An Overview on Osteoporosis Diagnosis and Management in a Primary Health Care Setting

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ABSTRACT

Background: Osteoporosis is a bone disorder which results in a low bone mineral density (BMD) resulting in an increased risk of fractures in affected patients. Patients with this disease will be asymptomatic and thus will not seek medical attention. Osteoporosis is a prevalent condition especially in the older population and is estimated to affect more than 14 million people in the US. Locally, this disease is prominent in the age group between 50 and 79 years affecting around 30.7% of Saudi men and 34% of Saudi women. Thus, early recognition and detection by primary care and family physicians is vital to limit the complications of this disease. **Objectives:** We aimed to review the literature regarding the pathophysiology of osteoporosis, clinical features, risk factors, diagnosis, and management. **Methodology:** PubMed database was used for articles selection, from which the papers were obtained and reviewed. **Conclusion:** Osteoporosis is a disease of age mainly and affects the bones in general, resulting in fractures, high morbidity, and affecting the quality of life. Thus, physicians shall be able to clinically suspect it, take a good history, in order to diagnose this disease, and form a good management plan. The importance of early diagnosis and screening is immeasurable since this disease is asymptomatic. Many treatment options are available with variable classes and proven results in decreasing the risk of fractures, thus providing better prognosis.

Key Words: *Osteoporosis, Diagnosis, Clinical Features, Management*

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INTRODUCTION

Osteoporosis is a bone disorder which results in a low bone mineral density (BMD) resulting in an increased risk of fractures in affected patients. This condition will result in an abnormal bone mineralization process, a change in its microarchitecture, usually resulting in a less overall bone strength. Patients with this disease are, unfortunately, asymptomatic and thus will not seek medical attention and remain undiagnosed as a result. Most common cause of suspecting and diagnosing this disease is presenting with its complications, such as fracture of the hip or spine, and/or history of fractures leading to hospitalization. Osteoporosis is a prevalent condition especially in the older population and is estimated to affect more than 14 million people in the US alone. Moreover, the prevalence increases with age, where women affected by the disease are around 2% at 50 years, however, this increases over 25% at 80 years [1]. Locally, this disease is prominent in the age group between 50 and 79 years affecting around 30.7% of Saudi men and 34% of Saudi women [2]. The complications of this disease affect the quality of life and increase the economic burden on the health care system overall due to higher hospitalization and medical visits

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rate. It is evident that fractures related to this disease cost approximately $17.9 and £4 billion yearly in the US and UK respectively [3]. Thus, early diagnosis and detection by primary care and family physicians is vital to limit the complications of this disease. In this paper, we will discuss this disease with its types, pathophysiology, clinical features, diagnosis, and management with a special focus on the primary health care setting.

METHODOLOGY

PubMed database was used for articles selection, and the following keys used in the mesh ((“Osteoporosis"[Mesh]) AND (“Diagnosis"[Mesh] OR "Management"[Mesh])). In regards to the inclusion criteria, the articles were selected based on inclusion of one of the following topics; Osteoporosis’ pathophysiology, evaluation, management and diagnosis. Exclusion criteria were all other articles that did not have one of these topics as their primary endpoint.

Review

ones are the main structures of the body as a whole and have many functions. These include protection for structures (organs), and acting as a storage for minerals important for the body as a whole (these include calcium and phosphorus). The stored minerals are also essential for the development and stability of these bones and disturbance in them plays a vital role in many diseases. Generally, the bones continue to be developed and built till reaching its peak –in terms of mass- at around 30 years of age. This peak is highly associated with and determined by many factors; some are non-modifiable such as genes, and others are modifiable like nutrition, exercises, medications, and some diseases. Nevertheless, the loss of the bones mass starts after this peak in a steadily manner over the years, and under some circumstances can even accelerate the process of such depletion. Moreover, bones constantly get remodeled and go through a continuous process of reabsorption (via osteoclasts), and are replaced with a new bone (via osteoblasts). These processes affect both the cortical bone, which is the hard outer part of the skeleton, and trabecular bone, filling the ends of the limb bones and the vertebral bodies (more commonly associated with osteoporotic fractures). Moreover, both processes are controlled and regulated with many factors and mechanisms to insure a balance, so, none of the processes overwhelms the other. Generally, both processes help the body to provide the minerals it needs, and maintain the mechanical strength of these bones, along with many other benefits. However, the main pathophysiological change seen in osteoporosis involves the imbalance in the remodeling process where the resorption exceeds the formation process.

