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Review Article

Osteoporosis: Exploring Causes, Pathophysiology and Advances in Treatment: A Comprehensive Review

Vijayakumar S[1,*], Parimalakrishnan S[1], Prem Anand DC[2], Kaviya E[3], Vijayakumar AR[4]

[1]Department of Pharmacy Practice, Annamalai Univeristy, Annamalai Nagar, Chidambaram, Tamil Nadu, INDIA.
[2]Department of Pharmaceutical Analysis, Padmavathi College of Pharmacy and Research Institute, Periyanahalli, Dharmapuri, Tamil Nadu, INDIA.
[3]Department of Pharmacy Practice, Srivijay Vidyalaya College of Pharmacy, Nallampalli, Dharmapuri, Tamil Nadu, INDIA.
[4]Faculty of Pharmacy, Department of Pharmacology, Sree Balaji Medical College and Hospital, BIHER, Chromepet, Chennai, Tamil Nadu, INDIA.

ABSTRACT

Osteoporosis diagnosis relies primarily on a clinical assessment involving the observation of signs and symptoms. The origins of this disorder may be either causative or risk-related, with some factors being preventable while others are not. Treatment modalities are diverse, constantly under study for improved outcomes and aimed at minimizing adverse effects from various therapeutic approaches. This study aims to comprehensively explore the etiology, pathophysiology and advancements in osteoporosis management. A thorough review was conducted, utilizing an extensive search of MEDLINE, PubMed and EMBASE databases spanning from January 1987 to March 2023. The search terms included "osteoporosis," "etiology of osteoporosis," "pathophysiology," "clinical features," and "treatment of osteoporosis." The osteoporosis treatment mainly combinations with or without drug therapy and ensure the sufficient intake of the calcium ion and assess the levels of vitamin D. diminish the polypharmacy, particularly with tranquilizer. Bisphosphonates are the main medicament for the treatment of osteoporosis but should be taken separately from food due to poor absorption. Recent years have witnessed the emergence of numerous treatment options, including novel drugs and their combinations with or without non-pharmacological therapies, demonstrating promising results. Further research is imperative to implement advanced regimens for the treatment of osteoporosis.

Keywords: Osteoporosis, Pharmacological, Non-pharmacological, Pathophysiology.

Correspondence:
Vijayakumar Subash
Research Scholar, Department of Pharmacy Practice, Annamalai Univeristy, Annamalai Nagar, Chidambaram, Tamil Nadu, INDIA.
Email: vijaykumarsasikala@gmail.com

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INTRODUCTION

Osteoporosis is a skeletal condition considered by decreased bone mass and deterioration of bone mineral density, which poses significant health risks, particularly among the aging population.[1] As individuals grow older, they become more susceptible to bone thinning, increasing the likelihood of fractures and bone fragility. Research suggests that over a third of women and one in five men worldwide will experience osteoporosis-related fractures during their lifetime, leading to chronic pain, reduced quality of life and potentially fatal outcomes. Vitamin D, particularly its active metabolite 1, 25-dihydroxy vitamin D (1, 25 $(OH)_2$ D), plays a crucial role in regulating calcium and phosphorus metabolism, as well as influencing key proteins involved in bone metabolism. Maintaining optimal vitamin D levels is essential for overall health, with serum metabolite assessment reflecting dietary intake and sunlight exposure. Between 2005 and 2013, the global burden of musculoskeletal disorders, including osteoporosis, increased by 17.7%, highlighting the growing public health concern.[2] The Bone Mineral Density (BMD) is a main parameter to the diagnosis of osteoporosis, with a T-score ≤-2.5 indicating osteoporosis, T-scores between -2.5 and -1 indicating osteopenia and T-scores above -1 considered normal BMD.[3]

The T-score, which indicates the deviation of an individual's Bone Mineral Density (BMD) from the peak bone mass of a healthy and young person of the same sex, is a primary diagnostic tool for osteoporosis in men aged 50 and above, as well as post-menopausal women. BMD is influenced by a variety of factors, both modifiable and non-modifiable, including age,[4] weight,[5] nutrition,[6] sunlight exposure, premature menopause,[7] smoking, alcohol consumption, genetic predisposition,[8] sex[9,10] and exercise.

