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OSTEOPOROSIS AND PERIODONTAL DISEASE: A COMPREHENSIVE GUIDE

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ABSTRACT

Osteoporosis and periodontitis affect a large number of men and women worldwide with increase in incidence with advancing age. Periodontitis has long been defined as an infection mediated destruction of the alveolar bone and soft tissue attachment of the tooth, responsible for tooth loss among adult populations. Several studies support an association of osteoporosis with the onset and progression of periodontal disease in humans. Systemic loss of bone density in osteoporosis including that of the oral cavity may provide a host system that is increasingly susceptible to infectious destruction of periodontal tissue. Understanding the association between these common diseases and the mechanisms underlying these associations will aid health professionals to provide improved means to prevent, diagnose and treat these very common diseases.

KEY WORDS: Osteoporosis, Osteopenia, Bone Mineral Density, Periodontitis.

INTRODUCTION

Osteoporosis is a skeletal disease characterized by reduction in bone mass and micro architectural changes in the bone, which leads to an increased bone fragility and an increased risk of fracture [1]. Osteoporosis results from an imbalance between the rate of bone formation and resorption that leads to loss of bone mineral mass. Loss of the mineral component of the bone leads to a greater tendency of the bone to be broken [2].

Periodontal disease and osteoporosis, both are chronic inflammatory disorders resulting in a gradual alveolar bone loss and higher risk of fracture, respectively. Periodontitis and osteoporosis are also influenced by age related endocrine disorders that directly or indirectly affect bone homeostasis. A difference between both diseases is that periodontitis is initiated by a localized bacterial infection[3]. Osteoporosis, in contrast, could be attributed to a “sterile inflammation” (indicating an absence of detectable pathogens) as a consequence of cellular senescence. However, in both conditions cells of the immune system, such as T cells, B cells, macrophages or dendritic cells become activated and produce inflammatory cytokines. These

secreted pro-inflammatory signals, such as IL-1 (Interleukin-1) and TNF-α (Tumor necrosis factor) not only promote osteoclast differentiation, but also oppose BMP-2 (Bone morphogenetic proteins) induced osteoprogenitor cells differentiation into osteoblasts. This immune inflammatory response favors bone loss by both an aberrant increased bone resorption and a diminished osteoblast bone formation. Periodontal diseases consist of a spectrum of disorders in the dento-gingival tissues with a predominant dysbiotic and inflammatory nature.

CLASSIFICATION OF OSTEOPOROSIS

Based on the confinement to a particular bone or group of bones

a. Regional Osteoporosis.

b. Generalized osteoporosis

Osteoporosis classification based on disease etiology

On the basis of etiology, osteoporosis can be classified into:

1. **Primary Osteoporosis:** Primary osteoporosis develops as a result of aging or menopause-related bone demineralization. In patients with primary osteoporosis, the bone density decreases as the age progresses.
2. **Secondary Osteoporosis:** Secondary osteoporosis results from more severe loss of bone mass due to pathologies associated with immobilization, medications (iatrogenic), endocrine dysfunction, cancer, and chronic kidney disease.

Osteoporosis classification based on disease severity

Osteoporosis may be classified based on the bone marrow density (BMD). The patients are classified according to the site and method of measurements. The used equipment and reference group of people may also be helpful in classification of osteoporosis. The major value used in the classification of osteoporosis is T-score. T-score may be defined as "patient measured BMD (bone marrow density) value minus the reference BMD value (sex-matched and with a preference for youth) divided by the reference standard deviation (SD) (sex-matched and with a preference for youth)".[4]

The classification of osteoporosis on the basis of BMD measured T-score is as follows:

- T-score less than -1 and more than -2.5: **Osteopenia**
- T-score equal to or less than -2.5: **Osteoporosis**
- T-score equal to or less than -2.5 with history of fracture: **Severe osteoporosis**

