Original Article

A Suggested Prototype for Assessing Bone Health

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Abstract

Background- Osteoporosis is becoming a health concern worldwide. Considering the fact that prevention plays an important role in reducing the burden of this silent disease and in view of the limited resources available, many countries have adopted certain programs to fight osteoporosis through shifting their attention towards at-risk individuals. The Iranian Multicenter Osteoporosis Study (IMOS) is one of these programs. The program aims to assess bone health and the prevalence of vitamin D deficiency in different parts of Iran with various altitudes, latitudes and lifestyle habits in a way that the results could be generalized to the country.

Method- The present article presents the protocol used in the third phase of the study. It was designed based on the experiences gathered in the previous phases to overcome the shortcomings particularly subject loss. The questionnaire applied in this study was developed based on a thorough literature review of the risk factors and secondary causes of osteoporosis and was approved by an expert panel. It should be added that while the majority of the existing studies aim to study a certain aspect of osteoporosis, the present protocol provides the information needed for policy makers and researchers to study different osteoporosis-related issues.

Conclusion- The authors believe the protocol, to be implemented with small modifications, can help policymakers in different parts of the world, particularly developing countries, gather accurate information on different aspects of bone health at the national level.

Keywords: Bone, osteoporosis, vitamin D deficiency

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Introduction

Osteoporosis is the most common bone disease, characterized by reduced bone mass and altered microarchitecture, therefore, associated with an increased fracture risk.[1] Considering the aging trend in the population worldwide, the prevalence of osteoporosis is increasing rapidly. It is estimated that the fragility rate, which was about 1.7 million in 1999, would reach 8.3 million in 2050.[2] Therefore, osteoporosis and its complications impose a heavy burden on the society. Figure 1 shows the high risk of a major osteoporotic fracture in a 65-year-old individual with a priority fragile fracture in different parts of the world.

Since the fracture is mainly the first symptom of osteoporosis, a large number of the patients, particularly in developing countries, remain undiagnosed and untreated, while osteoporosis is both preventable and treatable. [3]

In order to prevent the disease and its complications, the prevalence of the disease and its risk factors should be well known. This is while the majority of the studies conducted on this matter, in different parts of the world, suffer several shortcomings and discrepancies. Similarly, several studies have been conducted recently in different parts of Iran; their results revealed that osteoporosis is becoming a health priority in the country.[4] According to these results; the prevalence of osteoporosis and osteopenia is about 22% and 59.9% in women aged 50 years and over, respectively. As for men of the same age group, the rate is about 11% and 50.1%, correspondingly.[5,6]

These data are mainly based on the results of different phases of the Iranian Multicenter Osteoporosis Study (IMOS) conducted by the Osteoporosis Research Center of the Endocrinology and Metabolism Research Institute affiliated with Tehran University of Medical Sciences in collaboration with the Iranian Ministry of Health and Medical Education. This study aimed to assess bone health and the prevalence of vitamin D deficiency in different parts of Iran. Each phase was conducted in different provinces with various altitudes, latitudes and lifestyle habits; therefore the final results could be generalized to the country.

The first phase of the study was conducted in the five main cities in Iran, including: Tehran, Shiraz, Bushehr, Mashhad, and Tabriz in 2000.[7] The second phase was conducted in Sari and Yazd in 2003.[8] The third phase was conducted in Arak and Sanandaj in 2012.

