MINISTRY OF HIGHER EDUCATION AND SCIENTIFIC RESEARCH

BABYLON UNIVERSITY COLLEGE OF DENTISTRY

BONE RESORPTION

IN DIABETIC PATIENTS – TYPE II –

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شكر و عرفان :

اول مَن يُشكر و يُحمد اناء الليل و اطراف النهار هو الوهاب الذي اغرقنا بنعمه التي لا تُحصى واغدق علينا برزقه الذي لا يفنى وانار دروبنا وعلمنا ما لم نكن نعلم وحثنا على طلب العلم اينما وجد ووفقنا والهمنا الصبر على المشاق لانجاز هذا العمل المتواضع فله جزيل الحمد والثناء العظيم

والشكر موصول الى كل معلم افادنا بعلمه منذ اولى المراحل الدراسية حتى هذه اللحظة

كما نرفع كلمة الشُكر الى الدكتور المشرف (ايمن حميد) والدكتورة المشرفة (ملاذ عزيز) لمساعدتهم لنا انجاز بحثنا ولم يبخلوا علينا بالنصح والارشاد

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Introduction

Bone resorption is the destruction of bone tissues that promotes bone loss which is a decrease in bone mass and bone density (1) .

Bone resorption decreases post-prandially, a finding which is a significant contributor to increased CTX early morning, i.e., typically the longest fasting period. This post-prandial decrease in bone remodeling has been shown to result from the effects of gastrointestinal hormones, i.e., glucagon-like peptide-2, in reducing resorption . Bone formation markers appear to be less impacted by these factors . Also, calcium intake leads to a reduction in bone resorption markers. Accordingly, samples obtained following overnight fast (8–10 am) provide the most reliable results (2) .

Bone resorption results in lysis of bone and appears radiographically as radiolucency. This is most commonly focal in the horse, but can also be diffuse.

Focal lucencies :

- Changes in bone contour, e.g. flattening of trochlear ridges in cases of osteochrondrosis
- Well-defined lucencies within bone, e.g. osseous – cyst like lesions
- Subchondral bone lucencies, e.g. in osteoarthritis.

Diffuse lesions:

Diffuse bone resorption affecting whole bones is seen in association with disuse osteopenia. This is often best seen at the proximal sesamoid bones which have a honeycomb appearance in affected horses (3) .

Bone formation and resorption are regulated by systemic and local factors acting in concert to maintain bone mass. Calciotropic and steroid hormones have been studied extensively for their effects on bone remodeling. However, there is compelling evidence to support the concept that systemic and locally produced growth factors play a central role in the regulation of bone remodeling. Growth factors regulate the replication, differentiation, and function of bone cells. This is a somewhat arbitrary division since bone remodeling is coupled and osteoclastogenesis is dependent on osteoblastic signals. Furthermore,

cytokines with primary effects on cells of the osteoclast lineage also play a role in the process of bone formation (4) .

Bone formation and resorption are balanced in healthy adults, but formation becomes slower than resorption after menopause and also with aging in both men and women. In menopausal women, decreased estrogen production is associated with accelerated bone loss in the first 5 years after menopause, particularly from the lumbar spine. Evidence indicates that although increasing calcium intake at menopause does not prevent this bone loss, it is beneficial for reducing bone loss in compact bones (e.g., hips, legs, and arms). Furthermore, data suggest that calcium supplementation also reduces lumbar spine bone loss in women who are more than 5 years beyond menopause. In the US, the recommended calcium intake is 1000 mg day−1 for men and women aged 19–50 years and 1200 mg day−1 for men and women aged 51–70 years. Individuals who are not able to obtain this amount of calcium from foods should consider taking calcium supplements to help decrease the risk of reduced bone mass and osteoporosis (5) .

