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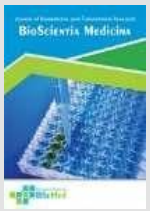

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Pathophysiology and Management of Primary Osteoporosis: A Narrative Literature Review

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A B S T R A C T

The pathophysiology of primary osteoporosis primarily involves changes at the cellular and bone tissue levels. This process involves an imbalance between the activity of bone-destroying cells (osteoclasts) and bone-constructing cells (osteoblasts). Osteoclasts are responsible for the resorption of old and damaged bone tissue, while osteoblasts build new bone. In osteoporosis, osteoclast activity increases and osteoblasts decrease, resulting in loss of bone mass. Treatment of primary osteoporosis involves a holistic approach that includes lifestyle changes, use of medications, and fracture prevention. The main goal of management is to slow down the decline in bone density, prevent bone fractures, and improve the quality of life of sufferers. Increasing your intake of calcium and vitamin D, as well as regular physical exercise, can help maintain bone mass. Meanwhile, drugs such as bisphosphonates and teriparatide can be used to inhibit bone breakdown or stimulate new bone formation.

1. Introduction

Osteoporosis is a bone health problem that is increasingly becoming a medical concern, especially among the elderly population. Osteoporosis is a condition in which bone fragility increases due to loss of bone mass and disruption of the microstructure. This condition can cause bones to become brittle and break easily, even from mild trauma. Osteoporosis usually has no symptoms in its early stages, so it is often known as the "bone thief" because it destroys bone strength and integrity without warning. At the primary level, osteoporosis is often related to natural aging and genetic factors. Factors such as gender (women are more susceptible), family history, and ethnicity can also influence a person's risk of developing osteoporosis. However, it is important to remember that although these factors can influence a person's predisposition to osteoporosis, lifestyle, and environmental factors also play an important role in the development of this disease. The pathophysiology of primary osteoporosis primarily involves changes at the cellular and bone tissue levels. This process involves an imbalance between the activity of bone-destroying cells (osteoclasts) and bone-constructing cells (osteoblasts). Osteoclasts are responsible for the resorption of old and damaged bone tissue, while osteoblasts build new bone. In osteoporosis, osteoclast activity increases, and osteoblasts decrease, resulting in loss of bone mass.[1-4]

Management of primary osteoporosis involves a holistic approach that includes lifestyle changes, the use of medications, and fracture prevention. The main goal of management is to slow down the decline in bone density, prevent bone fractures, and improve the quality of life of sufferers. Non-pharmacological treatments such as increasing calcium and vitamin D intake, as well as regular physical exercise, can help maintain bone mass. Meanwhile, drugs such as bisphosphonates and teriparatide can be used to inhibit bone breakdown or stimulate new bone formation. In addition, education and awareness about osteoporosis are very important, both for the general public and health professionals, to encourage early detection and appropriate preventive action.[5-7] This study aimed to further explore the pathophysiology and management of primary osteoporosis in order to better understand this condition and improve the treatment and prevention of osteoporosis in individuals at risk.

Pathophysiology of primary osteoporosis

Primary osteoporosis is a form of osteoporosis that occurs without a clear cause or underlying pathology. It is a common condition that occurs frequently in the aging population, especially in post-menopausal women, but can affect both young men and women. The pathophysiology of primary osteoporosis involves complex changes at the cellular and bone tissue levels that lead to loss of bone mass. As for some pathophysiology of primary osteoporosis:

Balance of osteoclast and osteoblast activity

The balance of osteoclast and osteoblast activity is a key concept in understanding the pathophysiology of osteoporosis and the regulation of bone health in general. Osteoclasts and osteoblasts are two types of bone cells that have opposing but complementary roles in the processes of bone rejuvenation and maintenance. Osteoclasts are bone cells whose main function is in bone resorption, namely destroying and absorbing old and damaged bone tissue. They release enzymes and acids that break down collagen and bone minerals. Osteoblasts are bone cells responsible for building new bone matrix. They produce new collagen and bone minerals, which form a strong, dense bone structure. The balance between osteoclast and osteoblast activity is important for maintaining bone integrity and strength. When osteoclasts are overactive, or osteoblasts are inactive, bone can decrease in density. In the growth period, osteoblast activity is usually more dominant, which allows an increase in bone mass. After a period of growth, this balance continues to maintain bone. Disturbances in this balance, such as an unbalanced increase in osteoclast activity, can result in the decreased bone mass that is characteristic of osteoporosis.[8,9]

