The Egyptian Journal of Hospital Medicine (July 2013) Vol. 52, Page 670–677

Diagnostic and Screening Utility of Biochemical Markers for Osteoporosis and Osteopenia in Saudi Women

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ABSTRACT:

Background and aim of the work: Postmenopausal osteoporosis is a major health problem worldwide and in Saudi Arabia as it leads to bone fragility and increased liability for fragile fractures, particularly in neck of femur and vertebrae. The present study was designed to determine the value of different screening tests to find out the most sensitive serum and urinary markers of osteoporosis among Saudi women and to clarify the relationship between E_2 deficiency and these markers in peri-menopause, early or postmenopausal women without hormonal replacement therapy.

Material and methods: This study included 37 Saudi women aged 40 to 60 years. They were categorized into 3 groups according to their bone mineral density (BMD): Group I: 15 Normal control (T-score up to -1.5), Group II: 12 Osteopenic women (T-score between –1.5 to –2.5)and Group III:10 Osteoporotic women (T-score below –2.5). For all subjects, dual energy X-ray absorptiometry (DEXA) was performed. Osteocalcin (OC), alkaline phosphatase (ALP), free galactosyl hydroxylysine (Gal-Hyl), calcium (Ca), inorganic phosphorus (P) and estradiol (E_2) were measured in serum, whereas, deoxypyridinoline (Dpd) and creatinine levels were measured in urine.

Results: Simultaneously both osteopenic and osteoporotic groups showed significant decreases in BMD when compared to the controls. Osteocalcin, ALP and Gal-Hyl showed significant increase ($p<0.0001$) among the osteopenic and osteoporotic groups versus the control group. Significant decrease in E_2 levels were obvious among the osteopenic ($p<0.0001$) and osteoporotic ($p<0.0001$) women when judged against the controls. Urinary Dpd was significantly increased in the osteopenic and osteoporotic groups ($p<0.001$). In osteoporotic group, significant negative correlations were observed between OC and BMD. Positive correlations were detected among the osteoporotic group between OC and ALP and between OC and Gal-Hyl. High significant negative correlations were confirmed between E_2 and OC among both the osteopenic and the osteoporotic groups. Also, a significant negative correlation was established between E_2 and Dpd in the osteoporotic group. In comparing between osteopenic and osteoporotic groups, significant decrease was recognized in BMD and significant increase was predicted regarding ALP, ($p<0.05$), Gal-Hyl ($p<0.0001$) and Dpd ($p< 0.001$).

Conclusion: Urinary Dpd may be a simple indicator for osteoporosis in postmenopausal women; however, screening should include the measurement of serum estradiol, galactosyl hydroxylysine, alkaline phosphatase and Osteocalcin to increase the sensitivity and specificity of primary screening to identify the groups at higher risk of osteoporosis which is the keystone in prevention of disabling fragility fractures.

Keywords: Bone turnover markers, osteoporosis, postmenopausal, Saudi women.

INTRODUCTION

Twenty five per cent of Saudi Arabian women over 50 years are reported to have osteopenia and the estimated prevalence of osteoporosis is 23-34% (1, 2). Studies have revealed that large number of middle aged and elderly Saudi women is unaware of osteoporosis risk factors as low calcium intake, lack of exercise and positive family history of the disease, moreover; it was found that less than 50% of them correctly identified calcium-rich foods (3). Osteoporosis is a multi-factorial disease and the role of estrogen deficiency in production of the disease in postmenopausal women was first described in 1940 by Fuller Albright (4). Riggs (5), found that, estrogen deficiency increases bone turnover and enhances osteoclast activity. Other studies have revealed that postmenopausal estrogen