Bone resorption involves both dissolution of bone mineral and degradation of organic bone matrix. Osteoclasts are highly specialized to perform both of these functions. Upon activation of mature multinucleated osteoclasts, the cells attach themselves firmly to the bone surface, using specialized actin-rich podosomes (actin ring), through cytoskeleton reorganization and cellular polarization. Within these tightly sealed zones of adhesion to the mineralized matrix, the osteoclasts form convoluted, villus-like membranes called “ruffled borders,” which substantially increase the surface area of the cell membrane facing the resorption lacuna (Howship’s lacuna). Via these ruffled membranes, the osteoclasts secrete abundant hydrochloric acid (involving the vacuolar H+-ATPase proton pump), mediating acidification of the compartment between the cell and the bone surface, as well as a myriad of enzymes such as lysosomal cathepsins, the phosphatase TRAP (tartrate-resistant acid phosphatase), and proteolytic MMPs (matrix metalloproteinases) . The acidity of the environment leads to dissolution of the mineral phase (crystalline hydroxyapatite), activation of lytic enzymes, and digestion of organic matrix compounds . The sealing mechanism allows localized dissolving and degrading of the mineralized bone matrix, while

simultaneously protecting neighboring cells from harm. During the resorption process, dissolution of hydroxyapatite releases large amounts of soluble calcium, phosphate, and bicarbonate. Removal of these ions is needed (e.g., to maintain the acidic pH in the resorption lacuna) and involves vesicular pathways and direct ion transport via different ion exchangers, channels, and pumps. The degradation products of the organic matrix after enzymatic digestion are transcytosed through the cell for secretion at the basolateral membrane.(6)

Bone resorption and bone formation do not occur randomly throughout the skeleton but are coupled together at discrete foci of functional assemblies termed basic multicellular units (BMUs). Over the course of 1 year, there are about 106 active foci, which follow the programmed temporal sequence of activation, resorption, and formation. At the cellular level, estrogen suppresses the activation ("birth rate") of BMUs and maintains a balance between the resorptive and formative phases. When estrogen is deficient, the activation frequency of new BMUs increases and, at each of them, the resorptive phase is more than the formative phase. The enhanced resorption phase during estrogen deficiency is mainly the result of prolongation of osteoclast life span due to inhibition of apoptosis , although an increase in osteoclast work potential may also contribute.

Although less well established than its effect on osteoclasts, some studies indicate that estrogen increases osteoblast formation, differentiation, proliferation, and function . In addition, two groups have demonstrated that estrogen antagonizes glucocorticoid-induced osteoblast apoptosis and, thus, extends osteoblast life span (7) .

Jaw bone resorption

Bones are not inert structures within the human body; they continue to change over the course of a lifespan. This process of skeletal change is known as bone remodeling, which both protects the structural integrity of the skeletal system and metabolically contributes to the body's balance of calcium and phosphorus(8) .

Jaw bone are known to keep their structure, size, and volume through natural activities such as chewing; however, once the teeth are no longer present, the body thinks that the calcium once in the teeth is no longer needed, which then causes the bone resorption process to occur. During resorption, the bone growth and maintenance stops at the site where a tooth or several teeth are missing. A section of the jaw bone that holds the teeth in the mouth, known as the alveolar bone, will no longer receive .stimuli which then causes bone resorption (9)

Bones are reinforced through osseointegration, where they are used the most. For the jawbone, when chew and bite, the force that exert through the teeth into the jaws sends signals to osteoblasts to keep that bone .strong

When missing a tooth due to tooth extraction, gum disease, or injury, the jawbone in the area of loss no longer receives stimuli, osteoclasts will begin to break down the jawbone, and osteoblasts will no longer prioritize rebuilding the bone structure there. According to Frontiers in Physiology, new bone will still form, but at a slower rate than the bone that is being destroyed. Wearing dentures may increase the rate at which the bone deteriorates. when wear dentures and they've become loose, it may be a result of bone loss, and may require refitting (10).

The Cells of Bone Remodeling:

The Major Players The bone remodeling cycle, which begins in early fetal life, depends on the interaction between two cell lineages. Osteoblast cells contribute to bone growth and derive from the mesenchymal origin. Mesenchymal cells are stem cells that can differentiate into various cell types, such as osteoblasts, chondrocytes, myocytes, and adipocytes. Osteoclast cells cause bone resorption and originate from a hematopoietic lineage, which includes various blood cell types from within the bone marrow. The cellular process of remodeling begins when osteoblast and osteoclast precursor cells fuse to form a multinucleated osteoclastic cell(11).

