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EVALUATION OF RECENT UPDATES REGARDING POST-MENOPAUSAL MANAGEMENT

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Abstract

Background: *Osteoporosis is a skeletal disorder characterized by low bone mineral density that increases fracture risk. The prevalence of osteoporosis is expected to increase even further due to the reported increase of life expectancy worldwide and the costs of osteoporotic fracture–related morbidity and mortality are going to burden the healthcare system. Optimization of bone health throughout life can help prevent osteoporosis and its consequences. Many studies have been published in order to examine osteoporosis management strategies and their efficacy.*

Objective: *A lot of literature have been done in order to provide a better outcomes for patients presented with post-menopausal osteoporosis, in our review we aim to discuss the recent literature that discussed the recent updates regarding its management.*

Method: *PubMed database were used for articles selection. All relevant articles related to our review were chosen to cover the following topics: Osteoporosis, Post-menopausal, Management and Diagnosis. We excluded other articles, which are not related to our objectives. The data have been extracted according to specific form to be reviewed by the authors.*

Conclusion: *The mainstay of prevention and treatment of postmenopausal osteoporosis is estrogen replacement therapy. In addition, increasing calcium intake and vitamin D is needed for bone growth and bone remodeling by osteoblasts and osteoclasts. Bisphosphonates are the most used anti-resorptive agents in the world for the treatment of osteoporosis and are in use for three decades. The most known anabolic therapy is PTH. Regarding prevention, exercise has the potential to be a safe and effective way to avert bone loss in postmenopausal women.*

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INTRODUCTION:

Osteoporosis is a skeletal disorder characterized by low bone mineral density (BMD) that increases fracture risk. An epidemiological analysis showed that 34% of healthy Saudi women, and 30.7% of men, 50-79 years of age are osteoporotic. The prevalence of osteoporosis is expected to increase even further due to the reported increase of life expectancy in KSA from 45-67 years in 1960 to 75.7 years in 2013 [1]. Lifestyle factors play a significant role in the high prevalence of this disease. The main factors are low calcium intake, lack of physical activity, and a higher prevalence of vitamin D deficiency. In KSA, there is approximately 8,768 femoral fractures each year costing billions, and being an endemic area for vitamin D deficiency, bone health is becoming a serious concern in the kingdom [2].

Risk factors consistently associated with bone loss in elders include female sex, thinness, and weight loss of 5% or more. On the other hand, gaining weight (5% or more) appears to protect against bone loss in both men and Women [3].

A population-based, large cohort study of 10-year incident osteoporosis-related fractures shows that hip fracture risks in the oldest men and women are similar. Forearm fractures are known to be associated with osteoporosis for women, but rib fractures appear to show a similar predominance as osteoporotic fractures in men [4]. Another study found that women with no regular walking were in more risk of osteoporosis [5]. Alcohol intake clearly has a harmful effect on bone density in young women, which until nowadays has not been recognized. Alcoholism is associated with osteoporosis perhaps due to a general toxic effect on the bone forming Cells [6].
Many studies have been published to improve the management strategies of osteoporosis and to test the used treatment plans. Therefore, in this review, we will discuss the recent literature published regarding osteoporosis and we will try to provide a sufficient review on the commonly used treatment methods.

METHODOLOGY:

Sample

We performed comprehensive search using biomedical databases; Medline, and PubMed, for studies concerned with Bronchiolitis management and diagnosis published in English language. Keywords used in our search through the databases were as {Osteoporosis, Post- menopausal, Management and Diagnosis}. More relevant articles were recruited from references lists scanning of each included study.

Analysis

No software was used, the data were extracted based on specific form that contain (Title of the study, name of the author, Objective, Summary, Results, and Outcomes). Double revision of each author outcomes was applied to ensure the validity of the findings.

DISCUSSION:

Peak bone density seems to have been achieved by the end of or soon after linear skeletal growth. There is no evidence of any increase in bone density in the third or fourth decade. There is a gradual age-related decline in bone density in the femoral neck and Ward's triangle before the menopause but no appreciable loss of vertebral bone density at this time. The menopause has the single greatest effect on bone density in any site [6].