DOI:10.12816/0000605

deficiency leads to a decrease in both cortical and cancellous bone mineral density through increasing osteoclastogenic cytokine production from immune cells, decreasing osteoblast proliferation, in addition to the increase in osteoblast and osteocyte apoptosis (6-8). The use of estrogen, either with or without progesterone as hormone replacement therapy (HRT) prevents and treats postmenopausal osteoporosis and deceases liability for bone fractures, however, its routine use has been diminished as it is associated with safety and tolerability concerns as increased risk of breast cancer, heart disease and stroke (9). Recently it has been proved that, Silymarin-rich milk thistle extract (MTE) and tissue-selective estrogen complexes (TSEC) are safe and effective for treating menopausal osteoporosis without endometrial or breast stimulation (9, 10, 11).Several studies indicated that screening for bone markers might be useful for improving the assessment and management of osteoporotic women in combination with bone mass measurement (12-14). As estrogen has a key role in normal physiology of the skeleton maintaining bone mass as long as the production is sufficient, it has been shown that serum bioavailable estrogen is independent predictor for bone density in postmenopausal women (15). Biochemical markers of bone turnover reflect either the rate of bone formation or the rate of bone resorption (12). The Gal-Hyl and Dpd are considered to be sensitive and specific markers of bone resorption and can provide better clinical utility as it allows direct comparison with markers of bone formation (16).The enzyme ALP is involved in making phosphate available for calcification of bone and some enzyme leaks into the serum where it can be measured, so, it can be used as an indicator of osteoblastic activity (17). Osteoblastic activity is associated with elevated serum OC, one of the proteins found in relatively high concentration in bone (18). Bone mineral density (BMD), measured by densitometry is used for the diagnosis of osteopenia and osteoporosis and dual energy X-ray absorptiometry is the diagnostic measure of choice for osteoporosis and provides a good diagnostic sensitivity for overall fracture risk with a relatively small precision error (13, 14). The present study was designed to determine the value of different screening tests to find out the most sensitive serum and urinary markers of osteoporosis among Saudi women and to clarify the relationship between E_2 deficiency and these markers in peri-menopause, early or postmenopausal women without hormonal replacement therapy.

Material and methods: This was a prospective controlled clinical trial conducted at the King Abdul Aziz Specialist Hospital in Taif, Saudi Arabia, after approval of the ethical committee of the hospital. Thirty seven women aged between 40 and 60 years were enrolled for the study from June 2012 to January 2013. They were selected to match as much as possible the same age, marital, educational and socioeconomic status. Informed consents for undertaking the research were obtained for all women. They were subjected to the following:

A): Clinical evaluation:

I. History and general examination: Clinical evaluation comprising full medical history laying stress on manifestations of osteopenia and osteoporosis.

II. Exclusion criteria:

1. Liver, kidney, endocrinal or rheumatologic diseases.
2. Drugs affecting bone and calcium metabolism.
3. Fractures within 6 months before the time of study.
4. Immobilization.

B): Investigations:

1. Assessment of BMD was done for every subject using DEXA. The usual regions measured are the lumbar spine and femur. The percentage and T-score of BMD were estimated in antero-posterior (AP) spine and left (Lt) femur.

The studied subjects were categorized into the following three groups according to the WHO (13), classification of their BMD into:

Group I: Fifteen normal women (control); T-score up to (-1.5).

Group II: Twelve osteopenic women; T-score between (-1.5 to – 2.5).

Group III: 10 Osteoporotic women; T-score below (-2.5).

2. Biochemical studies included the following: Osteocalcin (OC), alkaline phosphatase (ALP), free galactosyl hydroxylysine (Gal-Hyl), calcium (Ca), inorganic phosphorus (P) and estradiol (E_2)were measured in serum, whereas, deoxypyridinoline (Dpd) and creatinine levels were measured in urine.

Statistical analysis: Results were expressed as mean ± standard deviation and the analyses were performed using SPSS version 15. All data were expressed as mean ± SD. Pearson and spearman's correlation test were used to correlate each parameter with different variants in the same group to differentiate between positive and negative correlations and to find significant difference.

Results: The results were demonstrated through the following tables and figures:

Table (1) demonstrates a comparison between some laboratory data for the osteopenic groups and the controls. It is evident that there is no significant difference between both groups as regards the age. While significant decreases were observed as regards bone mineral density including AP Spine BD %, AP Spine BD T score, Lt Femur BD % and Lt Femur T score. Both OC, ALP and Gal- Hyl were significantly higher among the osteopenic women when compared to the control group. Furthermore, urinary Dpd was obviously increased among the osteopenic than the controls. No significant difference between the examined two groups was noticed in Ca levels while P levels showed slight decrease among group II when compared to the control. But for the E_2 value, a significant lower level was observed among the diseased group.

