IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

OSTEOPOROSIS: NUTRITIONAL MANAGEMENT STRATEGIES FOR A HOLISTIC APPROACH

[1]Aashka Desai*, [2]Divya Prajapati, [3]Pranali Panchal, [4]Yashvi Kachhiya, [5]Taufik Mulla
[1,2,3,4]UG Scholar, [5]Assistant Professor
[1,2,3,4,5]Krishna School of Pharmacy and Research, Affiliated with Drs. Kiran and Pallavi Patel Global University, Varnama, Vadodara, INDIA.

ABSTRACT: Osteoporosis is a chronic skeletal disease that is characterised by reduced bone mineral density (BMD) with an increased risk of fractures. Its occurrence is being observed increasingly in post-menopausal women and the elderly population. Primary prevention is the best way to combat this problem. Medical intervention in the form of allopathic remedies and in severe cases, surgery is required and is the traditional approach. Pharmacological treatment includes antiresorptive and bone anabolic drugs that may help restore mass and quality. However, these techniques are accompanied by an array of undesired side effects due to less researched long-term issues and patient incompatibility in many scenarios. Mainstream medical practice is centralised around healing through allopathic medicine and has not yet fully acknowledged nutrient strategies to enhance skeletal health. For a holistic approach to the treatment of this rampant disorder, a balance between lifestyle, nutritional, and dietary factors is essential. This article discusses the effects of the intake of adequate amounts of nutrients in a prophylactic as well as therapeutic role. The significance of calcium, phosphorus, proteins, fatty acids, magnesium, vitamin D, and vitamin K is reviewed. Incorporation of these nutrients in daily diet is imperative to curb this medical pandemic along with amendments in lifestyle.

Index Terms: Skeletal disease, Proteins, Fatty acids, Magnesium, Vitamin D, Vitamin K.

I. INTRODUCTION

The locomotion and structural integrity of the body is due to the musculoskeletal system. The adult skeleton is composed of 206 bones. Bones are a vital organ and connective tissue that provide structural support to the body and play an essential role in regulating mineral metabolism and storage. The major components of bone include bone matrix and bone cells. Bone is composed of 50 to 70% mineral, 20 to 40% organic matrix, 5 to 10% water, and <3% lipids. The mineral content of bone is mostly hydroxyapatite, with small amounts of carbonate, magnesium, and acid phosphate, with missing hydroxyl groups that are normally present [1].

Bone remodelling is the process of the creation and destruction of bone to maintain its strength and mineral levels. It is ideally a balance between two opposite mechanisms: bone formation and bone resorption. Osteoblasts are responsible for bone formation through the production of intercellular bone components. Osteoclasts take part in bone resorption. They secrete hydrolytic enzymes that can disintegrate bone constituents and cause phagocytosis and subsequent destruction [2, 3]. Osteoporosis means ‘porous bone.’ According to the definition of the World Health Organization, osteoporosis is a systematic skeletal disease, characterized by the loss of bone mass density (BMD) and damage to the microstructure of bone tissue, leading to increased bone vulnerability and risk of fracture [4, 5].

1.1. Classification

It is broadly classified into two types: primary and secondary osteoporosis. Primary osteoporosis includes idiopathic osteoporosis occurring in children and young adults, with an unknown etiology [6], and involutional osteoporosis which affects both men and women and is related to aging [7]. Involutional osteoporosis is divided into type I or postmenopausal osteoporosis and is characterized by rapid bone loss [8]. Type II or senile osteoporosis occurs above 75 years of age and is characterized by a loss of trabecular and cortical bone due to aging [9]. Secondary osteoporosis makes up less than 5% of all osteoporosis cases and is due to another disease or the use of medications [10].

1.2. Diagnosis

Assessment of existing bone mass, determining the fracture risk based on this clinical assessment, and making decisions regarding the appropriate therapeutic intervention are the ultimate goals when evaluating patients for osteoporosis [11]. Diagnosis of osteoporosis is based on the measurement of bone mineral density (BMD) with the help of dual X-ray absorptiometry. BMD results are observed as a comparison to a sex-matched young healthy adult (T-score) or a sex-matched and age-matched healthy population (Z-score). It is expressed in standard deviations [12]. The WHO has defined osteoporosis as a T-score of less or equal to −2.5.

