ORIGINAL ARTICLE

Diagnostic Accuracy of Procollagen Type I- N terminal Propeptide (P1NP) in women with Postmenopausal Osteoporosis

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ABSTRACT

Background: Osteoporotic fractures are pre-eminent matter of concern and high economic burden in Pakistan. The prevalence of osteoporosis is anticipated to rise to 11.3 million by 2020, which is alarming. Dual energy x-ray absorptiometry (DEXA) scan is a diagnostic tool for osteoporosis but it reveals static changes in bone metabolism which appears late. There is a need to identify dynamic markers in bone metabolism which can unmask early changes. Procollagen Type I- N terminal Propeptide (P1NP) is a recommended bone formation biomarker by International osteoporosis Foundation (IOF) and International Federation of Clinical Chemistry (IFCC) which is less affected by food intake and circadian rhythm variability, but its diagnostic accuracy needs to be assessed.
Aim: To evaluate the diagnostic accuracy of P1NP in osteoporosis and osteopenia.
Methods: This cross-sectional study with 267 postmenopausal women was conducted at Ziauddin University, Karachi, Pakistan. Demographic variables were taken by self-designed, structured questionnaire. P1NP levels were detected by using electrochemilluminescent technique while DEXA Scan was used to estimate bone mineral density (BMD). Cases were distributed into three groups on the basis of t-score from DEXA scan on hip and spine separately. Mean, median, SD and quartiles were used to describe P1NP levels in three groups and Box-plot was used to show the distribution of P1NP for three groups. Receiver Operative Characteristic Curve (ROC) was used to identify the cutoff of P1NP level for diagnosis of Osteoporosis and Osteopenia in comparison to normal by taking t-score spine as gold standard. Sensitivity, specificity, Positive predictive value (PPV), Negative predictive value (NPV) and accuracy were measured and were presented in percentages with 95% confidence interval. P-value ≤ 0.05 was considered significant.
Results: P1NP values for the diagnosis of osteoporosis were ascertained as 83.3% Sensitivity,70.8% specificity with diagnostic accuracy of 75.5% .When used for diagnosis of osteopenia the sensitivity, specificity and accuracy recorded were 56.0%, 70.8% and 65.11% respectively.
Conclusion: P1NP can be used as reliable marker to predict spinal osteoporosis.
Keywords: P1NP, DEXA, Osteoporosis, BMD

INTRODUCTION

Osteoporosis, a global disease, is defined as reduced bone mineral density (BMD) which leads to bone fragility and ultimately bone fractures[1,2]. Worldwide approximately 200 million people are affected by osteoporosis and 8.9 million fractures results due to fragile bones[1]. Data regarding osteoporosis is deficient in Pakistan. According to Sabit et al. frequency of osteoporosis is projected to rise to 11.3 million by 2020 in Pakistan which is alarming[3].Osteoporotic fractures are major health care concern and high economic burden of old age population[4,5]. Therefore early identification of osteoporosis is important to reduce the risk of fractures[1].

Although (DEXA) is commonly used to detect Bone mineral density (BMD) for risk identification of fractures its high cost and lack of accessibility decreases the feasibility of its use[6,7,8]. Moreover DEXA provides static measure or a snapshot of bone status[9]. Changes in BMD appears late on DEXA which is mostly unalterable at that point[4,10]. Bone being dynamically active continuously releases bone turn over biomarkers into the blood stream which provide dynamic details regarding bone status[11].These biomarkers reveal early changes in BMD and can be repeated at short intervals. In addition these can be beneficial to assess prognosis of osteoporosis, more importantly in estimation of drug holidays during bisphosphonate treatment[4]. In addition they provide better accessibility for bed ridden terminally ill patients. They are subject to biological and analytical variability[8], hence their diagnostic accuracy needs to be assessed.