Table (2): Clarifies a comparison between some laboratory data for the osteoporotic group and the controls. It is evident that there is a significant difference between both groups as regards the age. While significant decreases were observed as regards bone mineral density including AP Spine BD %, AP Spine BD T score, Lt Femur BD % and Lt Femur T score. Both OC, ALP, Gal-Hyl were significantly higher among the osteoporotic women when compared to the control group. Moreover, urinary Dpd was obviously increased among the osteoporotic than the controls. No significant differences between the examined two groups were noticed in Ca and P levels. But for the E_2 value, a significant lower level was observed among the diseased group.

Table (3): Reveales a comparison between some laboratory data for the osteopenic and the osteoporotic groups. Obviously, a significant difference was observed as regard the age between both groups. While significant differences were observed as regards bone mineral density including Ap Spine BD % and Ap Spine BD T score. Both ALP and Gal-Hyl were significantly higher among the osteoporotic women when compared to the osteopenics. In addition, urinary Dpd was clearly increased among the osteoporotic subjects. Apparently, E_2 value showed a significant lower levels among the osteoporotic group.

Figures (1, 2): illustrate the significant negative correlations between E_2 and OC in both osteopenic and osteoporotic groups respectively.

Figure (3): shows the significant negative correlations between E_2 and urinary Dpd in osteoporotic patients.

DISCUSSION

Osteoporosis is a major health care problem in Saudi Arabia especially, in postmenopausal women because of its high prevalence and its relation to fragility fractures (1, 2, 19). The incidence of these fractures in KSA particularly in vertebrae and femur has been increased from 2.9/1000 in 1999 to 6/1000 in 2007 and about 70% of the patients who were still alive remained disabled and non ambulatory (19). Proper screening and management of osteoporosis are the keystones in prevention of these disabling fragility fractures specially those of femur. Kanis *et al.* (12), reported that bone markers might be used to identify groups at higher risk of osteoporosis, predict osteoporotic (fragile) fractures in

postmenopausal women, and to monitor anti-resorptive therapy.

Biochemical markers of bone turnover allow clinicians to evaluate the risk of bone loss and provide insight into response to therapy (12, 13, 15-17).

The results of the present study revealed significant higher levels of OC in both osteopenic and osteoporotic groups compared to the controls, but no significant difference was detected between the osteopenic and the osteoporotic groups. These results agreed with that of Knapen *et al*.(20) who noticed that the serum OC level was 10% higher in postmenopausal osteoporosis. This study showed the presence of significant negative correlation between OC and BMD in osteoporotic women (OC and AP%: $r = -0.9091$ at $p< 0.001$and OC and left femur % $r = -0.9613$ at $p< 0.0001$). Thus, this came in accordance with that obtained by Chailurkit et al., (21)which might indicate that higher rates of bone turnover could be associated with more rapid bone loss in osteoporotic women.

The present study revealed a significant increase of serum ALP in both the osteopenic and osteoporotic comparing them with normal women, also a significant difference ($p<0.05$) was detected on comparing the diseased groups together. These results could be elucidated with those found by Brown et al. (22), who documented that, the increased levels of the two indices of bone turnover, ALP and OC suggested that the mean bone turnover was higher in osteoporotic women. This finding could explain the significant positive correlation between OC and ALP in the osteoporotic group ($r = 0.6937$ at $p< 0.05$). Atalay *et al.* (17), revealed in his study that serum OC levels and ALP, may be useful to monitor and follow-up osteoporotic changes that currently cannot be assessed with BMD.

