

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What are Glucocorticoids?

Glucocorticoids (GCs) are steroid hormones, secreted in a circadian rhythm from the adrenal glands, under the control of Hypothalamus-Pituitary-Adrenal Axis (HPA Axis) [1]. These hormones are rapidly secreted in response to stressful conditions and exert effects on various systems of our body. In detail, GCs regulate multiple, vital physiological and developmental functions, ranging from lung maturation, lipid, glucose and protein metabolism to inflammatory and immune response. GCs exert their action mainly through their glucocorticoid receptor (GR), which is being expressed in almost every human cell. Furthermore, GCs can, under specific circumstances, act through binding to the mineral corticoid receptor (MR). The main representative of GCs is cortisol, which is an especially important hormone for the maintenance of the homeostasis and integrity of almost all of the human tissues. Pharmacologically, GCs are been widely therapeutically used, mainly in case of acute or chronic inflammatory or autoimmune diseases. It is estimated that almost 1-3% of the adult population in the Western World is currently receiving therapy with GCs.

Physiological Role of GCs in Skeleton

Normal GC concentrations have a significant role in bone tissue homeostasis [2]. Endogenous GCs are essential for the achievement of peak bone mass (BM) in both the cortical and the trabecular bone. In detail they induce osteoblastogenesis and the maturation and differentiation of osteoblasts through direct actions. Also, GCs regulate the function of chondrocytes during skeletal development and remodeling and trigger chondrocytes' apoptosis during skeleton ossification. Lastly, GCs are necessary for cartilage regeneration and sufficient bone response/healing after wound in the adult life [1]. Conclusively, GCs through their actions on osteoblasts and chondrocytes determine skeletal development.

Effects of GCs' Excess on Bone and Muscle-Pathophysiology

Longterm exposure of human body to high GCs' concentrations correlate with various adverse effects in general, such as adipocytes hypertrophy, disturbance of glucose metabolism and insulin resistance, muscular atrophy, impaired healing capability after wound, psychological disorders, insomnia, depression and in bone specifically such as glucocorticoid induced osteoporosis (GIO) [3].

Excess of endogenous GCs or longterm use of (high dose) exogenous GCs have detrimental effects on bone tissue homeostasis and metabolism, as they are associated with high risk for GIO, which is the commonest cause of secondary/iatrogenic osteoporosis and is defined by higher risk for fractures and osteonecrosis [4].

Bone loss observed in GIO can be divided in 2 phases α) the initial phase, which is dominated by rapid bone loss and bone density (BD) reduction at a rate of 6-12% during the 1st year of GC therapy and β) the final phase, characterized by a slower rate of BM reduction at about 3% annually. The bone loss affects mainly the trabecular bone, but nonetheless femoral bone neck and other skeletal areas can also be affected.

The damaging action of GCs on bone tissue is mainly exerted through 3 direct actions [5]: a) bone resorption increase and bone loss acceleration in a dose dependent manner via decreased gonadotropins secretion, leading to suppressed estrogenic and androgenic production and

thus to increased RANKL and decreased osteoprotogerin levels, which result into increased activity and decreased apoptosis of osteoclasts; β) bone formation suppression via dose dependent osteoblastogenesis decrease and osteoblasts differentiation and aopotosis acceleration; γ) decrease of vascularization/angiogenesis and elasticity of bone tissue via increased apoptosis of osteocytes and decreased osteoblastic production of VEG, resulting into decreased bone and muscular strength.

Regarding the indirect effects of GCs on bone, the following are included [5]:: suppressed expression and consequently anabolic effect of growth hormone (GH) on bone; decreased transcription of IGF gene, leading to suppressed synthesis and increased collagen and osteoblastic apoptosis; reduced intestinal absorption and renal reabsorption; antagonizing action to that of vitamin D, which directly affects the secretion and skeletal action of parathyroid hormone (PTH), composing thus a peculiar state of secondary hyperparathyroidism, further deteriorating bone loss in GIO. Finally, GCs have a negative impact on muscle mass and strength, via increased gene expression and induction of various signaling pathways, related to muscular atrophy and increased muscle/fiber proteins, while they multiply the risk for falls and fractures via indirect actions such as higher risk for cataract and a variety of neuropsychiatric disorders.