Among these factors, heredity, sex and age cannot be changed, while weight, nutrition, exercise, sunlight exposure and lifestyle choices can be modified. Indicators of body composition, such as BMI and Skeletal Muscle mass Index (SMI),[11] are the result of both unchangeable and adjustable factors affecting the human body. Therefore, these indicators reflect the overall impact of

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these factors. SMI, which represents the proportion of skeletal muscle mass to concerning total body weight, is a recognized measure used to evaluate skeletal muscle health and diagnose sarcopenia.[12,13]

According to the World Health Organization (WHO), there is a relative scarcity of quantitative data regarding the occurrence and frequency of osteoporosis in developing nations.[14] In India, reported prevalence rates of osteoporosis among women exhibit a wide range, spanning from 8% to 62%.[15] This considerable disparity suggests notable variations in osteoporosis prevalence throughout the country. Women, especially during menopause, encounter a heightened susceptibility to osteoporosis compared to men.[16] Various other factors influence overall bone health, including advancing age, female gender, lower levels of formal education, reduced participation in occupational activities, higher body weight androgen deprivation therapy, duration of dairy product consumption and occurrence of recent fractures within a decade before study enrollment. Broadening understanding and awareness of osteoporosis among these demographic groups are critical measures for advancing osteoporosis management, enhancing excellence of life and alleviating the societal burden of osteoporosis.[17,18] Consequently, health professionals' possession of comprehensive and current knowledge regarding osteoporosis is paramount for optimizing patient care and well-being.

MATERIALS AND METHODS

This study was approved by the institutional ethical committee of Padmavathi College of Pharmacy and Research Institute and the Government headquarters hospital Krishnagiri. [EC/00108/2019]. The checklist was anonymous and included only raw data and statistics. Subjects were assured that their information would remain confidential and they are free to withdraw from the study at any stage of the research work.

ETIOLOGY OF OSTEOPOROSIS

Primary Osteoporosis

The primary osteoporosis is frequently associated with patient age and sex hormone deficiency. The age-related factors can result in the deterioration of trabeculae in bone tissue in both men and women. In post-menopausal women, decreased estrogen production can lead to increased bone loss. The liver secretes the Sex Hormone Binding Globulin (SHBG), which tightly binds to testosterone, estrogen and Dihydrotestosterone (DHT), while aging increases SHBG levels in men, it inactivates the sexual hormones which contributes to decreased BMD over time.[19]

Secondary Osteoporosis

Secondary osteoporosis can arise from various comorbid conditions and/or using drugs. The diseases linked to osteoporosis frequently involve mechanisms associated with imbalances in Ca^{2+}, vitamin D and sex hormones. The Cushing's syndrome is frequently associated with accelerated bone mineral loss due to the overproduction of glucocorticoid has well-known side effects. Moreover, many inflammatory circumstances such as rheumatoid arthritis require prolonged glucocorticoid therapy and are linked to secondary osteoporosis. It's noteworthy that Bone Mineral Density (BMD) decline can occur promptly within 3 to 6 months of initiating hormone treatment. In both genders various causes of secondary osteoporosis. An especially in men, factors such as too much alcohol consumption, glucocorticoid usage and hypogonadism are extra usually linked to osteoporosis. For instance, men undergoing Androgen Deprivation Therapy (ADT) for prostate cancer face an elevated menace of developing the disease.[20]

The following risk factors involved in an osteoporotic fracture.

Several risk factors can predispose to osteoporotic fracture (Figure 1).

Pathophysiology

The pathophysiology of osteoporosis encompasses a wide array of factors that can disrupt the bone remodeling process, leading to alterations in bone activity. The ailment is undeniably of complex cause, as genetic,[21,22] mechanical,[23] nutritional[24] and hormonal factors can all significantly impair bone remodeling.[25] This impairment results in decreased bone mass and micro-architectural deterioration, ultimately heightening the risk of fractures in typical skeletal sites. Specifically, we will explore hormonal factors, focusing on how glucocorticoids impact bone metabolism through various pathways.

Effect on Bone Cells

Glucocorticoids, being lipophilic, easily penetrate the cell membrane and bind to its receptor in the cytosol. The hormone receptor complex translocates into the nucleus, where it influences the transcription of genes crucial for cell functions.