The exclusive utilization of T-score and comparing the reference normative data of people aged 20-29 years, as world health organization (WHO) criteria, is very inconsistent. Compared to other classification systems, it is better to standardize the normative data, by including older people and individuals with other findings including BMD measurement at multiple sites, in order to obtain a comprehensive classification system.[4]

Osteoporosis in children[5]

- Bone mass, as measured by DEXA (Dual energy x-ray Absorptiometry), is reported as bone mineral content (BMC) (g) or areal BMD (g/cm2). These values are compared to reference values from individuals of similar age, sex, and ethnicity to calculate the Z-score, the number of SDs from the expected mean. Abundant pediatric reference data is now available for children and teenagers but not for infants.
- It is essential to select norms collected by using equipment from the same manufacturer as that used for the patient because of systematic differences in software. Peak bone mass is achieved in the second or third decade, depending on the skeletal site. Therefore, T-scores (which compare the patient's BMD with that of a healthy young adult) should not be used before 20 years of age.
- The appropriate interpretation of DEXA results may require more than the calculation of Z-scores.
- The Pediatric Development Conference (PDC) guidelines recommend that BMD in children with delayed growth or puberty be adjusted for height or height age or compared with reference data with age, sex, and height-specific Z-scores.
- The terms "osteopenia" and "osteoporosis" are used in older adults to describe degree of deficits (lesser or greater) in bone mass. These terms should not be used to describe densitometry findings in pediatric patients. Instead, a BMC or BMD Z-score that is > 2 SDs below expected (< - 2.0) is referred to as "***low for age***".

The following criteria for osteoporosis in a pediatric patient were agreed on in the 2013 PDC guidelines:[4]

- One or more vertebral fractures occurring in the absence of local disease or high-energy trauma (measuring BMD can add to the assessment of these patients but is not required as a diagnostic criterion);

- Low bone density (BMC or areal BMD Z-scores < - 2.0) and a significant fracture history (2 or more long bone fractures before 10 years of age or 3 or more long bone fractures before 19 years of age).

- Lastly, it is important to recognize that there are certain diseases in pediatric population (e.g., end-stage renal disease and spinal vertebral fractures) in which DEXA (Dual energy x-ray Absorptiometry) does not accurately reflect fracture risk or bone health.

EPIDEMIOLOGY OF OSTEOPOROSIS

According to statistics given by the World Health Organization (WHO), 30 percent of postmenopausal women suffer from osteoporosis [6]. It has been reported that 61 million people in India have osteoporosis and, out of these, 80 percent are women [7]. The peak incidence of osteoporosis in India occurs 10–20 years earlier than in Western countries, which impinges harshly on the health and economic resources[8]. Prevalence statistics of postmenopausal osteoporosis and knowledge regarding its independent predictors are lacking, especially in India, where every third woman and every eighth man is suffering from it [7].

Epidemiological studies show that at present more than 325 million individuals aged 65 years and older have osteoporosis worldwide [9]. Osteoporosis results in 2.5 million bone fractures annually, and it is predicted that this number will increase. Globally, it has been calculated that in 1990 thighbone fractures occurred in 560,000 individuals in Europe, in 360,000 in Northern America, and in 570,000 people in Asia.

RISK FACTORS INVOLVED IN OSTEOPOROSIS

1. Major modifiable risk factors:
   - Inadequate nutritional absorption
   - Lack of physical activity or fall risk
   - Weight loss
   - Cigarette smoking
   - Alcohol consumption
   - Air pollution
   - Stress

2. Major non-modifiable risk factors:
   - History of falls
   - Older age
   - Gender
   - White ethnic background
   - Prior fracture

- Reproductive factors (family history of osteoporosis)

3. Secondary causes of osteoporosis

- Chronic use of certain medications (prolonged corticosteroid use, and so on)
- Hypogonadism
- Hyperparathyroidism
- Chronic liver disease
- Inflammatory diseases (rheumatoid arthritis, and so on)
- Vitamin D deficiency
- Renal disease (history of kidney stones)
- Cardiovascular disease
- Diabetes mellitus
- Dementia