Cellular control of bone mass is done by osteoblasts and osteoclasts. Osteoblasts are bone-forming cells. They both secrete osteoid and conduct its mineralization. The collagen fibrils within the osteoid are arranged into linear columns, forming pores and holes. At these sites, mineralization is initiated. Osteoblasts have receptors for several factors that are known to control bone metabolism, most notably parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D [7].

Osteoporosis is a metabolic disorder with complex effects on bone and its homeostatic regulation. Endogenous hormonal changes and external mechanical loads resulting from physical activity are the factors controlling and influencing bone homeostasis. These impart their effects through regulation of the relative activities of bone cells, in particular osteoblasts which control bone deposition and osteoclasts which control bone resorption. Most simply, osteoporosis arises from an imbalance of bone formation and bone resorption. Peak bone mass is achieved between the ages of 16 to 25 years in most people. After this age, bone mass slowly, but continuously, decreases. Decreases in bone mass are inevitable with age. Primary osteoporosis related to aging has been classified as type II, or senile, osteoporosis. The type I disorder is related to the onset of menopause and is thus termed postmenopausal osteoporosis. Estrogen deficiency is the major contributing factor to bone loss after menopause. Estrogens decrease during the menopausal period induce an increase in Receptor activator of nuclear factor kB (RANK) ligand (RANKL) and a decrease in osteoprotegerin secretion from osteoblasts. RANKL activates its RANK receptor on the surface of the pre-osteoclasts, which

induces their differentiation and activation. This imbalance induces fast bone loss, and increases the risk of fractures. Other causes of osteoporosis can be secondary, such as that caused by long-term corticosteroid use or endocrinopathy [7,8].

DIAGNOSIS:

Screening and diagnosis use a BMD measurement that estimates bone strength [9]. Dual-energy X-ray absorptiometry (DXA) is the most widely used, validated technique to measure BMD. BMD is reported as a T-score, defined as the difference in number of standard deviations (SDs) from the mean BMD of a normally distributed, healthy adult reference population [10]. It is expressed as a negative number. The World Health Organization (WHO) defines osteoporosis as a BMD greater than 2.5 SDs below the average. Normal bone is no more than 1 SD below this value, and osteopenia is 1 to 2.5 SD below average. Severe osteoporosis is BMD greater than 2.5 SD below average and one or more fragility fractures [11,12].

MANAGEMENT:

- **Calcium**

The skeleton contains 99% of the body's calcium supply, which is mobilized when serum calcium levels are low. Adequate calcium levels are crucial for bone health and muscle performance, which are closely associated with balance and fall risk. Maintaining a calcium intake of at least 1000-1200 mg/day has long been recommended for older individuals to treat and prevent osteoporosis [13]. (Tai et al.) [14] published a meta-analysis on 51 RCTs to determine whether increasing calcium intake from dietary sources affects BMD. They found that increasing calcium intake from dietary sources increases BMD by a similar amount to increases in BMD from calcium supplements. In each case, the increases are small (1-2%) and non-progressive, with little further effect on BMD after a year. The small effects on BMD are unlikely to translate into clinically meaningful reductions in fractures. Long term use of calcium was suggested to be linked to increased cardiovascular risk. However, this recent debate has been opposed with a meta-analysis and a long-term follow-up randomized controlled trial disproving this theory [13,14].

- **Vitamin D**

Vitamin D status is best assessed by measuring levels of 25-hydroxyvitamin D. Many authors consider 30 ng/mL as the lower limit of the normal range, because this level is associated with lower PTH concentrations, with greatest calcium absorption, highest BMD, reduced rates of bone loss, reduced rates of falls, and reduced fracture rates. Doses higher than 1,000 IU/day of vitamin D3 are necessary to maintain 25-hydroxyvitamin D within normal range (> 30 ng/mL) in osteoporotic patients [8].