Hormonal changes

Sex hormones such as estrogen in women and testosterone in men play a key role in maintaining the balance between osteoclast and osteoblast activity in bone maintenance. Estrogen is the main sex hormone produced by the ovaries in women. During the reproductive years, estrogen helps maintain a balance between osteoclast and osteoblast activity, which results in the formation and maintenance of healthy bones. During the menopausal period, estrogen production decreases significantly as the ovaries stop functioning. This sharp drop in estrogen causes increased activity of osteoclasts (cells that break down bone) and decreased activity of osteoblasts (cells that build new bone). The combination of increased bone resorption and decreased bone formation leads to loss of bone mass, which is a hallmark of osteoporosis in post-menopausal women. Testosterone also has a role in maintaining bone density in men. Like estrogen in women, testosterone helps maintain a balance between osteoclast and osteoblast activity. A significant reduction in testosterone levels, as can occur in men with certain diseases or certain medications, can lead to increased bone resorption and decreased bone formation, which can lead to the development of osteoporosis in men.[10-13]

Genetics

A number of genetic polymorphisms or variations in certain genes can contribute to a person's risk of developing osteoporosis. Genetic polymorphisms are natural variations in the nucleotide sequence of DNA that can affect how genes work or interact with other factors in the body. The COL1A1 (collagen type I alpha 1 chain) and COL1A2 (collagen type I alpha 2 chain) genes are two very important genes in the regulation of bone metabolism and bone formation. Both are involved in the production of type I collagen, which is a major component of the bone matrix. The bone matrix is the extracellular framework that provides strength and structure to bones. The VDR (vitamin D receptor) gene has a key role in the regulation of bone metabolism and calcium absorption in the body. The role of the VDR gene in osteoporosis is critical because vitamin D is an essential nutrient for bone health, and the vitamin D receptor (VDR) enables the body to respond to and utilize vitamin D effectively. Mutations in the VDR gene influence its function and may interfere with the effective absorption of calcium and the metabolism of healthy bones. This can lead to reduced bone density and an increased risk of osteoporosis. In some individuals, polymorphisms or genetic variations in the VDR can influence the body's response to vitamin D, which in turn can contribute to the risk of osteoporosis.[14,15]

The genes RANKL (receptor activator of nuclear factor kappa-B ligand), RANK (receptor activator of nuclear factor kappa-B), and OPG (osteoprotegerin) have important roles in the regulation of bone metabolism and are key components in understanding the pathophysiology of osteoporosis. All three are involved in regulating the activity of osteoclasts (cells that break down bone) and osteoblasts (cells that build new bone) in bone. RANKL is a protein produced by many types of cells in the body, including bone cells. The main function of RANKL is to stimulate osteoclast activation. When RANKL binds to RANK receptors on the surface of osteoclasts, it stimulates osteoclasts to destroy bone tissue, which is called bone resorption. Increased production or activity of RANKL can increase bone resorption and reduce bone density. RANK is a receptor present on the surface of osteoclasts. When RANKL binds to RANK, it initiates osteoclast activation and triggers the process of bone resorption. Polymorphisms or genetic variations in the RANK gene can influence the body's response to RANKL and its effect on osteoclast activity. OPG is a protein that acts as a buffer or trap for RANKL. OPG competes with RANK for binding to RANKL, thereby inhibiting its activity in osteoclasts. OPG acts as a negative regulator of osteoclast activity. If the OPG concentration is high, then osteoclast activity will be suppressed, which supports the maintenance of bone mass. Genetic variation in the OPG gene can influence the OPG production rate in the body and, therefore, can influence bone resorption. In the context of osteoporosis, an imbalance between RANKL, RANK, and OPG can lead to increased osteoclast activity and decreased osteoblast activity. This results in loss of bone mass and thinning of the bones, which are the hallmarks of osteoporosis. Therefore, research on the genetic regulation of RANKL, RANK, and OPG and their role in bone resorption is an important area in the understanding and management of osteoporosis.[16,17]