DIAGNOSIS

Diagnosis of osteoporosis can be done by clinical features like neck and shoulder pain, lumbar and back pain, pain or numbness of extremities, fracture of fore arm, fracture on routine activities and also by using plain radiographs, dual energy x - ray absorptiometry (DXA), vertebral fracture assessment, quantitative CT, quantitative ultrasound, single energy x - ray absorptiometry.[10]

DXA (Dual x-ray Absorptiometry) is considered to be the gold standard for diagnosis. Dual X-ray absorptiometry is based on the quantification of axial bone mineral density (spine and hip) by measuring the transmission of a beam of X-ray photons with two energy peaks in the patient's body, which allows for the assessment of the calcium content of the bone.

The primary method for diagnosing osteoporosis and associated fracture risk relies on bone densitometry to measure bone mass. The bone densitometry reports are expressed as a T score (the number of SD above or below the mean bone mineral density for sex and race matched to young controls).The T-score or t-value, which is the number of standard deviations above or below the mean BMD (bone marrow density) of the normal young population of the same sex, has been taken into account for this classification. However, in the case of premenopausal women, men under 50 years of age and children, the Z-score will be considered (in relation to normal subjects of the same age and sex) such that "normal" will be considered up to −2.0.

On the other hand, general blood and urine tests provide information on the general health status and on the existence of elements causing secondary osteoporosis. These markers are really useful tools in identifying metabolic bone diseases, since they provide us with information that is not directly obtained with a bone density measurement or bone histomorphometry.[11] With respect to markers, another commonly used test is bone turnover markers (BMTs), which are capable of measuring peptides of the amino and carboxy-terminal ends in processes of bone matrix formation or degradation.Among these are formation markers that measure osteoblastic activity, i.e., bone-forming activity, such as ALP (Alkaline Phosphatase) and OC (Osteoclast). ALP (Alkaline Phosphatase) is secreted by different tissues (liver, bone, placenta), and its most frequent isoforms are from hepatic and bone (90%).

The most commonly used resorption markers that measure osteoclast activity are: (i) Pyridinolines (Pir) and deoxypyridinoline (Dpir), which link collagen molecules in the bone matrix through covalent bonds, thus forming fibrils [12]; and (ii) ICTP (C-terminal telopeptide of type I collagen), β-CTX (β-CrossLaps) and NTX (N-terminal telopeptide of type I collagen), which are peptides released during the process of bone resorption. β-CTX and NTX are considered to be the most useful resorption markers in clinical practice for the diagnosis of osteoporosis.

In addition, there are other methods, such as ultrasound based on measuring sound velocity and ultrasound attenuation in peripheral skeletal bones. However, it has not been demonstrated that the parameters obtained by this test are clinically useful for monitoring the disease; another assessment technique is quantitative computed tomography, which is based on the measurement of BMD (bone marrow density) volume in trabecular and cortical bones; however, this is a tool that is not recommended, since its economic cost is very high, and it exposes the patient to greater ionizing radiation than DEXA (Dual energy x-ray Absorptiometry). Finally, osteoporosis could be diagnosed through a biopsy of bone tissue. This is a very invasive technique in which a tissue sample is extracted, and it is only performed when evidence of tumors is detected.

INFLUENCE OF OSTEOPOROSIS IN PERIODONTAL DESTRUCTION

The relationship between osteoporosis and periodontal disease may be supported by the following mechanisms[13]:

1. **Systemic to local bone resorptive disease**: Other than the hormonal effect, the systemic to local bone resorptive disease is considered for describing the link between osteoporosis and periodontitis. Osteoporosis of the alveolar bone may lower the resistance of the periodontium to infectious challenge and may result in a local infection of the periodontium that first invades the cortical bone and results in a dimensional change in the alveolar ridge.