- **Calcium plus vitamin D**

It is well known that vitamin D promotes calcium absorption in the gut and helps to maintain adequate serum calcium concentrations to enable normal mineralization of the bone. Vitamin D is needed for bone growth and bone remodeling by osteoblasts and osteoclasts. Recently, Calcium plus vitamin D supplementation has been widely recommended to prevent osteoporosis and subsequent fractures. However, considerable controversy exists regarding the association of such supplementation and fracture risk. Therefore, (Weaver et al.) [15] conducted a meta-analysis of RCTs of calcium plus vitamin D supplementation and fracture prevention in adults. They found that combined calcium plus vitamin D supplementation is statistically significantly associated with reduced total and hip fractures across various populations. Their results indicated that supplementation could decrease the risk of total fractures by 15% and hip fractures by 30%.

- **Estrogen**

Perimenopause and postmenopause, an increase occurs in the lifespan of osteoclasts and a concomitant decrease in osteoblast lifespan. This was linked to estrogen deficiency. Moreover, it has been shown that breast cancer women treated with aromatase inhibitors are at increased risk of bone loss. Even the low residual levels of estrogen present in postmenopausal women are important in reducing bone resorption. Therefore, the mainstay of prevention and treatment of postmenopausal osteoporosis is estrogen replacement therapy [16,17]. A 2002 meta-analysis on a 57 RCTs found that hormonal replacement therapy has a consistent, favorable and large effect on bone density at all sites [18]. Nevertheless, BMD declines after cessation of HRT. (Yates et al.) [19] found that postmenopausal women who have discontinued HT within the past 5 years have a risk for hip fracture that is at least as high as that in women who have never used HRT. In addition, HRT can

be seen as an effective option for prevention of osteoporosis in peri- and postmenopausal women. The use of a standard dose of HRT for osteoporosis prevention is based on biology, epidemiology, animal and preclinical data, observational studies and randomized, clinical trials. It rapidly normalizes turnover, preserves BMD at all skeletal sites, leading to a significant, reduction in vertebral and nonvertebral fractures [20].

- **Selective Estrogen Receptor Modulator (SERM)**

Tamoxifen is the first SERM to be widely used for the treatment of breast cancer and has been demonstrated to reduce the risk of breast cancer in high-risk women. Raloxifene is a second-generation SERM that is FDA-approved for the prevention and treatment of osteoporosis. Like tamoxifen, raloxifene binds to the ER, imparting estrogenic effects on bone and lipid metabolism, and anti-estrogenic effects on the breast. Unlike estrogen, however, raloxifene displays anti-estrogenic effects on the endometrium. For this reason, it has been theorized that raloxifene could possibly serve as a safer alternative to tamoxifen in the prevention setting. Compared with with bisphosphonate therapy, the effects of raloxifene on BMD and markers of bone turnover have generally been more modest. Raloxifene therapy had no effect on non-vertebral fracture risk after 8 years and also showed an increased risk of fatal stroke and venous thromboembolism among postmenopausal women. The only advantages of raloxifene are it is associated with mild reduction of vertebral fracture risk and it reduces the risk of ER-positive invasive breast cancer and endometrial cancer [21].

- **Denosumab**

RANKL is a product of the osteocyte and a member of the tumor necrosis factor cytokine family. It is an osteoclast differentiating factor. Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor kappa-B ligand (RANKL). It inhibits osteoclast formation and increases BMD. The pivotal clinical trial leading to the approval of denosumab as a treatment of osteoporosis is known as Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) [22]. In this study, there was a 68% reduction in risk of new vertebral fractures, a 40% reduction in risk of hip fractures, and a 20% reduction in risk of non-vertebral fractures in the denosumab group compared with placebo [23]. However, the same trial found the incidence of eczema and cellulitis including erysipelas, to be significantly greater in denosumab-treated women compared to placebo. In addition, FDA warned individuals who have severe renal impairment or are receiving dialysis because denosumab can induce hypocalcaemia in them.

