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Review

Osteoporosis and its perspective in Pakistan: A review of evidence and issues for addressing fragility fractures



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ABSTRACT

Despite major advances in osteoporosis diagnosis and treatment, low rates of investigating and treating osteoporosis in patients with fragility fracture are reported in Pakistan. Cost of therapies, time and cost of resources for diagnosis, concerns about medications and lack of clarity regarding the onus of responsibility to undertake this care, are some of the barriers to osteoporosis identification and treatment. Data from our part of the world on osteoporosis as well as on fragility fractures is sparse. This review addresses the current screening and diagnostic strategies for osteoporosis and reviews the existing literature to highlight the issues prevalent in our society on this major public health problem.

1. Introduction

National Institute of Health (NIH) consensus development panel defines osteoporosis as a systemic skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture, where bone strength is reflected by integration of bone density and bone quality [1]. Osteoporotic fractures or fragility fractures are low trauma fractures occurring with a force equal to or less than falling from standing height. This definition arises because a normal human being ought to be able to fall from standing height without breaking any bones, and a fracture therefore suggests weakness of the skeleton. Pain and disability are the potential outcomes. Quality of life is affected with dependence on others [2] [3].

Despite major advances in osteoporosis diagnosis and treatment, low rates of investigating and treating osteoporosis in patients with fragility fracture have been reported internationally [4–7]. Practicing patterns in the diagnosis and treatment of osteoporosis after a fragility fracture [8], have shown that patients with fragility fractures are usually not always investigated or treated for the underlying osteoporosis. The rate of investigation of osteoporosis by bone densitometry has also been low. Even in the studies that reported high rates of osteoporosis diagnosis (35–100%), there was only moderate use of pharmacological and life style intervention. Studies on barriers to osteoporosis identification and treatment identifies cost of therapies, time and cost of resources for diagnosis, concerns about medications and lack of clarity regarding the responsibility to undertake this care, as some of the issues [8,9].

Data from our part of the world on osteoporosis as well as on

fragility fracture is sparse. Even in developed countries where osteoporosis is widely recognized, the practicing pattern of physicians in screening, diagnosing and then treating fragility fractures with focus on osteoporosis needs a lot to be done [8,10,11]. This review addresses the current screening and diagnostic strategies for osteoporosis and reviews the existing literature to highlight the issues prevalent in our society on this significant public health problem.

2. Methodology

Articles from Google scholar were selected by using the search terms “Osteoporosis”, “osteopenia”, “fracture risk assessment”, “fragility fracture”, “risk factors for osteoporosis”, “bone turn over markers”, “vitamin D” and “bone health” in “Pakistan”. Inclusion criteria were articles published in English in peer-reviewed journals, from Pakistan ranging from 1990 to 2017. The articles were further filtered in a team meeting, keeping in view the ideology behind this narrative review, i.e., current screening and diagnostic strategies for osteoporosis and review of the existing literature to highlight the issues prevalent in our society on this major public health problem.

2.1. Osteoporotic fracture risk assessment

Clinical history, physical examination and routine x-rays diagnose osteoporosis in its advanced stages. Occurrence of first fracture in a previously asymptomatic individual is often the first indication for the presence of osteoporosis. First fracture is a major risk factor for

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Table 1
Clinical evaluation of bone health based on risk factors.

Risk factors for low bone mass	Risk factors for fall	Risk factors for fracture
Intrinsic Causes	Fragility fracture	Low bone mineral density
Age (x2 risk/decade)	Reduced Vision	Advancing age
Female gender	Orthostatic	Prior fracture
Caucasian or Asian ethnicity	hypertension	Family history of osteoporosis or fragility fracture in a first degree relative
Thin body build (body mass index < 20)	Pain	Current smoker
Previous fragility fracture (x10 risk of future fracture)	Impaired ambulation and/or balance	Low body weight
Low trauma fracture in first degree relative	Muscle weakness	Falls
Endocrine Causes	Depression	Sarcopenia
Premature menopause (< 45 years) – natural or surgical	Long term disability	Dementia
Previous amenorrhea (> 6 months duration)	Living alone	Chronic illnesses
Cushing's syndrome	Use of drugs: sedatives, diuretic or anti-arrhythmic	Use of corticosteroids
Hyperparathyroidism (primary or secondary)	Foot problems (bunions, toe deformities, ulcers, deformed nails)	
Hypogonadism	Improper use of assistive device	
Thyrotoxicosis	Extrinsic factors: Lack of stair handrails, Lack of bathroom grab bars, Dim lighting	
Gastrointestinal and nutritional factors		
Life style		
Low level of physical activity		
Poor calcium intake (< 0.5 g/d)		
Alcohol excess (> 14 units/week)		
Cigarette smoking		