2. **Hormonal impact on bone homeostasis inflammation:** A major risk factor following menopause is estrogen deficiency that inevitably acts as a risk factor for osteoporosis. Deficiency of estrogen affects systemic bone homeostasis that further compromises absorption of calcium and increases excretion of calcium which increases overall requirements of the human body a marked decrease in levels of estrogen induces osteocyte apoptosis that is known to abruptly affect homeostasis of bone. On the other hand, estrogen is known to alter inflammatory responses.

Few studies conducted on hormone replacement therapy (HRT) carried out in humans have reported improved mandibular bone density by reducing gingival bleeding and mobility of the teeth. Another hormone associated with homeostasis of bone is Parathyroid hormone (PTH), which increases resorption of bone to ensure sufficient levels of calcium within the blood. Thus, intermittent PTH application also aids to improve healing of the periodontium thereby promoting bone regeneration.[14]

Together, these interactions suggest a possible link of interaction of hormones related to bone remodeling and inflammation may be a mechanism that links osteoporosis and periodontitis.

1. **Inflammation and bone homeostasis:** Individuals suffering from osteoporosis are known to have increased systemic levels of pro-inflammatory cytokines IL-1, IL-6 and TNF- α (Tumor necrosis factor). These cytokines in turn are associated with induction of bone resorption and altered tissue response to periodontal disease. Moreover, the cycle of bone remodeling involves “physiologic inflammation” that further recruits non-phlogistic macrophages for the clearance of osteoclastic apoptotic cells.

2. **Low bone density in the oral bone associated with low systemic bone:** Osteoporosis results in loss of BMD (bone marrow density) throughout the body, including the maxilla and the mandible. The resulting low density in the jawbones leads to increased alveolar porosity, microarchitectural deterioration of trabeculae, reduced remodelling rate,

reduction in volume of the residual ridge, and decrease in the cortical thickness following invasion by periodontal pathogens.

3. **Oral implications of osteoporosis**: Estrogen used in hormone replacement therapy of postmenopausal women is known to cause reduced gingival inflammation and a reduced frequency of gingival attachment loss in osteoporotic women in early menopause.

Role of genetics in bone mineral density

1. Vitamin D receptor gene (VDR): The first candidate gene to be studied in relation to BMD regulation was the VDR gene was and most attention has focused on polymorphisms situated on the 30 flank of VDR recognised by the restriction enzymes BsmI, ApaI and TaqI.[15]

2. Collagen type I αI (COLIA1) : The COLIA1 gene encoding the αI chain of type I collagen is an important functional candidate for the pathogenesis of osteoporosis, as type I collagen is the major protein of bone.

3. Estrogen receptor gene : The estrogen receptor encoded by the ESR1 gene, is another important functional candidate for the regulation of bone mass.

4. Transforming growth factor β-1(TGFβ-1): Langdahl et al. 1997 and Yamada et al. 2001 studied polymorphisms of the TGFβ-1 gene that encodes the growth factor TGFβ-1 have been studied and few of them have been associated with BMD and/or increased risk of osteoporotic fractures.

5. Lipoprotein receptor related protein-5: Gong et al 2001 assessed activating mutations and reported them to be associated with Lipoprotein receptor related protein-5 result in bone mass aggregations whereas inactivating mutations of the similar gene predispose individual to rare autosomal recessive disorders, for eg., osteoporosis pseudoglioma syndrome (Little et al 2002).

6. Sclerostin: Balemans et al 2001, 2002; Brunkow et al 2001 studied mutations affecting the SOST gene that encode sclerostin and further lead to sclerosing bone dysplasia's like Van Buchem disease, Sclerosteosis. Uitterlinden et al 2004 studied association of sclerostin with BMD in men and women and reported it to increase with age. These study mechanisms show SOST polymorphisms regulate BMD in aged individuals.