Osteoclasts

Once the fusion of osteoblast and osteoclastic precursors has occurred, the resulting multinucleated osteoclast attaches to the bone surface and commences resorption. These cells use a combination of lysosomal enzymes and hydrogen ions which work to break down the bone matrix. This bone matrix is comprised of an inorganic portion of calcium phosphate crystals (hydroxyapatite) and an organic portion comprised of collagen, proteoglycans, and glycoproteins. The resorption process leaves "scooped out" regions of the bone matrix (Howship lacunae). It is then believed that a "reversal" phase is conducted by mononuclear cells of macrophage lineage, which continue to degrade and deposit organic material while releasing growth factors to initiate the bone deposition phase(12).

Osteoblasts

The differentiated mesenchymal precursors fill the Howship lacunae by depositing new collagen and minerals. Once the osteoblast has completed the task, it will encounter three fates: flatten and become a cell to line the bone surface, become an osteocyte, or undergo cell death (apoptosis)

Osteocytes

Osteocytes are the most abundant cell type in mature bone. These cell types are situated within the bone matrix and occupy microscopic spaces called lacuna. They play a role in bone remodeling by transmitting signals to nearby osteocytes regarding bone stress (tendons pulling on the bone). Osteocytes are also involved in regulating fluid flow within the bone, so this cellular signal may be due to changes in fluid flow in response to mechanical stresses on the bone. These cells are involved in a process called mechanotransduction, where the mechanical forces are converted to biochemical signals. Osteocytes act as conductors for this signal (or lack thereof) and instruct surrounding cells on how to compensate for and adapt to the mechanical stress.

Symptoms Of Bone Resorption

In most of the cases, a person may not notice tooth resorption for years.

However, as resorption worsens, symptoms often develop, which include:

- swelling and redness of the gums
- pain stemming from the root, crown, or inside of a tooth
- teeth that are brittle and chip easily
- dark or pinkish discoloration
- cavity-like holes in the teeth
- unusual spacing between the teeth (13)

COMMON CAUSES OF JAW BONE DETERIORATION

Numerous events, dental conditions, oral disease, and a patient's choice of dental treatment can compromise

important jawbone characteristics. Some of the more common causes are listed here :

* **Extractions:** As soon as an adult tooth is removed, and not replaced, bone stimulation ceases for that particular site.

* **Trauma:** Events that cause a tooth to be knocked out or broken off to the extent that no biting surface exists (such as broken off at the gum line), bone stimulation ceases.

***Gross Malalignment:** Alignment issues due to growth factors, trauma, and untreated extractions can cause situations where certain tooth structures do not have an opposing tooth structure. The unopposed tooth may super erupt and also undergo underlying bone deterioration.

* **Bridgework:** Custom bridges are a popular treatment for replacing missing teeth. The bone structure underlying the span of missing teeth will undergo deterioration, while only the anchoring teeth continue to provide important bone stimulation.

* **Dentures:** Low cost, unanchored dentures are designed to ride or rest on top of gum tissue. Contrary to what many people want to believe, there is no direct stimulation of jaw bone material. Rather, there may be accompanying loss of gum tissue while the all important underlying bone structure slowly resorbs.

* **Bite Occlusion Abnormalities**: Dentists routinely maintain a close focus on bite and occlusion. Assessment of the biting surfaces assures normal bite characteristics, overall dental function, and patient comfort. Long standing occlusal issues arising from lack of treatment, normal wear and tear, and certain TMJ/TMD problems can cause abnormal physical forces that disrupt the balance of the occlusal relationship. Therefore, significant, bone deterioration can occur with certain tooth structures.

