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Consensus Article

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Middle East and North Africa consensus on osteoporosis

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Abstract

With the increasing life expectancy, osteoporosis is becoming a major worldwide health problem. The magnitude of the disease may become larger in developing countries, more particularly in the Middle East region where the prevalence of low bone mass is higher than in western countries. Although several local organizations and countries have developed guidelines for osteoporosis, no previous regional guidelines have been developed encompassing all Middle-Eastern and North African countries. The present document reviews all the regional published data on bone mineral density, risk factors, fracture prevalence and vitamin D status. It also gives simple recommendations applicable to all these countries.

This document was endorsed by leading members of all the different regional countries including, Iran, Egypt, Tunisia, Jordan, Palestine, Syria, Iraq, Libya, Oman, Kuwait, Saudi Arabia and Bahrain.

Keywords: Middle East, North Africa, Consensus, Osteoporosis

What is osteoporosis?

In 1994, the WHO defined osteoporosis as a "disease characterized by low bone mass and micro-architectural deterioration of bone tissue, enhanced bone fragility and an increase in fracture risk"[1,2]. Bone strength is determined by the material properties of bone (tissue mineral content, and collagen composition) and bone's structural properties (bone size, shape, distribution of cortical bone, trabecular number, thickness and connectivity). Non-invasive methods, such as bone densitometry, provide a measure of the bone mineral content (BMC) of a region expressed as grams of bone mineral, or bone mineral density (BMD) expressed as grams of mineral per unit projected area of the bone. The WHO definition of osteoporosis in women is based on a BMD value 2.5 standard deviation (SD) or more below the mean for young normal white women. BMD is a predictor of fracture but bone size, shape and micro-architectural features of bone are not captured by the measurement. Thus, although the measurement does identify a high-risk group it is not sensitive; about 50% of persons who will sustain fractures come from individuals with osteopenia (BMD value between -2.5 SD and -1 SD) or normal BMD[3].

A decline in BMD with age increases bone fragility because it reflects the progressive loss of bone mass and changes in the architecture of the bone such as cortical thinning, cortical porosity, thinning and loss of trabeculae with loss of connectedness of trabeculae. Bone loss is progressive and is not associated with symptoms until a fracture occurs – the main clinical feature of osteoporosis. According to the WHO, fractures are "caused by injury that would be insufficient to fracture normal bone". In other words, a fragility fracture can result from minor trauma, such as a fall from a standing height or less.

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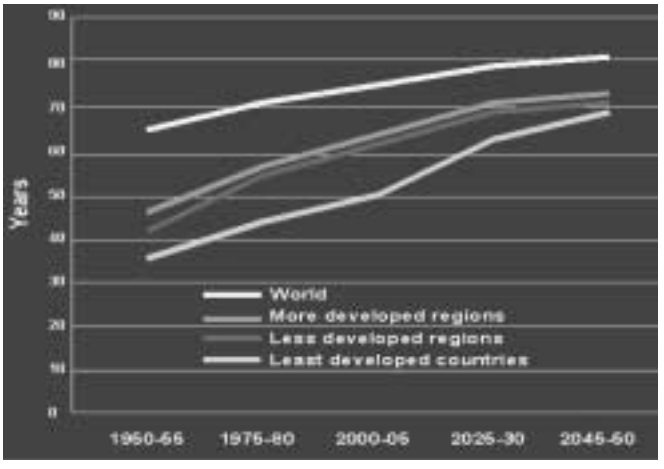

Figure 1. Life expectancy at birth (UN source, 2001).

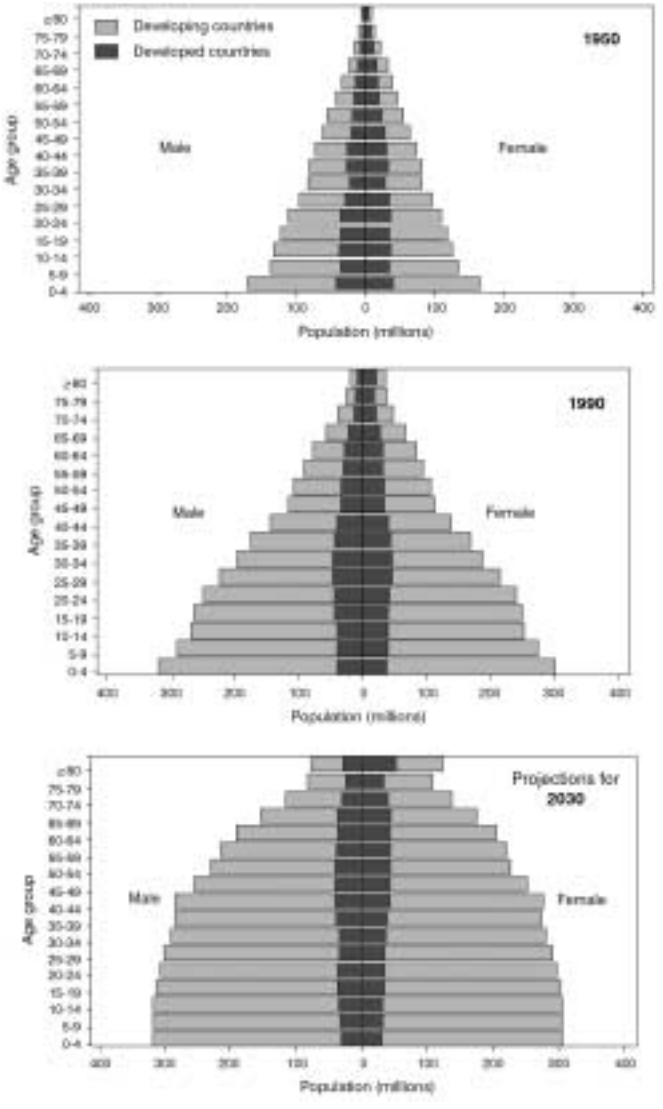

Figure 2. Age population distribution; 1950, 1990 and 2030 (UN source, 2001).

