Journal of Global Health Science
A Qatar Foundation Academic Journal

OPEN ACCESS

Review article

Osteoporosis: An under-recognized public health problem

Local and global risk factors and its regional and worldwide prevalence

Rajasree Vijayakumar, Dietrich Büsselberg*

Weill Cornell Medicine in Qatar,
Qatar Foundation-Education City,
PO Box 24144, Doha, Qatar
*Email: dib2015@qatar-med.cornell.edu

ABSTRACT

Over 200 million people suffer from osteoporosis worldwide, which occurs when bone tissues become structurally deteriorated and bone mass becomes fragile, resulting in an increased risk of fracture. This review aims to describe the underlying risk factors and provide guidance on changes in lifestyle for those at risk of developing osteoporosis. It highlights risk factors such as age, sex, genetic background, and other under lying illnesses (factors that are generally "non-modifiable"). Furthermore, it focuses on factors that are dependent on lifestyle and (local) habits (factors that are "modifiable"), such as diet, sunlight exposure, exercise, and medication. Clearly, osteoporosis is a multifactorial disease and multiple of these risk factors can occur simultaneously. Currently, the data available differ greatly between regions and some areas might be affected more seriously than others. This review suggests that this might be due to differing healthcare training systems and suboptimal awareness of osteoporosis. Importantly, osteoporosis and resulting bone fractures represent a significant economic burden for both individuals and the wider society. Therefore, improved awareness of the disease may influence personal habits, reduce suffering, and alleviate the burden on healthcare expenditure.

Keywords: osteoporosis, vitamin D, geographic variations, sun exposure, risk factors, genetic background

http://dx.doi.org/
10.5339/jlghs.2016.2

Submitted: 20 August 2015
Accepted: 24 January 2016
© 2016 Vijayakumar, Büsselberg, licensee HBKU Press. This is an open access article distributed under the terms of the Creative Commons Attribution license CC BY 4.0, which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

QSCIENCE.com
An Initiative of Qatar Foundation

Cite this article as: Vijayakumar R, Büsselberg D. Osteoporosis: An under-recognized public health problem, *Journal of Local and Global Health Science* **2016:2** http://dx.doi.org/10.5339/jlghs.2016.2

1. OSTEOPOROSIS: A GLOBAL PUBLIC HEALTH PROBLEM

Osteoporosis is recognized as a serious public health problem, with about 200 million people being affected worldwide. In the USA, about 10 million patients have been diagnosed with osteoporosis and another 34 million with a low bone mass, placing them at an increased risk of osteoporosis.[1] Osteoporosis is the cause of approximately 1.5 million fractures every year; among them, the most common are hip, spine, and wrist fractures. Globally, the economic burden of osteoporosis parallels expenditures for osteoporotic fractures.[2]

Bone loss and hip fracture was originally described by Sir Astley Cooper in 1822 [3], and the term "osteoporosis" was introduced by German and French physicians in the 19th century when the histology of osteoporotic bone was investigated.[4]

The Consensus Development Conference[5] characterized osteoporosis as a "systemic skeletal disorder characterized by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture". Today, osteoporosis is defined by the National Osteoporosis Foundation (NOF) as "a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased risk of fracture".[1]

Osteoporosis occurs due to an imbalance of bone remodeling, leading to a reduction in bone strength. Bones become fragile due to a disruption of the structure, resulting in an increased risk of fracture. Generally, bone loss develops over a prolonged time and its pathogenesis can occur without warning symptoms. The pathogenesis of osteoporosis is an aberration in normal bone turnover, involving an imbalance between the processes of bone resorption and bone formation.[6] Osteogenesis occurs rapidly during growth and leads to denser, longer, and heavier bones, resulting in skeletal growth. Bone density in adults is a reflection of modifiable conditions at puberty, with the highest bone mass being attained at 30 years of age. Thus, this benchmark age is considered to be an important predictor for the subsequent development of osteoporosis.

Currently, osteoporosis is a significant human and economic burden and will become even more significant in an aging society, giving rise to the decline in bone mass and an increased risk of fracture. Overall, hip fracture, one of the most serious outcomes of osteoporosis, is most frequent as life expectancy increases at a rate of 1–3% each year globally, and this is more pronounced in postmenopausal women.

Osteoporosis-related diagnosis, treatment and research have increased in Western countries; however, less attention is given to this issue in the Middle East and African countries. While osteoporosis has become a worldwide challenge, only a few countries within this region have accessible osteoporosis guidelines.

2. EPIDEMIOLOGY

The prevalence of osteoporosis has not yet been adequately documented in several parts of the world (e.g., South America, Australia, or China). In different parts of the world, the normal serum content of 25-hydroxyvitamin D (25(OH)D) among women with osteoporosis is 50–80 nmol/l (20–32 ng/ml). Serum 25(OH)D levels of postmenopausal women with osteoporosis undergoing medical care have been studied in 18 countries. The mean serum 25(OH)D levels have been reported to be 26.8 ng/ml, with a range as low as 7 ng/ml up to 243 ng/ml. It is evident that while regional values differ greatly, serum levels have been found to be highest in Latin America (29.6 ng/ml) and lowest in the Middle East (20.4 ng/ml). Overall, 64% of the women have been found to have serum levels <30 ng/ml, which is the normal level for serum 25(OH)D).

The following sections summarize the available information for specific regions and countries (while some information of specific regions is given in previous sections).

2.1. USA and Europe

In the USA and Europe, approximately 30% of postmenopausal women have been found to have osteoporosis. At least 40% of women and 15–30% of men have sustained fragility fractures in their lifetime.[7] Hadji et al.[8] determined the prevalence and incidence of osteoporosis and the frequency of osteoporotic fractures in a selected population of insurees, and extrapolated their findings to the overall German population. The prevalence of osteoporosis among individuals aged 50 years and above was 14%, with a sex-specific prevalence of 24% in women and 6% in men. This implies that

6.3 million people in Germany have osteoporosis and 2.1% of those will have an osteoporotic fracture within a year. Meanwhile, 85% will develop osteoporosis and 52% of the affected individuals will have sustained fractures (many being multiple). Overall, osteoporosis is still a common health problem in Germany.

2.2. Asia

In Japan, the number of people with osteoporosis is estimated to be 15 million, but only 20% are currently undergoing treatment.[9] A recent survey conducted in 2007 found that the incident rates of hip fractures were 5.1 cases in 10,000 men and 18.1 in 10,000 women, while the number of patients was approximately 130,000, of which 60,000 experienced functional decline. This indicates a 2.8-fold increase when compared with an initial survey conducted in 1987, which could be attributed to an increase in the elderly population. Data on the prevalence and incidence of vertebral fracture in Japan are vague compared with those of hip fracture. The prevalence rate of vertebral fracture was comparable with those in Caucasian populations (or was even higher), with approximately 30% in women aged 70 years and 40% in those aged 80 years.