* **Advanced Gum Disease**: Periodontitis, if left untreated, causes wholesale devastation of all tissues at the site of infection. Bone tissue, gingival tissue, and connective tissue all undergo destructive changes that may or may not be fully restorable

Types of bone loss

Horizontal bone loss : most common pattern and it occur when the path of inflamation is to thecrest bone . The crest of bone is peripendicular to the tooth surface and this type of bone loss produce suprabony pocket

vertical bone loss : less common pattern and it occur when pathway of inflamation travels directly into the pdl space . It occur interdentally and can see by radiograph and this type of bone loss can produce infrabony pocket . It increase with age

ossseous craters : are concavities in the crest of the interdental bone confind within the facial and lingual walls(14)

Reasons for high frequency:

The interdental area collects plaque and it difficult to clean

Normal flat or even concave faciolingual shape of interdental septum in lower molar

Vascular pattern

- **bulbous bone contours** : they are bony enlargments caused by exostoses ,adaptation tofunction or butteresting bone . and they are more in maxilla than mandible
- **reversed architecture** : they are produced by loss of interdental bone including the facial plates ,lingual plates or both without concomitant loss of radicular bone . More in maxilla
- **ledges** : are plateau like bone margins caused by resorption of thickend bony plates (15)

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Diseases and medications causes bone resorption

Type2 diabetes mellitus compromises bone microarchitecture by inducing abnormal bone cell function and matrix structure, with increased osteoblast apoptosis, diminished osteoblast differentiation, and enhanced osteoclast-mediated bone resorption. The linkage between these two chronic diseases creates a possibility that certain antidiabetic therapies may affect bone quality. Both glycemic and bone homeostasis are under control of common regulatory factors. These factors include insulin, accumulation of advanced glycation end products, peroxisome proliferator-activated receptor gamma, gastrointestinal hormones (such as the glucose-dependent insulinotropic peptide and the glucagon-like peptides 1 and 2), and bone-derived hormone osteocalcin. This background allows individual pharmacological targets for antidiabetic therapies to affect the bone quality due to their indirect effects on bone cell differentiation and bone remodeling process. Moreover, it's important to consider the fragility fractures as another diabetes complication and discuss more deeply about the requirement for adequate screening and preventive measures. This review aims to briefly explore the impact of T2DM on bone metabolic and mechanical proprieties and fracture risk (16)

Several conditions have been described to cause osteoporosis, including diabetes mellitus. While the relationship between type 1 diabetes and osteopenia is well documented in the literature, data on the presence of this complication in type 2 diabetes have not been well established. A study for a population composed of 66 post-menopausal women with type 2 diabetes and a control population. This study examined bone mineral density with the dual-energy X-ray absorptiometry (DXA) technique at the lumbar and femoral levels and, in a subgroup of patients, they also measured the levels of markers of bone remodelling. they found significantly higher levels of bone mineral density at the femoral (but not lumbar) level in the diabetic subjects compared with the control population in all the examined subregions, except Ward's triangle. Moreover, they found higher levels of some markers of bone resorption (urinary calcium and hydroxyproline, telopeptide) in the patients with diabetes, while urinary crosslinks were higher in the controls. On the basis of these results, they suggest that osteoporosis cannot be considered

a complication of type 2 diabetes and that, from a metabolic point of view, bone resorption is greater in diabetic patients than in normal subjects, as suggested by the high levels of most of the markers of osteoclastic activity (17)

Drug

A variety of medications can increase bone loss and/or fall risk:

1- SYNTHETIC GLUCOCORTICOIDS (E.G. PREDNISONE)
2- BREAST CANCER DRUGS
3- PROSTATE CANCER DRUGS
4- "HEARTBURN" DRUGS
5- DEPO-PROVERA
6- EXCESSIVE THYROID HORMONE REPLACEMENT
7- ANTI-SEIZURE AND MOOD-ALTERING DRUGS
8- BLOOD PRESSURE MEDICATION
9- DIURETICS
10- 10- PROSTATE DRUGS
11- Thiazolidinediones such as rosiglitazone (Avandia®) and pioglitazone (Actos®) are drugs used to treat type 2 diabetes. In men and women aged 40 years and older who were started on these drugs, there was an increased risk of fracture and this risk increased with longer duration of thiazolidinedione use (4 years or more) (18).