LRP5 (low-density lipoprotein receptor-related protein 5) and LRP6 (low-density lipoprotein receptor-related protein 6) genes are two genes that have important roles in the regulation of bone development and density. Mutations or variations in these genes can influence the regulation of the Wnt pathway, which is a key signaling pathway in the regulation of new bone formation by osteoblasts (cells that build new bone). The LRP5 and LRP6 genes are members of the receptor family of low-density lipoprotein receptor-related proteins. These two genes play an important role in regulating the activation of the Wnt pathway, which is a signaling pathway that controls bone development and bone maintenance. Wnt pathway activation triggers osteoblast differentiation and new bone formation. LRP5 and LRP6 act as receptors that enable bone cells to respond to Wnt signals. Mutations in the LRP5 or LRP6 genes can influence Wnt pathway

activation. Several mutations in LRP5, for example, have been associated with increased bone density and resistance to osteoporosis. In contrast, mutations that impair LRP5 or LRP6 function can impair the regulation of the Wnt pathway, which may contribute to reduced new bone formation and the development of osteoporosis.[18,19]

Hormone disorders

Hormonal disorders such as hyperparathyroidism, hyperthyroidism, and Cushing's syndrome can influence bone metabolism and contribute to the development of osteoporosis. Hyperparathyroidism is a condition in which the parathyroid glands produce too much parathyroid hormone (PTH). PTH plays a role in regulating calcium levels in the blood. When PTH levels are high, there can be increased absorption of calcium from the bones, leading to excessive bone resorption. As a result, bone density can decrease, and the risk of osteoporosis increases. Hyperthyroidism is a condition in which the thyroid gland produces too many thyroid hormones, such as thyroxine (T4) and triiodothyronine (T3). Thyroid hormone plays a role in regulating the body's overall metabolism. Hyperthyroidism can increase the rate of bone resorption, that is, the process where Bone is broken down faster than new bone is formed. This can lead to decreased bone density and an increased risk of osteoporosis. Cushing's syndrome is a condition associated with increased levels of cortisol in the body, usually caused by long-term use of corticosteroid drugs or by tumors that affect the adrenal glands. Cortisol plays a role in regulating metabolism and can inhibit the formation of new bone and stimulate bone resorption. This can lead to loss of bone mass and increase the risk of osteoporosis.[20,21]

Environmental and lifestyle factors

A diet that is low in calcium and vitamin D, as well as a lack of physical exercise or being underweight, are important risk factors that can lead to decreased bone density and bone strength. Calcium is an essential mineral required for the formation and maintenance of healthy bones. If the diet is low in calcium, the body may not get enough calcium to meet the needs of the bones. Vitamin D is also very important because it helps the body absorb calcium from the intestines into the blood. Vitamin D deficiency can inhibit calcium absorption and reduce the availability of calcium for bone formation. Lack of calcium and vitamin D can cause bones to become more fragile and more susceptible to osteoporosis. Physical exercise, especially weight-bearing exercises such as walking, running, or exercising with weights, stimulates the formation of new bone and maintains the strength of existing bone. Lack of physical exercise or an inactive lifestyle can cause decreased stimulation for new bone formation, thus causing a decrease in bone density. Physical exercise also helps in maintaining a balance between osteoclast and osteoblast activity, which is important for bone health. Being underweight, especially a lack of excess body fat, can cause a decrease in the production of the hormone estrogen in women and the hormone testosterone in men. The hormones estrogen and testosterone have an important role in maintaining bone health. A deficiency in this hormone can inhibit the formation of new bone and increase bone resorption (excessive bone destruction). Over time, this can cause a decrease in bone density and increase the risk of osteoporosis.[22,23]