Worldwide burden of osteoporosis

Osteoporosis is a worldwide problem because of the fractures that occur. The burden of fractures is increasing in direct correlation with life expectancy. This increase is greater in underdeveloped countries (Figure 1). By 2030, the increase in the aged population will affect developing countries more than developed ones (Figure 2), and this increase will occur in both sexes.

According to the National Osteoporosis Foundation (NOF), the number of postmenopausal women in the United States will double over the next 20 years, leading to a tripling of the number of osteoporotic fractures in 2040[3]. The International Osteoporosis Foundation (IOF) estimates that 200 million women suffer from osteoporosis across the world. Moreover, osteoporosis has been misconceived as a women's disease because it also affects men significantly. Indeed, at least one in five men compared to one in three women over the age of 50 will have an osteoporosis-related fracture in their remaining lifetime[4-6].

Over 1.3 million osteoporotic fractures occur each year in the United States (US)[7]. Osteoporotic fractures affect the quality of life and are associated with premature mortality[8]. Spinal fractures commonly cause pain, deformity, loss of height and disability and are associated with an increased risk of future fractures within the next year[9,10], while hip fractures are more painful and almost always require hospitalisation[11]. Many of those who suffer hip fractures never regain their normal mobility. The overall mortality rate of hip fractures is 20 to 24 percent, the majority of deaths occurring in the first six months after the fracture[8,12,13]. In addition, survival after a hip fracture is less in men than in women[14,15]. Both men and women lose about 7 years of life after a hip fracture; however, the seven-year lapse represents a greater proportion of the number of years of life left in men than in women[15]. The burden of disease may be even greater in developing countries, including the Middle East.

WHO definition of osteoporosis

The WHO has standardized the interpretation of BMD results, based on a comparison of a patient's BMD with the mean for a normal young adult population of the same sex and race[2]. The patient's BMD is calculated as a T-score, which is the number of standard deviations above or below the mean BMD for normal young adults as follows:

- Normal BMD: T-score no more than -1 SD below the young adult mean
- Osteopenia: T-score between -1.0 and -2.5
- Osteoporosis: T-score equal to or less than -2.5
- Severe osteoporosis: T-score below -2.5 for patients with a fragility fracture

The tendency to fracture is inversely correlated with BMD, confirming the importance of BMD measurement[16]. However, the WHO criteria were derived from European and North American postmenopausal women and may not be applicable to other races.

Risk factors for osteoporosis

Risk factors for osteoporosis suggested by the National Osteoporosis Foundation include[3,17]:

Major risk factors are:

- Personal history of fracture as an adult
- History of fragility fractures in a first degree relative
- Low body weight (<58 kg)
- Current smoker
- Use of oral glucocorticosteroid therapy for 3 months or more

These factors are mainly dependent on lower BMD.

Additional risk factors are[17,18]:

- Impaired vision
- Estrogen deficiency at an early age (age <45 years)
- Poor health/fragility
- Recent falls
- Low calcium intake
- Low physical activity
- Alcohol in amounts more than two drinks per day
- Excessive caffeine intake

Some of these factors such as impaired vision, poor health and recent falls are independent risk factors of BMD.

Medical conditions associated with increased risk of osteoporosis are:

Chronic obstructive pulmonary disease, gastrectomy, hyperparathyroidism, hyperthyroidism, hypercortisolism, vitamin D deficiency, hypogonadism, malignancy including multiple myeloma, renal disease, liver disease, malabsorptive states including celiac disease and rheumatoid arthritis.

Medications:

In addition to oral glucocorticoids, drugs that are associated with reduced bone mass in adults include anticonvulsants, GnRH agonists, chronic heparin therapy, T4 in excessive doses, chemotherapy, lithium and aromatase inhibitors.

Below is a simple guide useful for identifying those at risk found on the IOF website: www.iofbonehealth.org

For both men and women:

- Has either of your parents broken a hip after a minor bump or fall?
- Have you broken a bone after a minor bump or fall?
- Have you taken corticosteroid tablets for more than 3 months?
- Have you lost more than 3 cm in height?
- Do you regularly drink heavily (in excess of safe drinking limits)?
- Do you smoke more than 20 cigarettes a day?
- Do you suffer frequently from diarrhoea?

For women:

- Did you undergo menopause before the age of 45?
- Have your periods stopped for 12 months or more (other than because of pregnancy)?

For men:

- Have you ever suffered from impotence, lack of libido or other symptoms related to low testosterone levels?