Serum Gal-Hyl could be considered as a most sensitive biochemical marker of bone resorption, our results showed significant increases in both osteopenic and osteoporotic patients versus the control group. Also, a high significant increase was detected in the osteoporotic patients compared to the osteopenics ($p<0.0001$). In addition, a significant positive correlation between OC and Gal-Hyl was found in the osteoporotic women. Bettica, *et al.* (16), measured Gal-Hyl in the serum and they declared that the concentration of Gal-Hyl in both serum and urine discriminated between pre-menopausal women, pubertal girls and patients with untreated Paget's disease, concluding that; increased levels of Gal-Hyl reflects the high bone turnover.

As regards urinary Dpd, the present study demonstrated that the mean urinary Dpd level was significantly increased in osteopenic and osteoporotic women against the controls. Again, a high significant difference was obtained when comparing the osteopenic against the osteoporotic groups ($p< 0.0001$). Our data revealed a significant positive correlation between OC and Dpd ($r = 0.8817$ at $p< 0.001$). Yilmaz *et al.* (23) clarified that Dpd was significantly high in osteoporosis and its concentration increased with the severity of the disease. Bettica et al. (16), reported that bone resorption markers are more efficient than bone formation markers. They added that urinary Dpd level was more than 50% higher in postmenopausal osteoporosis than in premenopausal women.

Regarding Ca and P levels, the results of the current study revealed no significant difference in both Ca and P levels in cases of osteopenia and osteoporosis when compared to the controls. This came in accordance to the result of Yilmaz *et al.* (23) who reported that the serum Ca and P did not show any significant difference between normal and osteoporotic women. Moreover, the current data revealed a significant negative correlation between OC level and serum Ca in osteoporotic women ($r = - 0.9048$ at $p< 0.001$). These findings pointed out that the accelerated skeletal turnover rate, as shown by the high OC level was associated with a net loss of bone (21, 22).
This study showed a significant decrease in E_2 level in osteopenic and osteoporotic women when compared to the controls. Estradiol level was significantly inversely correlated with OC in both osteopenic ($r= -0.9036$ at $p< 0.0001$) and osteoporotic women ($r= - 0.7508$ at $p< 0.01$). Also, a significant negative correlation was

detected between urinary Dpd and E_2 (r= -0.8179 at $p< 0.05$) in the osteoporotic group. As well, a non-significant negative correlation was identified between Gal-Hyl and E_2 in the same group. All of these results could be explained on the fact that E_2 plays an important role not only suppressing bone resorption but also, as physiological regulators of osteoblastic activity (25). So, a very low serum E_2 level in postmenopausal women has been associated predominantly with enhanced bone resorption, measured by biochemical markers (Gal-Hyl) and to a lesser extent bone formation (12, 13, 16, 25) as well as rapid bone loss (12, 16). In conclusion; Urinary Dpd may be a simple indicator for osteoporosis in postmenopausal women; however, screening should include the measurement of serum estradiol, galactosyl hydroxylysine, alkaline phosphatase and Osteocalcin to increase the sensitivity and specificity of primary screening to identify the groups at higher risk of osteoporosis which is the keystone in prevention of disabling fragility fractures.

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Table (1):Comparison between osteopenic group and controls regarding some investigated parameters

Sub-Group / Variable	Normal (n= 15)			Osteopenic (n= 12)			*P value*
	Mean	**± SE**	**Range**	**Mean**	**±SE**	**Range**	
Age	52.27	1.4	40- 60	48.9	1.9	40 – 60	>0.05
Ap Spine BD %	101.2	2.3	86- 119	82.9	0.96	77 – 88	***<0.05***
Ap Spine BD T score	-0.09	0.23	-1.4 – 1.9	-1.8	0.1	-2.3 -1.5	***<0.001***
Lt Femur BD %	109.33	2.7	95 – 138	94.9	2.6	73- 110	***<0.001***
Lt Femur T score	.82	0.22	-0.4 – 3.2	-0.29	0.22	-2.2 – 0.8	***<0.05***
OC (ng/ml)	5.23	0.61	1.8 – 9.3	9.28	0.59	6.4 – 13.1	***<0.0001***
ALP (U/L)	209.5	6.1	178 – 255	275	5.8	257 – 331	***<0.0001***
Gal-Hyl (nmol/L)	61.18	1.2	53.4 - 70	80.25	0.95	74.1– 86.8	***<0.0001***
Calcium (mg/dl)	8.49	0.34	6.9 – 11.3	8.33	0.33	6.9 – 11.1	>0.05
Phosphorus (mg/dl)	3.45	0.19	2.2 – 4.9	3.0	0.81	2.3 – 3.5	>0.05
Dpd (nM/mMcreat.)	6.27	0.17	5.5 – 8.4	7.9	0.19	7.1- 9.4	***<0.0001***
Estradiol (pg/ml)	109.31	6	68 – 160	73.3	2.7	55 – 90	***<0.0001***