In India, hip fractures are common, and, surprisingly, men are more commonly affected than women. Nordin[10] analyzed 119 hip fracture cases and found that hip fractures occurred in almost all ages, but peaked between the ages of 30–39 and 50–70 years. Gupta et al.[11] analyzed 425 hip fracture cases in the Indian population. They reported the mean age of the occurrence of fracture as 49 years in men and 57 years in women. This finding was supported by a more recent study that examined 1393 hip fracture patients from different hospitals in Delhi, showing that fractures were common in both sexes and these fractures occurred mostly between 60–70 years of age.[12]

2.3. Middle East and Africa

In the Middle East and Africa, the highest incidence of rickets has been recorded.[13,14] Although these regions have ample sunshine throughout the year, sun exposure is limited partially due to the cultural practice of covering the whole body with clothes (parda), darker skin color, and prolonged breastfeeding without taking vitamin D supplements.[15,16,17] All these factors can indirectly contribute to vitamin D deficiency.[18]

However, concrete data from this region are scarce, largely due to the unavailability of methods (e.g., dual-energy absorptiometry) to measure bone mineral density (BMD), which can make the diagnosis of osteoporosis difficult for even well-trained primary healthcare professionals. The Middle East and Africa Regional Audit (released during the 1st Middle East and Africa Osteoporosis meeting) is a landmark report of the data collected from 17 countries in the Middle East and Africa by the International Osteoporosis Foundation.[19] It investigated the epidemiology, costs, and burden in individual countries as well as collectively across the region. The report concluded that osteoporosis is a serious problem throughout the regions of the Middle East and Africa.[19] From the available evidence, it is clear that the Middle East and Africa have very high incidences of osteoporotic fractures, with rates of fragility fracture incidence expected to quadruple in several countries. The report suggested that by 2020, 25% of the population will be over the age of 50 years, which will increase to 40% by 2050.[20] High prevalence for hypovitaminosis D has also been reported in the Middle East and Africa. Although the data from the Middle East (as summarized in Table 1) showed variations, overall, they clearly showed a widespread deficiency of vitamin D in men and women, albeit less pronounced in males.

In Lebanon, the incidence of vitamin D deficiency in school children and young individuals has been found to be high. A survey conducted in 251 Lebanese postmenopausal osteoporotic women has shown that vitamin D inadequacy was 84.9%. The level of 25(OH)D was negatively correlated with BMI and positively correlated with educational level.[37] Interestingly, no significant correlation with regard to age, season, sun exposure, or vitamin D-rich food consumption was observed in that study. However, the level of 25(OH)D was found to be strongly correlated with vitamin D supplement intake. The Muslim community had lower 25(OH)D levels compared with their Christian counterparts. They also had high BMI, low educational level, and low vitamin D supplement intake, and followed more frequently a dress code covering their arms. However, in Christians, the predictors were inadequate vitamin D supplements, high BMI, and low educational level.

Table 1. Percentage of vitamin D deficiency in different regions of the Middle East.

Serial no.	Country/region	Sex	Percentage of vitamin D deficiency (< 25 nmol/l)	Reference
1	Saudi Arabia (adolescent girls)	F	80	19,21
2	Saudi Arabia (mothers)	F	10–60	22
3	Saudi Arabia (neonates at delivery)		40–80	22
4	Iran	F	70	23
5	Iran	M	35	23
6	Iran	F	60–65	24
7	Lebanon (adolescent boys)	M	12	25
8	Lebanon (adolescent girls)	F	32	26
9	Israel (adults)		60–65	27
10	Lebanon (adults)	F	60–65	28,29
11	Jordan (adults)	F	60–65	
12	Iran (adults)	F	60–65	24
13	Lebanon (men)	M	37	30
14	Lebanon (elderly women)	F	56	30
15	Israel (elderly women with hip fracture)	F	80	31
16	Jordan	F	60–65	24,29
17	Kuwait (mothers)	F	10–60	32
18	Kuwait (neonates at delivery)		40–80	32
19	UAE (mothers)	F	10–60	33
20	UAE (neonates at delivery)		40–80	33
21	Tunisia	F	48	34
22	Lebanon (women)	F	35	26
23	Saudi Arabia	F	35	35
24	Emirates	F	35	36
25	Iran	F	35	23

3. RISK FACTORS

The following sections describe the risk factors that contribute to low bone mass and osteoporosis. We further divided these sections into "non-modifiable risk factors" (age, sex, concurrent illness, genetic background, and regional factors), which can be applied to any individual but are difficult (or impossible) to change, and "modifiable risk factors" (vitamin D status, medication (e.g., glucocorticoids or anti-epileptic drugs) and lifestyle (e.g., physical activity, diet, smoking habits, alcohol, and/or caffeine consumption), which are subject to change (Figure 1).

3.1. Non-modifiable risk factors

3.1.1. Lifespan

Classically, bone resorption exceeds formation after 30 years of age, with an average bone loss of 0.7% per year. Given the increase in life expectancy, it is expected that by 2050, a quarter of the world population will be over the age of 50 years, with a rise of 40% since 2005.[38] Thus, there is an increase in personal, social, and economic burden. As bone mass declines, the risk of fracture increases. Fractures in the elderly mostly result from a combination of falls and osteoporosis. Fall rates have been found to be higher in women than in men from Western communities and lower in East Asian populations. A meta-analysis conducted using statistically homogeneous datasets, extrapolated to the USA, has implied that low-impact falls can cause approximately 0.53 million osteoporotic fractures annually among the elderly in the USA.[39] A French study has estimated the present and future burden of postmenopausal osteoporosis in women (above 50 years), and observed that the number of postmenopausal osteoporotic women will increase from 3.0 million to 3.4 million between 2010 and 2020. The model predicted that the overall number of osteoporotic fractures will increase from 204,234 fractures in 2010 to 241,261 in 2020.[40] While these numbers are alarming, the IOF report[38] showed that solid epidemiological research on osteoporosis and fractures is scarce. Currently, the incidence of osteoporosis is highest in North America and Europe; however, it is expected to increase in developing countries compared with developing regions of the world as the elderly population grows at a higher rate.[3]

3.1.2. Sex

Women suffer from osteoporosis mainly due to the effects of menopause. Bone loss and/or fractures are attributed to causes such as estrogen deficiency, glucocorticoid exposure, or hyperparathyroidism.[41] In postmenopausal women, an acceleration of bone loss has been observed,