Assessing bone loss and bone turnover

BMD measurement methods

A BMD measurement using dual energy X-ray absorptiometry (DXA) has been the "gold-standard"[19,20] for diagnosing osteoporosis and evaluating fracture risk. Although DXA has proven to be a reliable predictor of future fracture, its high cost and its limited availability precludes its wide application in remote areas[21]. In the recently published NORA dataset[22], even if the one-year fracture rate and relative risk for fracture or SD reduction in BMD was greatest at T scores -2.5 SD or lower, the larger number of fractures was seen in the osteopenic category. This is partially related to the larger sample size of the population with T-scores between -1 SD and -2.5 SD. Moreover, it is also important to note that not all people who fracture have low BMD. In fact, the measurement of BMD overlaps between healthy women and those with fracture, perhaps because factors such as alteration of trabecular microstructure contribute to fragility. Other factors such as imprecision in the determination of "low trauma" fractures also contribute to this overlap. At the present time, there is no validated prospective data using the WHO cut-point and in which following a population prospectively we were able to determine the relationship between SD cut-points and 5-, 10-, or even 20-year fracture risk.

Quantitative ultrasound of bone (QUS) is an inexpensive, radiation-free method that provides information on fracture risk, and perhaps bone quality. It can be used to assess the risk of fractures at the spine, hip and non-vertebral sites[3]. However, the fracture risk relationship between QUS and fracture incidence has not been rigorously evaluated with this method[23]. Clinical trials of anti-resorptive agents have not found QUS to be helpful in identifying responders[24]. At the present time, QUS should not be used for the diagnosis of osteoporosis, but may become a useful tool when appropriate diagnostic cut-points have been established. Cut-off values of T-Score for the heel could be considered -1 SD[25].

Bone markers

Bone remodelling is a normal process, which enables maintenance of skeletal strength and repair of microfractures. During the remodelling process osteoblasts synthesize a number of molecules which are released into the circulation and reflect bone formation rates. These include osteocalcin, bone specific alkaline phosphatase and procollagen 1 carboxyterminal propeptide. Osteoclasts produce bone degradation products which are released into the circulation. These include hydroxyproline, pyridinoline, as well as collagen type 1 cross-linked N telopeptide (NTX) and C telopeptide (CTX)[24].

Bone markers are not used for the diagnosis of osteoporosis because there is a great overlap between values of osteoporotic and non-osteoporotic patients[26]. However, they are of value in estimating bone turnover rates. They can be helpful in identifying persons losing bone rapidly. Numerous cross-sectional studies have shown that bone markers increase at

menopause and remain elevated. Prospective studies have demonstrated faster and greater reductions in BMD in those with higher bone turnover[27]. Low BMD in the presence of high bone markers is more predictive of fracture then either risk factor alone[28]. Thus, bone markers have proven to be an additional tool to the assessment of the risk of fracture[26].

The IOF published recommendations regarding bone markers[29]. Because high levels of bone resorption markers are associated with a 2-fold increased risk of osteoporotic fractures, they can be used to assess fracture risk in patients in whom BMD and clinical risk factors are insufficient to make a treatment decision.

In addition, bone markers are important tools for monitoring the effect of treatment after a relatively short period of time (three to six months after the treatment has started) in order to decide whether or not patients are responders[26]. One resorption marker or the combination of one resorption and one formation marker can be used for this monitoring[29]. NTX and CTX as resorption markers, bone specific alkaline phosphatase and osteocalcin as formation markers are the most commonly measured markers. Serum or urine samples should be collected in the morning (before 09.00 hours) after an overnight fast, to avoid diurnal variations.

Secondary osteoporosis

Causes of secondary osteoporosis can be found in approximately one-third of postmenopausal women and one-half of men with osteoporosis. It is important to diagnose these causes in order to appropriately treat osteoporosis.

In addition to a comprehensive history and physical exam, the following tests are recommended[30]: a full blood count, ESR, serum calcium (corrected for albumin), phosphorus, alkaline phosphatase, 25 OH vitamin D ((25OH)D) and 24 urinary calcium. In addition, renal, liver, thyroid and gonadal function must be checked. If needed, special additional laboratory tests such as parathyroid hormone (PTH), serum and urinary protein electrophoresis and immunoelectrophoresis, 24-hour urinary free cortisol, anti-transglutaminase or anti-gliadin antibodies, are performed.

Which sites to test?

The WHO definition of osteoporosis applies only to DEXA assessments of the hip, spine and forearm. It does not apply to other skeletal sites or technologies. It also does not specify how many skeletal sites should be measured or which skeletal site should be used for diagnosis. The hip is the best site for measurement because over the age of 60, osteoarthritic changes artefactually increase spinal BMD. The forearm BMD should be measured when the hip and/or spine cannot be measured or interpreted, in patients with primary hyperparathyroidism or in very obese individuals. The following sites should be measured: L1-L4, proximal femur, femoral neck and total hip at either hip, and if needed, 33% radius of the non-dominant forearm.

How often should a patient be tested?

