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REVIEW ARTICLE

A comprehensive review on understanding and managing osteoporosis

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ABSTRACT
Osteoporosis, characterized by diminished bone mass and increased fracture susceptibility, stems from an intricate interplay of factors influencing bone remodeling, notably the activities of osteoclasts and osteoblasts. Advancing age, hormonal shifts, medication usage, and lifestyle choices all contribute to the gradual deterioration of bone density and structure. To counteract this process, preventative measures such as adequate calcium intake, weight-bearing exercises, and hormonal management are crucial. Complementary botanical supplements like dandelion, turmeric, guggul, and many more offer promising avenues for supporting bone health, though further research is needed to establish their efficacy and safety. By addressing these multifaceted aspects of osteoporosis, we can develop comprehensive strategies to mitigate its impact and enhance the well-being of affected individuals. This comprehensive review delves into the underlying mechanisms, risk factors, preventative measures, and treatment modalities associated with osteoporosis.
Keywords: *Osteoporosis, botanicals, management, bone remodelling, bone health.*

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INTRODUCTION

Osteoporosis is a medical condition that is a progressive weakening of bones. Osteoporosis is characterized by a decrease in bone mass, a deterioration of bone structure, and an alteration of the microstructure of the bone. This causes weakened bone strength and affects the health of individuals [1]. Although bone tissue is continually broken down and repaired, osteoporosis patients do not generate new bone at a rate that keeps up with the loss of existing bone. As a result, bones become porous and more prone to fractures, especially in the hip, spine, and wrist. They also lose density and strength [2]

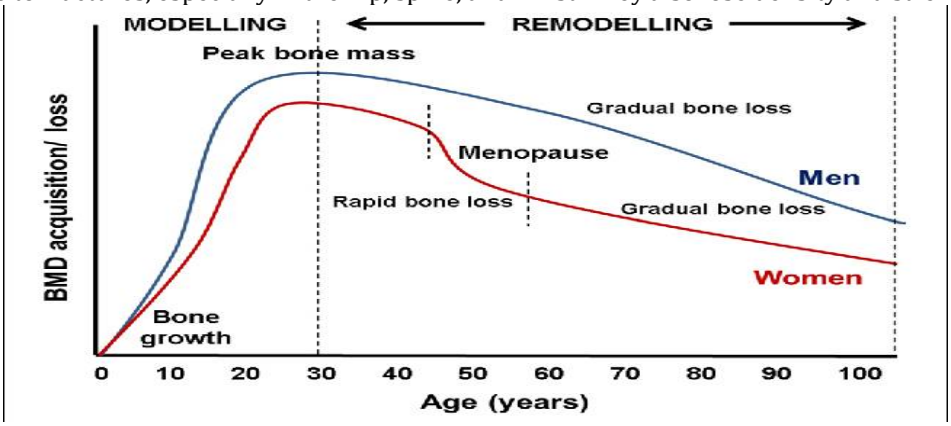

Figure 1: Bone loss as per age

Osteoporosis is again categorised into primary and secondary osteoporosis.

PRIMARY OSTEOPOROSIS:

Due to menopause and age factor

Hormones play a crucial regulatory role in bone remodeling by inhibiting bone resorption and promoting the development of bone. These include estrogen, testosterone, and parathyroid hormone (PTH). The zenith of bone mass is typically achieved between the ages of 25 and 30 in females. In elderly females, adverse bone remodeling affects both cancellous and cortical bone, disrupting bone microarchitecture and overall bone loss. Specifically, cancellous bone exhibits trabecular thinning, while cortical bone shows decreased thickness alongside increased cortical porosity [9].

SECONDARY OSTEOPOROSIS:

Drug induced osteoporosis:

Prolonged usage of glucocorticoids can give rise to complications, notably glucocorticoid-induced osteoporosis (GIO). The mechanism involves glucocorticoids fostering the distinction and development of osteoclasts while preventing bone formation by encouraging osteoblast and osteocyte cell death. This impact leads to increased decay of bones and decreased bone building. Furthermore, by inhibiting type I collagen synthesis, glucocorticoids limit insulin-like growth factor 1 (IGF1), a crucial component in bone development. This results in collagen breakdown with osteoblast apoptosis [10].