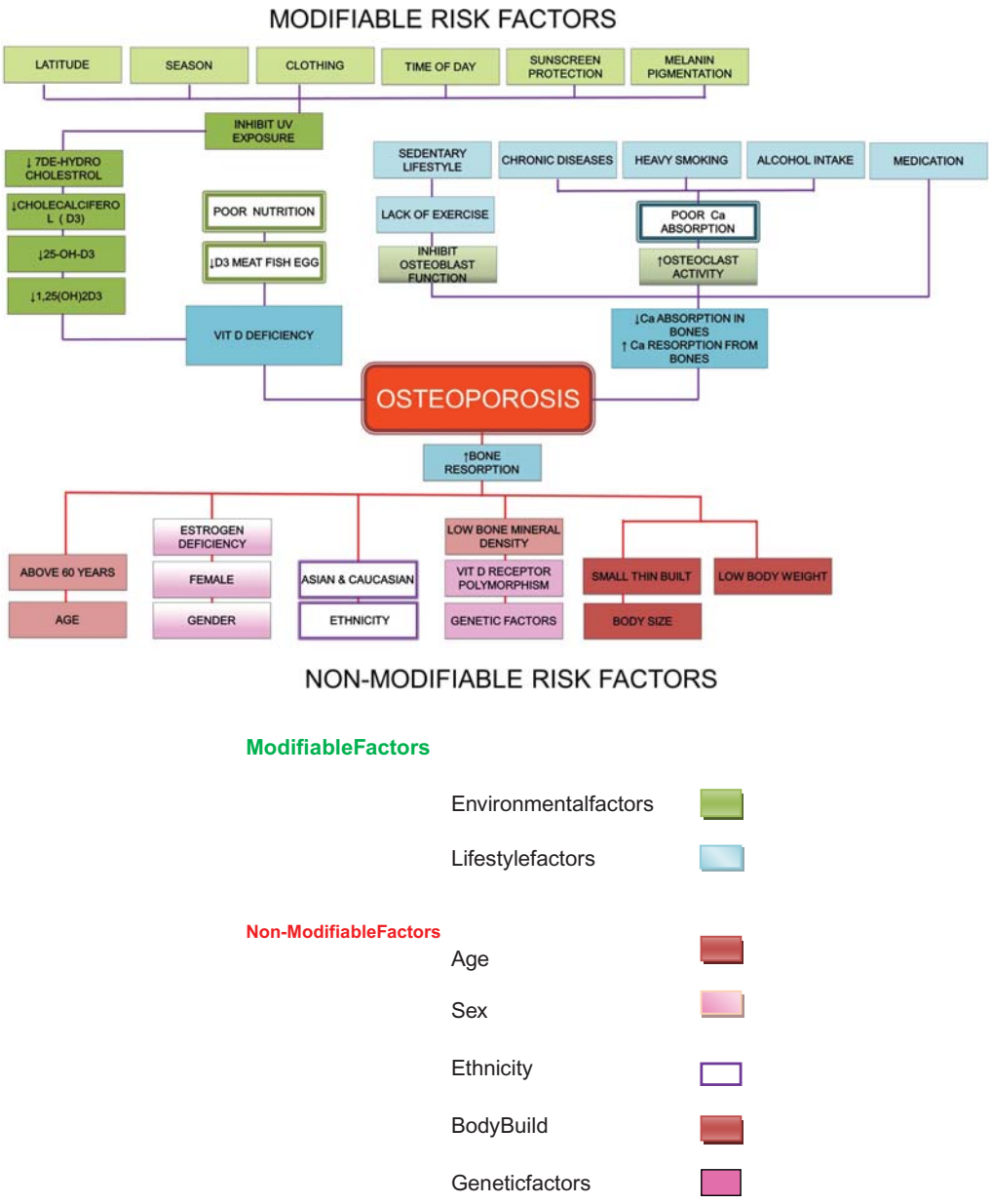

Figure 1. Factors influencing osteoporosis.

which is more common for those who attain menopause before the age of 45 years. The rate of bone loss remains elevated for up to 40 years after cessation of ovarian function, leading to continuous bone loss.[42] Studies have suggested that oral contraceptives, late menarche, and hormone replacement therapy are protective against the loss of bone density.[43] Over the past decades, male osteoporosis has also gained much attention, raising public health.[1] As in women, osteoporosis in males is associated with hormonal status and primary hypogonadism. Abnormal bone development plays an important role in osteoporosis of men with idiopathic hypogonadotropic hypogonadism.[44] Male hypogonadism causes both cortical and trabecular osteoporosis. In such people, a major risk factor for the development of osteoporosis is the reduction in plasma 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) levels, leading to malabsorption of calcium and reduced bone formation.[45]

3.1.3. Genetic factors

Recently, the effects of genetic traits that influence hormonal and environmental factors on susceptibility to osteoporosis development have been described,[46] which are discussed in the following sections.

3.1.3.1. Vitamin D receptor gene polymorphism: Polymorphisms are generally mutations that occur due to DNA damage and can grow in frequency over time and familial generations. Polymorphisms of the vitamin D receptor (VDR) gene are important for changes in the genetic regulation of bone mass. However, their specific roles within various ethnic (sub-) populations are not entirely clear. The VDR *BsmI* polymorphism affects BMD variation and levels of circulating osteocalcin.[47] A number of epidemiological studies have been performed to evaluate the association between the VDR *BsmI* polymorphism and its susceptibility to osteoporosis. It has been hypothesized that VDR genotypes are an important determinant of BMD, as a population of related osteoporotic individuals (mother–daughter or sister–sister relationship) exhibited a high prevalence of the *BB*, *tt*, or *AA* VDR polymorphic genotypes.[47,48] Ethnic variations in polymorphisms of VDR were also identified; however, the number of studies conducted in ethnic populations were fewer than those conducted in Caucasians. Allele frequency differences between ethnic groups most likely resulted from evolutionary processes, altering the "genetic behavior" of a population. The hereditary component of bone density has been mostly described as polymorphism of alleles within the vitamin D receptor gene. A study conducted by Mitra et al.[49] in postmenopausal Indian women confirmed that VDR gene polymorphisms were associated with BMD and influence determinants of bone metabolism.

