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Validation of Osteoporosis Scores with Urinary N-telopeptide Bone Marker in Assessment Bone Mineral Density in Autoimmune Rheumatic Diseases Patients

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Abstract

Introduction: Osteoporosis is a condition characterised by decreased bone strength. Many tools are used to assess osteoporosis e.g Dual-energy x-ray absorptiometry (DXA) and Fracture Risk Assessment Tool (FRAX). Also, different bone resorption marker can predict osteoporosis e.g Urinary N-telopeptide is a sensitive and specific marker of bone resorption.

Objective: assess the validity DXA and FRAX scores in early detection of osteoporosis in autoimmune diseases. Also, serum vitamin D and urinary N-telopeptide as marker for bone resorption in them.

Method: A cross sectional observational study where a (180) autoimmune rheumatic patients were assessed by DXA, FRAX scores, serum vitamin D, serum uric acid and Urinary N-telopeptide.

Result: The mean age of studied patients (180) was 46±12.6 years old, BMI 33.7 (29.4-37.8), S Uric acid 6 (5-7), S vitamin D 26 (13.3-32), urinary Telopeptide 105 (89-175), Lt femur neck T score -0.9 (-1.5…-0.3), Lt forearm T score -0.8 (-1.7….-0.1), osteoporosis 2 (1-2), FRAX score osteoporosis % 3.7 (2.6-7.5), FRAX score hip fracture % 0.2 (0.1-0.6) and risk hip fracture 1 (1-1). Left femur neck T score and Lumbar T score were significantly correlated with age, S uric acid, percentage of FRAX score osteoporosis and FRAX score hip fracture.

Conclusion: If we suspect osteoporosis, it is better to go for urinary N-telopeptide and those who test positive can go for current gold standard DXA scan. Combination of two diagnostic tools; urinary N-telopeptide with osteoporosis scores could help early identification of high risk for fracture in autoimmune diseases.

Keywords: Osteoporosis; Autoimmune Diseases; Fracture Risk Assessment (Frax); Bone mineral density (Bmd); Dual energy X-ray absorptiometry (Dexa).

Introduction

Osteoporosis is a condition characterised by decreased bone strength that culminates in an increased risk of fractures in response to minimal or low velocity force in autoimmune rheumatic diseases due to many factors; the disease itself, the age and side effect of medication used in treatment especially corticosteroid [16]. Many tools used to assess the osteoporosis in them e.g Dual-energy x-ray absorptiometry (DXA) san, is the gold standard test for diagnosing osteoporosis and monitoring its treatment [14]. It depends on the amount of x-ray energy passing through bone and

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correlates it with the amount of mineral present, so DXA is a valuable tool in assessment of quantity in bone, but it is poor assessment of quality of bone. Another important point; DXA is unquestionably a useful tool to detect early bone loss that fracture risk which can occur at any T-score [2].So; incorporation anew tool in evolution the risk of fracture in these vulnerable group based on clinical history to assess the risk factor e.g the Fracture Risk Assessment Tool (FRAX) [9]. FRAX has worldwide applicability and validation in different countries. Its calculations may be part of a DXA report, or clinicians may use web-based tools to run the calculations. It provides an intervention threshold for decision analysis. [8] it allows the use of trabecular bone score data to help calculate intervention thresholds for major and hip osteoporotic fractures [12] but it isn't validated to assess patients under the age of 40 years, may be restricted to specific geographic populations and they do not quantify factors in the calculations such as duration and amount of glucocorticoid use and the severity of secondary diseases [6]. Bone resorption markers are important indicators of disease activity in patients with osteoporosis. Urinary N-telopeptide has been used for monitoring treatment for osteoporosis for a long time [7], but now, clinicians are using it to predict the onset of osteoporosis. Urinary N-telopeptide is a sensitive and specific marker of bone resorption.

Aim of the work:

This study was conducted to validity of WHO fracture risk assessment tool (FRAX) and Dual-energy x-ray absorptiometry (DXA) scan in assessment of osteoporosis risk in autoimmune diseases. Beside assessment the role of serum Vitamin D and urinary telopeptide in predication of osteoporosis in them.