1.3. Causes And Risk Factors

Osteoporosis occurs when there is an improper balance between bone resorption and bone formation, which leads to a fall in skeletal mass. In most individuals, bone mass peaks in the third decade of life. During menopause and progressing age, bone resorption exceeds bone formation which destabilise the bone structure and increases the risk of fracture and decreases bone density.

Various diseases attribute to secondary osteoporosis like hyperparathyroidism, anorexia, malabsorption, hyperthyroidism, overtreatment of hypothyroidism and chronic renal failure.

Risk factors for osteoporosis include increasing age, body weight of under 128 pounds, smoking, family history of osteoporosis, white or Asian race, early menopause, low levels of physical activity, and a personal history of a fracture from a ground-level fall or minor trauma after the age of forty [14,15]. Cigarette smoking is related to a loss of bone mass and an increased risk of osteoporotic fractures [16]. Glucocorticoids cause profound effects on the skeleton, and glucocorticoid-induced osteoporosis is the most common secondary cause of osteoporosis [17]. Primary hyperparathyroidism is another calcium metabolic disorder that is observed largely in post-menopausal women. Several studies have shown decreased BMD in patients with this disorder [18]. Rheumatoid Arthritis is an inflammatory joint disease that is also associated with osteoporosis. Several studies reported that the rate of spine or hip fractures is higher in patients with RA compared with primary osteoporotic patients [19, 20]. High-calorie diets along with heavy alcohol consumption are also linked with increased chances of osteoporosis due to decreased bone density.

1.4. Complications

Pathological fractures, especially in the hip or spinal column, are the most serious complications of osteoporosis. Hip fractures occur due to falls and cause disability as well as an increased chance of mortality. Spinal fractures also occur, with compression fractures leading to back pain and a kyphotic posture.

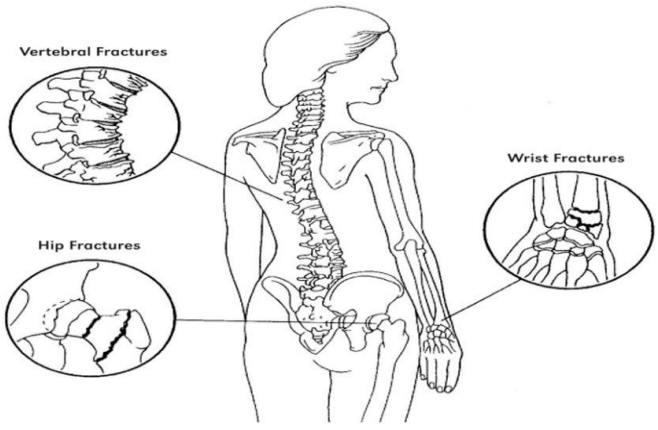

Figure 1 Common fracture sites

1.5. Fragility Fractures

A fragility fracture is defined as a fracture that occurs as a result of a low-energy force that is inadequate to break normal bone [21,22]. The most common locations for these fractures are the spine, hip, pelvis, humerus and wrist.

1.5.1. Hip Fractures

Hip fractures are the most serious fragility fractures in terms of morbidity and mortality as about half of the affected patients never regain their previous functional capacity. One-year mortality rates lie in the range of 14% to 36% [23, 24]. Hip fractures usually occur due to a sudden fall and commonly occur in older women of more than 65 years of age having no previous diagnosis of osteoporosis.

1.5.2. Vertebral Compression Fractures

Vertebral contraction fractures (VCFs) are common in cases with osteoporosis. In severe osteoporosis, the cortical and trabecular bone of the vertebral body weakens to the point where simple movements like changing posture or lifting light objects can cause a break in the bone [25]. Some fractures may spread from the original site of fracture in the anterior column whereas others can occur due to an impact causing the collapse of the entire vertebral body.