Diagnosis

Types of x-ray techniques for diagnosis of ridge resorption :

1- Magnetic Resonance Imaging Techniques :

in the water and the fat compartments of the bone marrow. removal of the RF radiation, the hydrogen atoms relax and emit an RF signal which is detected by information on the 3D organisation of bone by measuring the signal coming from the hydrogen atoms RF coils .These RF impulses provide information on the location and the microenvironment contained in the water and the fat compartments of the bone marrow, information on bone structure can be obtained indirectly by the magnetic field in combination with a radio frequency (RF), the hydrogen atoms can be excited and MRI signal after an image post-processing phase (19).

2- Computed Tomographic Imaging Techniques :

Computed tomographic (CT) imaging techniques allow for assessing the 3D bone organisation by irradiating the bone with an X-ray beam along different directions and by detecting the transmitted radiation. Since the attenuation of the X-ray beam depends on the density of the material crossed, the intensity profile of the revealed radiation contains the compositional information of the bone structure along the analysed direction (20).

3- Quantitative Computed Tomography (QCT) and High-Resolution Peripheral QCT (HRpQCT) :

Quantitative computed tomography (QCT) is a non-invasive CT technique used in clinics to assess the 3D bone geometry. In QCT, both the X-ray source and the detector rotate around the patient. By incorporating a mineral standard in the scan, as visible in , the volumetric BMD, expressed in g/cm3, can be additionally calculated . Many studies have shown a correlation between BMD calculated through QCT and the BMD obtained through DXA, making QCT a potential and alternative tool for osteoporosis screening .

4- Micro- and Nano-CT :

Micro-CT is the most powerful instrument for bone feature assessment at the laboratory scale, enabling the achievement of high isotropic resolutions of up to 1 μm., micro-CT equipment can distinguish between cortical and trabecular bone in a very reliable way. However, these high-resolution analyses are performed exclusively on sedated small animals or on bone biopsies since the scanning of whole bone would require extremely long durations and high radiation exposures, not applicable to patients (21)

5- Dual-energy X-ray absorptiometry (DXA or DEXA) :

In DXA, bone is irradiated by two X-rays for the assessment of fracture risk and for monitoring BMD changes during different energies in order to discriminate the contribution of two types of tissues, i.e., hydroxyapatite anti-osteoporotic drug treatment. In DXA, bone is irradiated by two X-rays with different energies (representative of the bone tissue) and soft tissues. representative transmitted by the bone sample and revealed by the detector provides a 2D greyscale image of the bone tissue and soft tissues. The further elaboration of the radiation transmitted by the bone representing a map of the BMD over the whole irradiated area(22)

level of bone :

The reproducibility of measurements on radiographs is influenced by the techniques by which the images as well as the measurements are obtained. Thus, bias resulting from errors in the image and image examinations at two points in time may result in wrongful registrations of true biological or pathological changes. The aim of the present study was to propose and evaluate an indirect radiological examination technique, by which bias, when measuring radiographic bone level, could be substantially reduced as compared to the technique using direct measurements(23).