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Table 1- Important studies assessing the relationship between osteoporosis and periodontitis

Author	Subjects And Study Setting	Type Of Study	BMD Assessment	Periodontal Parameters	Results
Mashalkar et al.(2018)[16]	94 post-menopausal women in Maharashtra	Cross sectional	DXA	OHI,PI, CAL	A statistically significant correlation was found between periodontitis and BMD
Silveria et al. (2016)[17]	4,678 subjects in Pomerania	Cross sectional	Quantitative ultrasound of heel	CAL, tooth loss	Reduced bone stiffness was associated with CAL and tooth loss in women but not in men
Richa et al.(2016)[18]	Post-menopausal women (aged 45 - 65 years) in Bangalore	Cross sectional	Quantitative ultrasound	CAL, BOP, gingivitis	Skeletal BMD is related to CAL, BOP, gingivitis
Ignasiak et al. (2016)[19]	91 post-menopausal women	Cross sectional	DXA of radial bone	Tooth number, PPD, gingival bleeding	BMD not significantly correlated with tooth number and gingival bleeding
Juluri et al. (2015)[20]	50 osteoporotic and 50 non osteoporotic women (aged 50 - 65 years)	Case control	DXA	PPD, CAL, ABL	Osteoporotic women had significantly greater PPD, CAL, ABL
Darcey et al. (2013)[21]	395 post-menopausal women (aged 45-70 years), Greater Manchster	Cross sectional	DXA	PPD, PI, GI	No significant association between osteoporosis status and moderate to severe periodontitis
Gondim et al. (2013)[22]	148 women	Cross sectional	DXA lumbar spine,femora	PPD. CAL, BOP, tooth loss	Inverse relationship of severe CAL

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			1 neck		with BMD of the femoral neck, positive association of severe CAL with tooth loss
Bertulucci et al. (2012)[23]	99 post menopausal women	Case control	DXA lumbar spine	PPD, PI, GI, CAL	Significant difference in periodontal status between normal and osteoporosis group and between osteoporosis and osteopenia group
Gomes-Filho et al. (2007)[24]	139 postmenopausal women in Brazil:	Case control	DXA of femur and/or lumbar column	PD, GR, CAL	Postmenopausal women with osteoporosis and low educational levels have a greater chance of having periodontal disease than do those without osteoporosis.
Wactawski-Wende et al.(2005)[25]	1341 post-menopausal women (aged 53 – 85),New York	Cohort	DXA	Alveolar crestal height (ACH)	Strong and consistent association between ACH and T score in post menopausal women
Yoshihara et al.(2004)[26]	600 subjects aged 70 years, Japan	Longitudinal	Ultrasound of heel bone	Probing attachment level (PAL)	Significant association between BMD and PAL

[DXA - dual-energy X-ray absorptiometry,OHI – oral hygiene index, GI – gingival index, PI – plaque index, BMD – bone mineral density, ABL – alveolar bone loss, PD –probing depth, CAL – clinical attachment loss, GR – gingival recession.]

CONCLUSION

Osteoporosis and periodontal disease both are silent diseases that manifest as poor bone density before a fracture occurs. As the Indian population ages, identifying the link between osteoporosis and periodontitis can encourage people to take preventive measures. There are various ways to lessen the burden of two chronic diseases while enhancing quality of life. Dentists should identify individuals with numerous risk factors, including aging and smoking, and offer a fracture risk assessment with their primary care physician based on their periodontal health. Longitudinal studies are needed to explore effective multidisciplinary management and therapy options for these disorders.

The complex relationship between oral and systemic health is shown by the association between osteoporosis and periodontal disease. Age, hormonal fluctuations, and inflammation are frequent risk factors for both illnesses, which results in a reciprocal relationship where one exacerbates the other.

Because of its reduced bone density, osteoporosis weakens the jawbone and increases its vulnerability to periodontal disease. On the other hand, the inflammatory disease known as periodontal disease, which affects the tissues that support teeth, can lead to bone loss in the skeleton as well as other parts of the body.

Moreover, new research indicates that periodontal disease and osteoporosis can be related by similar molecular mechanisms, especially those involving inflammatory cytokines and osteoclast activity. For dental and medical experts, this link has important clinical ramifications.

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