This section refers only to postmenopausal women, since no clear recommendations could be applied to men and premenopausal women. Frequency of testing depends on multiple factors and in particular the precision error of the testing center. The DEXA manufacturer reported precision is approximately 1% requiring a change of approximately 2-3% at the spine to be a statistically significant change. However, this precision is obtained in ideal experimental conditions using a phantom. Thus, a more realistic precision at the spine may be approximately 1 to 2%, thus requiring a larger rate of change of at least 3% to be a true change. At the hip the precision is poorer and the error is approximately 2% requiring a change of approximately 5 to 6% to be of statistical significance at 95% confidence interval. Considering that the rate of bone loss is generally 1% to 2% per year in postmenopausal women, scans should not be repeated with an interval of less than two years[31]. There are no available data or guidelines of the usefulness of follow-up BMD testing when the baseline BMD is normal. However, one approach in patients with "normal" baseline BMD (T-score more than -1.0), is to have a follow-up measurement every 3 to 5 years, even if many authors would disagree with this approach because of the absence of evidence of its cost-effectiveness. Patients whose bone density is well above the minimal acceptable level may not need further BMD testing[32]. Also, interpretation of the results needs to take into account the potential discordance obtained from the two main regions (spine and hip)[33]. Finally, the role of DEXA in monitoring treatment is controversial, since even with a modest increase in BMD, a decrease in the fracture risk can be observed.

Burdens of osteoporosis in the Middle East

The osteoporosis problem will soon be of greater importance in developing countries since there is an increase in life expectancy[34]. In the Middle East, the burden of this disease is expected to increase, considering the steady growth of the ageing population. In Iran, according to the Endocrinology and Metabolism Research Center (EMRC)[35], two million people are at risk of fracture, establishing osteoporosis as one of the chief health problems in the country.

According to the Ministry of Health, the yearly cost of hip fractures in Iran is between 8,000,000 and 16,000,000 USD[36].

Bone mineral density (BMD) in the Middle East

Several studies have been conducted in the Middle East, in an effort to evaluate BMD and adjust the means to that of Western populations. Indeed, reference ranges have been suggested for Lebanon[37-39], Saudi Arabia[40-42], Kuwait[43], Qatar[44] and Iran[36]. All these studies, conducted mainly on female populations, found lower BMD than the standard established for the US/European reference data, except the Kuwait study, where the BMD reference range was similar.

Female			Male	
	US/European reference	Lebanon reference	US/European reference	Lebanon reference
	Spine (L2-L4) (n=554)		*(n=69)*	
Osteoporosis	31%	11%	17%	9%
Osteopenia	49%	44%	46%	23%
	Femoral neck (n=565)		*(n=69)*	
Osteoporosis	13%	2%	22%	9%
Osteopenia	54%	44%	46%	38%
	Radius 33% (n=349)			
Osteoporosis	22%	13%		
Osteopenia	46%	31%		

Table 1. Prevalence of Lebanese subjects aged 50-79 years with osteoporosis and osteopenia using US/European and Lebanese reference data[37].

Age Bracket	Number	Average Age	Average Stiffness	Average T-score	% Normal	% Osteopenic	% Osteoporotic
20-24	77	22.00	94.31	0.17	90.91	9.09	0.00
25-29	144	27.09	89.35	-0.13	85.42	14.58	0.00
30-34	185	32.30	90.38	-0.07	88.11	10.81	1.08
35-39	312	37.06	88.12	-0.20	78.53	20.19	1.28
40-44	436	41.99	83.28	-0.48	71.56	26.61	1.83
45-49	500	47.18	83.11	-0.49	68.20	30.60	1.20
50-54	669	51.88	80.15	-0.67	62.18	35.87	1.94
55-59	604	56.89	73.70	-1.05	43.00	51.02	5.97
65-69	408	66.74	69.72	-1.28	33.33	58.82	7.84
70-74	245	71.52	65.83	-1.51	23.27	65.31	11.43
75-79	154	76.55	63.68	-1.64	24.03	58.44	17.53

Table 2. Percentage of osteopenic and osteoporotic population in Lebanon using QUS[39].

The Lebanese reference values established in 858 women and 165 men show a lower mean BMD at the spine, femoral neck and radius compared to the US/European reference data, particularly in the early adult years (age 10-49 years)[37]. This finding explains that in the Lebanese population, the prevalence of osteoporosis at the femoral neck for subjects aged 50-79 years was 13% using US/European reference values versus only 2% using the Lebanese reference population (Table 1).

Another Lebanese study[38], performed on a randomly chosen sample of 213 young healthy Lebanese subjects aged between 25 and 35 in the Beirut area, showed a lower peak bone mass (0.2-0.9 SD) and a higher prevalence of osteoporosis and osteopenia in the young population compared to the USA. Height, weight and total body fat were the most significant correlates of BMD/bone mineral content, while lifestyle factors had a very modest but significant contribution to BMD variance.

A third Lebanese study, using (QUS), looked at the prevalence of osteoporosis and osteopenia on a randomly selected sample of 4,320 women (ages ranging from 20 to 79, with a mean of 52.5)[39] (Table 2). Broadband ultrasound attenuation (BUA), speed of sound (SOS) and stiffness index (SI) of the calcaneus were measured. The study showed an overall decline of 19.2% for BUA, 3.1% for SOS and 30.3% for SI between late adolescence and old age. The SI value for the female Lebanese young adult reference was 8% lower than that of the North American and European women (92 SI units compared to 100). At the age of 42, the SI value in Lebanese women was 10.4% lower than North American women and 7.5% lower than European women (86 SI units compared to 96 and 93, respectively). The decline in SI for the Lebanese women between age 20 and 75 is about 30.3% compared to 32% for the North American or European reference curves.