P1NP is one of the bone formation biomarker recommended by International osteoporotic foundation (IOF) and International Federation of Clinical Chemistry (IFCC)[8]. Major advantage of using P1NP as a bone biomarker is its low individual variability and good essay precision[12]. In addition sample stability is well reported and it is less affected by food intake and circadian variability[11,12]. This study was designed to evaluate diagnostic accuracy of P1NP in osteoporosis and osteopenia of post- menopausal female population. Moreover we calculated difference of P1NP levels in four post- menopausal age quartiles.

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MATERIAL AND METHODS

A cross sectional study of 267 women aged 40 years[13] and above was conducted at Ziauddin Hospital Clifton Campus Karachi. This project was approved by ethical committee of Ziauddin University. Pregnant females, patients of any medical disorders or drugs affecting bone turnover,

malignancies, metastasis to bone, cholestatic liver disease (during previous 3 months) and patients with chronic renal failure were excluded from our study population. After taking informed consent a self-designed structured questionnaire was administered to evaluate age, weight , BMI, socioeconomic status, past and family history of fractures and drugs. Patients were selected on the basis of DEXA scan. According to WHO criteria t- scores of less than -1 was interpreted as normal, between -1 to -2.5 was osteopenic and more than -2.5 was osteoporotic.

For serum P1NP levels, 5ml of blood was taken by venipuncture. After centrifugation, samples were stored at -80 ˚C. Roche Elecsys 2010, Modular Analytics E 170 Cobas was utilized at Ziauddin Hospital, North Campus Karachi to measure P1NP. Analysis technique was electrochemeluminescense immune assay (ECLIA).

Statistics: Cases were distributed into three groups on the basis of t-score from DEXA scan on hip and spine separately. Data were entered and analyzed by SPPSS version 22. Median with inter quartile range (IQR) were used to describe P1NP levels in three groups and Box-plot was used to show the distribution of P1NP for three groups. The comparison of P1NP level was made among three groups by using Kruskal Wallis test and Post hoc analysis was performed by using Mann Whitney U test. Receiver Operative Characteristic Curve (ROC) was used to identify the cutoff of P1NP level for diagnosis of osteoporosis and osteopenia in comparison to normal by taking t-score spine as gold standard. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were measured and were presented in percentages with 95% confidence interval. P-value ≤ 0.05 was considered significant.

RESULTS

The study included 267 menopausal and post-menopausal women. They were grouped according to t-scores on DEXA scan as normal, osteopenia and osteoporosis. Detailed analysis was done on the basis of t-scores at hip and spine. 72(27%) women were diagnosed as cases of osteoporosis, 75 (28.1%) as osteopenia and remaining 120 as normal at the spine. On the basis of t-score measured from DEXA scan for hip, there were 9(3.4%) osteoporotic, 133(49.8%) as osteopenic and 125 as normal. The P1NP levels were measured for all these women and a highly significant difference was noticed among three categories based on spine t-score with p-value<0.001. When compared from normal, the osteoporosis and osteopenia group had significantly different P1NP level with p-values 0.021 and <0.001 respectively. The difference between osteoporosis and osteopenia was also significant with p-value 0.004. In the hip t-sores group the difference among three groups based on hip t-score was also significant with p-value 0.046, among osteoporotic and osteopenic patients and normal subjects. Osteoporosis and osteopenia was significant with p-value 0.044.The difference between normal group to osteopenia and normal group to osteoporosis were insignificant here. (Table.1) The difference of P1NP levels was not statistically significant among four age quartiles of the postmenopausal women with p-value 0.264. The first and last quarter of age had very high variation in P1NP levels. After applying ROC curve a value of 46.03 was considered an optimal cutoff based on this sample data taking t-score on spine as gold standard (Fig. On this basis the sensitivity of P1NP level to diagnose osteoporosis was 83.3% and specificity of 70.8% with an accuracy of 75.5%. When used for diagnosis of osteopenia in comparison to normal the sensitivity, specificity and accuracy recorded were 56.0%, 70.8% and 65.1% respectively (Table. 2, 3).