subsequent fractures and therefore the ultimate goal is to diagnose osteoporosis even before first fracture occurs. The value of bone densitometry in the management of individual patients is as a measure of risk and not as either or diagnostic criterion. Low bone mineral density (BMD) cannot always translate into enhanced fracture risk. Information on bone mass should be added to information on clinical risk factors and non-skeletal risk factors like potential to fall should be balanced against the benefits and risks of the intervention considered.

A number of BMD-independent risk factors for insufficiency fractures are now recognized. It is important to differentiate risk factors for low bone mass from risk factors for fracture and risk factors for falling (Table 1). None of the risk factors predict bone mass with sufficient accuracy in an individual patient. The best combination of risk factors accounts for 20% variability in bone mass and provide information about the risk of osteoporosis. They are used to target individuals for further investigations (BMD and bone turnover marker) and treatment. They also provide an opportunity to discuss with the patient those factors (life style and secondary causes of osteoporosis) that can be eliminated or altered.

The limited accuracy of BMD alone to predict fractures has led to the development of fracture risk assessment tools that utilize the combination of bone density and clinical risk factors to improve fracture risk prediction. The fracture risk assessment tools qualitatively predict the 10-year fracture probability of hip and major osteoporosis related fractures and can be used to define cost effective intervention strategies for primary and secondary fracture prevention. Available major osteoporosis screening instruments and algorithms include WHO Fracture Risk Assessment Tool (FRAX), the Garvan Institute fracture risk calculator (Garvan) and QfractureScores (Qfracture), simple calculated osteoporosis risk estimation (SCORE), Age, BOdy size, No Estrogen (ABONE), OSteoporosis Index of RiSk (OSIRIS), Study of Osteoporosis Fractures-Study Utilizing Risk Factors (SOF SURF), osteoporosis self-assessment tool (OST), National Osteoporosis Foundation

(NOF) guidelines, Weight-Only–EPIDOS (WO-E) and Osteoporosis Risk Assessment Instrument (ORAI) [12–25]. Most of these are based on non-Asian populations. Unfortunately no such tool is available for Pakistan where the risk factors are different from the Caucasians. Osteoporosis screening questionnaires have thus far not been validated in Pakistani community.

2.2. Value of bone mineral density

The definition of osteoporosis developed for World Health Organization (WHO) is based on bone densitometry. Normal bone mass is defined as BMD above or below 1 standard deviation (SD) from the premenopausal mean value (T-score), osteopenia as BMD below -1SD but above -2.5 SD and osteoporosis is as BMD below -2.5SD [26,27]. These definitions are used to provide diagnostic labels, but not necessarily indications for intervention.

It is useful for fracture risk assessment as BMD is correlated with bone; for each SD decrease in BMD there is an approximately two fold increase in risk of fracture, depending on site of measurement and the technique used [28]. Quantitative assessment of bone mass by DXA allows serial monitoring of patients. In untreated patients, significant loss may be an indication for treatment and is associated with an increased fracture risk. In treated patients, DXA is used to monitor response to therapy. An increase in BMD or stable BMD is encouraging and is associated with fracture risk reduction. Further evaluation is considered for those who are losing BMD. The National Osteoporosis Foundation (NOF), American College of Obstetricians and Gynecologists and International Society for Clinical Densitometry (ISCD) recommend BMD testing for women ≥ 65 years of age and for younger women with high risk of fracture [29]. Monitoring for treatment effects is recommended 1–2 years after starting or changing therapy, with consideration of longer testing intervals once a favorable treatment effect is confirmed. Table 2 shows the indications for BMD testing as per ISCD recommendations. The ISCD official position states that intervals between BMD testing should be determined according to each patient's clinical status.