The interaction between parathyroid hormone (PTH) levels and VDR gene polymorphisms is evident, which has been shown to be directly related to variations of BMD at the spine and the forearm in vitamin D-deficient Asian Indians.[50] In Indian women, polymorphisms of the estrogen receptor gene have also been shown to be associated with BMD, resulting in age-related bone loss.[51]

3.1.4. Intrauterine and early postnatal programming

At an early stage of development, environmental factors increase the risk of developing osteoporosis. Structural and functional changes initiated during that time have been shown to persist lifelong.[52] During intrauterine growth, cell number of any particular organ can be permanently reduced by nutritional deprivation (e.g., "rickets"). A significant correlation has been found between the weight of a child at 1 year and the bone mineral content at 21 years, which is independent of BMI, diet, or lifestyle. This observation reveals that bone mass in adulthood depends on the weight at infancy.[53] This conclusion was supported by a Swedish study that investigated this correlation in 15-year-old children.[54] Furthermore, it has been suggested that this correlation might even persist over the entire lifetime of an individual, as described for 189 women and 224 men (age 63–73 years).[55]

3.1.5. Concurrent illness

Many chronic diseases have been identified as contributors to bone loss, including endocrine diseases (e.g., hyperthyroidism), rheumatological conditions (e.g., rheumatoid arthritis or systemic lupus), chronic lung diseases, gastrointestinal conditions associated with malabsorption (e.g., celiac disease or inflammatory bowel disease), neurological diseases (e.g., Parkinson's disease, multiple sclerosis, or spinal cord injury), oncological diseases (e.g., multiple myeloma), and organ transplantation. Bone loss due to any of these diseases could be either related to multiple factors (e.g., use of medication, lack of nutrition, or reduced physical exercise) or directly to a disease (e.g., bone cancer has a high metabolic activity and increases the rate of bone loss by 3-fold due to both a shortening of the lifespan of osteoblasts and a prolongation of the lifespan of osteoclasts[6]).

Interestingly, a secondary effect of one initial fracture is that it can increase the risk of a new fracture by 86%.[56] Likewise, patients with a history of vertebral fracture have a 2.3-fold risk of future hip fracture and a 1.4-fold risk of distal forearm fracture.[57]

Intestinal failure occurs as a result of specific nutrient deficiencies. Serum levels of fat-soluble vitamins and bone density in outpatients with intestinal failure were studied by Ellegard et al. [58]. In that study, 106 outpatients with intestinal failure were assessed during routine visits and 78 patients underwent DXA scan for bone density, and the analysis revealed that 88% had low bone density. Moreover, the overall prevalence of vitamin D deficiency was found to be 67%. The authors concluded that vitamin D deficiency and osteoporosis are prevalent in patients with intestinal failure, which should be adequately treated.

Table 2. Synthesis of vitamin D as described by Holick et al.[59]

In the skin, 7-dehydrocholesterol is converted to vitamin D_3 in the presence of UV light
In the liver, vitamin D_3 is metabolized to 25(OH)D_3, the primary circulating form of vitamin D component
In the kidney, 25(OH)D_3 is converted to the active hormone 1α,25(OH)$_2D_3$ and the inactive hormone 24*R*,25(OH)$_2D_3$ and is transported to distal target organs
1,25(OH)$_2D_3$ is bound to a nuclear receptor, plasma membrane receptor, or both at the target organs for the generation of appropriate biological responses
Plasma vitamin D-binding protein carries vitamin D_3 and its metabolites to the target organs

3.2. Modifiable factors

3.2.1. Vitamin D

Vitamin D regulates the absorption of calcium (Ca^{2+}) and thus is important for bone health. There are two important types of vitamin D: Vitamin D_2 (synthesized by plants) and vitamin D_3 (cholecalciferol; present in egg yolk, fish oil, and a number of plants). Vitamin D is produced in the skin when UV light is absorbed by the precursor molecule 7-dehydrocholesterol.

3.2.1.1. Synthesis: Vitamin D_3 is synthesized endogenously in the mammalian skin exposed to UVA/B light. The mechanisms and sequence of chemical reactions involved in this process were elucidated by Holick.[59] The production of vitamin D begins with the synthesis of the sterol provitamin D_3 molecule 7-dehydrocholesterol (Table 2). In most vertebrates, including humans, it is produced in large quantities and incorporated into plasma membrane lipid bilayers of cells in the dermis and epidermis, when the skin is exposed to sunlight. This molecule absorbs UVB radiation (290 – 315 nm) and the absorbed energy promotes the formation of chemical bonds within the 7-dehydrocholesterol molecule, resulting in the production of previtamin D_3. In the skin, previtamin D_3 undergoes rapid, thermally induced transformation to vitamin D_3. The liver metabolizes vitamin D_3 to 25(OH)D (abbreviated 25(OH)D_3) and the kidney finally produces 1α,25-dihydroxyvitamin D_3 (1α,25(OH)$_2D_3$) and/or 24*R*, 25-dihydroxyvitamin D_3 (24*R*,25(OH)$_2D_3$).

The main regulatory factors are as follows:

1) the steroid hormone 1α,25(OH)$_2D_3$, which downregulates its own production;
2) PTH, which stimulates the renal production of 1,25(OH)$_2D_3$;
3) fetal growth factor 23; and
4) serum concentrations of calcium and phosphate, which are modulated according to the calcium and other endocrine needs of the organism.[60]

The activity of 25(OH)D-1α-hydroxylase is dependent on the nutritional status of vitamin D. When the concentration of 1α,25(OH)$_2D_3$ is low, there is enhanced production of 1α,25(OH)$_2D_3$ in the kidney. However, when its concentration is high, the production of 1α,25(OH)$_2D_3$ decreases in the kidney.

3.2.1.2. Vitamin D deficiency: Vitamin D deficiency reduces calcium uptake and leads to osteomalacia, a condition characterized by insufficient mineralization of the newly formed bone matrix, the osteoid. The symptoms of vitamin D deficiency are reduced muscle strength and weakness that are common among the elderly due to the decreased ability to synthesize the provitamin 25(OH)D_3.[61]

***3.2.1.2.1. Nutritional factors*:** *Calcium and vitamin D* An adequate vitamin D status combined with a sufficient intake of calcium is a requirement for good bone architecture and strength. Good dietary sources of vitamin D are milk, yogurt, margarine, cereals, fish (e.g., catfish, sardines, salmon, tuna), egg yolk, and mushroom. However, it can be difficult to obtain enough vitamin D and calcium unless the diet incorporates dairy products and fish that are rich in these minerals. Although the nutritional aspects related to bone development and subsequent bone loss are well established, they require further attention in an aging population (see Section 2.1). As with osteoporosis, vitamin D

deficiency is frequently observed in the elderly, particularly in those who are chronically ill, house-bound, and/or poorly nourished.

Alcohol consumption Consumption of alcohol increases the risk of osteoporosis by inhibiting osteoblast function and reducing bone formation, therefore resulting in more hip fractures. Nutritional deprivation of alcoholics also contributes to the specific toxic effects of alcohol on bone among other organ systems.