It must be highlighted that the overproduction of endogenous GCs and the consequent bone damage can potentially be partially limited via the endogenous deactivation mechanism of GCs through the 11βHSD2 enzyme, an action which is not possible in case of excess of exogenous synthetic GCs [6].

Endogenous Hypercortisolmia-Adrenal and ACTH-Dependent Cushing Syndrome

In cases of endogenous hypercortisolmia, such as adrenal (ACS) and ACTH-dependent (CD) Cushing syndrome (CS), a higher incidence of GIO is observed along with clearly reduced BM particularly in the vertebral column and to a lesser extent in the femoral bone, as bone areas rich in cortical bone are more resilient to the osteopenic action of GCs [6,7]. The prevalence of osteoporosis in patients with CS is about 50% while fracture risk is estimated at 30-50%,particularly in the vertebral column. The pronounced reduction of DHEA-S levels and its limited anabolic action on bone in case of ACS, in comparison to CD, could potentially explain this phenomenon.

Adrenal Incidentalomas

More than one third of the patients with adrenal incidentalomas (which affect 4-7% of the general population) suffer from subclinical hypercortisolism, which negatively affects bone metabolism [8]. Hypersecretion of cortisol is an independent prognostic factor for fractires at diagnosis and for occurrence of new verterbral fractures in the future. Positive linear correlation of cortisol with vertebral fractures in patients with adrenal incidentalomas is independent of BM, a fact that indicates that bone tissue quality is one of the most important if not the most important mechanism resulting into bone damage. Thus, the use pf vertebral fractures as a diagnostic criterion for subclinical hypercortisolism in patients with adrenal incidentalomas is proposed.

Glucocorticoid Replacement Therapy in Primary (PA) and Secondary (SAI) Adrenal Insufficiency

In case of replacement therapy with GCs (GCRT) in patients with primary (PAI) and secondary (SAI) adrenal insufficiency, the damaging effect of GCs is known and is dose-dependent, as the longer duration of GCRT is associated with increased bone damage [9]. During the last 2 decades, mean daily hydrocortisone (H/C) doses have gradually declined from 30 to 20mg. While in higher H/C doses (>20-30mg H/C) dose-dependent damaging bone effects have been observed, in lower H/C doses (< 20mg H/C), the damaging effect is disputed and in fact some studies have observed positive effects on BM arising from the use of low/normal H/C doses. Replacement therapy with prednisolone is related to lower BM in comparison with H/C, implying that bone tissue is more sensitive to synthetic GCs in comparison to other tissues but also a better long term prognostic factor of adverse effects due to exposure to GCs. It must be noted that patients with SAI present with increased bone loss and BM reduction, possibly because of the coexisting pituitary hormone deficiencies in comparison to patients with PAI. As a result, excellent regulation of the dosing schema of GCRT is of vital importance for the prevention of the damaging effects of GCs on bone and could potentially limit or even prevent GIO.

Epidemiology

Longterm use of GCs is associated with detrimental effects on bone tissue and GIO occurrence. Fractures and most notably the vertebral ones, are the most common and important adverse effects but also those which are easier to prevent [10]. Fracture risk rises rapidly with age, dose and duration of use and is higher in female patients of the white race aged under 55 years. Vertebral fracture risk increases during the first 3 months of GC therapy and reaches its peak at 12 months. Vertebral and femoral neck fractures risk rise proportionally to the dose of GCs. Intermittent GCs use has a lesser effect on fracture risk while high dose inhaled GCs for more than 4 years increases mildly fracture risk. Of note, after GC use interruption in established GIO, fracture risk declines rapidly.