Pathophysiology and Its Types:

Osteoporosis is characterized by the low bone mass and deterioration of bone structure, resulting in fragility of bones and a higher risk of fracture. Nevertheless, a clinical definition for this condition by WHO is when the bone mineral density (BMD) is below 2.5 standard deviations the normal mean for the population in the same age group and gender. As we mentioned earlier, the process of resorption and forming new bone is a tightly controlled and balanced process with many factors controlling and regulating it. Some of the most important factors in this process are hormones and growth factors. The main hormones controlling the regulation function are the estrogen and testosterone which have a primary -if not the most important- role in inhibition of the breakdown process. Overall, testosterone stimulates the bone formation process higher than what estrogen can, and a portion of it is converted into estrogen by the aromatase enzyme. Thus, postmenopausal women have an increased risk rates to develop this condition due to the low estrogen levels. As a result, there are two phases of bone loss in women that are age related; the first is regular –constant- phase we mentioned earlier which is slow and takes longer period of time –up to decades- to produce functional changes; the second phase is the rapid one that begins at menopause and takes around 4 to 8 years; while, men do not have it. As a result, females lose more bone density than men. In comparison, while men and women lose around 20 to 25 % of cortical and trabecular bone in the slow phase, women lose an extra 10% of cortical bone and 30% of trabecular bone in the fast phase. Nevertheless, there are other factors that help in maintaining the bone strength with increased age, such as the increased outside diameter of the bone. Other important factors that have been identified are cytokines and specifically receptor activator of the nuclear factor kappa-B ligand (RANKL). The production of RANKL is by osteoblasts, which bind to the RANK receptors on osteoclasts. As a result, maturation and activation of osteoclasts take place and further increase the bone resorption process. Recent studies have highlighted the role of apotent protease, cathepsin K (CatK), which is secreted by activated osteoclasts. This protease further aids the bone resorption process by degrading the bone matrix and breakdown the mineral components. Moreover, some hormones, such as parathyroid hormone (PTH), have a vital role in bone forming process and cause a feedback mechanism to control the whole process. Parathyroid hormone (PTH) indirectly increases the proliferation of osteoblasts, by means of regulating the calcium homeostasis, where they enhance it when enough calcium is available in the body. So, if there is any impairment of absorption (by intestine) and/or reduced ability to conserve calcium (by kidney) and the person is not consuming enough calcium to make up for it the calcium levels will drop, activating the PTH. High

PTH levels in the blood will cause bone resorption to increase in order to remove calcium from bones. Only a negative calcium balance of 50 to 100 mg per day over a long period will result in osteoporosis; in comparison, a single glass of milk contains 300 mg of calcium. [4-7]

Osteoporosis can be localized in a certain part of the skeleton and can be generalized all over the skeleton, which is the most common form. Usually, the localized form is a result of trauma, injury, or any condition affecting the muscle forces on the bone itself, for example paralysis. In terms of types, osteoporosis can be divided based on the etiology into primary and secondary osteoporosis. Primary osteoporosis is not caused by any other disorder and has its own modifiable and non-modifiable risk factors. On the other hand, secondary osteoporosis is caused by a certain disorder, condition or drug and can be developed even without any of the risk factors of the primary disease. A rare form of this condition is idiopathic osteoporosis where it can affect younger individuals with no obvious reason. Many patients with this variant can be diagnosed with a primary defect in the regulation mechanism affecting the bone formation, and resorption and/or both which result in a severe form of the disease. Moreover, some have a milder form of this condition and only fail to achieve the optimal skeletal mass during growth. [1, 4, 8]