Tobacco consumption Smokers generally weigh less than non-smokers. The inhaled toxins reduce osteoblast function, lead to an earlier menopause, and result in reduced production and accelerated degradation of estrogen.[62]

Use of statins *In vitro* studies have shown the beneficial effects of statins on bone formation; however, most of the clinical trials have not confirmed these findings.[63] Some investigators have highlighted the positive impact of statins on bone turnover; however, there are no conclusive data to recommend the use of statins either as a treatment or as the prevention of osteoporosis. Therefore, more longitudinal studies in different ethnicities with large sample sizes are needed.[64]

***3.2.1.2.2. Sun-exposure: Skin pigmentation, seasonal variations, and regional habits*:** In all vertebrates, including humans, most of the daily vitamin D requirement is met from brief exposure to sunlight. Despite sufficient sunshine in most regions, vitamin D deficiency remains a common problem due to poor dietary habits, unfavorable weather conditions (less outdoor activities), and cultural practices that limit sunlight exposure.[20,65]

Skin pigmentation (melanin) reduces the skin's ability to synthesize vitamin D from sun exposure; thus, the efficiency for the photosynthesis of pre-cholecalciferol is decreased.[66,67,68] As a result, people with darker skin need 5 to 10 times more sun exposure to synthesize the same amount of vitamin D as people with lighter skin.[69] When the skin is aging, there is a decrease in its thickness and a marked decrease in the epidermal concentration of the vitamin D precursor 7-dehydrocholesterol.[61,70] It has been found that serum PTH level increases with age, and may contribute to bone loss in postmenopausal women due to declining renal function, calcium absorption efficiency, and serum 25-hydroxyvitamin D (25(OH)D) levels.[71] A correlation between serum PTH and serum 25(OH)D_3 levels has been reported in the bone.[72] Serum PTH shows an inverse seasonal variation with highest values at the end of winter and lowest values at the end of summer when serum 25(OH)D_3 level is at its maximum.[73,74] During winter, in some parts of the world, outdoor activities are restricted and clothing limits sunlight exposure. Generally, vitamin D synthesis depends on latitude,[65] with less UV radiation from the sun reaching the earth surface closer to the poles. Therefore, it is not surprising that women in non-equatorial countries exhibit lower serum 25(OH)D levels in winter than during the summer months.[75]

Currently, a major health concern is skin damage following long-term exposure to sunlight, resulting in sunburn, and the risk of developing skin cancer (e.g., melanoma). Topical "sunscreen" agents with a high sun protection factor are used for protection; although there are benefits of using these agents in the prevention of skin damage, they also inhibit the production of pre-cholecalciferol.[76,77] Generally, moderate exposure to sunlight will not increase the risk of skin cancer.[69] Interestingly, vitamin D levels do not increase when exposed to moderate sunlight and UVB rays are mostly absorbed by clothing, particularly cotton, wool, or polyester fabrics.[78]

Overall, skin pigmentation, aging, and topical application of a sunscreen reduce the cutaneous production of cholecalciferol, which is also affected by latitude, season and time of day, and ozone content in the air.[65]

3.3. Combination of multiple factors

Studies have reported large geographic variations around the globe, pointing to a higher incidence of hip fracture in industrialized countries compared with developing countries. As mentioned previously, the population might be affected by this outcome at any age, which is particularly prevalent among elderly women. While life expectancy rises, the percentage of the elderly in any population will rise (see Sections 2.1 and 2.2). This is especially true for developing countries that have a relatively young population. Based on this information, it has been estimated that by 2050, half of hip fractures will occur in Asia and the Middle East.[19]

The multiple factors discussed here may occur simultaneously, and their effects may add to the severity of osteoporosis. For example, elderly people are less exposed to sunlight as they tend to stay more indoors and may have inadequate dietary intake. Therefore, depending on the aforementioned factors, the reasons for vitamin D deficiency can be numerous, compounding the problem in the elderly and/or vulnerable.

4. PREVENTION AND TREATMENT

Osteoporosis remains a poorly diagnosed and under-treated disease, and is often ignored even when the problem is severe. Despite the burden of fragility fractures, public awareness and training for healthcare professionals are suboptimal in many countries. The result is premature death, immense personal suffering, loss of productivity, and subsequent dependence on family members.

Screening of the elderly for vitamin D deficiency is easy, and supplement treatment will reduce the incidence of fractures. As the use of supplements could potentially be as expensive as medical treatment of fractures, epidemiological research is needed to identify individuals at high risk, thereby allowing careful allocation of expensive treatments to individuals who are most in need.

The diagnosis of osteoporosis and guidelines for the treatment of osteoporosis are based on bone mass in postmenopausal women and do not generally apply to pre-menopausal women. Overall, there are numerous guidelines and recommendations regarding the evaluation and management of osteoporosis in the population; however, some countries have failed to adopt those guidelines. In addition, any individual can reduce the risk of developing osteoporosis by undertaking some changes in their daily lifestyle,[5] as described below (see Figure 2).

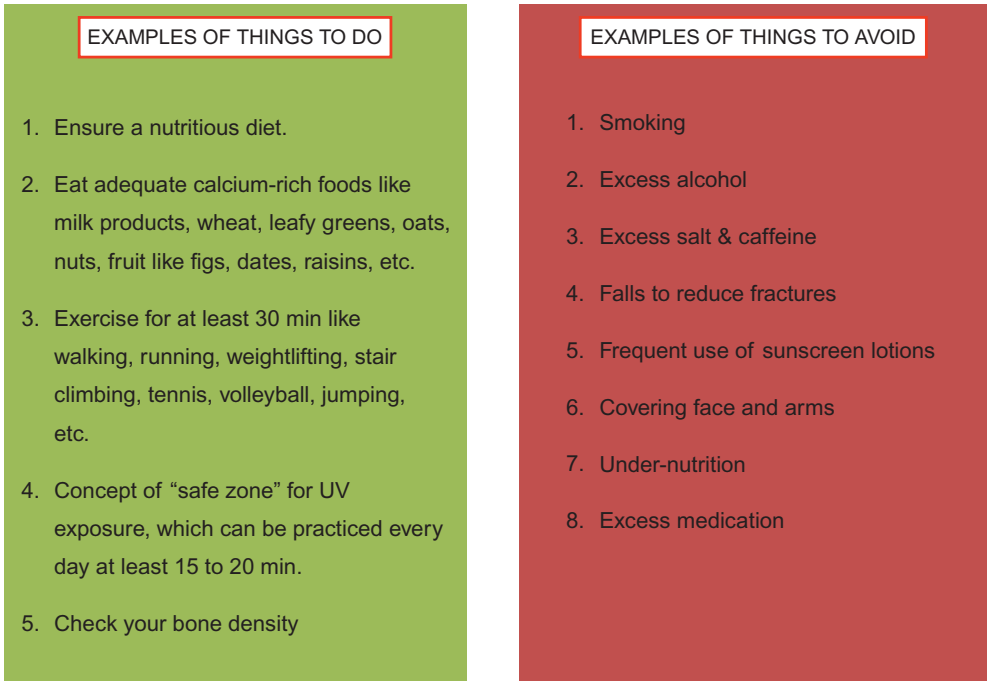

Figure 2. Fact box showing “Things To Do” and “Things To Avoid” to reduce the occurrence of osteoporosis.