Fracture Risk Estimation-Prevention

As GCs have an independent of BM effect on fracture risk, BMD exclusively is not the best prognostic factor for the estimation of fracture risk in GIO, thus GC use has been incorporated in the existing tools of fracture risk estimation such as FRAX Score. This estimation tool offers an estimation of 10year possibility of occurrence of a major osteoporotic or a femoral fracture in patients aged over 40 years. This tool includes GC use in combination with demographic and other clinical factors and BM in the area of femoral bone neck. Limiting factors are associated with the fact that FRAX [11]: Estimates a mean prednisolone dose and consequently

under- or overestimates the risk for those receiving low or high GC doses accordingly, requiring thus an adjustment of fracture risk in these patients categories; it does not apply to patients aged under 40 years; is based on the estimation of BM only in the cortical and not in the trabecular bone, which is mainly affected from GIO. The American College of Rheumatologists stratifies fracture risk in low, intermediate, and higher categories based on age, fracture risk based on FRAX Score, GCs dose, BMD and fracture risk. Of note, fracture risk rises and time duration before fracture occurrence minimizes remarkably, proportionally to the rising age of patients receiving GCs [12].

General Thoughts

As the use of GCs is the most common iatrogenic cause of osteoporosis, GIO is generally considered a preventable disease [13]. Consulting all patients, who are going to begin or already receive (high dose) GC therapy, is of vital importance. The first but especially important step is to limit GC use as far as dose and duration are involved. Inhaled GC therapies should be preferred in comparison to per os GC therapies while it should be attempted, if possible, to substitute GCs with other medications. Nonetheless every underlying inflammatory or autoimmune disease induces bone loss, so an adequate GC dose for the control of the underlying disease is equally important. In cases of necessary GC therapy, preventive treatment of GIO should be initiated, including early antiosteoporotic therapeutic interventions.

Therapy

Non Pharmacological Therapies

Non pharmacological therapeutic interventions in patients with GC therapy involve lifestyle changes such as exercise with weight, maintenance of normal body weight, healthy food diet, limitation of alcohol consumption and estimation and management of fall risk factors. Systematic intake, via diet or, if not possible, via substitution, of calcium (1-1,2gr daily) and vitamin D (600-800 IU daily) targeting sufficient calcium and Vitamin D levels should be advised, This advice is important because of the fact that decreased calcium urinary loss seems to be associated with limited BM loss in the vertebral column, particularly in low dose long term GC therapy, without though being enough as an intervention in order to achieve a sufficient prevention of bone loss in GIO [4].

Therapy

Despite high awareness, only partial successful treatment of GIO is achieved. It is estimated that only 25% of patients with GIO, receive antiosteoporotic therapy, with remarkable failure/lack of therapy in younger male patients. This therapeutic gap is almost identical to that observed in postmenopausal osteoporosis in the Western World.

Therapeutic Instructions

Pharmaceutical prevention of fractures Θεραπευτικές οδηγίες

The efficiency of the known antiosteoporotic therapies, applied to postmenopausal women with osteoporosis, is extremely difficult to be estimated via reliable studies in patients with GIO because of far greater heterogenity of underlying diseases, age range and comorbidities and also because of the variety regarding the type, dose and therapy duration with GCs.