Osteoblasts

Osteoblasts, originating from mesenchymal stem cells, are responsible for generating the bone matrix and ultimately becoming surrounded within it as osteocytes. Glucocorticoids disrupt several signaling pathways in osteoblasts, including the bone morphogenetic protein Runtrelated transcription factor 2 (Runx2) pathway, the Wnt signaling pathway and the peroxisome proliferator-activated receptor-gamma-2 (PPAR-gamma-2) pathway, all vital for osteoblast distinction. In the Wnt signaling pathway, glucocorticoids enhance the secretion of sclerostin and dickkopf-related protein 1 (Dkk-1) from osteocytes in a time- and dose-dependent manner. Both sclerostin and Dkk-1 inhibit Wnt binding to lipoprotein receptor-related proteins 5 and 6 (LPR 5/6), destabilizing B-catenin and prompting a shift in cell fate from osteoblast to adipocyte lineage, thus reducing osteoblastogenesis.

Glucocorticoids also impact osteoblast income in a dose-dependent manner. At physiological doses, they promote osteoblast autophagy, a lysosomal turnover procedure essential for osteoblast feasibility maintenance. At supra-physiological doses, glucocorticoids induce apoptosis, donating to decreased bone power and density.[26]

Osteocytes

Osteocytes act as mechanoreceptors in bone, responding to mechanical and metabolic demands and regulating osteoblast and osteoclast movement accordingly. Glucocorticoids induce osteocyte apoptosis, associated with skeletal vascularity loss, angiogenesis and disruption of the osteocyte-canalicular circulation network. This system is critical for bone construction and repair. Disruption of this network may explain the loss of bone assets and superiority observed before bone mineral density decline in glucocorticoid-treated bone.

Indirect Effects on Bone Metabolism

Glucocorticoids induce a negative calcium balance in the body by augmenting renal calcium elimination and reducing gut calcium reabsorption, thereby contributing to the ancillary hyperparathyroidism observed in glucocorticoid-treated patients. A contradictory sign exists regarding the impact of glucocorticoids on vitamin D metabolism and the balance of Parathyroid Hormone (PTH).

Sex steroids play a crucial role in bone metabolism and maintaining bone assets. Estrogens and androgens inhibit osteoblasts from releasing local motivating factors that encourage osteoclastogenesis. Decreased mixing levels of sex steroids result in increased osteoclast production, thereby enhancing bone resorption. Glucocorticoids hinder the synthesis and secretion of sex steroids, leading to a comparable effect and causal to Glucocorticoid-Induced Osteoporosis (GIOP).

Insulin-like Growth Factor 1 (IGF-1) fosters bone construction by stimulating type 1 collagen amalgamation, overwhelming bone collagen deprivation and inhibiting osteoblast apoptosis. Glucocorticoids suppress the transcription of the IGF-1 gene, further impacting bone metabolism.[27]

Genetics and Osteoporosis

Hereditary factors contributing to osteoporosis encompass genetic factors that dictate bone weight, size of the bone, architecture, microarchitecture and fundamental properties. The potential regulators like bone weight, Transforming Growth Factor B1 (TGF-B1), chloride channels, Vitamin D Receptor