Patients and Methods

A cross sectional observational study where a total of (180) autoimmune rheumatic patients were assessed for osteoporosis during one-year duration in the rheumatology and immunology outpatient clinic, Mansoura University Hospital (MUH).

Methods

Thorough autoimmune and rheumatic history (which one, duration, line of management and disease activity at that time).Osteoporosis assessment (DXA, FRAX score assessment) and Line of management (whether anabolic or antiresorptive therapy, duration and response to prescribed medication).Serum vitamin D and uric acid and Twenty-four hours urine was collected in a sterile plastic container and sent for analysis of urinary telopeptide.

Inclusion criteria

All patients diagnosed as autoimmune rheumatic diseases patients who fulfil the criteria of definition of osteoporosis attending Rheumatology &Immunology unit in internal medicine department and outpatient's clinic during the duration of the study.

Statistical analysis

Data were entered and statistically analyzed using the Statistical Package for Social Sciences (SPSS) version 23. Qualitative data were described as numbers and percentages. Quantitative data were described as means (SD) or medians, after testing for normality by Kolmogorov-Smirnov test.

Results

Our work target about 180 Rheumatic patients with the mean age of them was 46±12.6 years old, 92.8% (167/180) were female, more than fifty 57.2 (103/180) of studied patients were RA, 33 % (60/180) were SLE and less than 10% of them were Behcet 4.4%, Scleroderma 0.6%, Sjogren syndrome 1.7%, Vascuilitis 0.6% and 2.2% PSA. Most of them 86.1% (155/180) were controlled and 67.2% (121/180) of them had no complication. Majority of studied group 77.8% (140/180) were treated with DMARDs, 89.4% (161/180) were treated with corticosteroid Table (2). The median of height of studied patients was 160 (154-165) cm, weight 85 (75-95) kg, BMI 33.7 (29.4-37.8)cm/kg2, S Uric acid 6 (5-7)ng/dl, S vitamin D 26 (13.3-32)ng/dl, urinary Telopeptide 105 (89-175) nm BCE. It was noticed that more than Fifty of studied Rheumatic patients had normal bone density, 34% had osteopenia and about 14% of them had osteoporosis Figure (1), where Lt femur neck T score -0.9 (-1.5…-0.3), Lt femur neck z score -0.6 (-1.2….0), Lt forearm T score -0.8 (-1.7….-0.1), Lt forearm Z score -0.5 (-1.3…….0.3), osteoporosis 2 (1-2), FRAX score osteoporosis % 3.7 (2.6-7.5), FRAX score hip fracture % 0.2 (0.1-0.6) and risk hip fracture 1 (1-1). The mean of BMI (10-year probability of fracture) was 33.5±6.6, lumbar spine T score -1.1±1.3 and lumbar spine Z score -1.1±1.3 Table (1). Type of Osteoporosis treatment received by our studied patients varied where Bisphosphonate was used in 47.2%, Densoumab 5%, Tripeptide 2.2% while Calcium and vitamin D supplement was used alone in 37.2% and one year duration was used in 57.8% of treated patients, two year duration in 31.1% while three year duration was only in 7.8% of them. Majority of treated patients 91.1% had stationary course, fortunately no major osteoporotic fracture in majority of them 96.1% with mild side effect in the form FHMA and hypocalcaemia in about 35.6% Table (2). With correlation of osteoporosis score with other parameter, there was highly significant negatively correlated with age, percentage of FRAX score osteoporosis and BMI (10year probability of fractur), but positively significant correlation with risk hip fracture. Weight and BMI were positively significant correlated with age, BMI (10year probability of fractur) and risk hip fracture, but significant negatively correlated with percentage of FRAX score hip fracture. S Uric acid