II. PATHOPHYSIOLOGY

Osteoporosis occurs because of failure to achieve peak bone mass or excessive bone resorption and/or decreased bone formation during remodelling, leading to low BMD. An inverse relationship is seen between BMD and fracture risk. The bone remodelling process is regulated by systemic factors such as calcitonin, parathyroid hormone, etc. PTH regulates bone resorption by osteoclasts and bone formation by osteoblasts. Calcitonin affects both osteoclasts and the tubules of the kidney. In the kidney, it reduces serum calcium and phosphate by promoting diuresis and decreasing reabsorption. In the bone, it causes osteoclasts to contract, which reduces their motility and ability to resorb bone.

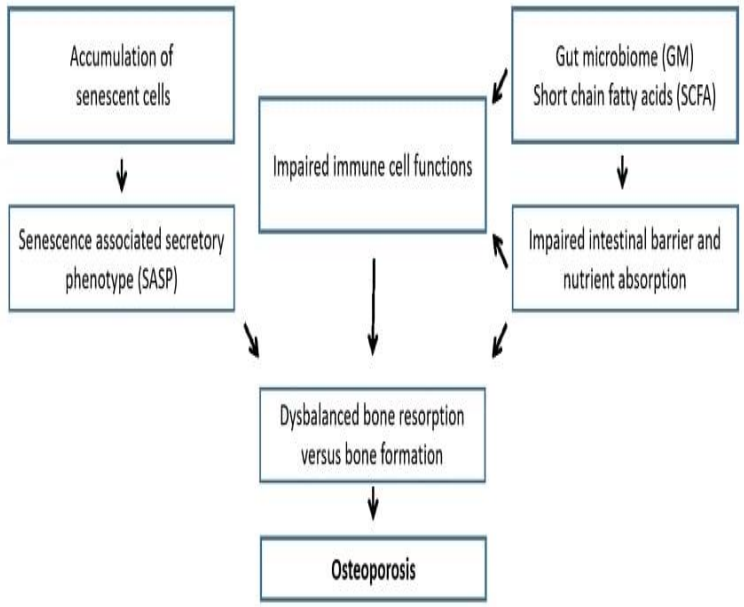

Figure 2 General pathophysiology of osteoporosis

2.1. Peak Bone Mass

Genetic factors are responsible for about 80% of the variance in peak bone mass, while the remaining are due to environmental factors, exercise, diet, and age at puberty [26, 27]. A variety of genes have been associated with BMD including vitamin D receptor, collagen 1α1, estrogen receptor, insulin-like growth factor 1 (IGF-1) and IGF-1 binding protein [28]. Intrauterine development has been denoted as a factor in the achievement of PBM, due to an association between birth weight, childhood growth rates, and peak BMD [29, 30].

2.2. Bone Loss

Involutional bone loss starts between the ages of 35 and 45 in both sexes but is accelerated after menopause in women. Bone loss then continues until the end of life in both sexes [31]. One of the causes of osteoporosis in women is the loss of sex steroids during menopause, which leads to increased bone turnover and bone loss. Oestradiol appears to be the dominant sex hormone regulating bone resorption in men [32].

III. ALLOPATHIC REMEDIES

The goal of pharmacological therapy is to reduce the risk of fractures. Medications to treat osteoporosis are categorized as either antiresorptive (bisphosphonates, estrogen agonist/ antagonists, estrogen, calcitonin, and denosumab) or anabolic (teriparatide). Antiresorptive medications primarily decrease the rate of bone resorption while anabolic medications increase bone formation more than bone resorption. Bisphosphonates are used as a first-line treatment for osteoporosis as they bind with the high affinity mineral matrix of the bone and inhibit osteoclast resorption of the bone [33].

