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Review Article

Stress: one of the cause for Diabetes that further leads to Osteoporosis

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ABSTRACT

Stress is characterised as a condition of anxiety or mental tension brought on by a challenging circumstance. Stress is a typical human response that drives us to confront challenges and threats in our lives. Everyone goes through periods of stress. Stress causes the body to release hormones that may raise blood sugar levels. Diabetes patients may experience negative symptoms from this, although they may be controlled. People who have Type 1 diabetes, in which the pancreas stops producing insulin, or Type 2 diabetes, in which the body cannot utilise insulin and the ability to generate insulin gradually declines, are more likely to experience bone fractures and osteoporosis. Women with Type 1 diabetes are 12 times more likely to fracture than women without diabetes, which is linked to lower bone mass. Osteoporosis Because it typically goes undiagnosed until a bone is shattered, and sometimes even then, osteoporosis is referred described as a "silent" illness.

Keywords: Stress, Osteoblastogenesis, Mental illness, Diabetes

INTRODUCTION

Stress is characterised as a condition of anxiety or mental tension brought on by a challenging circumstance. Stress is a typical human response that drives us to confront challenges and threats in our lives. Everyone goes through periods of stress.

Stress has a significant impact on our mood, sense of wellbeing, behaviour, and physical and mental health. Young, healthy people's acute stress reactions may be adaptive and normally have no negative effects on their health. The long-term impacts of stressors, however, can harm health if the threat is constant, especially in older or ill people. The type, quantity, and duration of the stressors, as well as the person's biological sensitivity (i.e., genetics, constitutional characteristics), psychosocial resources, and ingrained coping mechanisms, all have an impact on the association between psychosocial stresses and disease. Psychosocial therapies have been shown to be effective in treating problems caused by stress and may have an impact on how chronic diseases develop.

Oxidative stress is a phenomena brought on by an imbalance between a biological system's capacity to detoxify these reactive by products and the creation and build up of oxygen reactive species (ROS) in cells and tissues.

As the ER's ability to fold proteins reaches saturation, ER stress happens. In addition to conditions that hinder the formation of disulfide bonds or protein glycosylation, ER stress can also result from the overexpression or mutation of proteins that travel through the secretory route.

Diabetes mellitus (DM) is a condition where blood glucose levels are not properly controlled. Only a few of its numerous subtypes include type 1, type 2, maturity-onset diabetes of the young (MODY), gestational, neonatal, and steroid-induced diabetes. Type 1 and type 2 are the two main subtypes of DM; each has a different aetiology, presentation, and management, however both can lead to hyperglycemia.

In T1DM, beta cells in the pancreas are frequently destroyed as a result of an autoimmune process. Beta cells are completely destroyed as a result, and as a result, there is no or very little insulin in the body.

The development of T2DM is more subtly manifested, with an insulin functional deficit brought on by an imbalance between insulin levels and insulin sensitivity. Although insulin resistance has many causes, fat and ageing are the most frequent ones.

A significant risk factor for both types is the genetic background. Many loci have been discovered that increase risk for DM as the human genome is studied more thoroughly. Major Histocompatibility Complex (MHC) and Human Leukocyte Antigen polymorphisms have been reported to affect the risk for T1DM (HLA).

Genetics and lifestyle play a more intricate role in T2DM. There is unmistakable proof that T2DM has a greater hereditary profile than T1DM. Most illness sufferers have at least one parent who also has type 2 diabetes.

As people age, T2D and low-trauma fractures become increasingly frequent. T2D is linked to both increased weight and BMD. Both were originally believed to be protective against fracture, but as was already mentioned, a paradoxical increased risk of fracture has been seen in T2D, even if this risk is often lower than in T1D. Strotmeyer and colleagues discovered in the Health, Aging and Body Composition study that T2D was linked to greater hip, whole body, and volumetric spine BMD, independent of body composition and fasting insulin levels. Even after age, calcaneal BMD, BMI, and other factors were taken into account, the same cohort still found that people with diabetes had an elevated risk of fractures. Older age, poorer BMD, lower BMI, and falls are risk factors for fracture in T2D.

Osteoporosis Because it typically goes undiagnosed until a bone is shattered, and sometimes even then, osteoporosis is referred described as a "silent" illness. The primary cause of fractures in postmenopausal women and elderly men is osteoporosis. Any bone can break, however the most common broken bones are the hip, spine, and wrist vertebrae.When bone mass, bone mineral density, or the composition and strength of bone alter, osteoporosis, a disease of the bones, results. This may result in a loss of bone density and an elevated risk of fractures (broken bones).

Osteoporosis causes

Osteoporosis occurs when there is an excessive loss of bone mass and the structure of bone tissue is disturbed. Certain risk factors either increase your risk of developing osteoporosis or can actually cause it.

There are many risk factors for osteoporosis, but not everyone with the illness has them. Certain risk factors may be modifiable, while others may not be. But, by being aware of these variables, you might be able to prevent the illnesses and fractures.