This article presents the protocol used in the third phase of the

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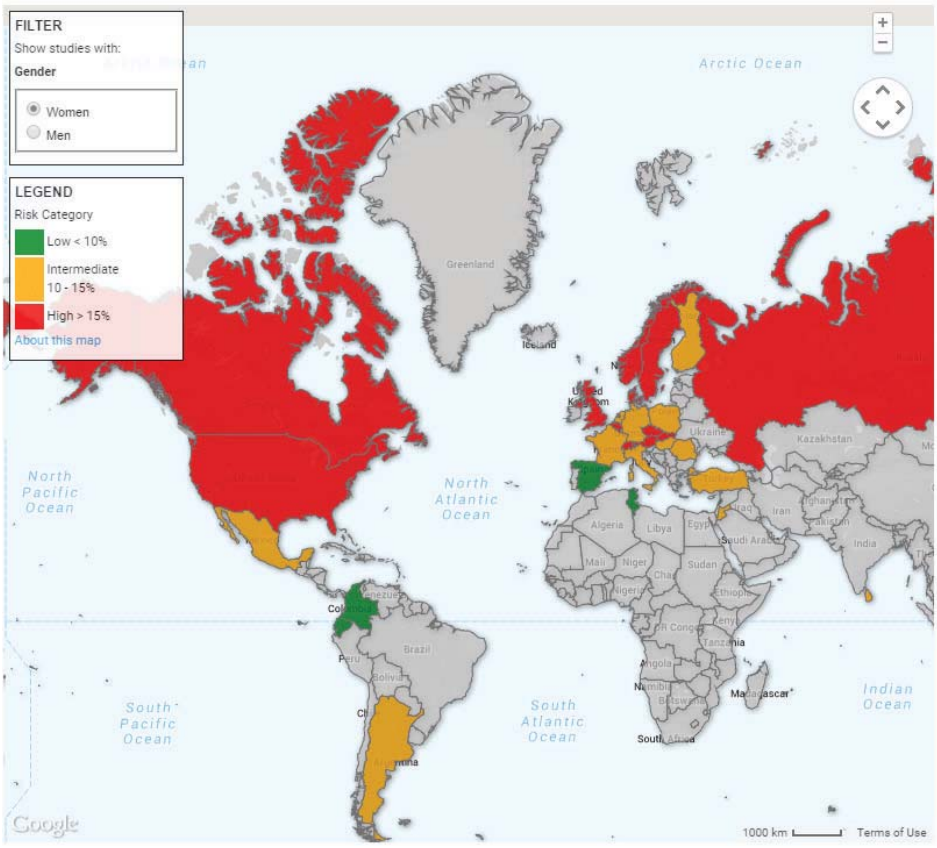

Figure 1. Ten year probability of a major osteoporotic fracture for a 65-year-old person with a priority fragile fracture adopted from International Osteoporosis Foundation website.[30]

study. It was designed based on the experiences gathered in the previous phases, to overcome the experienced shortcomings, particularly subject loss. The questionnaire applied in this study was developed based on a thorough literature review of the risk factors and secondary causes of osteoporosis, and was then approved by an expert panel.[9–11]

The majority of the existing studies aim to consider a certain aspect of osteoporosis however; this study provides the information needed for policy makers and researchers to study different osteoporosis-related issues. The authors of this study believe the protocol can help policymakers in different parts of the world, particularly developing countries, gather accurate information on different aspects of bone health.

Material and Methods

The third phase of IMOS was conducted in Arak and Sanandaj. Arak, located at 34°5'8"N/49°41'2"E, 1,718 m (5,636 ft) is the capital of Markazi Province, Iran. In the latest census, the population of this major Iranian industrial city was 526,182. Sanandaj, located at 35.2458° N, 47.0092° E, 1,538 m (5,046 ft), is the capital of the Kurdistan Province, Iran. According to the latest census performed in 2011, 311,446 people live in this city. The economy of Sanandaj is based upon the production of carpets, processed hides and skins, milled rice, refined sugar, woodworking, cotton weaving, metalware and cutlery.

This study was conducted through a one–stage cluster sampling technique in winter 2011. The protocol of this study was approved by the Ethics Committee of the Endocrinology and Metabolism Research Institute (EMRI) affiliated with Tehran University of Medical Sciences. Considering the results of the first phase (lumbar osteoporosis = 13%, accuracy 2.5%), 700 individuals were needed in each city. The sample size was increased by 1.5 times after design-effect adjustments for the used cluster sampling technique. Thus, 1050 individuals were needed in each city. As a result, 70 clusters with 15 individuals in each cluster were recruited.