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was positively significant correlated with age, percentage of FRAX score osteoporosis and FRAX score hip fracture, but significant negatively correlated with osteoporosis and S. vitamin D. S. Vitamin D was significant negatively correlated with percentage of FRAX score osteoporosis and FRAX score hip fracture and S. uric acid but significant positively correlated osteoporosis. Left femur neck T score was significant negatively correlated with age, S uric acid, S vitamin D, percentage of FRAX score osteoporosis and FRAX score hip fracture, but positively significant correlated with osteoporosis and risk hip fracture. Left femur neck Z score was significant negatively correlated with S uric acid and S vitamin D, but positively significant correlated with osteoporosis. Left forearm T score was significant negatively correlated with age, S uric acid, percentage of FRAX score osteoporosis and FRAX score hip fracture, but positively significant correlated with S vitamin D, osteoporosis, risk hip fracture and BMI (10year probability of fractur). Left forearm Z score was significant negatively correlated with S uric acid, percentage of FRAX score osteoporosis and FRAX score hip fracture, but positively significant correlated with osteoporosis, S vitamin D and BMI (10year probability of fractur). Lumbar T score was significant negatively correlated with age, S uric acid, percentage of FRAX score osteoporosis and FRAX score hip fracture, but positively significant correlated with S vitamin D and osteoporosis, risk hip fracture. Lumbar Z score was significant positively correlated with age, S vitamin D, percentage of FRAX score osteoporosis and FRAX score hip fracture, but negatively significant correlated with S uric acid and risk hip fracture. Table (3)

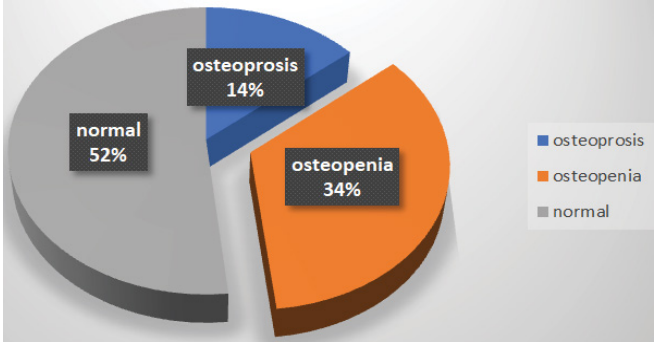

Figure 1: Percentage of osteoporosis among studied patients (n=180)

Table 1: Characteristics of studied patients (n=180):

Age	**Mean±SD**	**180**	**46.0 ± 12.6**		
Hight	Median (Q1-Q3)	180	160	154	165
weight	Median (Q1-Q3)	180	85	75	95
BMI	Median (Q1-Q3)	175	33.7	29.4	37.8
duration/years	Median (Q1-Q3)	180	5	3	8
S Uric acid	Median (Q1-Q3)	180	6	5	7
S Vit D	Median (Q1-Q3)	180	26	13.3	32
Urinary Telopeptide	Median (Q1-Q3)	180	105	89	175
LT femur neck T score	Median (Q1-Q3)	180	-0.9	-1.5	-0.3
LT femur neck Z score	Median (Q1-Q3)	170	-0.6	-1.2	0
Lt forearm T score	Median (Q1-Q3)	174	-0.8	-1.7	-0.1
Lt forearm Z score	Median (Q1-Q3)	162	-0.5	-1.3	0.3
lumbar spine T score	Mean±SD	177	-1.1 ± 1.3		
lumbar spine Z score	Mean±SD	175	-1.1 ± 1.3		
Osteoporosis	Median (Q1-Q3)	180	2	1	2
FRAX score osteoporosis %	Median (Q1-Q3)	180	3.7	2.6	7.5
FRAX score hip fracture %	Median (Q1-Q3)	180	0.2	0.1	0.6
Risk hip fracture	Median (Q1-Q3)	180	1	1	1
BMI (10year probability of fracture)	Mean±SD	180	33.5 ± 6.6		

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Table 2: demographic data of studied patients (n=180):

		n	%
Gender	Female	167	92.8
	Male	13	7.2
Rhematic disease	RA	103	57.2
	SLE	60	33.3
	Behcet	8	4.4
	Scleroderma	1	0.6
	Sjogran syndrome	3	1.7
	Vasculitis	1	0.6
	PSA	4	2.2
Controlled	Yes	155	86.1
	No	25	13.9
Complications	Yes	59	32.8
	NO	121	67.2
Medications DMARDs	Yes	140	77.8
	No	40	22.2
Corticosteroid	Yes	161	89.4
	No	19	10.6
Type of osteoporosis treatment	NO treatment	15	8.3
	Ca+Vit D	67	37.2
	Bisphosphonate	85	47.2
	Densumab	9	5
	Teripeptide	4	2.2
Duration of osteoporosis treatment	3 years	14	7.8
	2 years	56	31.1
	1 year	104	57.8
Response to osteoporosis treatment	Improved	16	8.9
	Stationary	164	91.1
	Worsen	0	0
Side effects osteoporosis treatment	FHMA	6	3.3
	pain site injection	3	1.7
	hypocalcaemia	14	7.8
	FHMA + hypocalcaemia	64	35.6
	hypocalcaemia + pain site injection	9	5
	No	84	46.7
Major osteoporotic fracture	Yes	7	3.9
	No	173	96.1