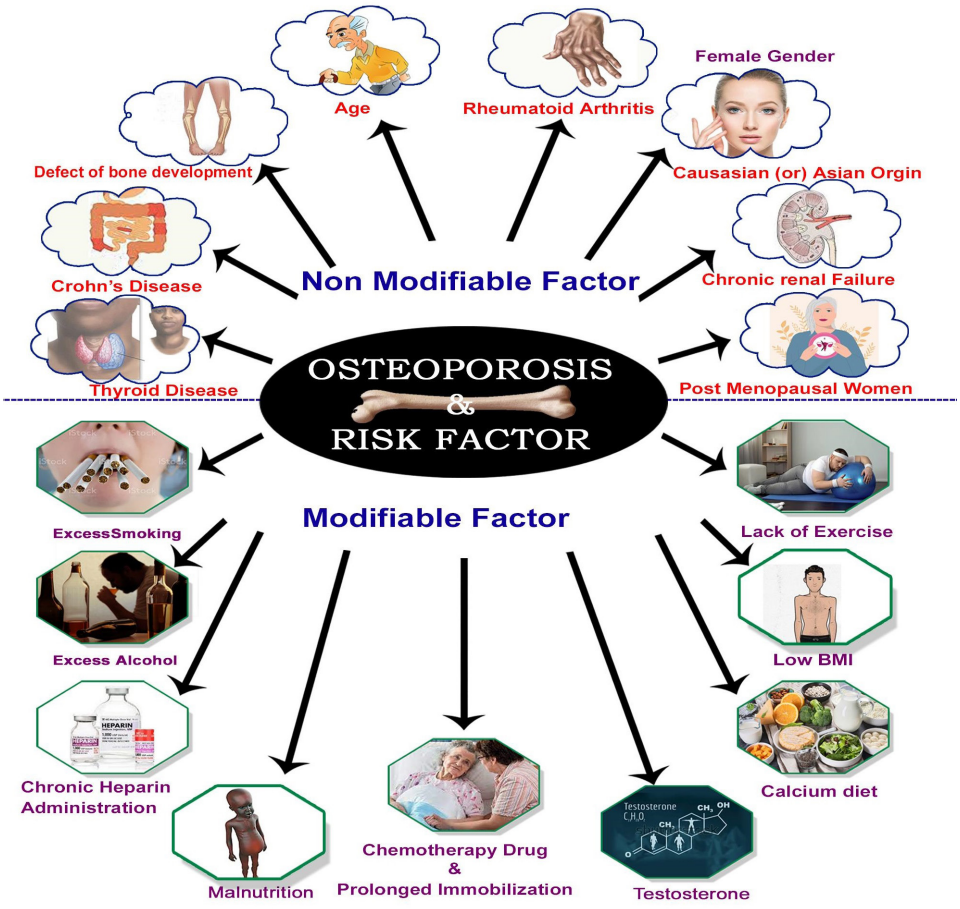

Figure 1: Risk factors involved in an osteoporotic fracture.

(VDR), Sclerostin (SOST), Bone Morphogenic Proteins (BMPs), Runt-related transcription factor 2 (Runx2), cathepsin K, Type 1 Collagen (TCIRG1), and Estrogen Receptor alpha (ER-α) was identified a multitude of the genes and polymorphisms.[28] However, despite the extensive list of genes associated with osteoporosis condition, many have not been consistently imitation and the instruments underlying these candidate genes remain ambiguous.

The genetic predisposition to osteoporosis arises from numerous gene polymorphisms and gene-environment interfaces, with each donating minimally to the alteration in Bone Mineral Density (BMD). Rarely does a single gene directly influence BMD and most of these instances result in clinically evident bone diseases. For example, transformations in COL1 (collagen, type 1) gene responsible for osteogenesis imperfect[29] and TCIRG1, the gene encoding a subunit in the osteoclast-specific proton pump, have been linked to osteoporosis.[30] Additionally, mutations in the SOST gene, which produces sclerostin, lead to sclerosing bone dysplasia, van Buchem disease and sclerosteosis.

One notable mutation is the glycine to Valine substitution at amino acid residue 171 (G171V) mutation of low-density Lipoprotein Receptor-related Protein 5 (LRP5), which results in exceptionally high bone weight devoid of any noticeable dysmorphic phenotype.[31] In contrast to other conditions with high bone mass, bones with this mutation maintain a normal shape without impinging on neural structures. Moreover, these bones function normally but exhibit heightened sensitivity to weight adaptation and increased bone mass.

Estrogen Hormone Deficiency: An Effect at the Cellular Level

The deficiency of estrogen during menopause removes its inhibitory effect on osteoclasts, leading to augmented osteoclast quantities and prolonged osteoclast lifetime, resulting in more widespread and profound bone structural remodeling sites.[32,33] It produces some advantages with increased osteoblastogenesis, this is counteracted by early osteoblast apoptosis,[34] ultimately causing trabecular thinning and perforation. However, the mechanism behind estrogen's inhibitory effect on osteoclasts remains poorly understood. One prevailing hypothesis suggests that estrogen optimizes skeletal tissue sensitivity to loading and its deprivation reduces this sensitivity, resulting in bone loss patterns resembling disuse.[35,36]

Aging and Oxidative Stress in Osteoporosis

Aging, characterized by intracellular Reactive Oxidative Species (ROS) accumulation, has been increasingly recognized as a contributing factor to osteoporosis, particularly in the elderly population. ROS generation occurs through fatty acid oxidation which is responsible for inflammatory cytokines, with the body's ability to counteract these effects declining with age. Studies manipulating ROS protection in mice have demonstrated osteoblast and osteocyte apoptosis and diminished bone mass. Additionally, sexual hormones like estrogens and androgens have protective effects against oxidative stress, shedding light on the interplay between aging, sex steroids and bone health.[37]