2.3. Value of bone turnover markers

High bone turnover as estimated by biochemical markers is associated with an increased rate of bone loss, and predicts the risk of fracture independently of BMD [30–32]. Markers of bone turnover can be allocated into two groups: markers of resorption and markers of formation. The primary markers of bone formation are total alkaline phosphatase, the bone isoenzyme alkaline phosphatase, osteocalcin, and the procollagen propeptides of type I collagen. The odds ratio for hip fracture seems to be increased around 2 fold in those with normal BMD but bone turnover biochemical marker above the premenopausal range [33]. Several assays are currently available that measure bone turnover markers. These assays measure collagen breakdown products and other molecules in blood and urine released from osteoclasts and

Table 2
Indications for bone mineral density (BMD) testing.

Women aged 65 and older
Post-menopausal women under age 65 with risk factors for fracture
Women during the menopausal transition with clinical risk factors for fracture, such as low body weight, prior fracture, or high risk medication use
Men aged 70 years or older
Men under age 70 with clinical risk factors for fracture
Adults with a fragility fracture
Adults with a disease or condition associated with low bone mass or bone loss
Adults taking medicine associated with low bone mass or bone loss
Anyone being considered for pharmacologic therapy
Anyone being treated, to monitor treatment effect
Anyone not receiving therapy in whom evidence of bone loss would lead to treatment

Table 3
Studies done on bone health statuses reported from different health centers of Pakistan.

Author [Reference]	Year	Location	Subjects/Age	n	BMD testing tool	Prevalence	T scores	Risk Factors evaluated	Follow-up DXA
Naeem [51]	2015	Karachi	Post-menopausal	203	DXA	44.8% osteopenic 28.6% osteoporotic	NA		NA
Ejaz [52]	2012	Karachi	Pre- menopausal Post-menopausal	1351 65	Heel ultrasound	63.8% osteopenic 17.8% osteoporotic 43.1% osteopenic 49.3% osteoporotic	NA	Daily calcium intake, 30 min or more work against per day.	NA
Lowe [46]	2011	Nahaqi, near Peshawar	Postmenopausal	140	Heel ultrasound	43% osteopenic 27% osteoporotic	0.00 -1.65 -2.8	Age of menopause and menarche, pregnancies, children, history of personal fracture and of siblings, history of smoking, drugs, occupation, income, 24-h dietary recall food and physical activity recall.	NA
Zahoor [41]	2010	Peshawar	Postmenopausal from outpatient clinics	240		44% osteopenic 24.5% osteoporotic	NA	Social history, past medical history, drug history, menarche, age at menopause, reproductive history and family history of osteoporosis.	NA
Jaleel [53]	2010	Karachi	Females (18–80 years) visiting Obstetrics and Gynecology health stall at Expo Center	170	Heel ultrasound	< 45 years (n = 124) 54% osteopenic 5.6% osteoporotic > 45 years (n = 46) 47.8% osteopenic 26.1% osteoporotic	NA	Age, marital status, parity and occupation.	NA
Mamji MF [47]	2010	Karachi	Hip fracture patients (45–80 years) who underwent surgery	103	Not mentioned	NA	NA	History of occupation, literacy, smoking, family history of osteoporosis, steroid usage, calcium intake, lactation, exercise and visual impairment.	NA
Lateef [54]	2010	Karachi	Females from osteoporotic clinics and healthy premenopausal females	150	Heel ultrasound	NA	NA	History of fracture, diet, BMI, menarche and years since menopause.	NA
Haq [55]	2009	Faisalabad	Postmenopausal females	300	Heel ultrasound	44% osteopenic 20% osteoporotic	NA	Reproductive and drug history, family history of osteoporosis and level of physical activity	NA
Hafeez [56]	2009	Medical College, Lahore	Healthy female volunteers	40 post- premenopausal	ultrasound ultrasound	Lower bone mineral density in postmenopausal	NA	NA	NA
Baig [45]	2009	Karachi	Healthy females random sampling from 800 households	925	Heel ultrasound	32.4% osteopenic 6.7% osteoporotic	NA	Knowledge, attitude and practices related to menopause.	NA
Fatima [44]	2007	Quetta	Outpatients and their attendants at obs./gynae unit of Bolan medical College/20–60 years	334	Heel ultrasound	43.7% Normal 43.4% osteopenic 12.9% osteoporotic	-0.29 -1.68 -2.95	Sociodemographic history, medical, smoking, menstrual history, history of low-trauma fracture, family history of fracture, use of steroids, surrogate markers of socioeconomic status and homeopathic medicines.	NA

osteoblasts during the process of bone resorption and formation. If bone turnover markers are used to monitor osteoporosis therapy baseline and post-treatment serum/urine samples should be obtained under standardized conditions and analysis should be performed from same laboratory.