The population-based study was conducted on all Iranian adults, aged 20 years and above, from the urban areas of Arak and Sanandaj. Non-Iranians and individuals, who had moved to these cities within the last 12 months, were not included in the study. Individuals with any mental/psychological problems, those unable to cooperate with the interviewers were excluded. Moreover, those with deformity in the spine, hip or lower extremities that would affect the BMD results, those who weighed more than 120 kg as well as those hospitalized for more than 2 weeks or immobilized for more than 3 consecutive months were dismissed. Individuals suffering from infertility, acute/chronic renal failure, advanced liver failure, any kind of cancer, chronic diarrhea (for more than 2 weeks) and mal-absorption as well as those taking any type of vitamin D in the past 6 months, were also excluded.

In this regard, a list of the households in each city was prepared based on the results of the latest census. A total of 70 households was randomly selected in each city. Each of these households was considered as a "cluster." All the adults who met the inclusion criteria in these families and adjacent households, based on the census list, were recruited until 15 individuals were included in each cluster.

The interviewers were asked to visit the households in the af-

ternoons, which was a better time for all family members. If each of the individuals were not present at home after three stopovers, another adult was included as said above. The individuals, who agreed to sign an informed consent form, were asked to fill a questionnaire at the time of the visit and then referred for laboratory and bone mineral density testing upon the arranged time.

In order to assess the knowledge of women regarding osteoporosis, a questionnaire was developed to be filled by the female head of household or the oldest woman living in the house.[12] In case the oldest woman living in the house was unable to answer the questions for any reason, after three visits, the questionnaire was filled out by the next oldest female family member. To the best of our knowledge, this is the first population-based study to measure the knowledge of the Iranian female family members on osteoporosis and its complications, risk and protective factors. It should be noted that to reduce the influence of implicit bias, this questionnaire was always filled prior to the main questionnaire.

The main questionnaire comprised of several sections including: demographic information (age, gender, level of education, and marital and socioeconomic status), reproductive factors (only in women), lifestyle habits (sun exposure, exercising, smoking and alcohol abuse habits), family and personal medical history and drug use (with focus on diseases and medications affecting bone metabolism). Sensible sunlight exposure was assessed with an index, calculated from the number of hours spent each day in the sun, weighted according to the amount of body (less/more than 5% (equal to hands and face) exposed to the light.[13] In the reproductive factors' section, the breastfeeding duration was calculated by adding the breastfeeding time in each pregnancy. Menopause was defined as the time when there has been no menstrual periods for 12 consecutive months and no other biological or physiological cause can be identified.[14] Glucocorticoid use was defined as the use of at least 7.5 mg of prednisolone or its equivalents for more than three months.[15] The individuals were also asked about possible history of osteoporosis (previous BMD testing, the use of calcium and vitamin D supplements and anti-osteoporosis drugs and compliance with treatment) and fracture in themselves and first-degree families. Fragility fracture is defined by the WHO as "a fracture caused by injury that would be insufficient to fracture a normal bone...the result of reduced compressive and/or torsional strength of bone".[16] Clinically, fragility fracture can be defined as one, which occurs as a result of a minimal trauma, such as a fall from a standing height or less. The interviewers were also asked about the 3-month dietary intake of calcium and vitamin D through a Food Frequency Questionnaire (FFQ). The questionnaire also assessed the individual's habit of drinking tea, coffee and soft drinks.[17] It should be added that the questionnaires were designed in a way that would facilitate the interview process and reduce the data entry error.

The individuals were sent to a certain laboratory, where 20 cc of fasting venous blood samples were taken. About 15cc of the blood was kept in plain tubes and 5cc in Ethylenediaminetetraacetic acid (EDTA) tubes. Samples (plain tube) were centrifuged at 3000 RPM for 10 minutes and serum was extracted. Serum and whole blood samples were kept at -70 °C and then sent to the reference laboratory in Tehran.