- *Calcium- and vitamin D-rich diet.* Milk and other dairy products (e.g., cottage cheese, yogurt, or hard cheese) and green vegetables (e.g., kale and broccoli) are the main dietary sources of calcium. One of the primary sources of dietary vitamin D is milk products and eggs. Mushrooms also contain significantly high amount of vitamin D.
- *Supplements of calcium and vitamin D.* Experts have recommended at least 1000 mg calcium and 600 IU vitamin D per day (total diet plus supplement) for pre-menopausal women and younger men. Postmenopausal women and men aged >70 years should consume 1200 mg calcium and 800 IU vitamin D per day (total diet plus supplement).

- *Exercise*. A moderate-intensity physical activity for at least 30 min three times per week is helpful. Weight-bearing exercises such as brisk walking, jogging, tennis, golf, and netball are particularly good for bone health.[79] As bone adapts to the loads that are applied, increased mechanical load associated with exercise leads to an increase in bone density, particularly during childhood. The best benefit to bone health is the exercise that is associated with high impact force and the weight-bearing exercise that is associated with increased peak bone mass. For example, gymnasts have greater bone density than runners. Moreover, jumping, in the form of rope jumping and jumping off from a platform, appears to be an efficient way to improve peak bone mass.
- *Avoid smoking*. Various substances in the cigarette smoke can cause reduced bone growth and thus reduced bone mass.
- *Avoid falls (especially among the elderly)*. The risk of fracture can be lowered by preventing frequent falls.
- *Consult a physician before taking medications*. Medications such as glucocorticoids can cause bone thinning.
- *Consult a physician before possible hormone replacement therapy*. Occasionally, hormone therapy is administered to pre-menopausal women with abnormal concentrations of estrogen. In other cases, PTH administration is used to treat osteoporosis. Overall, a variety of supplements improve bone health and reduce the incidence of fractures. It is advisable to monitor the bone response to the treatment of osteoporosis by bone mass density testing.

Furthermore, "Osteoporosis-Forums" help to increase the knowledge and understanding in order to support its prevention, diagnosis, and treatment and to increase general awareness. Forums could focus on the screening of people for risk factors such as those with fragility fractures, steroid use, heavy smokers, and postmenopausal and elderly men and women. Women should be advised to undertake regular bone health check-up.

Overall, osteoporosis develops slowly over years without any noticeable symptoms. As no cure is yet known for the disease, only the symptoms can be managed and prevention is key. As with any lifestyle-related disease, the development of osteoporosis depends largely on the choices made as well as on socio-economic and environmental factors. Awareness will help understand the underlying factors, hopefully resulting in lifestyle changes to reduce the occurrence of osteoporosis.

5. CONCLUSION

According to the IOF President Professor Kanis, "Despite the severity of the problem, osteoporosis is being dangerously ignored as it competes with other diseases for scarce healthcare resources and recognition. Notwithstanding the burden of fragility fractures, osteoporosis remains greatly under diagnosed and under treated, and both health professional training and public awareness is suboptimal in most countries in the region. The result is premature death for many hip fracture sufferers, immense personal suffering, lost productivity and long-term dependence on family members".[19] A deeper understanding of the different changing variations will help policy makers and healthcare providers to develop strategies that will reduce the burden of osteoporosis, especially in developing countries and in countries with a dramatic change in their population structure. Although significant gaps in knowledge still exist and more research is required to improve the treatment of established osteoporosis, better availability of information can support healthcare professionals in their critical role in guiding individuals to make the right choices to reduce the risk.

REFERENCES

[1] National Osteoporosis Foundation (NOF). America's bone health: The state of osteoporosis and low bone mass in our nation; 2002. [http://www.nof.org/advocacy/prevalence].
[2] Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet*. 2002;359(9319): 1761–1767.
[3] Cooper A, Cooper BB. *A treatise on dislocations, and on fractures of the joints*. London, United Kingdom: Churchill; 1822:p.425.
[4] Jordan KM, Cooper C. Epidemiology of osteoporosis. *Best Pract Res Clin Rheumatol*. 2002;16(5):795–806.
[5] Anonymous. Consensus development conference: diagnosis, prophylaxis and treatment of osteoporosis. *Am J Med*. 1993;94:646–665.