OSTEOCLAST:

Once monocyte/macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor kappa B (RANK) with its ligand (RANKL) are activated, osteoclasts are differentiated from hematopoietic stem cells (HSCs). Numerous other elements may regulate the differentiation and activity of osteoclasts, like inflammatory cytokines including interleukin 1 (IL-1), IL-6, tumour necrosis factor-α (TNF-α), and αVβ3 integrin [4,5,11].

OSTEOBLAST:

In the growing skeleton and during the process of bone remodeling, osteoblastic cells are in charge of building new bone [6]. Numerous cytokines and growth factors are secreted by bone cells alongside other cells in the bone marrow segment. These substances exert their effects on osteoblasts through both autocrine and paracrine mechanisms, influencing cell proliferation, differentiation, and viability. The secreted factors and signaling pathways either stimulate or inhibit the expression of transcription factors crucial for osteoblast differentiation [7,8].

MECHANISM:

It is an intricate procedure for OCs to differentiate from hematopoietic stem cells, influenced by several factors. Its mechanism is divided into five different stages

1. **Differentiation Stimuli:**
   The commencement of osteoclast differentiation is triggered by the action of colony-stimulating factor for macrophages and monocytes (M-CSF). M-CSF acts upon hematopoietic stem cells, facilitating their transition into osteoclast precursors [11].
2. **RANK-RANKL Signaling:**
   RANKL, a crucial component in osteoclast biology, plays a central role by being essential for both osteoclast formation (osteoclastogenesis) and the process of bone resorption [12]. One of the most important phases in the distinction between osteoclasts is the activation of the RANKL. Through such interaction, signaling pathways are set in motion, causing these precursors to differentiate into fully grown osteoclasts [13].
3. **Inflammatory Cytokines:**
   IL-1, IL-6, and tumour necrosis factor-alpha (TNF-α) are examples of inflammatory cytokines that regulate osteoclast function and development [11,13]. These cytokines can augment RANKL-mediated signaling, thereby facilitating osteoclast formation and function.
4. **αVβ3 Integrin:**
   The αVβ3 integrin plays a crucial role in anchoring osteoclast precursors to the bone surface. Additionally, this integrin is instrumental in the assembly of the sealing zone, a specialized structure that promotes the resorption process by establishing a microenvironment conducive to efficient bone degradation. [10,14].
5. **Resorption Process:**
   After differentiating, osteoclasts attach themselves to the edge of the bone and release enzymes and acid to start the process of forming a resorption lacuna. This resorption lacuna serves as a site for the dissolution of bone matrix, facilitating the release of calcium and other minerals into the bloodstream. [14]

THE PATHOLOGICAL MECHANISM:

The interplay of M-CSF, RANK-RANKL signaling, inflammatory cytokines, and integrins orchestrates the intricate process of osteoclast differentiation and function in bone remodelling. Moreover, epigenetic modifications such alterations in the methylation of DNA and non-coding RNA can lessen the generation of osteogenic genes [15,16].

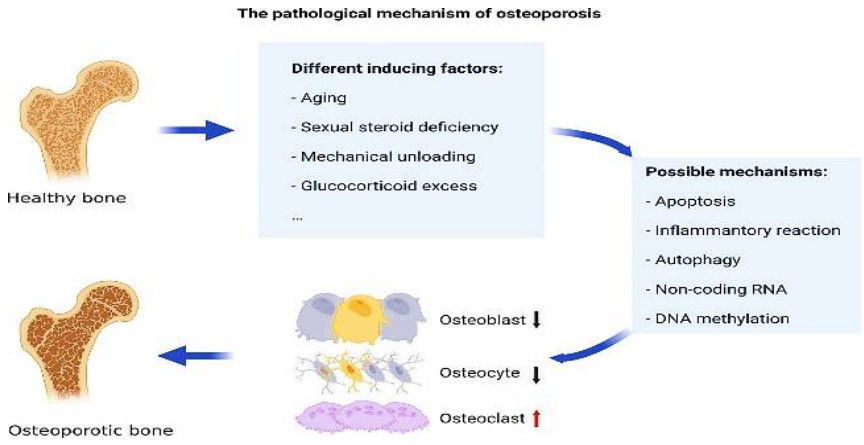

Figure *2*: Pathological mechanism of osteoporosis

MOLECULAR MECHANISM OF OSTEOPOROSIS:

It includes the binding of parathyroid hormone to parathyroid receptor which are present on the osteoblasts. Which causes the rank ligand (RANKL) binding on premature osteoclasts.