Figure 1: ROC curve to decide cutoff of P1NP for diagnosis of Osteoporosis

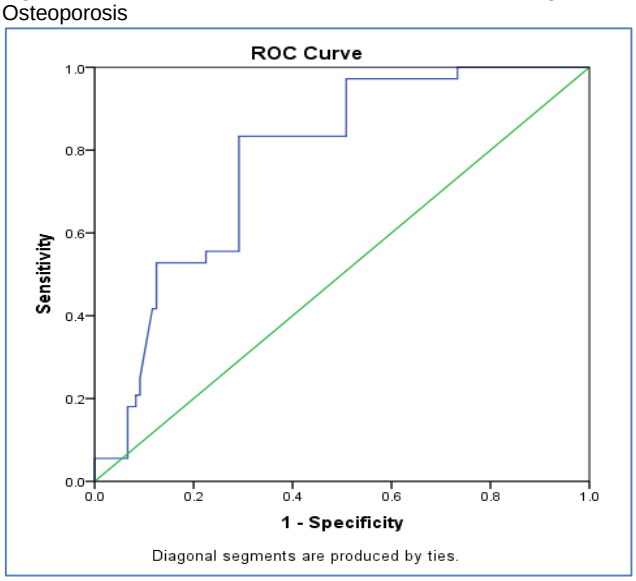

Table1: P1NP levels for each category of cases as per status against spine and hip t-score

	n	Q1	Median	Q3	*p value
Spine					
≤ -2.50	72	46.05	51.24	58.48	0.001
-2.49 – -1.00	75	33.62	49.01	54.54	
> -1.00	120	28.20	43.90	47.11	
Hip					
≤ -2.50(A)	9	51.10	51.37	51.37	0.046
-2.49 – -1.00(B)	133	42.52	46.05	57.45	
> -1.00(C)	125	38.91	42.91	52.19	
Group wise comparison Spine	A - B	p-value 0.001	B - C	**p-value 0.004	
Group wise comparison Hip	A - B	p-value 0.057	B - C	**p-value 0.125	

A= osteoporosis, B= osteopenia, C=normal, * p value calculated by Kruskal Wallis, **p value calculated by Mann Whitney U test

Table 2: Distribution of cases as per P1NP and its diagnostic power for detection of osteoporosis against spine t-score on DEXA

	Osteoporosis	Osteopenia	Normal	
	≤ -2.50	-2.50 – -1.00	> -1.00	Total
P1NP>46.03	60	42	35	95
P1NP≤46.03	12	33	85	97
Total	72	75	120	192

Procollagen Type I- N terminal Propeptide (P1NP)

Table 3: Diagnostic measures through P1NP for osteoporosis taking DEXA t-score of spine as gold standard

	Osteoporosis		Osteopenia	
Measure	Value%	95% CI	Value%	95% CI
Sensitivity	83.3	(74.7 – 91.9)	56.0	(44.8–67.2)
Specificity	70.8	(62.7 – 78.9)	70.8	(62.7–78.9)
PPV	63.2	(53.5 – 72.9)	54.5	(43.4–65.6)
NPV	87.6	(81.0 – 94.2)	72.0	(63.9–80.1)
Accuracy	75.5	(69.4 – 81.6)	65.1	(58.4– 71.8)

Positive predictive value (PPV), Negative predictive value (NPV), Confidence interval (CI)

DISCUSSION

Although DEXA is gold standard to assess BMD but its major limitations i.e. high cost, low accessibility and poor prognostic marker for terminally ill patients, reduces its feasibility. On the other hand bone biomarkers emerge relatively as a new strategy to assess low BMD[1,14,15]. Bone biomarkers can identify changes in bone metabolism at earlier stage (3-6 months) as compared to DEXA which detects these changes at a later stage (1-2 years)[16,17]. These bone biomarkers are subjected to biological and analytical variabilities[18]. P1NP is one of the upcoming promising biomarker as it is less affected by these changes[8].