Serum Albumin, Alkaline-phosphatase, Calcium and Phosphorus levels were analyzed by Bromocresol green, DGKC, Arsenazo and molybdate methods respectively using Pars Azmoon Kit; Iran. Creatinine levels were analyzed by the Jaffe method using Man Kit, Iran. Serum levels of PTH, and Bone alkaline phosphatase were measured by ELISA method using Immunodiagnostic system kits. Competitive ELISA using Enzymoimmunoassay with CV of 8% was used for 25(OH)D. Immunodiagnostic systems were used in all the three tests and calibration and quality control were performed based on the manufacturers' guideline and using the available kits in the package. The whole blood sample was collected in an EDTA tube and used for genetic studies. Genomic DNA was extracted using the phenol chloroform technique. After designing the appropriate primers, Restriction Fragments length polymorphism (RFLP) was applied for genotyping to assess the frequency of the Vitamin D Receptor Gene (VDR) variants at end 3' gene (EcoRV, Bsm I, Taq I ApaI) and the 5' region (FokI) in general Iranian population. The genotyping results were validated and approved by Sequencing.

Quality control was carried out regularly. Unacceptable range results, based on Westgard rules, were re-investigated. High-concentration samples (according to reportable range claimed by the manufacturers) were diluted to a concentration suited to measurement based on the kit instructions.

The individuals were then sent to a BMD clinic, where they underwent an L2–L4 antero-posterior lumbar spine, hip and its sub-regions DXA study by a trained operator according to the manufacturer's instruction. A Hologic Discovery-Wi (Hologic Inc, Waltham, Massachusetts, USA) and a Norland XR46 (Norland Corp., Fort Atkinson, WI) were used in Arak and Sanandaj, respectively. Results were expressed as T- and Z-scores. Quality control procedures were carried out in accordance with the manufacturer's recommendations. In each city, the instrument variation was determined regularly by a weekly calibration procedure using a phantom supplied by the manufacturer (the phantom equilibrium was sent from one city to another after each testing). The interdevice variance was checked several times during the study period. There was an irrelevant small difference between the reported measures, which was negligible. Precision error in BMD measurements was 1% – 1.5% in the lumbar and 2% – 3% in the femoral regions. Standardized BMD (sBMD), which would not differ by more than 3% – 5 % of the different machines, were used to compare the results between the cities.[18,19]

Based on the World Health Organization Study Group recommendation, BMD values were classified as normal, osteopenic and osteoporotic.[20]

In the clinic, the anthropometric measurements were also performed. The measurements, including weight, height, waist and hip circumferences were obtained with light clothing and without shoes by trained technicians using similar instruments and following international guidelines.[21] Quality control for all measurements was monitored regularly.

The height (to the nearest 0.1 cm) and the weight (to the nearest 0.1 kg) were measured using a wall-mounted stadiometer (Seca) and a mobile digital scale (Seca, Hamburg, Germany), respectively. The BMI was calculated by dividing body weight by the height squared (kg/m2). The waist and hip circumference were measured using a non-elastic flexible anthropometric tape (to the nearest 0.1 cm) in the standing position. The tape was applied horizontally midway between the lowest rib margin and the iliac crest for WC and the widest point over the buttocks for HC measurements. The waist to hip ratio (WHR) was calculated by dividing WC by the HC.[22] Individuals were then categorized according to their baseline BMI values (underweight < 18.5, normal weight 18.5 – 24.9,

overweight 25 – 29.9, and obese ≥ 30 kg/m2).

All the questionnaires were checked in two steps by the provincial supervisor (in each province) and the administrative supervisor (in the EMRI in Tehran). The questionnaires with missing or unacceptable data were returned to the interviewers for recheck. The finalized questionnaires along with the BMD and laboratory results were entered in an Access Databank developed for this project.

Statistical analysis

All statistical analyses were performed with SPSS 13.0 for Windows (SPSS, Chicago, IL, USA). Means ± SD were used to express standard descriptive statistics. Categorical variables were expressed as percentages. The normality assumption was checked using Kolmogorov-Smirnov test. The skewed or not-normally distributed variables were transformed and then ANOVA or t-test was used to compare quantitative variables, whereas chi-square was used for the qualitative ones.