2.4. Screening for secondary causes of osteoporosis

Certain medical conditions and medications completely unrelated to osteoporosis can nevertheless have the effect of causing osteoporosis. In patients with symptomatic vertebral fractures, secondary causes of osteoporosis should be identified by careful history, physical examination and appropriate investigation. Underlying secondary causes of osteoporosis should also be sought in men and women presenting with low trauma hip and other non-vertebral fractures. Tests to exclude secondary causes of osteoporosis include complete blood count, erythrocyte sedimentation rate, serum calcium, phosphate, vitamin D, parathyroid hormone, liver and kidney function tests, serum thyroid stimulating hormone and 24-h urinary calcium levels. Routine biochemical profile is probably worthwhile, as hypocalcaemia & hypophosphatemia may indicate possible osteomalacia. In a multinational cohort study (GLOW) by Dennison et al., in 2012, it is shown that comorbidities contributed significantly to fracture risk and suggested greater awareness of the relationship between co-morbidities and fracture risk in improving fracture-prediction algorithm [34].

2.5. Treatment goals for prevention and treatment of osteoporosis

The treatment goals in the first place include decreasing the fracture risk by stabilizing or increasing bone mass and maintaining or improving bone quality and strength. Therapy is targeted to pathophysiological risk factors for fractures such as calcium/vitamin D deficiency and factors such as estrogen deficiency that cause loss of bone mineral. Patients with osteoporosis are also at risk for fracture because of a tendency to fall; most fractures are the result of a fall onto a fragile bone. Observational studies show that low levels of physical activity and poor muscle strength are risk factors for future fracture, and randomized trials show that exercise will improve muscle strength and reduce the risk of falling [35,36].

There are three components to the non-drug treatment of osteoporosis: diet, exercise, and cessation of smoking. The universal recommendations for improvement of bone health from NOF include adequate intake of dietary calcium and vitamin D, regular weight bearing and muscle strengthening exercises, avoidance of smoking and excess alcohol and fall prevention in elderly. Many studies suggest that calcium and vitamin D supplementation decreases the risk of fractures. The incidence of non-vertebral fractures in 3270 ambulatory elderly women who were randomized to receive either 1200 mg of calcium and 800 IU of vitamin D or placebo; incidence of hip fractures and all non-vertebral fractures was significantly lower in the supplemented group [37]. In a different study of 389 adults age > 65, who were randomized to receive either 500 mg of calcium or 700 units of VD daily or placebo. Treatment was associated with an improvement in BMD and a decrease in incidence of all non-vertebral fractures [38]. While not all randomized trials agree that treatment with calcium and vitamin D will reduce the risk of fractures, there are enough data to suggest safety and efficacy to recommend 800 Units of vitamin D and 1200 mg of calcium daily. Though the changes in BMD that occur with treatment with calcium and vitamin D are small, but still resulted in a substantial and significant reduction in fracture risk. There is therefore speculation that treatment with calcium and vitamin D reduce the incidence of fractures by other means as well like reducing falls.

There are many things to think about when choosing the right osteoporosis treatment option such as gender, age, the severity of osteoporosis and patient's personal preference. The drugs approved for osteoporosis treatment include bisphosphonates, calcitonin, selective

estrogen receptor modulators, parathyroid hormone and RANK ligand inhibitors. Drugs approved for treatment of osteoporosis have been proven in randomized clinical trials to improve BMD and decrease the rate of non-vertebral fractures compared to calcium and vitamin D alone. Data from different trials are not directly comparable, because the clinical trials differed in number and types of patients enrolled [39].