Treatment

The net amount of bone lost during aging is determined by the difference between the amount of bone removed from the endocortical, trabecular and intracortical components of its endosteal (inner) envelope and formed beneath its periosteal (outer) envelope. Endosteal bone loss is determined by the remodeling rate (number of basic multicellular units, BMUs) and the negative balance (the difference between the volumes of bone resorbed and formed in each BMU). Bone loss already occurs in young adult women and men and is probably due to a decline in the volume of bone formed in each BMU. The rate of loss is slow because the remodeling rate is low in young adulthood. Bone loss accelerates in women at menopause because remodeling intensity increases and BMU balance becomes more negative as estrogen deficiency reduces osteoblast lifespan and increases osteoclast lifespan. The high remodeling rate also reduces the mineral content of bone tissue. The negative BMU balance results in trabecular thinning, disappearance and loss of connectivity, cortical thinning and increased intracortical porosity. These changes compromise the material and structural properties of bone while concurrent age-related subperiosteal bone formation increases the cross-sectional area (CSA) of bone partly offsetting endosteal bone loss and the loss of structural and material strength. Thus, treatments aimed at reducing the progression of bone fragility, and reversing it, should reduce activation frequency and so reduce the number of remodeling sites, reduce osteoclastic resorption in the BMU, and so reduce the volume of bone resorbed on each of the three components of the endosteal surface thereby reducing the progression of trabecular thinning, loss of connectivity, cortical thinning and porosity. If treatment also increases periosteal bone formation, the CSA of the whole bone and its cortical area will increase. If treatment also increases endosteal bone formation in the BMU, bone balance will be less negative, especially if resorption depth is reduced. This may produce thickening of trabeculae provided activation frequency is not too low. If treatment can increase de novo bone formation at quiescent endosteal surfaces, this will increase cortical and trabecular thickness, and reduce intracortical porosity. In this way, drugs directed at both the resorptive and formative aspects of remodeling, and bone modeling may (i) increase compressive and bending strength of cortical bone by increasing the diameter of the whole bone, its CSA and

the distance the cortical mass is placed from the neutral long bone axis; (ii) maintain or increase peak compressive stress and peak strain in trabecular bone, preventing microcracks and buckling; and (iii) increase the material density of bone tissue, an effect that probably should not be permitted to reach a level which reduces resistance to microdamage accumulation and progression (toughness)(25)

Geminal bisphosphonates (BPs) are a class of drugs considered to be stable analogs of pyrophosphate (P–O–P), a physiological regulator of calcification and bone resorption. A number of BPs have been approved for clinical use in Paget's disease, hypercalcemia of malignancy, and osteoporosis. The major disadvantage of the clinically utilized BPs is their poor oral absorption from the GI tract, typically less than 1% is absorbed. In addition, the BPs have been associated with adverse gastrointestinal effects in humans. The challenge for novel drug delivery systems is to achieve improved bioavailability and safety(26)

How is bone resorption treated؟

Bone resorption treatment depends on the reason for your bone deterioration, so it's important you work with a dental professional to give you clarification on your tooth or jawbone condition .so in DM treatment of bone resorption is bone augmentation

Two techniques of ridge augmentation using onlay bone graft alone or associated with a non-resorbable membrane

Severe cases of bone atrophy in the maxilla or mandible are often reconstructed using bone from extraoral donor sides. Most commonly, grafts from the iliac crest are used for augmentation, however, frequently associated with bone resorption as possible late complication. Calvarial bone grafts, often reported to show less resorption, are an alternative. The aim of this study was to compare the bone stability of vertical bone grafts from the iliac crest and the calvarium. Bone augmentation techniques may be used for the applications of extraction socket defect grafting, horizontal ridge augmentation, vertical ridge augmenta- tion, and sinus augmentation. To maximize the results for each of these applications, a variety of different techniques is employed. They include particulate grafting, membrane use, block grafting, and distraction osteogenesis, either alone or in combination.(27)

Conclousion

Bone resorption is the destruction of bone tissues that promotes bone loss which is a decrease in bone mass and bone density

bone resorption is natural process during life occur by osteoclast cells while new bone is formed by osteoblast cells this called bone remodeling but there is another factors cause bone resorption e.g (extraction , trauma ,denture and bone pathology .There is types of bone loss (vertical ,horizontal and osseous craters)

Type2 diabetes mellitus compromises bone microarchitecture by inducing abnormal bone cell function and matrix structure andA variety of medications can increase bone loss and fall risk :

SYNTHETIC GLUCOCORTICOIDS (E.G. PREDNISONE) , BREAST CANCER DRUGS ، PROSTATE CANCER DRUGS , HEARTBURN DRUGS .

in DM treatment of bone resorption is bone augmentation Best Types of x-ray techniques for diagnosis of ridge resorption is Magnetic Resonance Imaging Techniques And bone level measure .

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