This interaction activates the premature osteoclasts. Resulting in formation of pits and trails on bone by prompting acid to hydroxyapatite (mineral compound of bone) and release the enzyme causing the bone degradation. [17].

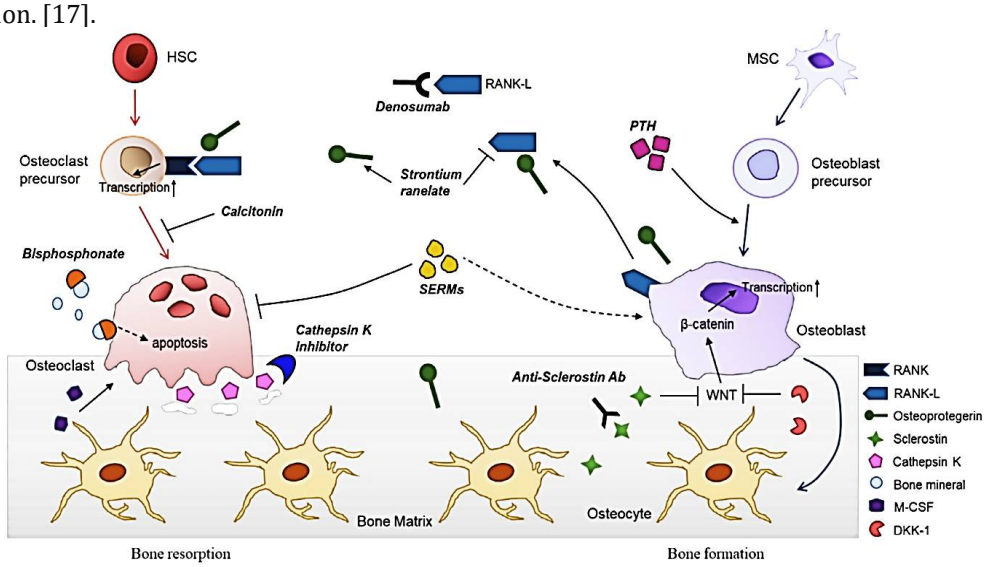

Figure *3*: Molecular mechanism of osteoporosis

COMMON RISK FACTORS

Aging
Hormonal changes / Imbalance
Hypogonadism
Low body weight
Improper diet
Adrenal gland hyperplasia
Certain medications or medical conditions.
E.g.: Medical conditions like: Hypoxia

A hypoxic environment promotes bone formation and increases the osteoclasts' ability to resorb bone. This will directly result in bone resorption or more breaking down of bone tissue hence there will be less bone mineral density. Leading to Secondary Osteoporosis [18]. Also, Age-related bone loss is accelerated by low estrogen following menopause [30].