Table 1 Drugs for treatment of osteoporosis

CLASS	DRUG
First line treatment	
Antiresorptive/bisphosphonate	Alendronate (Fosamax, Binosto)
Antiresorptive/bisphosphonate	Risedronate (Actonel, Atelvia)
Antiresorptive/bisphosphonate	Zoledronic acid (Reclast)
Antiresorptive/RANK Inhibitor	Denosumab (Prolia)
Antiresorptive/Raloxifene	Raloxifene hydrochloride
Antiresorptive/Conjugated estrogen	Bazedoxifene/Conjugated estrogens (BZA/CE)
Antiresorptive/Calcitonin	Miacalcin, Fortical
Alternate treatment	
Anabolic /Recombinant human parathyroid hormone	Teriparatide (Forteo)
Antiresorptive/bisphosphonate	Ibandronate (Boniva)

IV. NUTRITIONAL MANAGEMENT

Traditional pharmacological treatment through the use of bisphosphonates and antiresorptive agents has many adverse effects. Oral bisphosphonates have been proven to showcase several complications. When administered in patients with pre-existing gastrointestinal reflux, upper GI adverse effects like ulcers, esophagitis, and bleeding were observed [34, 35]. Osteonecrosis of the jaw is commonly seen in an oncology setting [36]. Due to this, control of diseases through nutritional management is preferred. Vitamin D and K, calcium, magnesium, phosphorus, proteins, and fatty acids play an important role in bone metabolism.

4.1. Calcium

Calcium is the traditional and preferred nutrient supplement for both prophylactic use and the treatment of osteoporosis. Some studies illustrated that calcium supplementation played a protective role in bone health, improving bone mass density (BMD) and decreasing morbidity of osteoporosis and osteoporotic fractures in different genders and age groups [37]. Many OTC calcium supplements are available in the form of calcium carbonate, calcium citrate, calcium lactate, calcium gluconate, etc. They are usually taken without medical supervision and hence exhibit cases of constipation, kidney stones, hypercalcemia, and worsening of kidney functions in susceptible individuals [38, 39]. Foods fortified with vitamin D are preferred to maintain bone health. Most of the dietary intake of calcium is obtained through dairy products like milk, yogurt, and cheese. The fruits and vegetables rich in calcium include broccoli, kale, French beans and dried figs. The animal sources of calcium include sardines, salmon and pilchards.

4.2. Vitamin D

VD promotes calcium absorption in the gut, especially the small intestine (ileum and jejunum). It is important to maintain adequate serum calcium concentrations, required for the normal mineralization of the bone [40]. VD is involved in bone growth and remodelling by osteoblasts and osteoclasts [41], and its deficiency accelerates bone turnover, bone loss, and osteoporotic fractures [42]. In a Cochrane review that spanned over

11 studies and 27,000 patients, reliable evidence was found that taking vitamin D only is unlikely to prevent fractures. However, evidence showed that vitamin D taken with additional calcium supplements slightly reduced the likelihood of hip fractures and other types of fractures [43]. The principal source of vitamin D for most of the population is synthesis following exposure of the skin to UVB radiation. The Endocrine Society states, for example, that to maintain serum 25(OH)D levels above 75 nmol/L, adults need at least 37.5 to 50 mcg (1,500–2,000 IU)/day of supplemental vitamin D, and children and adolescents might need at least 25 mcg (1,000 IU)/day [44]. Not many naturally-occurring food substances contain Vitamin D. Fish liver oils and the meat of fatty fish like salmon, tuna and trout are high sources. The amount of vitamin D is variable in different types of mushrooms. In some countries, the main sources of dietary vitamin D are fortified foods, of which, milk, butter, margarine, and breakfast cereals, enriched with either ergocalciferol or cholecalciferol, are mainly used.

4.3. Vitamin K

It regulates bone remodelling by the promotion of conversion of osteoblast to osteocyte and controlling osteoclast production. There are 3 vitamin K-dependent proteins in bone: osteocalcin, matrix Gla protein, and protein S. Vitamin K is found in 3 forms: phylloquinone (vitamin K_1), Menaquinone (vitamin K_2), and menadione (vitamin K_3) which is synthetically produced only for animals. K_1 is found in green, leafy vegetables like kale, spinach and vegetables in the Brassica genus like brussels sprouts and broccoli. It is also found in fruits such as avocado and kiwi and herbs like parsley and cilantro. Other dietary sources are plant oils such as soybean, canola, and olive oils. K_2 is a bacterial by-product formed by the gut microbiota but may also be found in dairy products like cheese and yoghurt, and meat like chicken, beef and salmon. According to evidence, vitamin K supplementation, especially vitamin K_2, in addition to vitamin D and calcium helps to increase lumbar spine BMD in comparison to the standard combination of calcium and vitamin D alone [45].