These three studies suggest that the age-related female Lebanese reference data are different from the North American and the European curves used by the instrument manufacturer. Therefore, the use of these standardized ref-

	Women		Men	
	US/European reference	Saudi reference	US/European reference	Saudi reference
Spine (L2-L4)				
Osteopenia	39.1%	42.2%	32.8%	19.1%
Osteoporosis	47.7%	30.5%	38.3%	49.6%
Femoral neck (total)				
Osteopenia	57.0%	58.6%	32.3%	56.7%
Osteoporosis	7.8%	4.7%	6.3%	1.2%
Either (Spine or Femur)				
Osteopenia	41.4%	43.4%	46.5%	54.1%
Osteoporosis	44.5%	28.2%	33.2%	37.8%

Table 3. Prevalence of osteopenia and osteoporosis in Saudis (>50 years) using US/European and Saudi reference data[40].

	Women		Men	
	US/European reference	Iranian reference	US/European reference	Iranian reference
Spine (L2-L4)				
Osteopenia	44.8%	37.4%	46%	33.9%
Osteoporosis	28.8%	41.7%	17%	10.2%
Femoral neck (total)				
Osteopenia	52.4%	47.6%	58%	56.5%
Osteoporosis	12.5%	3.6%	13.7%	0.8%

Table 4. Prevalence of osteopenia and osteoporosis in Iran using different references.

erence data rather than the US or European database reduces the chance of overestimating osteoporosis in the Lebanese population (Table 1).

Similarly, in Saudi Arabia[41], the prevalence of osteoporosis was studied in a randomly selected group of 1980 Saudi males and females aged 20 to 79 years. The prevalence of the disease in Saudi women was 44.5% using the manufacturer's reference values compared to only 28.2% when the Saudi reference values were used (Table 3). On the other hand, less Saudi men are diagnosed with osteoporosis when the manufacturer's reference values are used compared to the prevalence when the Saudi Arab reference value is used. Thus, the prevalence of osteoporosis in the Saudi Arab population is overestimated in women and underestimated in men when using the US/European data reference rather than the Saudi Arabian reference value. On the other hand, the Kuwaiti normative data is higher than the Saudis and is equivalent to the US/European value[43]; no differences were observed in BMD between Kuwaiti subjects and the Caucasian normative values. Finally, in 574 Qatari women aged 20 to 69 years, BMD values at the spine and femur were found lower than Caucasians and Kuwaitis at the spine in the age group 60-69 years, but are higher at the total femur in the age group 40-59 years[44].

In Iran, the Iranian Multicenter Osteoporosis Study (IMOS) establish the osteoporosis prevalence according to the manufacturer's reference values and to the Iranian reference values. The results are shown in Table 4.

1. Patient has been postmenopausal for a period greater than 2 years
2. Patient suffers from back pain
3. Patient engages in low physical activity
4. Family history of osteoporosis or hip fracture
5. Loss of height or presence of kyphosis
6. Patient experienced early menopause (at an age less than 45 years)
7. Smokes more than 20 cigarettes per day
8. Thin, small build
9. History of rheumatoid arthritis, thyroid disease, liver disease, anorexia nervosa or cushing syndrome
10. Patient has undergone oopherectomy
11. Previous use of chronic corticosteroids
12. Chronic alcohol intake

Table 5. Risk factors assessed in patients.

The above findings confirm significant differences among the countries in the region and suggest the need for establishing, in each country, separate reference values for diag-

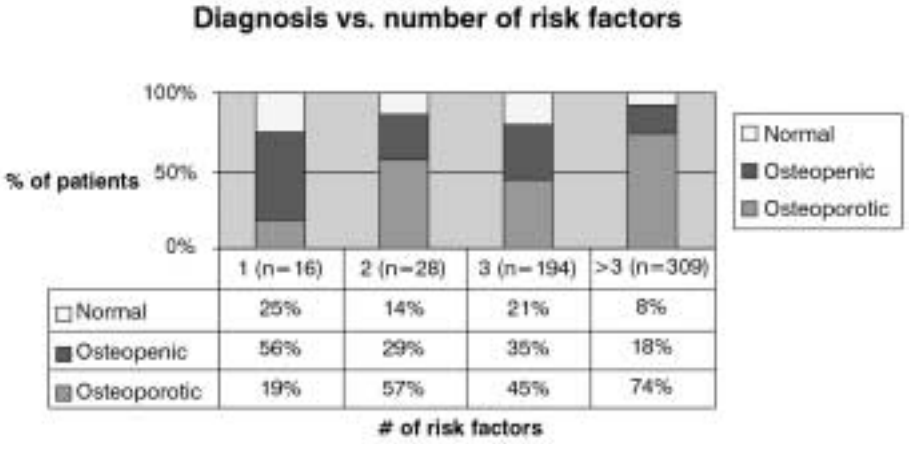

Table 6. Diagnosis of osteoporosis or osteopenia in the Lebanese population based on number of risk factors.

nosing osteoporosis and osteopenia as published by a Saudi group[41]. The region is still lacking studies that focus on the prevalence of osteopenia and osteoporosis in males.

In conclusion, even if it seems that BMD is lower in most Middle Eastern countries compared to Western countries, at the present time, it is of the utmost importance to study the relationship between BMD and fracture risk in order to decide or not the use of local reference data in our populations.