[6] Manolagas SC. Birth and death of bone cells: basic regulatory mechanism and implications for the pathogenesis and treatment of osteoporosis. *Endocr Rev*. 2000;21:115–137.
[7] Reginster JY, Nansa B. Osteoporosis: A still increasing prevalence. *Bone*. 2006;38:S4–S9.
[8] Hadji P, Klein S, Gothe H, Haussler B, Kless T, Schmidt T, Steinle T, Verheyen F, Linder R. The epidemiology of osteoporosis –Bone Evaluation Study (BEST): An analysis of routine health insurance data. *Deutsches Ärzteblatt Int*. 2013;110(4):52–57.
[9] Iki M. Epidemiology of osteoporosis in *Japan*. *Clin Calcium*. 2012;22(6):797–803.
[10] Nordin BEC. International patterns of osteoporosis. *Clin Orthop*. 1966;45:17–30.
[11] Gupta AK, Samuel KC, Kurian PM, Rallan RC. Preliminary study of the incidence and aetiology of femoral neck fracture in Indians. *Indian J Med Res*. 1967;55:1341–1348.
[12] Vaishnava H, Rizvi SNA. Frequency of osteomalacia and osteoporosis in fractures of proximal femur. *Lancet*. 1974;1:676–677.
[13] El-Rassi R, Baliki G, Fulheihan CGE. Vitamin D status in Middle East and Africa. *Dermato-endocrinology*. 2013;5(2):274–298.
[14] Prentice A. Nutritional rickets around the world. *J Steroid Biochem Mol Biol*. 2012;136:201–206.
[15] Baroncelli GI, Bereket A, El Kholy M, Audì L, Cesur Y, Ozkan B, Rashad M, Fernández-Cancio M, Weisman Y, Saggese G, Hochberg Z. Rickets in the Middle East: Role of environment and genetic pre disposition. *J Clin Endocrinol Metab*. 2008;93:1743–1750.
[16] Kimball S, Fuleihan GEH, Vieth R. Vitamin D: A growing perspective. *Crit Rev Clin Lab Sci*. 2008;45:339–334.
[17] Fuleihan GCE. Vitamin D deficiency in the Middle East and its health consequences. In: Holick MF, ed. *Vitamin D: Physiology, Molecular Biology, and Clinical Applications*. Second Edition: Humana Press; 2009.
[18] Pettifor JM. Nutritional rickets: deficiency of vitamin D, calcium, or both? *Am J Clin Nutr*. 2004;80:1725S–1729S.
[19] International Osteoporosis Foundation (IOF). Burden of osteoporotic fracture increases dramatically in the Middle East and Africa; 2011. [http://www.iofbonehealth.org/publications/me-a-audit-2011.html].
[20] International Osteoporosis Foundation. Vitamin D deficiency is widespread and on the increase; 2012. [http:/www.osteofound.org/bonehealth/vitamin-d-deficiency-widespread-and-increase].
[21] Ola Al-Ghazawy. The growing danger of osteoporosis in the Arab world. *Nature Middle East*. 2011;158.
[22] Bassir M, Laborie S, Lapillonne A, et al. Vitamin D deficiency in Iranian mothers and their neonates: a pilot study. *Acta Paediatr*. 2001;90:577–579.
[23] Arabi A, Baddoura R, Awada H, et al. Hypovitaminosis D osteopathy: Is it mediated through PTH, lean mass, or is it a direct effect? *Bone*. 2006;39:268–275.
[24] Mishal AA. Effects of different dress styles on vitamin D levels in healthy young Jordanian women. *Osteoporos Int*. 2001;12:931–935.
[25] El-Hajj Fuleihan G, Nabulsi M, Choucair M, et al. Hypovitaminosis D in healthy schoolchildren. *Pediatrics*. 2001;07:E53.
[26] El-Hajj Fuleihan G, Nabulsi M, Tamim H, et al. Effect of vitamin D replacement on musculoskeletal parameters in school children: a randomized controlled trial. *J Clin Endocrinol Metab*. 2006;91:405–412.
[27] Goldray D, Mizrahi-Sasson E, Merdler C, et al. Vitamin D deficiency in elderly patients in a general hospital. *J Am Geriatr Soc*. 1989;37:589–592.
[28] El-Hajj Fuleihan G, Deeb M. Letter to the Editor. Hypovitaminosis in a Sunny Country. *N Engl J Med*. 1999;340:1840–1841.
[29] Hashemipour S, Larijani B, Adibi H, et al. The status of biochemical parameters in varying degrees of vitamin D deficiency. *J Bone Miner Metab*. 2006;24:213–218.
[30] Snijder MB, van Dam RM, Visser M, et al. Adiposity in relation to vitamin D status and parathyroid hormone levels: A population based study in older men and women. *J Clin Endocrinol Metab*. 2005;90:4119–4123.
[31] Weisman Y. Vitamin D deficiency rickets and osteomalacia in Israel. *Isr Med Assoc J*. 2003;5:289–290.
[32] Ainy E, Ghazi AAM, Azizi F. Changes in calcium, 25(OH) vitamin D3 and other biochemical factors during pregnancy. *J Endocrinol Invest*. 2006;29:303–307.
[33] Molla AM, Al Badawi M, Hammoud MS, Molla AM, Shukkur M, Thalib L, Eliwa MS. Vitamin D status of mothers and their neonates in Kuwait. *Pediatr Int*. 2005;47(6):649–652.
[34] Meddeb N, Sahli H, Chahed M, Abdelmoula J, Feki M, Salah H, Frini S, Kaabachi N, Belkahia Ch, Mbazaa R, Zouari B, Sellami S. Vitamin D deficiency in Tunisia. *Osteoporo Inter*. 2005;16:180–183.
[35] Gannagé-Yared MH, Chemali R, Yaacoub N, Halaby G. Hypovitaminosis D in a sunny country: relation to lifestyle and bone markers. *J Bone Miner Res*. 2000;15(9):1856–1862.
[36] Saadi HF, Nagelkerke N, Benedict S, Qazaq HS, Zilahi E, Mohamadiyeh MK, Al-Suhaili AI. Predictors and relationships of serum 25 hydroxyvitamin D concentration with bone turnover markers, bone mineral density, and vitamin D receptor genotype in Emirati women. *Bone*. 2006;39(5):1136–1143.
[37] Gannag-Yared MH, Maalouf G, Khalife S, Challita S, Yaghi Y, Ziade N, Chalfoun A, Norquist J, Chandler J. Prevalence and predictors of vitamin D inadequacy amongst Lebanese osteoporosis women. *Br J Nutr*. 2009;101(4):487–491.
[38] International Osteoporosis Foundation (IOF). *The facts about osteoporosis and its impact*. International Osteoporosis Foundation (2005).
[39] Morrison A, Fan T, Sen SS, Weisenfluh L. Epidemiology of falls and osteoporotic fractures: A systematic review. *Clin Econ Outcome Res*. 2013;5:9–18.
[40] Cawston H, Maravic M, Fardellone P, Gauthier A, Kanis JA, Compston J, Borgstrom F, Cooper C, McClosKey E. Epidemiological burden of postmenopausal osteoporosis in France from 2010 to 2020: Estimations from a disease model. *Arch Osteoporosis*. 2012;7:237–246.
[41] Harper KD, Weber TJ. Secondary osteoporosis: Diagnostic considerations. *Endocrinol Metab Clin North Am*. 1988;1:325–348.
[42] Garnero P, Sornay-Rendu E, Chapuy M-C, Delmas PD. Increased bone turnover in late postmenopausal women is a major determinant of osteoporosis. *J Bone Miner Res*. 1996;11:337–349.