Non significant = P > 0.05 **Significant = P < 0.05**
Highly significant = P < 0.001 **Very highly significant = P < 0.0001**

Table (2): Comparison between osteoporotic group and controls regarding some investigated parameters

Sub-Group / Variable	Normal (n= 15)			Osteoporosis (n= 10)			*P value*
	Mean	**± SE**	**Range**	**Mean**	**± SE**	**Range**	
Age	52.27	1.4	40- 60	57.9	0.66	55 – 60	***<0.05***
Ap Spine BD %	101.2	2.3	86- 119	75.8	1.2	72 – 86	***<0.0001***
Ap Spine BD T score	-0.09	0.23	-1.4 – 1.9	-2.67	0.1	-3.2 - -2.5	***<0.0001***
Lt Femur BD %	109.33	2.7	95 – 138	88.2	5.1	70 – 127	***<0.001***
Lt Femur T score	.82	0.22	-0.4 – 3.2	-1.01	0.42	-2.5 – 2.2	***<0.001***
OC (ng/ml)	5.23	0.61	1.8 – 9.3	9.19	0.83	2.5 – 12.1	***<0.0001***
ALP (U/L)	209.5	6.1	178 – 255	319.5	13.3	263 – 383	***<0.0001***
Gal-Hyl (nmol/L)	61.18	1.2	53.4 - 70	110.29	1.4	103.1 – 116.8	***<0.0001***
Calcium (mg/dl)	8.49	0.34	6.9 – 11.3	8.79	0.4	7.1 – 11.1	*>0.05*
Phosphorus (mg/dl)	3.45	0.19	2.2 – 4.9	3.11	0.09	2.8 – 3.7	*>0.05*
Dpd (nM/mMcreat.)	6.27	0.17	5.5 – 8.4	11.5	0.6	8.1 – 13.5	***<0.0001***
Estradiol (pg/ml)	109.31	6	68 – 160	51.15	3.0	40 – 70	***<0.0001***

Non significant= P > 0.05 Significant = P < 0.05
Highly significant = P < 0.001 Very highly significant = P < 0.0001

Table (3): Comparison between osteopenic and osteoporotic groups regarding some investigated parameters

Sub-Group / Variable	Osteopenia (n= 12)			Osteoporosis (n= 10)			*p value*
	Mean	**± SE**	**Range**	**Mean**	**± SE**	**Range**	
Age	48.9	1.9	40 – 60	57.9	0.66	55 – 60	***<0.001***
Ap Spine BD %	82.9	0.96	77 – 88	75.8	1.2	72 – 86	***<0.001***
Ap Spine BD T score	-1.8	0.1	-2.3 - -1.5	-2.67	0.1	-3.2 - -2.5	***<0.0001***
Lt Femur BD %	94.9	2.6	73- 110	88.2	5.1	70 – 127	>0.05
Lt Femur T score	-0.29	0.22	-2.2 – 0.8	-1.01	0.42	-2.5 – 2.2	>0.05
OC (ng/ml)	9.28	0.59	6.4 – 13.1	9.19	0.83	2.5 – 12.1	>0.05
ALP (U/L)	275	5.8	257 – 331	319.5	13.3	263 – 383	***<0.05***
Gal-Hyl (nmol/L)	80.25	0.95	74.1– 86.8	110.29	1.4	103.1 – 116.8	***<0.0001***
Calcium (mg/dl)	8.33	0.33	6.9 – 11.1	8.79	0.4	7.1 – 11.1	>0.05
Phosphorus (mg/dl)	3	0.81	2.3 – 3.5	3.11	0.09	2.8 – 3.7	>0.05
Dpd (nM/mMcreat.)	7.9	0.19	7.1- 9.4	11.5	0.6	8.1 – 13.5	***<0.001***
Estradiol (pg/ml)	73.3	2.7	55 – 90	51.15	3.0	40 – 70	***<0.0001***