Risk factors for osteoporosis in the Middle East

A recent public survey was conducted in Lebanon in order to determine risk factors for osteoporosis and osteopenia in the Lebanese female population. The sample was composed of 551 postmenopausal women aged 61 +/- 8.9 years old and with at least one risk factor for developing osteoporosis. The diagnosis of osteoporosis and osteopenia was based on local reference ranges. These women had no history or evidence of systemic disease and were not on current or prior treatment for their osteoporosis. Table 5 lists the risk factors that were assessed in patients. The mean number of risk factors reported was 6±3. Table 6 identifies the percentage of normal, osteopenic or osteoporotic patients in each of the following sub-groups: one, two, three or more risk factors. The results show that the more risk factors the patient has, the lower the BMD: while 25% of the patients with one risk factor have a normal BMD, only 14-21% of patients with 2 to 3 risk factors have a normal BMD, and as few as 8% of those having more than 3 risk factors have a normal BMD. Looking at the percentage of osteoporotic women with each risk factor, the study found that 90% of the sample was composed of postmenopausal women for a period greater than two years, 70% suffered from back pain, 55% had a low physical activity, 35% had a family history of osteoporosis or hip fracture, 35% suffered from loss of height or kyphosis, 25% experienced an early menopause, 24% were heavy smokers (>20 cigarettes per day), 23% were thin and of small built, 16% had a history of rheumatoid or thyroid disease, 12% were previously taking corticosteroids chronically and 6% were chronic alcohol consumers.

Another Lebanese multimember study[45] showed that hip fractures occur at a younger age in Lebanon (between the ages of 65 and 75) compared to Western populations (above 75), and that 60% of patients with hip fractures have osteopenia rather than osteoporosis. Mean hip axis length in normal subjects was 92 mm versus 102 mm in patients with hip fractures. Hip axis length may be a predictor for hip fractures, even in patients with osteopenia. Hip fracture subjects weighed less than controls. Femoral neck angle variation between the right and left hips in the same subjects was also more prominent in the hip fracture subjects compared to controls. Also, hip deviation from the mean was greater in fractured subjects as compared to controls (Table 7). All femur BMD variables were lower in hip fracture subjects compared with subjects without fracture.

In addition, in a study carried out in Qatar[46], on a healthy female population aged 20 to 70, risk factors for osteoporosis were similar to those known to influence BMD in other populations; female sex, age, early menopause, excessive and smoking. This study further suggested other risk factors of great importance in the Qatari population and probably also in the Gulf region, those factors being: high number of pregnancies, prolonged lactation and vitamin D deficiency, prevalent in the region and that may account for the reported lower axial BMD in the region compared to European and North American women.

Fracture data in the Middle East

In Saudi Arabia, the prevalence of hip fracture was reported to be lower than the incidence reported in many other countries[47]. This anticipated incidence is according to the same authors expected to be higher than was observed with the population increase in life expectancy. However, in Kuwait, the incidence of hip fractures was reported to be

Measurement	Hip Fracture	Control	p-Value
Mean weight (kg)	63.9	68.3	=0.07
Right hip axis length (mm)	104	100	<0.001
Left hip axis length (mm)	101	99.4	<0.05
Neck angle degree variation (degree)	1.3	3.01	=0.02
Right upper neck BMD (g/cm^2)	0.51	0.61	<0.001
Right hip deviation	3.32	-0.3	<0.001
Left hip deviation	0.79	-1.7	=0.02
BMD spine (g/cm^2)	0.88	0.96	<0.01
T-score L2L	-2.0	-1.5	<0.04
Total femur BMD (g/cm^2)	0.69	0.82	<0.001
T-score femur	-2.1	-1.1	<0.001
Right upper neck BMD (g/cm^2)	0.51	0.61	<0.001
Left upper neck BMD (g/cm^2)	0.53	0.6	=0.02
Right hip BMC (G)	1.25	1.52	<0.001
Left hip BMC (g)	1.32	1.46	<0.05

Table 7. Hip deviation from the mean was significantly greater in fractured subjects as compared to controls.

higher than in some Asian countries, but comparable to the incidence in the US and Western Europe[48]. In Iran according to the Ministry of Health Registration, approximate 8000 hip fractures occur annually.

Besides two small studies carried out on fractures incidence in Lebanon[49,50], and the ones performed on morphometric vertebral fracture[51,52] no inferences concerning the burden of hip fracture can be made in the absence of a fracture registry of all types of fragility fractures (shoulder, wrist, ankle, etc.). We encourage the establishment of a fracture registry for the Middle East.

The mortality rate of hip fracture is 7% in the Lebanese population after one year and 18% after 5 years[53]. These rates are lower than the rates related to Western populations. One explanation for this could be the lack of nursing care homes that are so widely used in Western countries and the presence in our country of the extended family that assumes the responsibility of taking care of its own patients.

The association between BMD and the prevalence of fractures in the Middle Eastern populations is understudied. There is no real fracture registry in any country except Iran.

Vitamin D insufficiency in the Middle East

The biochemical criteria for vitamin D deficiency are problematic. While many laboratories report normal values of 10 to 50 ng/ml, in cross-sectional studies, the 25(OH)D threshold below which vitamin D supplementation resulted in a fall in a serum PTH is around 30 ng/l. It was previously considered that serum concentrations between 10 and 20 ng/ml is suggestive of vitamin D insufficiency and that levels below 10 ng/ml of vitamin D deficiency. However, more recently a threshold of serum 25(OH)D below 30 ng/ml was considered as evidence of vitamin D insufficiency.