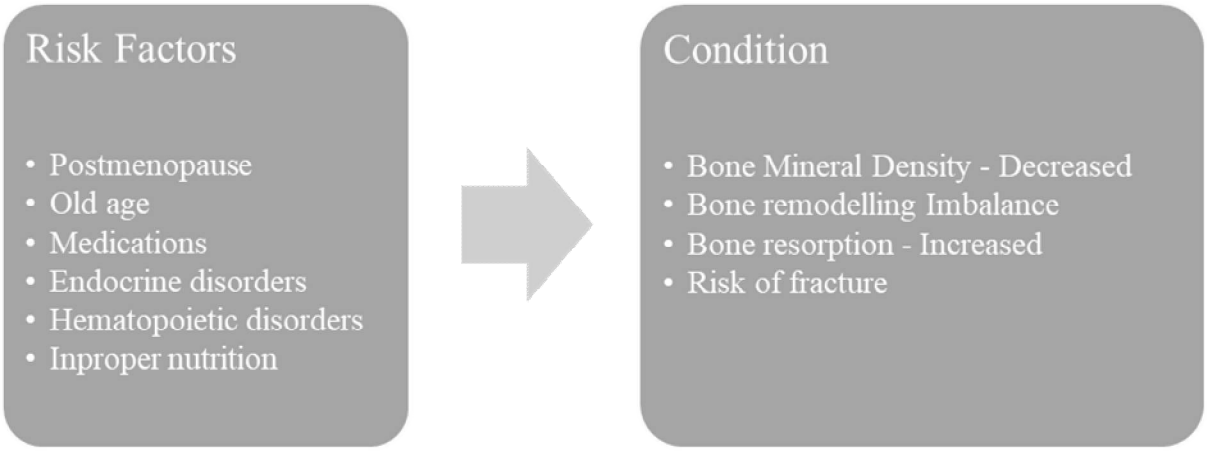

Figure 4: Risk factors leading to osteoporosis

PREVENTION AND MANAGEMENT:

Research / recent studies on calcium and bone development suggest that efforts to prevent osteoporosis should commence around puberty, particularly at the onset of menarche, as peak bone mass can be achieved up to the age of 20.

1. **Lifestyle modification:**

Inhibiting osteoclast activity often involves a combination of pharmacological interventions, lifestyle modifications, and close medical supervision. Therapeutic selection is influenced by several variables, including the extent of bone loss, the patient's features, and possible adverse effects.

2. **Proper nutrition & diet:**

In postmenopausal women, supplements with 800 mg/d may be able to stop bone loss. Clinical research results also indicated that such supplementation may help older people avoid hip and spinal fractures [21,22].

3. **Physical activity:**

Weightlifting activities help to improve the strength of the bones. The risk of fractures is decreased and bone health is preserved by early detection and care.

4. **Medication:**

Bisphosphonates:

A class of medications known as bisphosphonates attaches themselves to the surface of bones and is taken up by osteoclasts during the process of bone resorption. Once inside the cell, they interfere with various intracellular pathways, leading to reduced osteoclast activity [19]. Eg: Alendronate, Risedronate, Ibandronate, etc

Denosumab (Monoclonal Antibody):

The monoclonal antibody called denosumab attacks and suppresses RANKL. An essential signaling molecule for the development and stimulation of osteoclasts is RANKL [20].

Calcitonin:

Calcitonin inhibits osteoclast activity by directly affecting these cells. It also has a short-term effect in reducing bone resorption.

Selective Estrogen Receptor Modulators:

SERMs, like Raloxifene, have estrogen-like impact on bone, reducing osteoclast activity and preventing bone loss.

Hormone Replacement Therapy (HRT):

Estrogen replacement can have a positive effect on bone density by inhibiting osteoclast activity. It is used cautiously due to potential side effects after long-term use.

Anabolic Agents:

Teriparatide and Abaloparatide are parathyroid hormone analogues that stimulate bone formation while also inhibiting osteoclast activity, resulting in a net gain in bone mass. Typically used in specific cases, such as severe osteoporosis.

USEFUL HERBS FOR OSTEOPOROSIS:

Table 1: Useful Herbs for Managing Osteoporosis

BOTANICAL NAMES	COMMON NAMES	USES
Taraxacum officinale	Dandelion	May support bone health and mineral absorption
Curcuma longa	Turmeric	May aid in reducing inflammation and promoting bone health
Trifolium pratense	Red Clover	May support bone health and density
Cissus quadrangularis	Hadjod	Used traditionally for bone fractures and healing
Terminalia arjuna	Arjuna	May have cardioprotective effects, indirectly benefiting bone health
Commiphora wightii	Guggul	May support bone health and reduce inflammation
Withania somnifera	Ashwagandha	May promote bone healing and density
Asparagus racemosus	Shatavari	Traditional use for bone health and strength
Saraca asoca	Ashoka	Traditional use for women's health, potential benefits for bone health
Zingiber officinale	Zingiber	May have anti-inflammatory properties, indirectly supporting bone health

1. DANDELIONS

Taraxaci Herba (TH) or "dandelion" belongs to the Asteraceae (Compositae) family, thrives in warmer regions and is primarily found across USA, Asia and Europe [23]. *Taraxaci Herba* (TH) exhibits a suppressive effect on osteoclast function and bone resorption. Research has shown a significant effect on the improvement of bone microstructure by reduction in RANKL-mediated osteoclast differentiation, development, fusion, and resorption. Furthermore, it prevents the femur's lowered trabecular area [24].