Non significant = P > 0.05 Significant = P < 0.05
Highly significant = P < 0.001 Very highly significant = P < 0.0001

Fig (1): Correlation between E_2 and

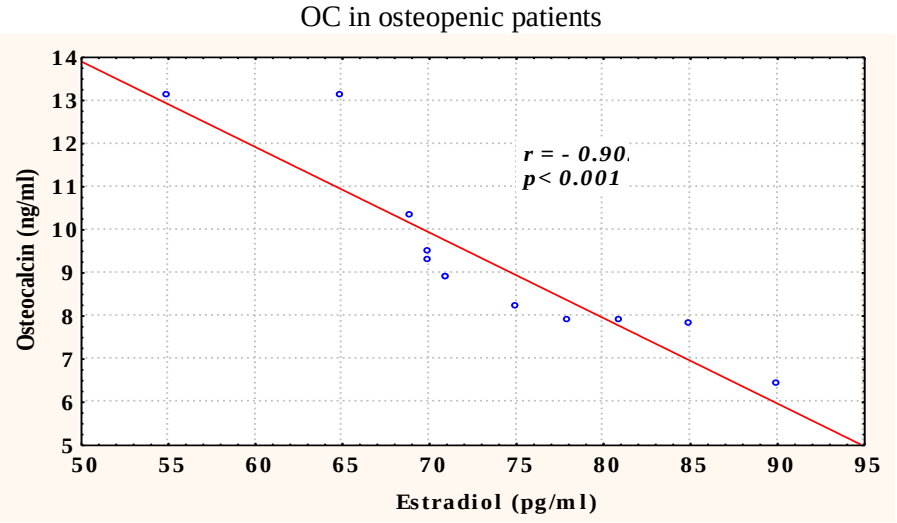

Fig (2): Correlation between E_2 and OC in osteoporotic patients

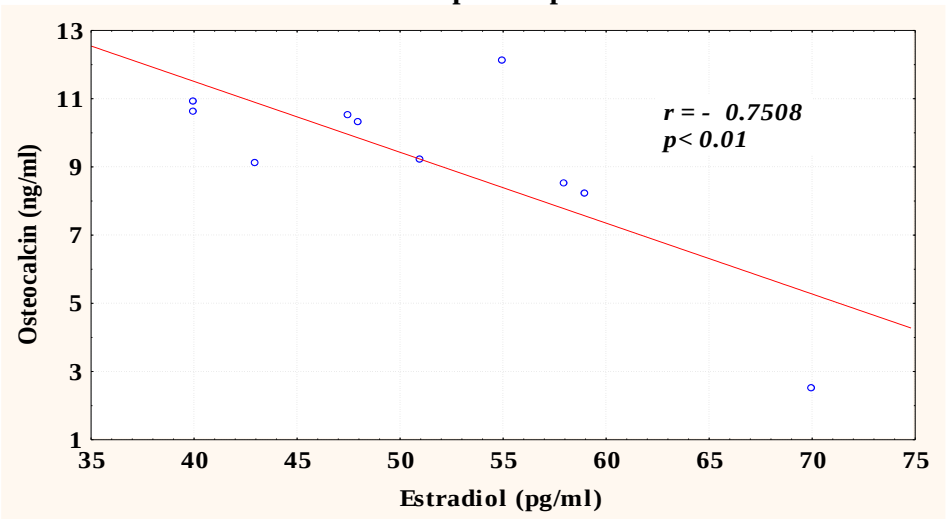

Fig (3): Correlation between E_2 and Dpd in osteoporotic patients