Hypovitaminosis D is highly prevalent in Middle Eastern countries. Several studies have been performed in Lebanon, in young people[54], schoolchildren[55] or in elderly people[56]. The study performed in 316 young people aged 30 to 50[54] emphasises the importance of the problem in the region. Indeed, it appears that 72.8% of this population is affected by Vitamin D insufficiency (defined by a 25(OH)D value below 15 ng/ml), and that it is significantly more common in women than in men (83.9% against 48.5%). Moreover, the same study showed that, in women and in men, inadequate vitamin D intake and urban dwelling are independent predictors of hypovitaminosis D. In addition, in women, veil wearing and high parity are predictors of hypovitaminosis D.

The second study was carried out on 385 schoolchildren[55] aged 10 to 16 years old, with different socio-economic backgrounds and at different seasons (spring and fall); the results showed that 52% of the children were Vitamin D insufficient (defined by a 25(OH)D value below 20 ng/ml). The proportion of vitamin D insufficiency was 65% in the winter and 40% at the end of the summer. Girls, especially those with a lower SES (socio-economic status), are at particular risk.

The results of those 2 studies confirm the fact that even in a sunny country, hypovitaminosis D is common, even if it is more so in winter. Low vitamin D intake probably explains the findings observed in these 2 sub-groups of the Lebanese population, adults[54,57] and schoolchildren[58].

Other studies from the region revealed low vitamin D levels in the Saudi population[43]. In that study performed in 321 Saudi young women with a mean age of 35.4 years old, severe hypovitaminosis D (25OHD level </=8 ng/ml) was present in 52% of the subjects. In Iran[59], vitamin D was studied in a sample population of 1,210 subjects aged 20 to 64. 81.3% of the population have vitamin D insufficiency (defined respectively as 25(OH)D levels below or equal to 14

ng/ml). The prevalence of the severe and moderate forms (defined respectively as 25(OH)D levels below or equal to 5 ng/ml and between 5 and 10 ng/ml), was 9.5% and 57.6%. In that study, neither sun exposure nor clothing habits were predictors of vitamin D deficiency.

The results of all these studies emphasize the need for urgent measures in our part of the world to avoid long-term complications related to vitamin D deficiency; these measures include vitamin D supplementation of some food. In Lebanon, dairy products derived from natural cow's milk, which are highly consumed, could be a target for this fortification. Awaiting these measures to be effective, and because of the very high prevalence of vitamin D insufficiency in our countries, vitamin D supplementation is imperative in all postmenopausal women living in our part of the world.

Treatment options

Non-pharmacological intervention as well as a wide range of pharmacological treatments should be considered. The choice of treatment depends "on the patient's age, the presence or absence of prevalent fractures, especially at the spine, and the degree of bone mineral density measured at the spine and hip"[60]. The two main classes of pharmacological treatments include anti-resorptive drugs and anabolic agents. Non-pharmacological intervention consisting of ensuring adequate calcium and vitamin D intake as well as ensuring exercise programmes and prevention of falls for elderly patients is a vital component of the treatment program.

Anti-resorptive drugs

Bisphosphonates are pyrophosphate analogues. Alteration of the various side chains results in different chemical compounds of varying potency and safety. They are potent inhibitors of bone resorption increasing BMD and decreasing the incidence of fracture. The different bisphosphonates available are quite similar in their efficacy, side effects and possible routes of administration, thus offering a flexible range of therapeutic options. Alendronate has been studied in randomized controlled clinical trials at a daily dose of 10 mg or a weekly dose of 70 mg[61,62]. It increases BMD at all skeletal sites and reduces the incidence of fracture by around 50% in both the hip and spine[61,62]. A newer bisphosphonate, risedronate, at a daily dose of 5 mg or a weekly dose of 35 mg, shows similar results[63,64]. Other bisphosphonates, such as ibandronate and zoledronate, have been recently developed[65]. In the US, ibandronate has been approved by the Food and Drug Administration in a daily dose of 2.5 mg as well as a monthly dose of 150 mg. It has also been approved for IV uses once every 3 months[66].

Selective Estrogen Receptor Modulators (SERMS) mimic estrogens in some tissues and anti-estrogens in others providing the bone-protecting effects of estrogen without its unwanted side effects. Currently, the only marketed SERM is raloxifene. In the largest randomized trial with raloxifene (the MORE study), the drug prevented bone loss and decreased the incidence of new vertebral fractures in postmenopausal women by 30-50%[67]. A reduction of 50% of these fractures occurred in subjects with or without vertebral fractures at baseline[67]. No significant reduction in non-vertebral fractures has been reported. In addition, raloxifene lowers serum cholesterol and does not increase the risk of endometrial cancer. *Post hoc* analysis of secondary endpoints found no overall change in cardiovascular risk. The incidence of new breast cancer was significantly decreased[67]. The results from the 8-year follow-up core trial have confirmed an ongoing beneficial effect on the reduction of breast cancer. The RUTH trial is expected to confirm the effects of raloxifene on the incidence of coronary and cardiovascular events. Other SERMs, such as bazedoxifene, lasofoxifene, and arzoxifene are in clinical development.