- **Bisphosphonates**

Bisphosphonates are the most used anti-resorptive agents in the world for the treatment of osteoporosis and are in use for three decades. (Watts et Diab) [24] reviewed the pharmacology and mechanism of action of bisphosphonates and the clinical studies that support their efficacy. They found that bisphosphonates can remain as long as 10 years in the skeleton for the reason that they accumulate in bone and provide some residual anti-fracture reduction when treatment is stopped. Basically, bisphosphonates decrease bone turnover leading osteoclasts to apoptosis. Alendronate was the first bisphosphonate approved by the FDA for the prevention and treatment of osteoporosis. Alendronate is also approved for treatment to increase bone mass in men with osteoporosis and for the treatment of osteoporosis in men and women taking glucocorticoids [25,26]. Alendronate reduces the incidence of spine and hip fractures by about 50% over 3 years in patients with a prior vertebral fracture or in patients who have osteoporosis at the hip site. It reduces the incidence of vertebral fractures by 48% over 3 years in patients without a prior vertebral fracture [23,13]. In addition, (Eriksen et al.) [27] systematic review showed that long-term use of bisphosphonates resulted in persistent anti-fracture and BMD increasing effects beyond 3 years of treatment. Therefore, Bisphosphonates are the first line treatment for osteoporosis postmenopausal, glucocorticoid-induced and male osteoporosis. However, bisphosphonate treatment is not without its issues. They predispose to esophageal irritation and gastrointestinal side effects when administered orally and leads to discontinuation of the drug in up to 20% of subjects. Intravenous bisphosphonate infusion is associated with transient flu-like symptoms in about 20–30% of cases. Moreover, intravenous bisphosphonates are not advised in those with renal dysfunction because their clearance occurs via the kidney and

because they have high affinity for bone mineral results in prolonged skeletal retention and accumulative drug exposure. Therefore, the sole use of bisphosphonates as treatment for osteoporosis is imperfect [25,26,27]

- **PTH**

It was noted that combinations of anabolic and anti-resorptive agents have potential to improve bone density and bone strength more than either agent as monotherapy. The most known anabolic therapy is PTH. Teriparatide is a recombinant form of human PTH (1–34 N-terminal fragment) and is FDA approved for use in postmenopausal women with osteoporosis, hypo-gonadal or primary osteoporosis in men and in both men and women suffering from glucocorticoid-induced osteoporosis. Teriparatide reduces the risk of vertebral fractures by about 65% and non-vertebral fragility fractures by about 53% in patients with osteoporosis, after an average of 18 months of therapy [25,26].

- **Anabolic and Anti-resorptive Combinations**

(Felicia Cosman) [28] reviewed and summarized the key combination trials and the evolving concepts regarding combination treatment using anabolic and anti-resorptive agents together. The effects of combination therapies are site-dependent. The most consistent effect of combining anti-resorptive agents with teriparatide is a superior hip BMD. This is most evident when teriparatide is combined with a bisphosphonate or denosumab. In contrast to findings in the hip, there is no benefit to spine BMD with combination therapy vs monotherapy in the majority of studies.

- **Exercise**

As mentioned earlier, a study found that women with no regular walking were in more risk of osteoporosis [5]. In 2011, a cochrane systematic review found that exercise has the potential to be a safe and effective way to avert bone loss in postmenopausal women. The most effective type of exercise intervention on BMD for the neck of femur appears to be non-weight bearing high force exercise such as progressive resistance strength training for the lower limbs [29]. In addition, weight-bearing and muscle-strengthening exercise is recommended because it improves agility, posture, balance, and strength to prevent falls [30].

CONCLUSION:

Perimenopause and postmenopause, an increase occurs in the lifespan of osteoclasts and a concomitant decrease in osteoblast lifespan. This was linked to estrogen deficiency. Therefore, the mainstay of prevention and treatment of postmenopausal osteoporosis is estrogen replacement therapy. Also, increasing calcium intake from dietary sources increases BMD but by this increase is small and non-progressive. Vitamin D is needed for bone growth and bone remodeling by osteoblasts and osteoclasts. Recently, calcium plus vitamin D supplementation has been widely recommended to prevent osteoporosis and subsequent fractures. Bisphosphonates are the most used anti-resorptive agents in the world for the treatment of osteoporosis and are in use for three decades. However, the sole use of bisphosphonates is imperfect. It was noted that combinations of anabolic and anti-resorptive agents have potential to improve bone density and bone strength more than either agent as monotherapy. The most known anabolic therapy is PTH. Regarding prevention, exercise has the potential to be a safe and effective way to avert bone loss in postmenopausal women.

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