The antiosteporotic therapy should be early initiated and continued for the duration of high dose GC therapy in patients with high fracture risk [14,15]. The therapy 'toolbox' for the treatment of GIO involves antiabsorptive agents that inhibit osteoclastic activity and reduce bone metabolism such as: α) per os and intravenous (iv) bisphosphonates (BPH), which are the most common therapy of GIO, mainly aledronic/risedronic acid (per os) and zoledronic acid (iv). In patients with adverse gastrointestinal effects, iv BPH should be preferred. BPH have a solid effect on vertebral fracture decrease, something not proved in femoral bone. Osteonecrosis associated with BPH and atypical femoral fractures have greater importance in GIO, as GCs themselves are associated independently with these adverse effects. Jaw osteonecrosis occurs early and is often more severe in patients with GIO, so mouth hygiene is of significant importance for the prevention of this adverse effect. Radiological imaging in patients with suspicion of atypical femur fractures should be implied; b) denosumab, which seems to be superior to BPH in 6 moth therapy regarding BM improvement in verterbral column. Interruption of denosumab therapy is associated with rapid BM loss and return to pre-therapy fracture risk, thus initiation of another antiosteoporotic therapy is needed, with the best possible choice being unclear. Osteonecrosis and atypical femoral fracture risk in patients therapy with denosumab is identical to that observed in therapy with BPH [14] and osteoanabolic agents, which stimulate .bone metabolism favoring bone formation such as teriparatide [15], which outmatches BPH, with higher BMD increase in the vertebral column (in patients with higher GC doses) and in the femur and higher reduction of vertebral fracture incidence. The high cost of therapy with teriparatide is a negative factor for the initiation of this therapy. The soon to be available generic teriparatide or bioequivalent anabolic therapies such as abaloparatide and rosozumabe will potentially stimulate the use of anabolic therapies in GIO.

Follow-up of Antiosteoporotic Therapies

The goal of antiosteoporotic therapy in GIO is the reduction of fracture risk, whose estimation is complicated [12], At the initiation of the therapy, Vit D, calcium and creatinin levels, body height, BMI, BMD and fracture risk should be estimated while control for vertebral fractures should be applied. BMD estimation should be repeated every 2 years or earlier under the suspicion of a vertebral fracture in addition to radiologic imaging of the vertebral column. The use of bone metabolism markers in the follow-up of antiosteoporotic agents is disputed. The definition of failure of antiosteoporotic therapy in GIO is identical to that of postmenopausal osteoporosis, though stricter criteria are proposed, aiming at therapy adjustment

at patients agent over 40 years under therapy with oral BPH, who present with vertebral fractures in less than 18 months of therapy or bone loss over 10% in 1 year. If failure therapy is attributed to poor absorption or low compliance with the therapy, initiation of iv BPH therapy is proposed. Patients over 40 years, who have completed 5 years of therapy with BPH therapy per os and have high or intermediate fracture risk should either continue the therapy or revert to iv therapy with BPH or other category of therapy. Patients over 40 years with low fracture risk, receiving antisoteoporotic therapy, vit D and calcium supplements should discontinue the antiosteoporotic therapy in contrast to those with intermediate or high fracture risk, who should conclude the therapy. Failure of therapy raises the need for reevaluation of the compliance of the patient to the therapy, mostly in case of per os BPH and the need for therapy adjustment f.e. to an iv from a per os BPH therapy or to an anabolic from an anticatabolic antiosteoporotic therapy [13].

Conclusion

GCs are steroid hormones with a vital role in the regulation of the physiology and homeostasis of bone tissue. They are widely used therapies for a variety of inflammatory and autoimmune diseases as well as in cases of adrenal insufficiency. On the other hand, multiple pathological conditions are associated with excess of endogenous GC secretion such as in adrenal incidentalomas, ACS and CD. Of note long term use of GCs and/or high GCs doses and excess of endogenous GCs are associated with profound damaging effects on bone, leading to GIO and increased fracture risk. Though the mechanisms of this phenomenon are unclear and complex, they involve increased ostoclastic activity in the initial phase followed by bone formation reduction due to osteoblastic and osteocytic apopotosis. GIO is considered a disease, which can potentially prevented. Till now, various prognostic tools have been developed regarding fracture risk estimation in GIO, without promising results, Treatment strategies in GIO include limitation of GCs doses in combination with reduction of therapy duration and management of endogenous GCs excess in combination with non pharmaceutic therapeutic interventions such as life style changes. Pharmaceutic interventions are necessary in all patients with high fracture risk while strict/close monitoring of the response to the therapy is needed, followed by early therapy adjustment if necessary.

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