[43] O'Neill TW, Silman AJ, Naves Diaz M, Cooper C, Kanis J, Felsenberg D. Influence of hormonal and reproductive factors on the risk of vertebral deformity in European Women. *European Vertebral Osteoporosis Group, Osteoporos Int.* 1997;7:72–78.
[44] Finkelstein JS, Klibanski A, Neer RM, Greenspan SL, Rosenthal DI, Crowley WF Jr. Osteoporosis in men with Idiopathic Hypogonadotropic Hypogonadism. *Ann Intern Med.* 1987;106(3):354–361.
[45] Francis RM, Peacock M, Aaron JE, Selby PL, Taylor GA, Thompson J, Marshall DH, Horsman A. Osteoporosis in hypogonadal men: role of decreased plasma 1,25-dihydroxyvitamin D, calcium malabsorption, and low bone formation. *Bone.* 1986;7(4):261–268.
[46] Seremak-Mrozikiewicz A, Drews K, Mrozikiewicz PM, Bartkowiak Wieczorek J, Marcinkowska M, Wawrzyniak A, Slomski R, Kalak R, Czerny B, Horst-Sikorska W. Correlation of vitamin D receptor gene (VDR) polymorphism with osteoporotic changes in Polish postmenopausal women. *Neuro Endocrinol Lett.* 2009;30(4):540–546.
[47] Jia F, Sun RF, Li QH, Wang DX, Zhao F, Li JM, Pu Q, Zhang ZZ, Jin Y, Liu BL, Xiong Y. Vitamin D receptor BsmI polymorphism and osteoporosis risk: a meta-analysis from 26 studies. *Genet Test Mol Biomarkers*. 2013;17(1): 30–34.
[48] Fountas L, Moutsatsou P, Kastanias I, Tamouridis N, Tzanela M, Anapliotou M, Sekeris CE. The contribution of vitamin D receptor gene polymorphisms in osteoporosis and familial osteoporosis. *Osteoporos Int.* 1999;10(5): 392–398.
[49] Mitra S, Desai M, IkramKhatkhatay M. Vitamin D receptor gene polymorphisms and bone mineral density in postmenopausal Indian women. *Maturitas*. 2006;55(1):27–35.
[50] Vupputuri MR, Goswami R, Gupta N, Ray D, Tandon N, Kumar N. Prevalence and functional significance of 25-hydroxyvitamin D deficiency and vitamin D receptor gene polymorphisms in Asian Indians. *Am J Clin Nutr.* 2006;83(6):1411–1419.
[51] Malhotra N, Mithal A. Osteoporosis in Indians. *Indian J Med Res*. 2008;127:263–268.
[52] Barker DJP. Programming the baby. In: Barker DJP, ed. *Mothers, babies and disease in later life*. London: BMJ Publishing Group; 1994:14–36.
[53] Cooper C, Cawley MD, Bhalla A, et al. Childhood growth, physical activity and peak bone mass in women. *J Bone Miner Res*. 1995;10:940–947.
[54] Duppe H, Cooper C, Gardsell P, Johnell O. The relationship between childhood growth, bone mass and muscle strength in male and female adolescents. *Calcif Tissue Int.* 1997;60:405–409.
[55] Cooper C, Fall C, Egger P, et al. Growth in infancy and bone mass in later life. *Ann Rheum Dis*. 1997;56:17–21.
[56] Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas PD, Eisman JA, Fujiwara S, Garnero P, Kroger H, McCloskey EV, Mellstrom D, Melton LJ, Pols H, Reeve J, Silman A, Tenenhouse A. A meta-analysis of previous fracture and subsequent fracture risk. *Bone*. 2004;35(2):375–382.
[57] Melton LJ III, Atkinson EJ, Cooper C, O'Fallon WM, Riggs BL. Vertebral fractures predict subsequent fractures. *Osteoporosis Int.* 1999;10:214–221.
[58] Ellegard L, Kurlberg G, Bosaeus I. High prevalence of vitamin D deficiency and osteoporosis in out-patients with intestinal failure. *Clin Nutr.* 2013;32(6):983–987.
[59] Holick MF, MacLaughlin JA, Clark MB, Holick SA, Potts JT Jr. Anderson RR, Blank IH, Parrish JA, Elias P. Photosynthesis of previtamin D3 in human skin and the physiological consequences. *Science*. 1980;210:203–205.
[60] Adams JS, Clemens TL, Parrish JA, Holick MF. Vitamin D synthesis and metabolism after ultraviolet irradiation of normal and vitamin D- deficient subjects. *N Engl J Med*. 1982;306:722–725.
[61] Mac Laughlin J, Hollick MF. Aging decreases the capacity of human skin to produce vitamin D3. *J Clin Invest.* 1985;76:1536–1538.
[62] Grainge MJ, Coupland CA, Cliffe SJ, Chilvers CE, Hosking DJ. Cigarette smoking, alcohol and caffeine consumption, and bone mineral density in postmenopausal women. The Nottingham EPIC Study Group. *Osteoporos Int.* 1988;8:355–363.
[63] Jadhav SB, Jain GK. Statins and osteoporosis: New role for old drugs. *J Pharm Pharmacol.* 2006;58(1):3–18.
[64] Sharif PS, Abdollahi M. A systematic review on the relation between use of statins and osteoporosis. *Int J Pharmacology.* 2011;7(2):180–188.
[65] Holick MF. Environmental factors that influence the cutaneous production of vitamin D. *Am J Clin Nutr.* 1995;61(Suppl.):638S–645S.
[66] Holick MF. Photobiology, Physiology and clinical applications for vitamin D. In: Goldsmith LA, ed. *Biochemistry and physiology of the skin*. 2nd ed. New York: Oxford University Press; 1991:928–956.
[67] Holick MF, MacLaughlin JA, Doppelt SH. Factors that influence the cutaneous photosynthesis of previtamin D3. *Science*. 1981;211:590–593.
[68] Clemens TL, Henderson SL, Adams JS, Holick MF. Increased skin pigment reduces the capacity of skin to synthesis vitamin D3. *Lancet.* 1982;1:74–76.
[69] Adams JS, Hewison M. Update in Vitamin D. *J Clin Endocrinol Metab*. 2010;95:471–478.
[70] Holick MF. The photobiology of vitamin D and its consequences for humans. *Ann N Y Acad Sci.* 1985;453:1–13.
[71] Need AG, O'Loughlin PD, Morris HA, Horowitz M, Nordin BE. The effects of age and other variables on serum parathyroid hormone in postmenopausal women attending an osteoporosis clinic. *J Clin Endocrinol Metab.* 2004;89(4):1646–1649.
[72] Cheng S, Tylavsky F, Kröger H, Kärkkäinen M, Lyytikäinen A, Koistinen A, Mahonen A, Alen M, Halleen J, Väänänen K, Lamberg-Allardt C. Association of low 25-hydroxyvitamin D concentrations with elevated parathyroid hormone concentration and low cortical bone density in early pubertal and pre pubertal Finnish girls. *Am J Clin Nutr.* 2003;78:485–492.
[73] Outila TA, Karkkainen MU, Lamberg-Allardt CJ. Vitamin D status affects serum parathyroid hormone concentrations during winter in female adolescents: Associations with forearm bone mineral density. *Am J Clin Nutr.* 2001;17: 513–516.

[74] Guillemant J, Cabrol S, Allemandou A, Peres G, Guillemant S. Vitamin D dependent seasonal variation of PTH in growing male adolescents. *Bone*. 1995;7:513–516.
[75] Lips P, Hosking D, Lippuner K, Morquist JM, Wehren L, Maalouf G, Ragi-Eis S, Chandler J. The prevalence of vitamin D inadequacy amongst women with osteoporosis; an international epidemiological investigation. *J Intern Med*. 2006;260(3):245–254.
[76] Matsuoka LY, Ide L, Wortsman J, Mac Laughlin J, Holick MF. Sunscreen suppress cutaneous vitamin D_3 synthesis. *J Clin Endocrinol Metab*. 1987;64:1165–1168.
[77] Matsuoka LY, Worsman J, Hanifan N, Holick MF. Chronic sunscreen use decreases circulating concentrations of 25-hydroxyvitamin D: A preliminary study. *Arch Dermatol*. 1988;124:1802–1804.
[78] Matsuoka LY, Wortsman J, Dannenberg MJ, Hollis BW, Lu Z, Holick MF. Clothing prevents ultraviolet- B radiation-dependent photosynthesis of vitamin D. *J Clin Endocrinol Metab*. 1992;75(4):1099–1103.
[79] National Osteoporosis Foundation (NOF). 2013. Washington US. Exercise for your bone health. Bone Basics [http://nof.org/files/nof/public/content/resource/3239/files/958.pdf].