Considering the population-based nature of the study, the weight of age and sex groups were implemented during data analysis based on the latest population census data carried out at national level in 2010.[23] In this regard, age and sex-adjusted prevalence of vitamin D deficiency or insufficiency were calculated. In order to study different factors affecting the risk of developing osteoporosis, the individuals were categorized into four main groups: premenopausal and postmenopausal women, men aged less than 50 and men aged 50 years and over. WHO classification (normal, osteopenia and osteoporosis) was used to categorize BMD values in postmenopausal women and men aged 50 years and over.[24] This is while BMD values were divided into normal and low bone mass in the other two groups.

In accordance with the sampling method, survey Data Analysis was used to calculate points and interval estimation of the primary outcome (prevalence of vitamin D deficiency and insufficiency as well as the mean and standard deviation of serum levels of vitamin D in the studied population), using STATA ver. 11.1. Logistic regression, using survey data analysis commands in STATA Package, was applied to assess the risk or protective factors for osteoporosis and vitamin D deficiency. P-values lower than 0.05 were considered as statistically significant.

Socioeconomic status (SES) is the combination of an individual's level of education and work experience as well as the individual's and family's economic and social position based on income, education, and occupation.[25] When analyzing SES, the individual and household income as well as the education level and occupation of each of the family members were assessed. Considering the fact that an accurate estimate on individual's income is not always possible, personal and household asset assessments were used in the study. Thus, SES was measured based on four variables: level of education, residence place index (calculated by multiplying 10 percent of living area square footage to 5 for owned houses and 1 for rental, company and government houses), individual (five items with similar weights) and household assets (six items with similar weights). The assets mentioned in this section are included in the list only if they belong to the individual or shared by the family members and are not applied for work purposes. The resulted variable, calculated as a Z-score, was designated as the socioeconomic status and was used to divide patients into SES tertiles (low, medium, high). The use of a constant C (C = 2 in both provinces) greatly reduced the possibility of a negative Z-score in our study. A detailed explanation of the SES model can be found elsewhere.[26]

Based on 25(OH)D values, subjects were classified as those suffering from vitamin D deficiency (≤ 20 ng/mL), - insufficiency (mild deficiency) (20 to 30 ng/mL) and - sufficiency (higher than 30 ng/mL).[27]

Discussion

Before any decision targeting osteoporosis could be made at national level, policymakers should have sufficient information on the prevalence of osteoporosis and vitamin D deficiency, its risk factors and compliance with treatment in the studied population. Therefore, the final aim of many national programs such as IMOS is to assess bone health in different geographical areas, ethnicities, races and lifestyles. These studies should be designed not only to gather accurate data but also to reduce data loss. Moreover, in view of the limited available resources, they should help provide policy makers and researchers with comparable and generalizable results.

To the best of our knowledge, while many studies have been conducted on various aspects of osteoporosis in different parts of the world, there are not many published protocols for the assessment of risk factors and secondary causes of osteoporosis and vitamin D deficiency exist.[28]

The present protocol was developed by an expert panel in ORC in collaboration with MoHME, the two main organizations to study bone health in Iran.

This protocol was developed based on a literature review and the experience gained by the members of these two institutions in the first two phases of the population-based IMOS. These studies were conducted in different Iranian provinces located in different altitudes and latitudes, where the habitants had different genetic backgrounds and living habits. As a result, phase 3 was designed to take into account such diversities.

In this phase, we have tried to improve the protocol to overcome deficits in the study design, variability in measurements particularly in measuring circulating levels of 25-hydroxyvitamin D [25(OH)D].[29] In addition, blood samples were obtained in midwinter, when the individuals were exposed to insufficient sunlight for at least four months and experienced little or no cutaneous synthesis of vitamin D. We also recommended the use of standard BMD, so that the BMD results could be compared regardless of the device. However, it should be noted that the personal medical history and drug use in this questionnaire is based on self-report and may not be accurate.

In conclusion, several studies have assessed bone health in different populations, but many of them suffer from various deficiencies and bias. The authors believe their questionnaire can be applied as a reference questionnaire in all similar studies, as its reliability and validity has been studied. Data gathered through this questionnaire could provide the policymakers with more accurate and comparable information on the nature and the prevalence of the disease; therefore area-specific measures would be adopted to overcome the condition and its burden, which poses a heavy burden on the society.

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