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Review Article

Excess intake of Glucocorticoids leading to Osteoporosis

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ABSTRACT

Glucocorticoids are potent medications that reduce inflammation and boost your immune system to treat a variety of illnesses. Basal GC levels are crucial for intermediate metabolism and play a role in the growth and homeostasis of a variety of bodily tissues, including the skeleton, from a physiological standpoint. Numerous investigations on mammals have shown that GC hormones play a beneficial effect in bone remodelling and modelling by promoting osteoblastogenesis, which preserves the bone architecture. Although the so-called stress hormones' pharmaceutical effects have received considerable attention, little is known about the impact of endogenous GCs on bone mineral metabolism as a result of the endocrine stress response in vertebrates. Additionally, stress reactions differ among vertebrate lineages and depend on the stressor (such as mineral requirements, physical stress, and psychological stress), life cycle events (such as migration and ageing), and stressor (such as starvation, predation, and environmental change). This review aims to provide an overview of how endogenous GCs affect bone metabolism. Osteoporosis is a medical disorder that causes bones to become brittle and more prone to breaking. Stress, which causes physical, emotional, and intellectual reactions, is a typical bodily response to change.

Keywords: Glucocorticoids, Stress, Osteoblastogenesis, Osteoporosis

INTRODUCTION

Glucocorticoids are potent medications that reduce inflammation and boost your immune system to treat a variety of illnesses. Actually, your body produces glucocorticoids on its own. These

hormones perform a variety of functions, including regulating how your cells utilise sugar and fat as well as reducing inflammation. They don't always suffice, though. The created versions can be useful in those situations.

The Nobel Prize in Physiology and Medicine was given for the discovery of glucocorticoid (cortisone) in 1950. Glucocorticoids are stress-response hormones that bind to the glucocorticoid receptor and are essential for many physiological functions, including inflammation, metabolic equilibrium, and cognitive function. The nuclear receptor superfamily of steroid, thyroid, and retinoic acid includes the glucocorticoid receptor (GR). Heat-shock proteins FKBP51 and FKBP52 are what GR binds to inactively when glucocorticoids are not present. When GR attaches to glucocorticoids, it undergoes conformational changes, separates from the chaperone proteins, and translocates into the nucleus. There, it binds to target genes' promoter DNA and either stimulates or inhibits the transcription of response genes. [1]

The adrenal glands secrete hormones called natural glucocorticoids, such as cortisone or hydrocortisone, which are named for their functions in preserving glucose homeostasis. Systemic functions in immune response, metabolism, cell growth, development, and reproduction are affected by the release of glucocorticoids into blood circulation. Glucocorticoids are among the most often given medications because of their anti-inflammatory and immune-suppressive effects. Glucocorticoids are frequently used to treat some autoimmune, inflammatory, and allergy conditions, such as rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, transplant rejection, and asthma.

Prednisone, prednisolone, triamcinolone, methylprednisolone, dexamethasone, and other glucocorticoids are frequently utilised. To increase their anti-inflammatory actions, they undergo modifications to the cortisone (hydrocortisone) backbone's chemical structure. [2]

Side effects

The particular medication or dose you take will determine how glucocorticoids affect you. For instance, if you just use one occasionally to treat flare-ups of joint inflammation, you might not have any negative side effects.

Typical issues include:

- Gaining weight
- I'm quite hungry.

- Retention of water or enlargement
- Mood changes
- Distorted vision
- Being uneasy or uncomfortable
- Difficulty sleeping
- Muscle tremor
- Acne
- Anxiety in the stomach

Osteoporosis is a medical disorder that causes bones to become brittle and more prone to breaking. It takes years to grow slowly, and frequently, a bone fracture or break is the sole sign that it has occurred.

Osteoporosis patients most frequently sustain the following wounds:

i) wrist fracture

ii) hip fracture (broken hip)

iii) vertebral (spinal) bones shattered

Minerals like calcium and phosphorus found in bones give them their hard, thick texture. The body also needs the right levels of many hormones, including parathyroid hormone, growth hormone, calcitonin, oestrogen in women, and testosterone in males, to maintain bone density.[3]

The inner network of bones gets thinner, weaker, and more fragile after menopause and the loss of oestrogen. However, an individual would not be diagnosed with osteoporosis unless there has been an abnormal amount of bone loss, as can be determined by a bone density scan, for example.

Causes

Even though bone loss is a typical aspect of becoming older, some people experience it considerably more quickly. Osteoporosis and a higher chance of breaking a bone can result from this.

In the initial years following menopause, women also experience rapid bone loss. In instance, women who experience the menopause early (before the age of 45) or who have had their ovaries removed are more vulnerable to osteoporosis than men.

However, males, younger women, and children are also susceptible to osteoporosis.