Nutrition

The elderly commonly experience malabsorption of calcium, attributed to either a general decline in intestinal mucosa function or, more significantly, reduced biosynthesis of 1, 25(OH) 2D3 with age, prominent to decreased calcium transfer-allocation *via* the vitamin D-induced transcellular pathway. Since the calcium malabsorption owed to slight vitamin D shortage is a concern in osteoporosis pathogenesis, correcting this defect by administering vitamin D is a logical treatment approach. Nonetheless, preclinical research suggests that in old age, calcium absorption decreases, along with reduced volume to acclimatize to a less -calcium intake.[38]

Early diagnosis and investigation of osteoporosis involve assessing Bone Mineral Density (BMD), which denotes the mineral content in a particular bone region and provides insight into overall bone health. BMD tests compare an individual's results to the ideal bone density of a healthy young adult of the same sex. These assessments are non-invasive and typically involve central Dual-Energy X-ray Absorptiometry (DEXA) scanning, although Computed Tomography (CT) or ultrasound radiographic findings can also be utilized.[39]

DEXA scanning quantifies bone mineral amounts in the distal forearm, hip and lumbar spine with nominal radiation exposure, making it the most generally used method for measuring bone strength. Additionally, Quantitative Ultrasound (QUS) is considered to imitate structural bone properties such as the elasticity of the bone and the trabecular arrangement, as ultrasound velocity is influenced by these features.[40]

Other screening tests may be performed to identify risk factors such as the patient's family member's history, daily consumption of the alcohol, or rheumatoid arthritis. Additionally, screening tests are recommended to identify treatable underlying causes in osteoporosis patients, including the patient's Complete Blood Count (CBC) and Erythrocyte Sedimentation Rate (ESR), electrolytes and renal function tests (Urea and Electrolytes), Liver Function Tests (LFTs), Thyroid Function Tests (TFTs), serum calcium, Alkaline Phosphatase (ALP) levels, testosterone/ gonadotropins in men and serum immunoglobulins and paraproteins, as well as urinary Bence-Jones' protein. The various diagnostic tools in the early diagnosis of the osteroporois was well documented.[41]

MANAGEMENT

While etidronate was the initial option, is replaced by the additional potent alendronate and risedronate administered daily or weekly The novel option, Ibandronate, is administered monthly. The Following treatment options for osteoporosis[42] authorized by the Food and Drug Administration (FDA, USA), are shown in Table 1.

DISCUSSION

The discourse on osteoporosis presents a thorough examination of its multifaceted nature, encompassing its etiology, risk factors, pathophysiology, diagnostic methodologies and therapeutic interventions. Osteoporosis emerges as a pressing public health challenge, particularly in light of its escalating prevalence worldwide, notably among elderly demographics. The interplay of various determinants such as age, gender, genetic predispositions, hormonal dynamics, lifestyle choices and concurrent health conditions underscores the complexity inherent in osteoporosis development and progression.[8-10,43]

Central to the discourse is the pivotal role of early detection and intervention in mitigating the adverse outcomes associated with osteoporosis. Diagnostic tools like bone mineral density testing and comprehensive risk assessment protocols are underscored as essential components in identifying individuals at risk and initiating timely interventions.[44] Moreover, the comprehensive management paradigm advocated emphasizes the integration of pharmacological modalities with lifestyle modifications,

Table 1: Treatment options for osteoporosis authorized by the Food and Drug Administration (FDA, USA).