Intranasal or injectable calcitonin is an alternative. The results of the PROOF show that salmon calcitonin nasal spray reduces the incidence of vertebral fractures by 25-35% at a daily dose of 200 IU[68]. Patients may benefit from the analgesic effect intranasal calcitonin. Reduction of non-vertebral fracture has not been demonstrated with calcitonin. Problems with the trial execution and a high drop-out rate reduced the power of the trial, making the results difficult to interpret.

Hormone Replacement Therapy (HRT): HRT reduces vertebral and non-vertebral osteoporotic fractures. The "Heart and Estrogen/Progestin Replacement Study (HERS)"[69], and the "Women's Health Initiative" (WHI)[70] suggest an increase in the risk of coronary heart disease and invasive breast cancer, gall bladder disease, deep vein thrombosis, pulmonary embolism and strokes. However, the Health Initiative Estrogen Only Study[71] did not show the same adverse event profile as the HRT study, since conjugated equine estrogen does not affect CHD incidence despite the fact that they increase the risk of stroke; thus, estrogen replacement therapy in the WHI seems to be safer than HRT. At the present time, the role of HRT in osteoporosis treatment is questionable. HRT should only be used for women suffering from severe menopausal symptoms and for a short-term treatment.

Bone-forming drugs

Parathyroid Hormone (Teriparatide): The bone-forming effects of parathyroid hormone (PTH) are known for more than 70 years. However, it is only in the last 5-10 years that data have emerged that provide consistent and encouraging results in animals and humans. A recent multinational study[72] on postmenopausal women with prior vertebral fractures demonstrates that the synthetic fragment of PTH (1-34 amino acids fragment) reduces spine and non-spine fractures. The results showed that the risk of vertebral fracture was reduced by 65% within 18 months of treatment. Non-vertebral fracture risk was reduced by 50%. The incidence of hip fracture was very small making it difficult to discern a clear impact on hip fractures with teriparatide therapy.

Strontium ranelate has been shown in animal models to

decrease bone resorption and increase bone formation. It has also been shown to have a stabilizing effect on the hydroxylapatite crystal. Following positive effects in a phase II clinical study, phase III clinical studies of strontium ranelate show a reduction in vertebral and non-vertebral fractures[73].

In conclusion, in addition to the evidence-based efficacy of the different drugs, safety, tolerability and patient preference should also be taken into account in the determinants of treatment choice. In general, biphosphonates are well tolerated; rare cases of severe chemical esophagitis have been reported with alendronate. Side effects with calcitonin are minimal and include flushing and pain at the injection site (with injections) and rhinorrhea (with nasal spray). Raloxifene increases the risk of deep venous thrombosis similar to the use of estrogen, along with hot flushes and leg cramps. Finally, headache and nausea may occur in 10% of subjects receiving a daily dose of 20 μg of teriparatide.

Non-pharmacological interventions

Nutrition and lifestyle play an important role in prevention and treatment. Other factors, like fall prevention techniques, or hip protectors to reduce the impact in case of a fall, are also important[74].

Calcium, vitamin D, and protein. Calcium supplements (0.5-1 g/day) and low doses of vitamin D (800 IU per day) reduce the risk of hip fracture in elderly women in nursing homes[75]. The recommendations are a daily intake of more than 400 IU of vitamin D for women aged 50 to 70 years old and of more than 600 IU for women older than 70 years old[76]. Calcium and vitamin D supplementation is often part of the treatment regimen for osteoporosis in younger patients. Sufficient protein intake may also be beneficial.

With the high prevalence of vitamin D deficiency in the Middle East, one could consider giving higher vitamin D doses. Supplementation once a month or once every 6 months[77] (oral or injection) could be an easier way to achieve good vitamin D status.

Vitamin D analogues (calcitriol, alfacalcidiol) are not approved by the FDA for the treatment of osteoporosis. Their use should be limited to renal insufficiency, gastrointestinal malabsorption or post-organ transplantation. Fracture efficacy is limited and conflicting in postmenopausal women[78-80].

Exercise. Regular weight-bearing exercise may maintain BMD and muscle strength and induce better balance and agility contributing to fall prevention. The type of exercise should be tailored to the individual's needs and abilities. People with osteoporosis must take special care when exercising to reduce the risk of fracture due to impact or falls[81].

Psychological and practical support. Rehabilitation following fractures, strategies for the prevention of falls, and psychological and practical support are important in treatment. Patient support groups help in alleviating the feelings of isolation and depression experienced by many patients with osteoporosis.

Osteoporosis in men

Few treatments have been confirmed to be of value in fracture prevention and approved for use in men. The most commonly used drug is alendronate[82]; there is also evidence for risedronate use in corticosteroid osteoporosis[83] and for parathyroid hormone[84]. Testosterone increases BMD in men with hypogonadism[85].

Recommendations

1. Use evidence-based treatment.
2. Use risk factors for requesting testing, mainly DXA.
3. Be aware of the Vitamin D deficiency in our countries.
4. Establish in each country, the local BMD reference data and its relation to fracture risk.
5. Work, in each country, preferably with the WHO, to include the fracture registry program in the health system.
6. In the absence of prospective data on BMD and fracture risk in our populations there is clearly some uncertainty to use local reference ranges when defining the prevalence of osteoporosis.
7. Use the Middle East website www.iofbonehealth.org to include your local data.
8. Share your experiences with other regional and international ones.

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