Your risk for osteoporosis could be impacted by the following factors:

- Sex. If you are a woman, your risk of having osteoporosis is higher. Compared to men, women's bones are smaller and have lower peak bone mass. Men are still at risk,

though, particularly after the age of 70.

- Age. As you get older, bone loss happens more quickly and bone development is slower.The risk of osteoporosis can rise as your bones deteriorate over time.
- Body weight. Thin, slim women and men are more susceptible to osteoporosis due to the fact that they have less bone to lose than individuals with stronger bones.
- Race. Women who are white and Asian are more at danger. Women who are African American or Mexican American are at decreased risk. Compared to Mexican American and Black American men, white men are more at risk.
- Family background. According to research, if one of your parents has experienced osteoporosis or a hip fracture, you may be more susceptible to fractures and osteoporosis.
- Adjustments to hormones. The risk of developing osteoporosis may rise if you have low levels of specific hormones. For instance:

  i) After menopause, low oestrogen levels in women.

  ii) Low levels of oestrogen from premenopausal women's abnormal lack of menstruation brought on by hormone abnormalities or excessive physical exercise.

  iii) Low testosterone levels in males. For males with disorders that reduce testosterone, osteoporosis is a risk. However the progressive decline of testosterone with age is probably not the main factor in bone loss.

- Diet. The risk of osteoporosis and fractures can rise from childhood into old age if you eat a diet low in calcium and vitamin D. If you overeat or don't get enough protein, your risk of bone loss and osteoporosis may increase.
- Other health problems. Certain medical illnesses, such as various endocrine and hormonal disorders, gastrointestinal disorders, rheumatoid arthritis, specific types of cancer, HIV/AIDS, and anorexia nervosa, that you might be able to

cure or control can raise the risk of osteoporosis.

- Medications. Long-term use of several drugs, such as glucocorticoids and adrenocorticotropic hormone, which are used to treat disorders including asthma and rheumatoid arthritis, may increase your risk of developing bone loss and osteoporosis.

  i) medications used to treat epilepsy and other neurological conditions.

  ii) hormone-based cancer medicines to treat breast and prostate cancer.

  iii) inhibitors of the proton pump, which reduce stomach acid.

  iv) SSR inhibitors, which are used to treat anxiety and depression.

  v) Treatment for type 2 diabetes using thiazolidinediones.

- Lifestyle. By living a healthy lifestyle, bone strength can be preserved. Together with other variables, low levels of physical activity and prolonged periods of inactivity can hasten bone loss. Also, they put you in poor physical shape, raising your risk of fracturing a bone if you fall.

  i) Alcohol abuse is a substantial risk factor for osteoporosis when it occurs frequently.

  ii) According to studies, smoking increases the risk of osteoporosis and fractures. Tobacco use alone may have harmful impacts on bone health, but researchers are also investigating if smoking may increase the risk of osteoporosis.

Oxidative stress in diabetes mechanism of action

Reactive oxygen species (ROS) generation and oxidative stress brought on by hyperglycemia are linked to the pathophysiology and development of this metabolic disorder. Exogenous or endogenous antioxidants in the body neutralise ROS to prevent its detrimental effects and uphold homeostasis in the body. Diabetes develops as a result of oxidative stress, which is caused by an imbalance

between the cellular antioxidant system and ROS generation under hyperglycemic circumstances. The mitochondrial electron transport chain (ETC) plays a crucial role in the production of these ROS, which are also formed in the endoplasmic reticulum, phagocytic cells, and peroxisomes. Proteins, lipids, and nucleic acids can all undergo structural and functional changes as a direct result of the increased ROS generation. Moreover, it affects a number of intracellular signalling pathways that result in insulin resistance and reduced -cell activity. Moreover, the creation of ROS brought on by hyperglycemia aids in the development of both micro- and macrovascular problems in diabetes.

1) Autoreactive T cells in type 1 diabetes recognise their own self because of inborn ER stress in pancreatic islet β cells

An autoimmune condition known as type 1 diabetes (T1D) is defined by the death of pancreatic cells brought on by islet reactive T cells that have eluded central tolerance. Endoplasmic reticulum (ER) stress and dysfunction are caused by a variety of physiological and environmental stimuli in T1D patients, which raises the possibility of aberrant post-translational modification (PTM) of proteins. β cell ER stress brought on by physiological and environmental factors produces abnormally-modified proteins that trigger the T1D autoimmune response. Cell ER stress increased the activity of the tissue transglutaminase 2 (Tgase2) calcium (Ca2+)-dependent PTM enzyme, which is required for complete stress-dependent immunogenicity. Indeed, BDC2.5 T cells reacted to their antigen more robustly following Tgase2 alteration.