2. HADJOD:

The perennial climber Cissus quadrangularis (CQ) belongs to the Vitaceae family and is typically found in the hottest regions of India commonly referred to as Hadjod, a traditional medicinal herb known for its bone-setting properties, demonstrates the potential to preserve bone health, particularly in conditions such as osteoporosis and fractures [31]. As a natural matrix of excellence, it possesses verified bioactivity. Numerous studies conducted on cell lines and animals have highlighted its protective properties against various diseases, including osteoporosis and arthritis [32].

3. TURMERIC:

Curcumin and alendronate have advantageous impacts on resorption indicators and bone mass in postmenopausal osteoporosis patients. Curcumin, extracted from the turmeric plant (Curcumin longa L.), has demonstrated anti-inflammatory, antioxidant, antifungal, and chemotherapy-preventive effects in clinical trials [25]. Nuclear factor-κB and activator protein-1 are transcriptional factors that curcumin potently inhibits. Thus, transcriptional factors might be functionally important for osteoclast persistence [26]. Further research has shown that curcumin improves bone mass and mobility [27].

4. RED CLOVER:

High concentrations of isoflavones (genistein, daidzein, biochanin A, and formononetin) found in red clover can effectively reduce bone loss resulting from ovariectomy. This reduction in skeletal turnover is likely achieved by inhibiting the degradation of bone [28]. Due to its perceived safety, potential for controlling symptoms related to menopause, promotion of cardiac wellness, and purported positive effects regarding breast, endometrial, and neurological structure, its herbal preparations have garnered a lot of interest recently [29].

5. ARJUNA:

Terminalia arjuna is a commonly found plant in India, particularly recognized for its bark's ability to promote bone remineralization. In the realm of traumatic bone damages, bone substitutes play an essential role [33,34]. Similar to estrogen, it also has a clear antiosteoporotic activity that is particularly useful in preventing bone fractures brought on by low estrogen levels [35]. The current findings support the traditional claims of Terminalia arjuna's curative properties and show that its ethanolic extract has a positive effect on fracture healing [36].

6. GUGGUL:

Gum guggul is a resinous derivative of the Commiphora Mukul plant. Ayurvedic papers consisting of the Charaka Samhita (1000 BC), Sushruta Samhita (600 BC), and works by Vagbhatta (7th century AD) has revealed performance in the therapies of ailments like bone fractures, arthritis, and hyperlipidemic disorders [37]. The study's conclusions showed a significant improvement in bone strength and nearly

total recovery of bone microstructure, along with a decrease in TRAP levels, suggesting that the extract may be able to prevent bone resorption [38]. Research on Laksha Guggulu has demonstrated beneficial effects on fracture restoration, as demonstrated by several scientific measures, including radiographic, serological, and histological research carried out in clinical rat models [39].

7. ASHWAGANDHA:

Ashwagandha (*Withania somnifera*) is studied for its beneficial effects on various ailments, including osteoporosis. Some studies suggest that ashwagandha may help increase bone mineral density, which is a key factor in preventing osteoporosis [40]. By balancing hormone levels, ashwagandha may support bone health [41]. Moreover, ashwagandha possesses anti-inflammatory and antioxidant properties, which may further contribute to its potential benefits for bone healing by reducing inflammation and oxidative stress, both of which can impair the healing process [42].

8. SHATAVARI:

Shatavari contains phytoestrogenic chemicals that link to the estradiol receptor. Reduction in estradiol may trigger osteoporosis and sarcopenia, especially in women who have gone through menopause. After menopause, the estrogen-like properties of Shatavari supplements have an impact on the condition of muscles and bones [43]. Additionally, Shatavari's anti-inflammatory and antioxidant properties may contribute to overall bone health by reducing inflammation and oxidative stress, which can negatively impact bone density and strength.

CONCLUSION

Osteoporosis presents a significant health concern due to its progressive weakening of bones, leading to increased fracture risk. The main cause can be a postmenopausal condition leading to a decreased level of estrogen. Secondary reasons can be considered due to medications and poor diet of an individual. Early identification of risk factors and symptoms in an individual may assist in avoiding the progression of the disorder. Management strategies encompass lifestyle modifications, proper nutrition, physical activity, and medication. Additionally, botanical supplements like dandelion, turmeric, guggul, and others show promise in supporting bone health.

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