Numerous additional elements can further raise the risk of developing osteoporosis, such as:

- taking high-dose steroid medications for longer than three months;

- various health issues, such as inflammatory disorders, hormone-related conditions, or malabsorption issues;
- having or having had an eating disorder like anorexia or bulimia having a low body mass index (BMI) having
- a family history of osteoporosis, particularly a hip fracture in a parent long-term use of certain medications that can affect bone strength or hormone levels, like anti-oestrogen tablets that many women take after breast cancer
- Regularly skipping workouts, abusing alcohol, and lighting up

Exercise, vitamin and mineral supplements, as well as prescription drugs, may be used as treatments for osteoporosis that has already progressed. It's frequently advised that you avoid osteoporosis by exercising and taking supplements. Exercises including resistance, weight bearing, and balance are all crucial.

Stress, which causes physical, emotional, and intellectual reactions, is a typical bodily response to change. You may deal with changes in a better way by taking a stress management course.

A typical response to regular demands is stress, but when it interferes with your daily activities, it can become unhealthy. Nearly every system in the body experiences changes as a result of stress, which has an impact on how people feel and act.[6]

Stress lowers quality of life by affecting mental and physical health and by altering the mind-body connection, which directly contributes to physiological and psychological dysfunction and disease.

A short while to many hours after an occurrence, acute stress sets in. It lasts for a brief length of time, usually less than a few weeks, and is quite intense. Following a distressing or unanticipated event is when it can occur. Suddenly passing away, being attacked, or experiencing a natural calamity are a few examples.

Long-lasting or recurring stress is referred to as chronic stress. If you are frequently stressed out, you might experience this. If you live in poverty or have a rough daily existence, for example, if you are a caretaker, you may also have chronic stress.

Stress manifests physically as:

i) Pains and discomfort.

ii) Experiencing heart palpitations or chest pain.

iii) fatigue or difficulty falling asleep.

iv) headaches, woozyness, or trembling.

v) excessive blood pressure.

vi) tension in the jaw or the muscles.

vii) intestinal or stomach issues.

viii) Having a hard time getting laid.

ix) immunologically compromised.

Symptoms of emotional and mental distress include:

i) apprehension or irritation.

ii) Depression.

iii) Attacks of panic.

iv) Sadness.

Free radicals and antioxidants in your body are not balanced, which causes Oxidative stress. Oxygen-containing molecules called free radicals have an unbalanced number of electrons. The unequal distribution of electrons makes it simple for free radicals to interact with other molecules. Because they interact with other molecules so readily, free radicals can trigger lengthy chemical chains in your body. Oxidation is the name for these processes. They might be helpful or dangerous. [7]

Antioxidants are substances that can give an electron to a free radical without becoming unstable themselves. The free radical stabilises as a result and becomes less reactive.

Oxidative stress is a damaging process that can destroy many cellular components, including membranes, lipids, proteins, lipoproteins, and deoxyribonucleic acid (DNA). It is caused by free radicals and other oxidants. When there is an imbalance between the production of free radicals and cells' capacity to eliminate them, oxidative stress results. [9]

Free radicals can begin harming the fatty tissue, DNA, and proteins in your body when there are more of them than can be controlled by antioxidants. Your body is largely composed of proteins, lipids, and DNA, thus any damage can eventually result in a wide range of illnesses. Diabetes, atherosclerosis, or the hardening of the blood vessels, and inflammatory diseases are some of them.

Intake of Glucocorticoids

It is believed that 1-2% of the population is undergoing long-term glucocorticoid medication, which is used to treat a variety of disorders. Glucocorticoid (GC) excess and osteoporosis have been linked for about 80 years, but it has only lately been realised

how important this relationship is for clinical practise. Oral glucocorticoids cause fast bone loss, which is followed by a dose-dependent rise in fracture risk within a few months. Within 3 to 6 months after starting, continuous oral glucocorticoid medication is related to dose-dependent fast bone loss and an increase in fracture risk. The higher glucocorticoid doses and increased disease activity in the early stages of treatment can, at least in part, be attributed to this time cycle.

Glucocorticoids causing Osteoporosis

High concentrations of GCs significantly reduce the rate of bone production, the number of osteoblasts, and the quantity and activity of osteocytes. The increase in osteoblast and osteocyte apoptosis is linked to caspase 3 activation, and the decrease in osteoblast differentiation includes the expression of adipogenetic transcription factors (PPAR) and suppression of Wnt protein signalling. Additionally, the antianabolic actions of GCs, such as the decline in GH, IGF1, and IGFBP3-4-5, reduce osteoblast function. On the other hand, GCs boost IGFBP6 transcription, which reduces IGF2, a local regulator of osteoblast activity. Changes in the matrix's characteristics around the osteocyte lacunae are also linked to GCs and a decline in osteocyte viability.[11]

In stromal and osteoblastic cells, GCs cause an increase in the expression of RANK-ligand and a decrease in the expression of osteoprotegerin. As a result, osteoclasts are seen to have a longer lifespan (in contrast to osteoblasts, which have a shorter lifespan). Despite the fact that this enhanced resorption has been observed, the decreased bone formation that lasts the duration of GC administration is what accounts for the majority of the GC-related bone loss.