Natural aging process

Natural aging is one of the main risk factors for osteoporosis. During the aging process, changes occur in bone metabolism, which can lead to decreased bone mass and increased bone resorption. During the aging process, there is a natural decrease in bone density. It is caused by a variety of factors, including decreased activity of osteoblasts (cells that form new bone) and increased activity of osteoclasts (cells that break down bone). As a result, bones become more brittle and more prone to fractures. During aging, women experience menopause, which is a dramatic decrease in the production of the hormone estrogen. This can inhibit new bone formation and increase bone resorption.

Men can also experience decreased levels of the hormone testosterone, which can influence bone health. During aging, the absorption of important nutrients such as calcium and vitamin D from food can decrease. This can reduce the availability of calcium for bone formation and inhibit the function of vitamin D in calcium absorption.[21,23]

Management of primary osteoporosis

Antiresorptive agents, including estrogens, bisphosphonates/BP (e.g., alendronate, risedronate, ibandronate, and zoledronic acid; selective estrogen receptor modulator (SERM) raloxifene; human monoclonal antibody against receptor activator NF-κB ligand (RANKL) denosumab; and strontium ranelate/SR). All antiresorptive agents increase bone mass, but only alendronate, risedronate, zoledronic acid, and SR have been shown to reduce vertebral and hip fractures. However, the residual efficacy is only for vertebral fractures. Nonetheless, hip fractures cause increased morbidity, mortality, and healthcare costs compared to vertebral fractures. All of these antiresorptive therapies do not stimulate bone formation, with the exception of currently available anabolic agents (i.e., PTH), which increase bone strength and bone formation. PTH is especially helpful for those with severe osteoporosis.[24]

Table 1. Drugs for the prevention and management of osteoporosis.

	Postmenopausal osteoporosis		Osteoporosis due to glucocorticoids		
Drugs	Prevention	Therapy	Prevention	Therapy	Therapy
Estrogen	Some regiments				
Denosumab		60mg SC/6 month			
Raloxifene	60mg PO/day	60mg PO/ day			
Ibandronate	2.5 mg PO/day 150mg /month	2.5 mg PO/ day 150 mg PO/ month 3mg IV/3 month			
Alendronate 5-10-70 mg	5 mg PO/day 35mg PO/week	10mg PO/day 70mg PO/week 70mg PO+VD		5 mg PO/ day 10mg PO/ day	10mg PO/ day 70mg PO/week
Risedronate 5-35-75 mg	5 mg PO/day	5 mg PO/day 35mg po/week 150mg/PO/month	5 mg PO/ day	5 mg PO/ day	35 mg PO/week 150mg PO/ month
Strontium ranelate 2gr PO	2gr/day		2gr/day	2 gr/day	
Zoledronic acid	5mg IV/2 year	5mg IV/year	5mg IV/ year	5 mg IV/ year	5mg IV/ year
Teriparatide		20ug SC/day		20ug SC/ years	20ug SC/ year

Table 2. Drugs that can reduce the risk of fracture.

Drugs	Vertebral	Nonvertebral	Pelvis
Alendronate	Yes	Yes	Yes
Risedronate	Yes	Yes	Yes
Zoledronic acid	Yes	Yes	Yes
Denosumab	Yes	Yes	Yes
Teriparatide demonstrated	Yes	Yes	No effect
Ibandronate demonstrated	Yes	Yes	No effect
Raloxifene demonstrated	Yes	Yes	No effect