4.4. Phosphorus

Phosphorus deficiency, or its insufficient supply, causes bone resorption and inhibits bone mineralization and bone formation. On the contrary, an oversupply of phosphorus, particularly with insufficient Ca intake, results in excessive PTH excretion and the loss of bone mass [46]. Phosphorus is also a crucial element in the drug class of bisphosphonates that are used for osteoporosis treatment. The RDA phosphorus is 700 mg/d for adults aged 19 years or older [47]. Organic phosphorus sources include red meat, seafood, and dairy. Plant food like grains, seeds, and legumes have phosphorus in the form of phytic acid which has decreased absorption in the body as it cannot be digested. Phosphorus can be incorporated into the diet by additives in canned food and beverages. An increase in phosphorus additives such as in Cola has been shown to harm bone integrity [48].

4.5. Magnesium

Several small epidemiologic studies have found that increased magnesium intake is associated with higher BMD in elderly men and women [49]. It is necessary for bone development and mineralization as it stimulates osteoblasts and phosphatase enzymes. Hypomagnesaemia prevents the release of PTH and reduces sensitivity to circulating PTH in target organs, thus affecting BMD. Supplementation of Mg has been shown to correct the levels of PTH and $1,25(OH)_2 D_3$ in osteoporotic postmenopausal women [50]. Increased Mg intake has however been linked to increased wrist fracture risk [51, 52]. The RDA is 400-420mg for men and 310-320mg for women. Green vegetables like spinach, nuts like cashews and peanuts, chia and pumpkin seeds, beans, unprocessed grains, and legumes contain large amounts of Mg.

4.6. Proteins

Dietary protein is crucial for the maintenance of bone tissue as well as for bone growth. Bone is 35% protein and requires a supply of amino acids to be used for protein turnover. Protein intake causes the release of the hormone IGF-1, which increases muscle mass and bone growth [53]. Protein supplementation studies have shown an improvement in BMD, BMC, or other indices or bone size or strength in some studies but not others. High protein sources include dairy products, meat, poultry, fish, tofu, legumes, nuts, and seeds.

4.7. Fatty Acids

Recent research confirms that adequate and balanced levels of EFAs in the diet positively impact bone health and that EFA deficiency may be a major contributor to osteoporosis. Essential FAs are necessary for maximal vitamin D-dependent calcium absorption [54]. There are two categories of EFAs: omega-3 fatty acids (o3FAs) and omega-6 fatty acids (o6FAs). While o6FAs are found in foods such as cereal grains, processed foods, meat, milk, eggs, and some vegetable oils, o3FAs are found in significant quantities in only a few seeds and nuts, as well as in fish oil. Increased BMD of both lumbar and femoral bones was observed by omega-3 fatty acids in elderly females [55].

V. CONCLUSION

For those suffering from osteoporosis, effective prophylactic action as well as efficient management and treatment strategies are preferred. An equal balance of lifestyle, dietary, and allopathic changes and regimes is necessary for the optimum treatment of bone diseases. Although many routes of pharmacological treatment are available, they entail side effects and may not be suitable for all patients. Dietary and nutritional management is a key factor to optimise bone health and is preferred due to low risk and ability to treat secondary symptoms effectively. A balanced diet with enough amount of nutrients found to be effective in the treatment of osteoporosis should be adopted. However, they should be taken under medical supervision and in the right doses to prevent toxicity and further disease progression as sufficient data and research on their long-term effects is not yet established. The nutritional management of osteoporosis through supplements and dietary interventions shows promise for a disease that is prevalent amongst a large chunk of the population.