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Table 3: Correlation of osteoporosis scores: -

		Age	Osteoporosis	FRAX score osteoporosis%	FRAX score hip fracture %	BMI (10year probability of fractur)	Risk hip fracture	SUricacid	SVitD
Hight	Rho	-.214**	0.046	-.161*	-0.13	-.157*	.213**	-0.078	0.142
n=180	**P**	**0.004**	**0.543**	**0.031**	**0.082**	**0.035**	**0.004**	**0.297**	**0.057**
Weight	Rho	.187*	0.076	-0.119	-.183*	.865**	.199**	-0.069	0.124
n=180	**p value**	**0.012**	**0.314**	**0.112**	**0.014**	**0.000**	**0.007**	**0.355**	**0.098**
BMI n=180	Rho	.245**	0.095	-0.085	-.155*	.964**	.157*	-0.091	0.116
	p value	**0.001**	**0.211**	**0.264**	**0.041**	**0.000**	**0.038**	**0.229**	**0.125**
S.uric acid n= 180	Rho	.177*	-.230**	.259**	.237**	-0.055	0.066	1	-.747**
	p value	**0.017**	**0.002**	**0.000**	**0.001**	**0.463**	**0.38**		**0.000**
SvitD	Rho	-0.137	.266**	-.227**	-.223**	0.077	0.068	-.747**	1
n=180	**p value**	**0.066**	**0.000**	**0.002**	**0.003**	**0.305**	**0.365**	**0.000**	
LT femur neck T score	Rho	-.274**	.890**	-.379**	-.395**	0.047	.210**	-.245**	.299**
n=180	**p value**	**0.000**	**0.000**	**0.000**	**0.000**	**0.529**	**0.005**	**0.001**	**0.000**
LT femur neck Z score	Rho	0.015	.357**	-0.092	-0.069	-0.092	-0.024	-.343**	.299**
n=180	**p value**	**0.851**	**0.000**	**0.234**	**0.374**	**0.235**	**0.752**	**0.000**	**0.000**
Lt forearm T score	Rho	-.356**	.270**	-.443**	-.443**	.155*	.224**	-.338**	.410**
n=180	**p value**	**0.000**	**0.000**	**0.000**	**0.000**	**0.041**	**0.003**	**0.000**	**0.000**
Lt forearm Z score	Rho	-0.029	.164*	-.160*	-.157*	.167*	-0.042	-.366**	.399**
n=180	**p value**	**0.717**	**0.037**	**0.042**	**0.047**	**0.034**	**0.594**	**0.000**	**0.000**
lumbar spine T score n=180	Rho	-.193*	.259**	-.288**	-.260**	0.065	0.128	-.794**	.862**
	p value	**0.010**	**0.001**	**0.000**	**0.000**	**0.388**	**0.089**	**0.000**	**0.000**
lumbar spine Z score	Rho	.266**	0.115	.151*	.170*	-0.09	-.165*	-.620**	.661**
n=180	**p value**	**0.000**	**0.131**	**0.046**	**0.025**	**0.238**	**0.029**	**0.000**	**0.000**