2) Endoplasmic reticulum stress and diabetes-related ischemic brain injury

Cardiovascular disease is one of the many secondary consequences of chronic diabetes that can be fatal. Diabetes has a high incidence of cerebral ischemia-related mortality, morbidity, and the severity of brain injury. Yet, it is unclear how diabetes causes an increase in ischemic brain injury. The increase in ischemic brain injury caused by diabetes hyperglycemia and hypoglycemia is mediated by a number of mechanisms. During ischemia-reperfusion injury, endoplasmic reticulum (ER) stress mediates both brain damage and brain preservation. With diabetes, the ER stress pathways are altered. The routes of ER stress are known to be stimulated by free radical production and mitochondrial dysfunction, two of the key processes behind the diabetes elevation of ischemic brain injury. Diabetes results in a greater activation of ER stress, which is

accompanied by an increase in ischemic brain injury. Due to the numerous metabolic alterations brought on by diabetes, severe ischemic brain injury in diabetic people may be caused by differential ER stress pathway activation.

Diabetes and Osteoporosis mechanism of action

- Although both T1D and T2D include poor bone turnover, osteoblast dysfunction, and significantly less bone production, their respective pathophysiologies for increased fracture risk are distinct.
- Diabetes and hyperglycemia are linked to hyperlipidemia, impaired insulin signalling, reduced levels of insulin-like growth factor 1 (IGF-1), generation of reactive oxygen species, and inflammation, all of which have the potential to depress osteoblast function. Obesity and diabetes by themselves can both heighten bone marrow inflammation, which impairs osteoblast activity. The inflammation favours an increase in osteoclast number and activity, resulting to greater bone loss. Inflammatory cytokine levels have been found to be higher in T1D41 and T2D.
- Chronic hyperglycemia and skeletal advanced glycation end products (AGES), which irreversibly accumulate from the nonenzymatic addition of sugar moieties to the amine groups of proteins and then negatively affect skeletal integrity, are two potential causes of deteriorated bone quality and microarchitectural defects.
- Hyperglycemia causes oxidative stress to increase by two different mechanisms: first, glucose overloads the mitochondria, and second, AGEs and polyol signalling. The maturation of osteoblasts is significantly impacted by this oxidative stress, which may also result in an increase in osteoblast apoptosis. AGE levels are correlated with the severity of diabetic problems because they enhance collagen cross-linking, which alters the structural and functional characteristics of proteins and contributes to overall decreased bone strength and increased brittleness.

- Patients with diabetes have particularly high levels of AGEs because decreased bone turnover makes it easier for proteins to build up. Chronically high glucose levels encourage the glycation of the bone matrix while hindering collagen turnover and matrix renewal, ultimately decreasing bone production and making bones more brittle containing higher levels of AGEs per gram of collagen.
- These collagen alterations stiffen the bone matrix and alter the material characteristics of the bone, which causes brittleness and mechanical failure when exposed to physiological amounts of stress.
- To explain the skeletal fragility and impairments in BMD, bone geometry, bone microarchitecture, and biomechanical characteristics in T1D, a number of explanations have been put forth. Reduced bone production as a result of diminished osteoblast activity is the main bone disorder. Procollagen type 1 amino-terminal propeptide (P1NP) and IGF-1 levels, which are lower in those with T1D, may also be significantly important. The appearance of more pentosidine, an AGE marker, on bone histomorphometry in people with T1D who frequently fracture as opposed to those who do not fracture, is indicative of the negative effects of AGEs on bone tissue in vivo.
- Serum osteocalcin and diabetes: a possible relationship has been proposed. Serum osteocalcin levels in people with T1D or T2D are lower than in non-diabetic controls. Moreover, in T1D patients, osteocalcin levels are inversely linked with glycosylated haemoglobin levels. It has been proposed that altered Wnt signalling contributes to the impaired bone turnover and osteoblast activity associated with diabetes. Increased levels of the osteocyte product sclerostin, which blocks the Wnt signalling pathway and inhibits bone growth, lead to the decoupling of bone creation and resorption.

CONCLUSIONS

People respond to stress in different ways. Your body's reaction to stress can vary depending on the kind you experience. People with type 2 diabetes typically notice a rise in their blood glucose levels when

they are under emotional stress. People with type 1 diabetes could react differently. This indicates that their blood glucose levels may either rise or fall. Your blood sugar can rise as a result of physical stress. This may occur as a result of an illness or accident. Both type 1 and type 2 diabetics may be impacted by this. Falls, fragility, and low-impact fractures are all risks that osteoporosis and various other DM symptoms (such as vision impairment and gait imbalance) exacerbate. It is clear that in diabetes mellitus (DM), hyperglycemia directly inhibits osteoblast-mediated bone formation while favouring osteoclast-mediated bone resorption, adipogenic differentiation of mesenchymal stem cells (also precursors of osteoblasts), and fat accumulation in the marrow cavity, all of which worsen bone quality and strength and raise the risk of fracture**.**

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