VI. ACKNOWLEDEGEMENTS

We would like to express our sincere gratitude to Drs. Kiran and Pallavi Patel Global University, Varnama, Vadodara. Gujarat, India for its encouragement and plentiful resources that made this review article possible. We are thankful to the faculty and staff of Krishna School of Pharmacy and Research, KPGU for their constant guidance, expertise and support that played a significant role in shaping the content presented here. Furthermore, we would like to acknowledge the contributions and support of Mr. Taufik Mulla, our academic guide, for his invaluable insights, feedback, and assistance in the preparation of this review article. Last but not least, we appreciate the continued support and encouragement from our colleagues and peers at Krishna School of Pharmacy and Research, who have contributed to the academic environment that enabled this work.

VII. REFERENCES

[1] Clarke B. Normal bone anatomy and physiology. Clin J Am Soc Nephrol. 2008; 3 Suppl 3 (Suppl 3): S131-S139.

[2] Ross MH, Pawlina W. Histology. 5th ed. Lippincott Williams & Wilkins, Philadelphia, 2006; 202–238.

[3] Sawicki W, Malejczyk J. Histologia. 6th ed. Wydawnictwo Lekarskie PZWL, Warsaw, 2012; 192–196.

[4] Melton LJ, Chrischilles EA, Cooper C, Lane AW, Riggs BL. How many women have osteoporosis? Journal of bone and mineral research. 2005; 20 (5): 886–892.

[5] Shahbazi R, Akbari ME, Hashemian M, Abbasi M, Jalali S, Homayounfar R, et al. High body mass index and young age are not associated with post-mastectomy pain syndrome in breast cancer survivors: A case-control study. Iranian journal of cancer prevention. 2015; 8(1): 29

[6] Peris P, Martínez-Ferrer A, Monegal A, Martínez de Osaba MJ, Alvarez L, Ros I et al. Aetiology and clinical characteristics of male osteoporosis. Have they changed in the last few years? Clin. Exp. Rheumatol. 2008; 26 (4): 582–588

[7] Sözen T, Özışık L, Başaran N. An overview and management of osteoporosis. Eur. J. Rheumatol. 2017, 4 (1); 46–56

[8] Jiménez EG, Ferre JA, Pozo Cano MD.; Navarro Jiménez MC, Aguilar Cordero, Tristán Fernández JM. Osteoporosis involutiva tipo I en la mujer posmenopáusica: Diagnóstico y manejo clínico. REEMO. 2009; 18 (4): 77–84.

[9] González LA, Vásquez GM, Molina JF. Epidemiología de la osteoporosis. J. Rev. Colomb. Reumatol. 2009; 16, 61–75.

[10] Khosla S, Lufkin EG, Hodgson SF, Fitzpatrick LA, Melton LJ 3rd. Epidemiology and clinical features of osteoporosis in young individuals. Bone. 1994; 15 (5): 551-555

[11] National Institutes of Health. NIH consensus statement: osteoporosis prevention, diagnosis, and therapy. NIH Consens Statement 2000;17 (1): 1-45.

[12] Sandhu SK, Hampson G. The pathogenesis, diagnosis, investigation and management of osteoporosis. Journal of Clinical Pathology. 2011; 64: 1042-1050.

[13] Kanis JA, Melton LJ 3rd, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res. 1994;9(8):1137-1141

[14] Varacallo MA, Fox EJ. Osteoporosis and its complications. Med Clin North Am. 2014;98(4):817-xiii.

[15] Greenstein AS, Gorczyca JT. Orthopedic Surgery and the Geriatric Patient. Clin Geriatr Med. 2019;35(1):65-92.

[16] Ortego-Centeno N, Muñoz-Torres M, Jódar E, Hernández-Quero J, Jurado-Duce A, de la Higuera Torres-Puchol J. Effect of tobacco consumption on bone mineral density in healthy young males. Calcif Tissue Int. 1997;60(6):496-500.

