ASSOCIATION OF SERUM MATRIX METALLOPROTEINASE-9 (MMP-9) ENZYME WITH BONE MINERAL DENSITY (BMD) IN A SAMPLE OF IR2AQI OSTEOPOOROTIC POSTMENOPAUSAL WOMEN

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ABSTRACT

Objective: Measurement of the serum level of (MMP-9) and their association with bone mineral density (BMD) in postmenopausal women with osteoporosis.

Methods: A case-control study which included a total of 90 postmenopausal Iraqi women 45-70 years who were attending AL-Imamain AL-Kadimian and Baghdad teaching hospital, in medical city complex, Iraq. during the period between February to March 2021. subjects were divided into groups: those with osteoporosis (N=30), those with osteopenia (N=30) and those free from osteopenia and osteoporosis (N=30).

Serum levels of MMP-9 were determined using an ELISA immunological method. bone mineral density was measured by Dual-energy xray Absorptiometry (DEXA) and body mass index was calculated. The receiver operating characteristic (ROC) curve was used to evaluate the diagnostic value of MMP-9 in the detection of osteopenia and osteoporosis cases.

Results: There is significantly higher mean patient’s age in the osteopenia group (p=0.002), there was also significantly higher mean patient’s weight in the control group (p=0.018), however, there was no significant difference between the study groups regarding patient’s height and BMI. The results of BMD on the contrary of T-score showed higher levels in healthy control group versus lower levels in women with osteoporosis with a highly significant difference between the study groups (p < 0.001). Post hoc test of ANOVA also demonstrated significant differences in BMD and T-score between (control & osteopenia groups), (control & osteoporosis groups) and (osteopenia & osteoporosis groups) with p < 0.001.

The comparison of serum matrix metalloproteinase -9 (MMP-9) between the study groups show significantly higher levels in osteoporosis patients versus the healthy control group (p < 0.001). Post hoc ANOVA test of MM-9 also showed significant differences between every two groups separately (p < 0.001).

The interpretation of MMP-9 ROC curve results also demonstrated the cut-off value of osteoporosis was more than 4698 ng/L, normal bone density less than 4065 ng/L, and osteopenia present when MMP-9 levels between 4065 – 4698 ng/L.

Conclusion: The matrix metalloproteinase-9 is increased and significant predictors of osteopenia and osteoporosis at an early stage in postmenopausal women, helpful in differentiation between osteopenia and osteoporosis in postmenopausal women. The matrix metalloproteinase-9 are negatively correlated with bone mineral. The bone mineral density of postmenopausal women is affected by many factors one of them is serum zinc level.

Key words: post-menopausal Osteoporosis ,Matrix metalloproteinase -9,bone mineral density.

INTRODUCTION:

Osteoporosis (OP) is a disorder characterized by reduced bone mass, which causes bone frailty and an increased risk of fractures, particularly in the hip, spine, and wrist. Under a microscope, the bone resembles a honeycomb.
The healthy bone resembles a spongy honeycomb structure, but the gaps and spaces in the honeycomb structure in osteoporotic bone are much larger than in healthy bone (Nazia et al., 2020).

Osteoporosis is a "silent epidemic of the century" since it is not recognized until a fracture occurs (Al-Hariri M et al., 2020).

In the Western World, one in every three women over the age of 50 will suffer a fracture due to osteoporosis, and this rises to one in every two in those over the age of 60. Worldwide, osteoporosis causes more than 9 million fractures per year, implying that a fragility fracture occurs every three seconds (Borgström F et al., 2020). Osteoporotic fractures account for more hospitalizations in women than myocardial infarction, stroke, or breast cancer, and they are more costly than breast cancer (Williams SA et al., 2020). Postmenopausal osteoporosis (PMOP) is the most frequent kind of osteoporosis, characterized by decreased bone mineral density (BMD), skeletal microstructure disintegration, increased bone fragility, and susceptibility to fracture (Pouillès et al., 2021). Reduced estrogen levels enhance the homeostatic imbalance of the bone remodeling process, resulting in increased bone resorption, deterioration of the microarchitecture, loss of bone mass, and increased expression of matrix metalloproteinases. This is referred to as osteopenia. This can lead to osteoporosis and structural failure (Pontes et al., 2019). Some research has shown that matrix metalloproteinases (MMPs) play a role in the occurrence and progression of OP (Filipović T et al., 2020; Kodama et al., 2018). MMPs are an important family of zinc-dependent endopeptidases that are responsible for the degradation or resorption of all Extracellular matrix (ECM) components (Filipović T et al., 2020; Paiva KBS et al., 2017). They play important roles in ECM remodeling, bone development, and osteoclast bone resorption. MMPs are required for early bone resorption because they break down the collagen layer of the bone surface before demineralization (Filipović T et al., 2020; Zheng X et al., 2018).