Risk Factors and Etiology:

Primary osteoporosis is regarded as a disease of the elderly, so age is the main risk factor in this disease. This is reflected as younger population – children and young adults- do not usually develop the disease (except in the rare idiopathic variant). Menopause and any estrogen deficiency disorder is a major risk factor and thus women are more affected by osteoporosis up to three more times, especially in primary variant. Nevertheless, not all postmenopausal women develop this disease, and the reason behind this is not completely understood. However, males and females show the same risk rate for idiopathic osteoporosis, especially in the younger population. Some modifiable risk factors such as diet, physical activity, along with calcium and vitamin D intake can all slow down or fasten the course of losing the bone due to age. Genetics is associated with primary osteoporosis, moreover, some disorders such as the most commonly, cystic fibrosis and idiopathic hypercalciuria cause the secondary variant. Other disorders that are associated with osteoporosis include hypogonadal causing diseases (like androgen insensitivity), some gastrointestinal, renal, and endocrinal pathologies among others (Table 1). In addition, many drugs contribute to the development of this disease and the main examples are mentioned in Table 1. In summary, hyperparathyroidism and calcium metabolism disorders make up 78% of causes of secondary osteoporosis. Nevertheless, patients with primary osteoporosis can still have factors associated with secondary osteoporosis and these will further increase the bone loss resulting from the disease. [9, 10]

Table 1: Main Conditions and Medications Contributing to Secondary Osteoporosis

Genetic Disorders	Cystic Fibrosis, Glycogen Storage Diseases, Ehlers-Danlos syndrome, Hemochromatosis, Idiopathic Hypercalciuria, Homocystinuria, Marfan's Syndrome
Hypogonadal States	Anorexia Nervosa, Androgen Insensitivity, Athletic Amenorrhea, Turner's syndrome, Klinefelter's Syndrome, Hyperprolactinemia, Premature ovarian failure
Gastrointestinal Diseases	Inflammatory Bowel Disease, Gastrectomy, Celiac Disease, Primary Biliary Cirrhosis
Endocrine Disorders	Adrenal Insufficiency, Diabetes Mellitus (Type 1), Acromegaly, Cushing's Syndrome, Thyrotoxicosis , Hyperparathyroidism
Rheumatic and Auto-Immune Diseases	Rheumatoid Arthritis, Systemic Lupus Erythematosus, Ankylosing Spondylitis
Hematologic Disorders	Leukemia, Lymphoma, Hemophilia, Multiple Myeloma, Sickle Cell Disease
Miscellaneous	Congestive Heart Failure, Alcoholism, Chronic Metabolic Acidosis, End Stage Renal Disease, Amyloidosis, Muscular Dystrophy, Sarcoidosis
Medications	Glucocorticoids, Androgen-deprivation Therapy,Cyclosporine A, Anticonvulsants, Anticoagulants (heparin), Tacrolimus, Chemotherapies, ACTH, Gonadotropin-Releasing Hormone Agonists, Lithium, Thyroxine, Methotrexate.

Clinical Features and Screening:

Unfortunately, osteoporosis is asymptomatic and usually is presented with its complications, mainly fractures. These can vary from one or two collapsed bones in the spine, to multiple fractures involving the skeleton (e.g. whole spine or hip). The severity of such fractures depends on the severity of the disease and the forces causing the fracture. Classically, the disease –if not treated- only gets more severe with time, but in some cases, the disease can go into remission. This is seen in juvenile osteoporosis, which affects children and usually goes into a spontaneous remission when the patient is close to puberty. However, the patient may have a lasting hypnosis or even be incapacitated for life depending on the severity of the disease and complications. The primary health care physician shall request all adults over 50 to do the BMD screening if they have a history of fracture according to most guidelines [11]. Moreover, the clinician shall require

a full history from the patient in order to pick up any associated factors related to osteoporosis. Any chronic diseases history, including COPD, kidney problems, intestinal disorders (e.g. malabsorption), and family history, shall be all asked by the physician. Medication usage and history shall be taken in full details as well. Moreover, lab tests may reveal high calcium levels in the blood (in cases of high PTH due to adenoma for example), low vitamin D, and other chronic diseases reflecting inflammatory factors shall be alarming to the clinician. Genetic testing and some disease focused testing (like sweat test for cystic fibrosis) can be done in some cases when confirming a specific underlying cause is needed, but usually this is done after referring and not in primary health care center [12].

Diagnosis:

Diagnosing this disease starts with a high threshold of suspicion, especially when the patient is presented with a history of fractures, is elderly, and the fracture is more severe than the incident behind it. As we mentioned earlier, diagnosing osteoporosis depends on the BMD of the patient and comparing it to the standard deviation of population of the same age and gender. The golden standard for BMD measurement is dual-energy x-ray absorptiometry (DXA) mainly in the hip or lumbar spine. However, some studies have suggested the occurrence of non-traumatic hip or vertebral fractures as means to start therapy in elderly people. DXA scan yieldsT-scores, which are used to interpret the BMD and it correlates to the risk of fracture as well. The higher negative the T-score is the lower the BMD score, and the higher risk of fracture. Osteoporosis is diagnosed when the BMD is less than 2.5 times the standard deviation of the patient's similar population in age and gender. Severe osteoporosis has the same definition with the addition of one or more fragility fractures. For the purpose of screening, DXA is used as well; however, if the scan is negative, there is some controversy on when to repeat the scan, with some guidelines stating that repeated scans for screening shall be done after a two to five years after the first negative scan [13]. Another instrument to help for diagnosis is a risk-assessment tool called FRAX (Fracture Risk Assessment Tool) which can be used by primary health care physicians. It assesses many risk factors such as age, gender, race, body mass index, prior personal (or parental) history of fracture, alcohol usage, smoking history, glucocorticoids usage, among others in order to predict 10-year probability of major osteoporotic fractures (e.g. hip fracture). Fracture Risk Assessment Tool (FRAX) can reflect the probabilities based on the local population thanks to the epidemiological data for more accurate results. The family physician can use this tool to refer the patient to a higher center, or use it in conjunction with DXA (or other diagnostic tools), in order to determine the best treatment plan for the patient. However, FRAX does not make any recommendations on whom to treat, so further testing is needed before initiation of the therapy. Nevertheless, there are many limitations to FRAX such us not being valid with total hip or lumbar spine BMD, ethnic minorities, people younger than 40 or older than 90 years old, and people who started treatment. Another point of concern of this tool does not include history of falls as a risk factor due to lack of a standardized evidence connecting it to fracture risk. If the clinician diagnosed osteoporosis in a patient, but excluded all the common causes behind this disease s/he shall consider genetic disorders and may need further genetic testing to confirm [11, 14].

Management:

As many other diseases, management of this disease has a nonpharmacological and a pharmacological aspect, but both aim to reduce the risk of fractures. However, every clinician shall be aware of the main headlines of the management, especially primary health physicians. The nonpharmacological therapy approach focuses on the adequacy of calcium and vitamin D intake. The recommended daily calcium consumption should be limited to one gram per day for men (between 50 to 70 years old) and to 1200 mg per day for women (above 50 years old) and for men (older than 70 years old). However, there is still some controversy about the risk of kidney stones but the calcium intake from diet shall be differentiated from supplements. Although, high supplement calcium intake is associated with higher risk of kidney stones, some studies showed a protective effect of dietary calcium against renal stones. Thus, a family physician shall encourage and advice the patient to increase the dietary calcium intake before prescribing any supplements. Regarding vitamin D, which is vital for calcium absorption, it is recommended to take 600 IU per day for men and women, between 51 and 70 years. This dose increases to 800 IU daily for men and women older than 70 years. Sun exposure is important in this matter as well; however, supplements are available and they reduce fracture risk when taken in the recommended values. Some studies have shown relationship between the risk of falls and higher doses of vitamin D; thus, the clinician shall not overprescribe the doses. In addition, multiple management options proved effective in osteoporotic patients including exercises (weight bearing), smoking cessation, limiting alcohol (and caffeine) consumption, and teaching the patient (or caregiver) fall-prevention techniques [15, 16].