Bisphosphonates are the drugs most widely used for the treatment of osteoporosis. Alendronate is used in the prevention and treatment of cases of postmenopausal osteoporosis, glucocorticoid-induced osteoporosis, and cases of osteoporosis in men. Trials spanning 10 years have been reported in postmenopausal osteoporosis, but efficacy and safety beyond 10 years have not been established. Drug holiday for 1 or 2 years is recommended after 4-5 years of therapy (and longer for those with severe osteoporosis). Risedronate is used in men and women for the prevention and treatment of osteoporosis and glucocorticoid-induced osteoporosis. It has been suggested drug holidays up to 1 year after 7 years of therapy. Ibandronate is another BP used for the prevention and treatment of postmenopausal osteoporosis, which has proven efficacy in reducing the risk of fracture in postmenopausal women with osteoporosis but has not been shown to reduce non-vertebral or hip fractures except in higher-risk subgroups. Zoledronic acid is used for the prevention and treatment of postmenopausal and male osteoporosis and glucocorticoid-induced osteoporosis. Zoledronic acid is given once a year, given intravenously, as a 5 mg infusion over at least 15 minutes.[24,25]

Raloxifene has been shown to reduce the risk of vertebral fractures in women with postmenopausal osteoporosis, but its efficacy in reducing non-vertebral or hip fractures has not been proven. Facial flushing is contraindicated in fertile women and those who have had venous thromboembolic disease. Estrogen replacement therapy (ERT) is used for the prevention of postmenopausal osteoporosis in patients who demonstrate a significant osteoporosis risk, but estrogen has never been approved for the treatment of osteoporosis. Strontium ranelate reduces the risk of vertebral and non-vertebral fractures in postmenopausal osteoporotic women, regardless of age or the severity of the underlying disease. It has been demonstrated that SR increases BMD and reduces fracture risk in postmenopausal women and men with osteoporosis. While SR has not been approved by the FDA, it has been approved by the European Medicines Agency (EMA) in the treatment of osteoporosis in men with an increased risk of fracture. Denosumab (human monoclonal antibody against RANKL) is used in the treatment of postmenopausal women at high risk of fracture, patients who have a history of fracture due to osteoporosis, or patients who have failed or are intolerant of other available osteoporosis therapies. It has been shown to reduce the risk of vertebral, pelvis, and non-vertebral fractures. Hypocalcemia should be corrected before starting therapy. Serious infections, dermatitis, rashes, and eczema may occur. Discontinuation of the drug is recommended if severe symptoms appear. To date, the efficacy and safety of denosumab for more than 6 years has not been established.[24,25]

Teriparatide (recombinant human PTH 1-34) is used in the treatment of postmenopausal osteoporosis with high fracture risk, patients who have failed or were intolerant of previous osteoporosis therapy, and to increase bone mass in men with idiopathic or hypogonadal osteoporosis. Teriparatide is also approved for the treatment of men and women with glucocorticoid-induced osteoporosis. Serum calcium, PTH, and 25(OH)D levels should be checked prior to treatment. Teriparatide has a warning" black box due to the appearance of osteosarcoma in rats treated with very high doses of teriparatide. This drug is contraindicated in patients at increased risk of osteosarcoma (those with Paget's disease of bone), have exposed epiphyses, history of irradiation involving the skeleton, or unexplained elevated alkaline phosphatase levels. of skeletal origin, or patients with primary or other disease.[23,24]

To maintain serum calcium at a constant level, an adequate external calcium supply is required; conversely, low serum calcium levels promote bone resorption to bring calcium levels to normal. Calcium requirements increase among the elderly, so the older population is particularly vulnerable to calcium deficiency. Institute of Medicine (IOM) recommends a daily intake of 1000 mg/day for men aged 50-70 years and 1200 mg of calcium for women over 50 years and

men over 70 years. Vitamin D is needed for calcium absorption, bone health, muscle performance, and balance. The IOM recommends a dose of 600 IU/day until age 70 in adults and 800 IU/day thereafter. Major food sources of vitamin D include V-D–fortified milk, juices and cereals, salted fish, and liver. Supplementation with V-D2 (ergocalciferol) or V-D3 (cholecalciferol) may be used.[24,25]

2. Conclusion

The pathophysiology of primary osteoporosis is related to changes in bone density and strength resulting from an imbalance in bone formation and resorption. Management of primary osteoporosis aims to prevent further bone loss and prevent pathological fractures. In principle, primary osteoporosis therapy works by inhibiting bone resorption or increasing bone formation.

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