Bone formation markers	Findings
Alkaline phosphatase	Increased in osteoporosis
Osteocalcin	Decreased in osteoporosis
Bone resorption markers	
Urinary hydroxyproline	Increased in osteoporosis
Nutritional factors	
Calcium	Calcium supplementation 0.5-2g/day reduces BMD
Vitamin D	600-800 IU of vitamin D along with calcium supplement reduces BMD
Dual x-ray absorptiometry T Score	
T-score > -1.0	Normal
T-Score between -1.0 and -2.5	Osteopenia
T Score < -2.5	Osteoporosis
BMI	
18.5>BMI<25	Normal weight
25>BMI <30	Overweight
BMI>30	Obese
BMI of 20-25kg/m2	Decreased BMD
Mandibular cortical index (MCI)	
C1	The cortical layer for heavy endosteal cortical residues, porous
C2	The endosteal margin shows semilunar defects
C3	The endosteal margin of the cortex is even and sharp on both sides 0.31-0.38mm in osteoporotic patients
Panoramic mandibular index (PMI)	
MI or Mandibular cortical width (MCW) at Mental for amen region	Osteoporotic patient with thin MCW <3mm Decrease indicates BMD
Oral manifestations in osteoporosis	Periodontitis Tooth loss

nutritional interventions, physical activity regimens and fall prevention strategies.

However, the discussion does not shy away from addressing the inherent challenges in managing osteoporosis effectively. It acknowledges the potential adverse effects associated with pharmacological agents like bisphosphonates and emphasizes the imperative of patient compliance with prescribed treatment regimens. Moreover, the discourse underscores the ongoing need for scientific inquiry and innovation to advance our understanding of osteoporosis pathophysiology and refine therapeutic approaches.[42,45] The pursuit of novel pharmacological agents and the exploration of non-pharmacological interventions are posited as promising avenues for enhancing bone health and alleviating the burden of osteoporotic fractures in affected populations.

CONCLUSION

The management of osteoporosis requires a comprehensive approach that incorporates both non-pharmacological and pharmacological interventions. Regular physical activities and a well-balanced diet enhance bone health and it is not only in calcium intake but also involves other important essential minerals, proteins and antioxidant-rich foods. It is crucial to avoid smoking and excessive alcohol consumption, as these habits can negatively impact bone density and increase the risk of fractures. This is especially important for older individuals, who are more susceptible to fragility fractures. Implementing measures to prevent falls and ensuring sufficient vitamin D levels are essential components of osteoporosis management in this demographic.

Looking to the future, further research is vital to develop advanced treatment strategies for osteoporosis. This includes exploring new pharmacological agents, optimizing existing therapies and investigating innovative non-pharmacological approaches to augment the benefits of bone and diminish the load of osteoporotic fractures. By continuing to advance our understanding of the basic mechanisms of osteoporosis and emerging more real treatments, we can improve outcomes and eminence of life for persons affected by this condition.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVATIONS

%: Percentage; **<:** Less Then; **1, 25(OH)$_2$ D$_3$:** 1, 25, dihydroxy vitamin D$_3$ or Calcitriol; **adt:** Androgen deprivation therapy; **ALP:** Alkaline phosphatase; **BMD:** Bone mineral density; **BMPs:** Bone morphogenic proteins; **Ca^{2+}:** Calcium $^{2+}$ ion; **CBC:** Complete blood count; **COL1:** Collagen, type 1; **CT:** Computed tomography; **DEXA:** Dual-energy X-ray absorptiometry; **dht:** dihydrotestosterone; **DKK-1:** Dickkopf-related protein 1; **EMBASE:** Excerpta Medica Database; **ER-α:** Estrogen receptor alpha; **ESR:** Erythrocyte sedimentation rate; **FDA:** Food and Drug Administration, USA; **G171V:** Glycine to valine substitution at amino acid residue 171; **g:** gram; **giop:** glucocorticoid-induced osteoporosis; **IGF-1:** Insulin-like growth factor 1; **IU:** International unit; **LFTs:** Liver function tests; **lpr 5/6:** Lipoprotein receptor related protein 5 and 6; **LRP5:** Low-density lipoprotein receptor-related protein 5; **medline:** Medical Literature Analysis and Retrieval System Online; **ppar:** Peroxisome proliferator activated receptor gamma-2; **PTH:** Parathyroid hormone; **PubMed:** Player Unkinown Battle Mantra Ending in Domination; **QUS:** Quantitative ultrasound; **ROS:** Reactive Oxidative Species; **ruNX2:** Runt-related transcription factor 2; **shbg:** Sex hormone binding globulin; **smi:** Skeletal muscle mas index; **SOST:** Sclerostin; **TCIRG1:** Type 1 collagen; **TFTs:** Thyroid function tests; **TGF-B1:** Transforming growth factor B1; **VDR:** Vitamin D receptor; **WHO:** World health organization; **WNT Signaling:** Wingless related integration site.

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