[17] Buehring B, Viswanathan R, Binkley N, Busse W. Glucocorticoid-induced osteoporosis: an update on effects and management. J Allergy Clin Immunol. 2013;132(5):1019-1030.

[18] Wishart J, Horowitz M, Need A, Nordin BE. Relationship between forearm and vertebral mineral density in postmenopausal women with primary hyperparathyroidism. Arch Intern Med. 1990;150(6):1329-1331.

[19] Nampei A, Hashimoto J, Koyanagi J, et al. Characteristics of fracture and related factors in patients with rheumatoid arthritis. Mod Rheumatol. 2008;18(2):170-176.

[20] Arai K, Hanyu T, Sugitani H, et al. Risk factors for vertebral fracture in menopausal or postmenopausal Japanese women with rheumatoid arthritis: a cross-sectional and longitudinal study. J Bone Miner Metab. 2006;24(2):118-124.

[21] Bukata SV, Digiovanni BF, Friedman SM, et al. A guide to improving the care of patients with fragility fractures. Geriatr Orthop Surg Rehabil. 2011; 2(1): 5-37

[22] Gosch M, Kammerlander C, Roth T, Doshi HK, Gasser RW, Blauth M. Surgeons save bones: an algorithm for orthopedic surgeons managing secondary fracture prevention. Arch Orthop Trauma Surg. 2013; 133 (8): 1101-1108

[23] Dell R, Greene D. Is osteoporosis disease management cost effective? Curr Osteoporos Rep. 2010;8(1):49-55.

[24] Miyamoto RG, Kaplan KM, Levine BR, Egol KA, Zuckerman JD. Surgical management of hip fractures: an evidence-based review of the literature. I: femoral neck fractures. J Am Acad Orthop Surg. 2008;16(10):596-607.

[25] Picazo DR, Villaescusa JR, Martínez EP, Pérez FD. Late collapse osteoporotic vertebral fracture in an elderly patient with neurological compromise. Eur Spine J. 2014;23(12):2696-2702.

[26] Compston JE. Risk factors for osteoporosis. Clin Endocrinol (Oxf). 1992;36(3):223-224.

[27] Scane AC, Francis RM. Risk factors for osteoporosis in men. Clin Endocrinol (Oxf)1993;38:15–16.

[28] Bilezikian JP. Osteoporosis in men. J Clin Endocrinol Metab. 1999;84(10):3431-3434.

[29] Cooper C, Walker-Bone K, Arden N, Dennison E. Novel insights into the pathogenesis of osteoporosis: the role of intrauterine programming. Rheumatology (Oxford). 2000;39(12):1312-1315.

[30] Cooper C, Eriksson JG, Forsén T, Osmond C, Tuomilehto J, Barker DJ. Maternal height, childhood growth and risk of hip fracture in later life: a longitudinal study. Osteoporos Int. 2001;12(8):623-629.

[31] Jones G, Nguyen T, Sambrook P, Kelly PJ, Eisman JA. Progressive loss of bone in the femoral neck in elderly people: longitudinal findings from the Dubbo osteoporosis epidemiology study. BMJ. 1994;309(6956):691-695.

[32] Siddiqui JA, Partridge NC. Physiological Bone Remodeling: Systemic Regulation and Growth Factor Involvement. Physiology (Bethesda). 2016;31(3):233-245.

[33] Tu KN, Lie JD, Wan CKV, et al. Osteoporosis: A Review of Treatment Options. P T. 2018;43(2):92-104.

[34] Ralston SH, Kou TD, Wick-Urban B, Steinbuch M, Masud T. Risk of upper gastrointestinal tract events in risedronate users switched to alendronate. Calcif Tissue Int 2010; 87: 298–304.

[35] Favus MJ 2010. Bisphosphonates for osteoporosis. N Engl J Med 363:2027–2035

[36] Skjødt MK, Frost M, Abrahamsen B. Side effects of drugs for osteoporosis and metastatic bone disease. Br J Clin Pharmacol. 2019;85(6):1063-1071.

[37] Straub DA. Calcium supplementation in clinical practice: a review of forms, doses, and indications. Nutr Clin Pract. 2007;22(3):286–296.