Individual susceptibility to glucocorticoids varies, and extended exposure to low dosages of these steroids increases the risk of fractures. Following glucocorticoid therapy, there is an initial rapid loss of bone that is likely caused by increased bone resorption followed by a later, more gradual loss that is likely caused by decreased bone remodelling. Due to their stimulation of the expression of colony stimulating factor-1 and receptor activator of NF-B ligand, as well as their suppression of osteoprotegerin, a soluble decoy receptor for receptor activator of NF-B ligand, glucocorticoids reduce gastrointestinal calcium absorption and increase bone resorption by increasing osteoclastogenesis. Under specific circumstances, glucocorticoids may increase the lifespan of mature osteoclasts.[10]

By eventually reducing the number of osteoblasts, glucocorticoids reduce bone remodelling. This happens as a result of a reduction in osteoblastogenesis and an increase in mature osteoblast and osteocyte apoptosis. In addition to inhibiting the activity of mature osteoblasts, glucocorticoids postpone the development of immature stromal cells into osteoblasts. Instead, glucocorticoids promote adipogenesis, which most likely happens at the price of differentiation into osteoblasts. The effect is secondary to the stimulation of the anti-osteoblastic peroxisome proliferator-activated receptor gamma, CAAT enhancer binding protein beta, and CAAT enhancer binding protein delta. Because of these results, it appears that glucocorticoids are involved in the exchange of osteoblasts and adipocytes.

Glucocorticoids on Oxidative stress in Osteoporosis

Specialised bone-forming cells called osteoblasts have a variety of tasks in bone remodelling. Runt-related transcription factor 2 (RUNX2) and osterix are regulatory transcription factors that help osteoblasts form from multipotent mesenchymal cells, which can also evolve into other cell lineages such adipocytes, myocytes, and chondrocytes. During skeletal modelling and bone remodelling, osteoblasts create organic bone matrix (osteoid) and later mineralize it. Numerous signalling mechanisms, including the well-known Wingless and Int-1 (Wnt) signalling system, control the development and operation of osteoblasts. When Wnt1 and Wnt3a protein bind to Fizzled and low-density lipoprotein receptor-related protein 5/6, it is activated. As a result, glycogen synthase kinase-3 beta is inhibited, which causes the breakdown of cytoplasmic beta-catenin via phosphorylation.

Additionally, osteoblasts release RANKL, a ligand that interacts with RANK on the progenitors of osteoclasts to promote osteoclast development. Osteoblasts also release osteoprotegerin (OPG), a RANKL decoy receptor, at the same time to stop RANKL from binding to RANK and restrict the growth of osteoclasts. Different endogenous and exogenous variables, such as inflammatory cytokines, oxidative stress, and glucocorticoids (GCs), have an impact on these signalling pathways. [12]

Through the generation of reactive oxygen species (ROS), downregulation of cytoprotective antioxidant proteins, and antioxidant enzyme activity, GCs can result in oxidative stress. High ROS levels impair osteoblast function and development, killing osteoblast cells and reducing growth. By decreasing the capacity of all

antioxidants while increasing the production of ROS and lipid peroxidation, DEX therapy causes oxidative damage. Additionally, it significantly lowers the expression of RUNX2 mRNA, which is what leads to high-dose DEX-induced osteotoxicity. Due to increased caspase activity, DEX therapy also causes a considerable reduction in the mitochondrial membrane potential. Antioxidant therapy can increase the expression of these osteogenic markers and decrease the expression of caspase, reducing the apoptotic effect of DEX. This finding points to oxidative stress' potential role in DEX-induced osteoporosis.

A low GC level has stimulating effects on bone, whereas a high GC level has inhibiting effects. By inhibiting cytokines like IL-11 through the interaction of the monomeric GR with AP-1 but not nuclear factor kappa B (NF-B), GCs have an anti-inflammatory effect on osteoblasts. The attenuation of osteoblast development caused by GCs' suppression of cytokines contributes to bone loss during GC therapy.

CONCLUSIONS

Bone appears to be a target organ for stress-induced GCs in response to a range of stressful events and/or stimuli that test the internal homeostasis. Over time, GC levels that are sustained cause bone resorption, which disrupts the mineral balance and harms the bone structure. There is a knowledge gap regarding the cellular and molecular pathways involving the stress response, cortisol, and bone mineral metabolism, even though this information shows that stress-induced GCs may work similarly to therapeutic GCs. There is currently no information available about the effects of stress-induced GCs on bone cells or the interactions between GCs and other elements affecting bone homeostasis

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