The pharmacological medications that can be used in these diseases can be divided into antiresorptive or anabolic. Antiresorptive medications include bisphosphonates, estrogen agonist/antagonists –EAAs-, estrogens, calcitonin, plus denosumab that aim to decrease the rate of

bone resorption. On the other hand, anabolic ones such as teriparatide, increase bone formation rate to overcome the resorption rate. However, Food and Drug Administration (FDA) approve not all drugs in the treatment of osteoporosis in men, post-menopausal osteoporosis, and/or glucocorticoid-induced osteoporosis. As a result, the clinician shall not confuse the drugs and give the same drug for all osteoporotic cases, and this highlights the importance of an accurate diagnosis. American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) recommend alendronate, risedronate, zoledronic acid, and denosumab as a first line treatment for most high fracture risk post-menopausal osteoporotic cases. However, if the patient cannot take oral therapy, and is a high-risk case, teriparatide, denosumab, or zoledronic acid usage is recommended. American College of Physicians (ACP) recommends that this management plan is carried for five years in these women, and strongly advices against estrogen therapy, with or without progestogen and raloxifene. Moreover, men with osteoporosis can be treated with bisphosphonates as a first line of treatment according to ACP guidelines. Clinicians shall always be careful with usage of glucocorticoids and shall give it in the lowest possible dose for as short a time as possible and to use it locally when feasible. Treating osteoporosis cases due to glucocorticoids can be done with bisphosphonates like alendronate, risedronate, zoledronic acid, and teriparatide. For prevention, most guidelines recommend bisphosphonates, with exception of ibandronate, to be used as a first-line option for men and postmenopausal women [11, 13, 16].

There are many opinions about the recommended frequency of BMD monitoring during follow-up of treatment. Some foundations like National Osteoporosis Foundation (NOF) recommend monitoring one to two years after initiation of therapy and every two years after the first scan. Other studies recommend a four-year interval of follow up after initiation of therapy. Moreover, North American Menopause Society (NAMS) recommend one to two years before doing the scan again after starting the treatment. However, ACP guidelines in 2017 were against monitoring BMD in the whole five-year treatment period [4, 16, 17].

CONCLUSION

Osteoporosis is a disease of age, mainly, and affects the bones in general, resulting in fractures, high morbidity, and affecting the quality of life. This disease is increasing in prevalence due to the aging of population as a whole. Thus, physicians shall be able to clinically suspect it and take a good history in order to diagnose this disease and form a good management plan. The importance of early diagnosis and screening of suspected cases is immeasurable, since this disease is asymptomatic and almost exclusively presented with complications (fractures); if not picked up during routine checkups in the primary health care center. Many treatment options are available with variable classes and proved results in decreasing the risk of fractures and better prognosis for these patients. Nevertheless, new basis for treatment is being developed and may provide better options in some cases and change guidelines and the way we treat osteoporosis in the future.

REFERENCES

[1] Tu KN, Lie JD, Wan CKV, Cameron M, Austel AG, Nguyen JK, Van K, Hyun D. Osteoporosis: A Review of Treatment Options. Pharmacy & Therapeutics J. 2018; 43(2):92-104.