3. Osteoporosis in Pakistan

3.1. Prevalence of osteoporosis

Due to lack of national registries and lack of published data there is a paucity of epidemiological data on osteoporosis in Pakistan. The diagnostic facilities of osteoporosis are meagre and there are limited numbers of DXA machines available only in large towns and cities. In last 5 years, several hospital based studies have shown prevalence of osteoporosis using heel ultra sound and the data on BMD using DXA is scarce. Table 3 summarizes studies done on bone health on Pakistani population in the last decade. Available evidence suggests that the burden of osteoporosis is high in this part of the world ranging from 5.6 to 17.8% in pre-menopausal females and 20–49.3% in postmenopausal females. A study conducted in Peshawar on postmenopausal women (n = 1000) for simple calculated osteoporosis risk estimation, found that 75.3% were predisposed to osteoporosis and the risk increased with age (97% in women of 75–84 years of age compared to 55% in women of 45–54 years of age) [40]. Accurate data on osteoporosis prevalence is lacking and all these studies have used heel ultrasound and not DXA as their research tool. Almost all the studies have been reported from urban areas of the country. There are the concerns that the estimation of osteoporosis burden using available published data underestimates the number of people with the disease.

3.2. Status of knowledge about osteoporosis

There is generally a low level of osteoporosis awareness in the country. Though there have been individual efforts, but no government policy and osteoporosis is still not recognized as a major health issue in Pakistan. The low awareness levels is linked to low level of education, infrequent contact with the health service, large family size and poor economic conditions. In addition, people are not aware of importance of calcium intake in peri-menopausal period [41]. A study on healthy females attending a tertiary care hospital reported that Pakistani women from higher socioeconomic status had significantly better knowledge about osteoporosis than women of lower socioeconomic status but this knowledge did not improve life style/preventive habits for osteoporosis [42]. A study from a tertiary care hospital showed low rates of calcium and vitamin D supplementation for patients discharged after surgery for hip insufficiency fractures [43].

3.3. Osteoporosis risk factors in Pakistan

There is a scarcity of solid epidemiological data on osteoporosis in Pakistan but the osteoporosis risk factors, multi-parity, increased postmenopausal years, decreased calcium intake, vitamin D deficiency and lack of physical activity are on the rise [44,45]. Risk factors included from research work from Peshawar included age of menopause and menarche, pregnancies, children, history of personal fracture and of siblings, history of smoking, drugs, occupation and income while the mean calcium intake in these 140 postmenopausal females was significantly lower than the World Health Organization's dietary recommended intake of 1300 mg/day [46].

Significant osteoporosis risk factors found in 103 post-menopausal females having hip fracture; were early menopause, longer duration of menopause, low BMI, poor socioeconomic conditions, multi-parity, smoking, illiteracy, lack of calcium supplements, injudicious use of steroids and poor visual acuity. The mean age of the study group was

64.6 years and average duration of menopause was 9.9 years and the study also reported that 70.9% women did not exercise [47].

3.4. Bone turnover

Although relatively little is known about the osteoporosis risk factors in Indian & Pakistani, osteoporotic fractures usually occur 10–20 years earlier in Indian men and women compared with their western counterparts. In a cross sectional study the relative contributions of ethnicity, reproductive history, body size and composition, bone turnover, serum 25 OHD, dietary intake of calcium, fiber & alcohol & energy expenditure to femoral BMD & hip axis length were studied in Indians/Pakistanis and Caucasians. Findings revealed that Indian/Pakistani women had lower BMD than their American counterparts, placing them at greater risk of fracture. Shorter hip axis length of the Indian/Pakistani vs American Caucasians might attenuate hip fracture risk in the former group. Some of the significant contributors to proximal femur BMD were calcium intake and usual alcohol intake. Although serum 25OHD & urinary NTx concentration did not contribute to femoral BMD in the regression models, the lower serum 25OHD & higher NTx values in Indian Pakistani versus American Caucasian, respectively coupled with their lower BMD, places them at higher risk of osteoporosis. In one of our studies to assess bone health in healthy females, high bone turnover was seen with vitamin D deficiency and secondary hyperparathyroidism.

3.5. Vitamin D status

The two main determinants of bone health are calcium and vitamin D. Recently, studies from different cities of Pakistan has shown very high prevalence of vitamin D deficiency and insufficiency in randomly selected healthy and patient population (Table 4). According to the 'National Nutrition Survey 2011' of Pakistan, 66.2% of the non-pregnant and 68.5% of the pregnant mothers were found D deficient [48]. Despite ample sunshine, Pakistan has the highest rates of vitamin D deficiency worldwide. In a recent study to assess bone health in healthy adult population high bone turnover was seen in healthy premenopausal community females [49].