The current study was designed to assess the status of P1NP in osteoporosis and found statistically significant difference in osteoporotic and osteopenic group as compared to the normal. Physiologically, P1NP being bone formation biomarker reflects bone anabolic activity. Its levels decline with age but there is an incline in postmenopausal age and in osteoporosis because of increased bone resorption coupled with increase bone formation and consequently increased P1NP levels. Our results are in line with, Shetty et al. from India and Zhao et al. from china. They concluded significant association of P1NP and BMD at femur neck and spine and total hip in post-menopausal women[19,20]. Similarly Scariano et al. declared that osteoporotic women had increased P1NP levels as compared to normal subjects[21]. Contrarily, Liu et al. concluded no significant difference in the blood PINP concentration among osteoporosis, normal bone mass and osteopenia groups[22].

Detailed analysis revealed significant difference in normal, osteopenic and osteoporotic groups at spine as compared to hip. We found significant difference in osteopenic and osteoporotic group but no significant difference in normal to osteoporotic and normal to osteopenic groups at hip level. The less-significant association between serum P1NP and BMD at total hip can be explained by the fact that there are anatomical and physiological differences in spinal and proximal femur bones. Anatomically more trabecular bone is present at spinal level as compared to proximal femur bone which is subject to rapid bone loss at lumber region in postmenopausal period and leads to higher prevalence of lumber osteoporosis. Moreover physiologically weight bearing is a known cause of dissimilarity leads to better BMD at hip and femur level[23,24].

There is diversity in results all over the world, which can be due to different geographies. We evaluated sensitivity, specificity, positive and negative predictive values of P1NP in our study. We found good sensitivity and specificity with overall diagnostic accuracy of 75% patients for spinal osteoporosis; true positive and true negative cases were 63.2% and 87.6% respectively. In contrast, CD Cabrera et al conducted a study in India on postmenopausal osteoporotic women and reported poor sensitivity with good specificity. This study found sensitivity of P1NP 50% with a specificity of 100%. Interestingly when specificity was lowered from 100% to 94%, sensitivity increased from 50% to 73%. Serum PINP was measured by a RIA (Orion Diagnostica, Finland)[25]. Elma Kučukalić et al conducted a study in Bosnia and revealed that at the cut-off value of 37.1ng/mL, the sensitivity and specificity of P1NP were 70.8 and 38.5% respectively. While at the cut–off value of 22.1ng/mL, the sensitivity increased to 93.98 while specificity greatly decreased. This study was conducted by using Elecsys 2010 automated analyzer (Roche Diagnostics GmbH)[6]. They stated poor accuracy of P1NP and recommended further studies. A Chinese study concluded by LIU Gang et al revealed diagnostic sensitivity of P1NP 65.9% and specificity of 85.7% .The study was conducted by Roche Diagnostic. This study also suggested further studies with larger sample size but they mentioned PINP as useful tool in identifying postmenopausal women with osteoporosis[26]. With female population of decreased BMD, Scariano et al in Mexico reported diagnostic sensitivity of 83% and specificity of 64% at the cut off level of >45.0µg/L for PINP. The study was conducted[27,28].

The all above mentioned studies showed diversity in their results but still in our opinion P1NP can address successfully the difficult cases such as bed ridden terminally ill patients, especially patients with metastasis and to estimate length of drug holidays for bisphosphonate treatment. A combined approach with BMD and clinical factors forms a suitable strategy to predict the risk of fractures.

Limited number of cases in osteoporotic, osteopenic and normal groups at hip level is limitation of our study, so we recommend further studies with larger sample size.

CONCLUSION

This study concludes P1NP can be used as a reliable diagnostic biomarker to identify post-menopausal spinal osteoporosis.

Conflict of interest: Nil

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