Discussion

Due to impact of autoimmune diseases and medication used in management especially corticosteroid, most of them had low bone density with different degree of fracture, early predication of low bone mineral density is the main preventive tool to prevent fracture in these vulnerable group [19]. Our study revealed that half of studied autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Bechet, psoriatic arthritis (PSA), Scleroderma and Sjogren syndrome had low bone mass that in line with(Weitzmann, et al) [18] stated that rapid bone loss and increased fracture risk are implicated in a range of autoimmune diseases. The older age of studied autoimmune patients with average age of them was 46±12.6 years old that put them in high risk for osteoporosis and fracture as in agreement with (Marques A et al) who concluded that Age is a variable in all clinical risk calculators and with aging, fracture rates rise exponentially as bone density decreases. Added that fractures are less likely to occur in younger people than in older people, even with similar bone density measurements. Clinical data show that this paradox reflects age-dependent microarchitecture degradation [11]. It was noticed that S. vitamin D is low, median 6 (5-7)ng/ml that may a risk factor for low bone density in studied patients as mentioned by (Pietschmann, P et al 2016) that Osteoporotic hormones such as 1,25 dihydroxy vitamin D3 (1,25(OH)2 D3), parathyroid hormone (PTH) and prostaglandin E2 (PGE2) are responsible for upregulating expression of RANKL which represents the central process through which bone loss is regulated [13]. It was observed that usefulness of osteoporosis treatment in autoimmune studied patients with stationary course without risk of atypical fracture that in line to A 2019 meta-analysis [1] that Osteoporosis drugs produce a spectrum of changes in vertebral bone density, added that a strong correlation between improvements in BMD and greater reductions in rates of vertebral and hip fracture, reassuring practitioners of the usefulness of DXA to monitor treatment.

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Assessment of bone density can be done by different tools; DEXA scan, FRAX score for fracture risk assessment each one has advantage and disadvantage [10]. DEXA scan in autoimmune studied patients detected that osteopenia in 34%, osteoporosis 14% while the median of FRAX score osteoporosis % was 3.7 (2.6-7.5) with high risk for osteoporosis that was in consistent with (Humes, D.H et al) stated that risk of osteoporosis increases significantly in autoimmune patients with each standard deviation below peak bone mass (or 1 unit decrease in T-score), it is reported a woman's risk of fracture approximately doubles [4]. Our studied autoimmune patients had high risk of fracture according to 10-year probability of major osteoporotic fracture and 10-year probability of hip fracture based on thresholds in the USA as described in the National Osteoporosis Foundation (NOF) Clinician's Guide (Tosteson AN et al) [17] For clinical use, the International Osteoporosis Foundation proposed different markers that reflect bone metabolism or turnover, but these are not diagnostic tools for osteoporosis and are not a substitute for DXA analysis. (Eastell R et al) [8]. The N-telopeptide is specific to bone due to its unique amino acid sequence. Bone density as measured by DXA provides a static snapshot of bones and does not distinguish if bone loss is ongoing or not (Jayaram N et al). But urinary N-telopeptide is a dynamic measurement of what is happening in bone at any given time [5] The median urinary Telopeptide was high in studied autoimmune patients 105 (89-175) which is important tool in the evaluation of quality of bone and a predicator for fracture as in agreement with (Singer FR et al) [15] stated that urinary N-telopeptide can be considered as a new diagnostic tool for diagnosing osteoporosis.

Conclusion

Although urinary N-telopeptide is a valuable marker for bone metabolism and predication of risk of fracture, it is not a substitute for DXA and FRAX score. So, If we suspect osteoporosis, it is better to go for urinary N-telopeptide and those who test positive can go for current gold standard DXA scan. Thus, combination of these two diagnostic tests could be useful to improve the identification of high risk for fracture.

Limitations of our analysis: include the cross-sectional nature of the data collected, to some extant small sample size, single Centre experience and lack of long-term follow-up to evaluate the incidence of fractures.

Declarations:

DOI (Declaration of conflict of interest): Marwa A Besar, Youssef Abulatta, Mohamed Hussein and Mahmoud Abdelhadi have no conflict of interest.

Ethics approval: Ethical approval was taken by Mansoura Medical Ethics Research committee (MMERC) of faculty of Medicine, IRB Mansoura

Code number: R.22.10.1908 Date: 5/11/2022.

Human Ethics and Consent to participate: Ethical approval from the patients were taken to share their data and for publication.

Availability of data and materials: All data are confidential.

Competing interests: Marwa A Besar, Youssef Abulatta, Mohamed Hussein and Mahmoud Abdelhadi have not competing interest

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Authors' contributions

Main author; Corresponding author; (Marwa A Besar) Marwa Abo Elmaaty Besar; Lecturer of Internal medicine, Rheumatology& Immunology unit. Collected main data wrote, main paper and added supplementary data. besarmarwa@mans.edu.eg

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