Consistent predictors of low levels of 25OHD are duration of sun exposure and practice of wearing veil. Entire need for vitamin D can be met by adequate exposure to sunlight. Exposure of arms & legs for 5–30 min (depending on time of day, season, latitude & skin pigmentation) between 10am and 3pm twice a week is often adequate. In the absence of adequate sun exposure the body depends on dietary supply for vitamin D. Unlike many Western countries that have a vitamin D food fortification policy, Pakistan does not have a mandatory vitamin D fortification policy in place. With longer exposure to UVB rays, an equilibrium is achieved in the skin, and the vitamin simply degrades as fast as it is generated.

International recommendations and guidelines regarding desirable doses and levels may not readily apply to population from our region. On the other hand the calcium intake is assessed to be low based on food frequency questionnaire.

Table 4

Prevalence of vitamin D deficiency in Pakistani population residing in different geographical areas.

Authors (ref)	Year	Place of study	Study population	Sample size	Vitamin D deficiency %
Khan [50]	2012	Karachi	Premenopausal women from community	305	90.5
Dar [49]	2012	Karachi	Premenopausal healthy women	200	82
Hossain [57]	2011	Karachi	Women in labor	75	89
Mansoor [58]	2010	Karachi	Apparently healthy adults	123	90%
Zuberi [59]	2008	Karachi,	Ambulatory care adult patients	119	92% (female: male ratio of 5:1)
Masud [60]	2007	Lahore	Pre-menopausal women	195	81%

3.6. Fractures

Despite the high prevalence of osteoporosis and osteopenia in Pakistan, there is not enough information regarding the prevalence of osteoporosis-related fractures and the burden of the diseases. Published data on incidence rates for hip fractures is not available.

Mortality rates post hip fractures are not known from this region. While such rates vary between 25 and 35% in western population, they are 2–3 folds higher in Middle East. Information on social costs and quality of life is practically non-existent.

3.7. Life style variables

According to The National Osteoporosis Foundation, lifestyle adoptions effect 20–40% of adult bone mass. Therefore, modification of lifestyle factors is a key strategy intended at reducing risk of osteoporosis in advanced age.

A recently published community based study from our center done on females showed that the significant predictors of vitamin D deficiency were aging, housing structure and town of residence [50].

4. Conclusion

Economic development has resulted in rapid socioeconomic changes. Non-communicable diseases have become the leading cause of mortality and morbidity. It is important that concerned stakeholders should establish a priority list of objectives and a time table for a plan of action to develop appropriate programs and advocate for policy change, to render the diagnosis and treatment of osteoporosis accessible to all at risk. There is now sufficient evidence to develop action plans. The challenge is to stimulate young audience and to conduct effective education programs to increase general awareness of the problem. Public awareness programs regarding prevention, diagnosis and management of osteoporosis and fragility fractures should be a priority strategy.

As patients with osteoporosis-related fractures are at higher risk of subsequent re-fractures multiple programs have studied the efficacy of systems for the prevention of secondary fractures, often referred to as a fracture liaison service (FLS). Specifically, the FLS is a coordinated care model of multiple providers who help guide the patient through osteoporosis management after a fragility fracture to help prevent future fractures. Keeping in mind its efficiency and cost effectiveness Fracture Liaison Services and development of national database is also dire need of time.

4.1. Recommendations

- 1) It is recommended to cater the rampant Vitamin D Deficiency and calcium intake in Pakistan through promotion of life style modification strategies and implementing food fortification policy.
- 2) Awareness campaigns at community level advocating role of physical activity in promoting bone health to create mindfulness about attaining the peak bone mass disease and its implications are needed.
- 3) Promoting osteoporosis training through medical education

curriculum to physicians should be initiated.

- 4) Screening for high risk individuals, provision of adequate diagnostic facilities for DXA scanning for effective management and prompt diagnosis at low cost should be targeted.
- 5) Coordinated care model of fracture liaison service (FLS) should be promoted at Institutional level for prevention of secondary fracture and appropriate follow-ups.
- 6) At national level, osteoporosis should be included in the national action plan for the non-communicable diseases. So efforts to promote development of regional and national data base for fracture can be initiated.

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Author contribution

Dr Aysha Habib Khan, conceive the idea, design the study, data gathering, analysis & write up.

Dr Lena Jafri, data gathering, analysis & write-up.

Dr Sibtain, data gathering & write-up.

Dr Shahryar Noordin, critical review of the manuscript and write-up.

Conflicts of interest

None.

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