[2] Al-Moaibed G, AlHamam N, Alfayez E, Alfayez E, Al-Mubaddil M, Alramadhan N. Prevalence and risk factors for osteoporotic fracture among adults with comorbidities in Al-Ahsaa, Saudi Arabia. Journal of Family Medicine and Primary Care. 2020;9(2):877-882.

[3] Michael A Clynes, Nicholas C Harvey, Elizabeth M Curtis, Nicholas R Fuggle, Elaine M Dennison, Cyrus Cooper. The epidemiology of osteoporosis. British Medical Bulletin, 2020; 133 (1):105–117.

[4] Das S, Crockett J. Osteoporosis—a current view of pharmacological prevention and treatment. Drug Des DevelTher. 2013;7:435–448.

[5] Raisz LG. Pathogenesis of osteoporosis: concepts, conflicts, and prospects. Journal Clin Invest. 2005;115(12):3318–3325.

[6] Adami, G., Saag, K.G. Osteoporosis Pathophysiology, Epidemiology, and Screening in Rheumatoid Arthritis. CurrRheumatol Rep. 2019; 21, 34.

[7] Föger-Samwald U, Dovjak P, Azizi-Semrad U, Kerschan-Schindl K, Pietschmann P. Osteoporosis: Pathophysiology and therapeutic options. EXCLI J. 2020;19:1017-1037.

[8] Sutton RAL, Dian L, Guy P. Osteoporosis in men: an underrecognized and undertreated problem. BCMJ. 2011;53(10):535–540.

[9] Ibrahim NA, Nabil N, Ghaleb S. Pathophysiology of the Risk Factors Associated with Osteoporosis and their Correlation to the T-score Value in Patients with Osteopenia and Osteoporosis in the United Arab Emirates. J Pharm Bioallied Sci. 2019;11(4):364-372.

[10] Bijelic R, Milicevic S, Balaban J. The Influence of Non-preventable Risk Factors on the Development of Osteoporosis in Postmenopausal Women. Mater Sociomed. 2019;31(1):62-65.

[11] Camacho PM, Petak SM, Binkley N, Clarke BL, Harris ST, Hurley DL, Kleerekoper M, Lewiecki EM, Miller PD, Narula HS, Pessah-Pollack R. American Association of Clinical Endocrinologists and

American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis—2016. EndocrPract. 2016;22: 35-40.

[12] Jeremiah MP, Unwin BK, Greenawald MH, Casiano VE. Diagnosis and management of osteoporosis. American family physician. 2015 Aug 15;92(4):261-8.

[13] Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R. Clinician's guide to prevention and treatment of osteoporosis. Osteoporosis international. 2014 Oct 1;25(10):2359-81.

[14] Kanis JA, Harvey NC, McCloskey E, Bruyère O, Veronese N, Lorentzon M, Cooper C, Rizzoli R, Adib G, Al-Daghri N, Campusano C. Correction to: Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. Osteoporosis International. 2020;31(4):797-8.

[15] Kopecky SL, Bauer DC, Gulati M, Nieves JW, Singer AJ, Toth PP, Underberg JA, Wallace TC, Weaver CM. Lack of evidence linking calcium with or without vitamin D supplementation to cardiovascular disease in generally healthy adults: a clinical guideline from the National Osteoporosis Foundation and the American Society for Preventive Cardiology. Annals of internal medicine. 2016 Dec 20;165(12):867-8.

[16] Qaseem A, Forciea MA, McLean RM, Denberg TD. Treatment of low bone density or osteoporosis to prevent fractures in men and women: a clinical practice guideline update from the American College of Physicians. Annals of internal medicine. 2017 Jun 6;166(11):818-39.

[17] Abdelhalim MO, Mahmoud HM, Yacoub MF, Mohammad AS. The antiresorptive effect of neostigmine in ovariectomy-induced osteoporosis in rats. J. Adv. Pharm. Educ. Res. 2020;10(1):26-39.