[38] Reid IR, Mason B, Horne A, et al. Randomized controlled trial of calcium in healthy older women. Am J Med. 2006;119(9):777-785.

[39] Machado MC, Bruce-Mensah A, Whitmire M, Rizvi AA. Hypercalcemia Associated with Calcium Supplement Use: Prevalence and Characteristics in Hospitalized Patients. J Clin Med. 2015;4(3):414-424.

[40] Bischoff-Ferrari, H.A.; Willett, W.C.; Wong, J.B.; Stuck, A.E.; Staehelin, H.B.; Orav, E.J.; Thoma, A.; Kiel, D.P.; Henschkowski, J. Prevention of nonvertebral fractures with oral vitamin D and

dose dependency: A meta-analysis of randomized controlled trials. Arch. Intern. Med. 2009, 169, 551–561.

[41] Bouillon, R.; Marcocci, C.; Carmeliet, G.; Bikle, D.; White, J.H.; Dawson-Hughes, B.; Lips, P.; Munns, C.F.; Lazaretti-Castro, M.; Giustina, A.; et al. Skeletal and Extraskeletal Actions of Vitamin D: Current Evidence and Outstanding Questions. Endocr. Rev. 2019, 40, 1109–1151.

[42] Hewison, M. An update on vitamin D and human immunity. Clin. Endocrinol. 2012, 76, 315–325.

[43] Avenell A, Mak JC, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. Cochrane Database Syst Rev. 2014;2014(4):CD000227.

[44] Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911-1930.

[45] Kanellakis S, Moschonis G, Tenta R, et al. Changes in parameters of bone metabolism in postmenopausal women following a 12-month intervention period using dairy products enriched with calcium, vitamin D, and phylloquinone (vitamin K(1)) or menaquinone-7 (vitamin K (2)): the Postmenopausal Health Study II. Calcif Tissue Int. 2012;90(4):251-262.

[46] Mazierka, A.; Pasternak, K. Calcium and phosphorus in medicine and treatment. J. Elem. 2013, 18, 529–539.

[47] Calvo MS, Uribarri J. Public health impact of dietary phosphorus excess on bone and cardiovascular health in the general population. The American journal of clinical nutrition. 2013; 98(1): 6-15.

[48] Ahn H, Park YK. Sugar-sweetened beverage consumption and bone health: a systematic review and meta-analysis. Nutr J. 2021;20(1):41.

[49] Tucker KL, Hannan MT, Chen H, Cupples LA, Wilson PW, Kiel DP. Potassium, magnesium, and fruit and vegetable intakes are associated with greater bone mineral density in elderly men and women. Am J Clin Nutr. 1999;69(4):727-736.

[50] Sahota O, Mundey MK, San P, Godber IM, Hosking DJ. Vitamin D insufficiency and the blunted PTH response in established osteoporosis: the role of magnesium deficiency [published correction appears in Osteoporos Int. 2006 Dec;17(12):1825-6]. Osteoporos Int. 2006;17(7):1013-1021.

[51] Nieves JW. Skeletal effects of nutrients and nutraceuticals, beyond calcium and vitamin D. Osteoporos Int. 2013;24(3):771-786.

[52] Orchard TS, Larson JC, Alghothani N, et al. Magnesium intake, bone mineral density, and fractures: results from the Women's Health Initiative Observational Study. Am J Clin Nutr. 2014;99(4):926-933.

[53] Rizzoli R, Bonjour JP & Chevalley T. Dietary protein intakes and bone growth. International Congress Series. 2007; 1297: 50–59.

[54] Hay AW, Hassam AG, Crawford MA, et al. Essential fatty acid restriction inhibits vitamin D dependent calcium absorption. Lipids. 1980; 15(4):251–254.

[55] Kruger MC, Coetzer H, de Winter R, Gericke G, van Papendorp DH. Calcium, gamma-linolenic acid and eicosapentaenoic acid supplementation in senile osteoporosis. Aging (Milano). 1998;10(5):385-394.