Matrix metalloproteinase -9 (MMP-9), which has a high specific degrading activity for denatured collagen in the ECM, is highly expressed in osteoclasts and may play a role in osteoclast implantation and bone-resorbing activity (Filipović T et al., 2020).

This finding suggests that MMP-9 play important roles in bone resorption and formation, and that serum concentrations of these enzymes may be negatively correlated with BMD in osteoporotic women, serving as a biochemical marker for the diagnosis of postmenopausal osteoporosis.

The aim of this study:

1 - Estimate the concentration of MMP-9 in osteopenic, osteoporotic women, and healthy postmenopausal women.

2- To assess whether the level of MMP-9 is significantly effective in the diagnosis of osteopenia and osteoporosis and differentiation between both which can be of great help in diagnosis and treatment to decrease c

3- Assess the concentration of MMP-9 and its correlation with bone mineral density in postmenopausal women with osteopenia and osteoporosis

Patients and method:

A case-control study which included a total of 90 postmenopausal Iraqi women 45-70 years who were attending AL-Imamain AL-Kadimian and Baghdad teaching hospital, in medical city complex, Iraq during the period between February to March 2021. subjects were divided into three groups, The study is approved by the institutional review board of medicine college / Al-Nahrain university.

Grouping of Patients:

According to the T-score for bone mineral density obtained from the DEXA scan, we divided the patients into three groups:

- Group, I consist of 30 postmenopausal women with osteoporosis (T-score < -2.5 standard deviations or more below).

- Group, II consists of 30 postmenopausal women with osteopenia (T score between -1 and -2.5).

- Group III 30 post-menopausal women free from osteoporosis and osteopenia (T score > -1 and above).
**Inclusion criteria:** The postmenopausal women 45-70 years having osteoporosis and osteopenia diagnosed by DEXA scan according to T-score value at the lumbar spine (L1-L4).

**Exclusion criteria:** The patients with oligo menorrhea or amenorrhea before the age of 40 years or early menopause, previous history of osteoporotic fracture, Hyperparathyroidism, corticosteroid therapy applied longer than 3 months, hormonal therapy, liver and kidney dysfunction, rheumatoid arthritis, malignant tumors, hematologic diseases, and previous pathological fractures, Myocardial infarction.

**Blood sample collection and storage:**
All blood samples were collected from AL-Imamain AL-Kadimian and Baghdad teaching hospital in the medical city complex.
1. Five to ten milliliters of venous blood had taken from all participants which were placed in normal gel, tubes were left for 20 minutes at room temperature.
2. after clot formation, centrifugation had undergone at 3800 x g for 20 min to obtain serum.
3. the separated serum had then immediately stored at -40ºC in capped labeled aliquot to analyze them later for measurement of MMP-9 was determined using an ELISA immunological method.

**Methods**

**Calculation of body mass index (BMI)**
Calculation of BMI was done by dividing the body weight in (kilograms) by the height squared (in meters): 
\[ \text{BMI} = \frac{\text{Mass (kg)}}{\text{height (m)}^2} \]

**Bone mineral density measurements**
Dual-energy x-ray Absorptiometry (DEXA, DXA, Rarely also called QDR, DPX, DER) today DEXA is the most completely developed, reliable, and popular method in use, the “gold standard”. the skeletal site is exposed to two x-ray beams of different intensities, and the mineral content of the bone is calculated using computer programs from the amount of radiation. using the results of two measurements, the effect of soft tissue components (different quantities of muscle and fatty tissue) can be calculated and discarded. the hip joint and lumbar spine are routinely measured from the front (AP) or the side (lateral). In this study, BMD was measured from lumbar spine L1-L4.

**Determination of serum human MMP-9/Gelatinase A (Matrix metalloproteinase 9/Gelatinase A) by ELISA technique**
(MMP-9) was determined using the enzyme-linked immunosorbent assay (ELISA) according to the manufacturer’s recommendations.

Briefly principle of measuring Total serum matrix metalloproteinase enzyme9(MMP9) using an Enzyme-Linked Immunosorbent Assay kit (ELISA kit)( BT LAB/china). The plate has been pre-coated with a Human MMP-9 antibody. MMP-9 present in the sample was added and binds to antibodies coated on the wells. And then biotinylated human MMP-9 Antibody was added and binds to MMP-9 in the sample. Then Streptavidin-HRP was added and binds to the Biotinylated MMP-9 antibody. After incubation unbound StreptavidinHRP was washed away during a washing step. The substrate solution was then added and color developed in proportion to the amount of human MMP-9. The reaction was terminated by the addition of acidic stop solution and absorbance was measured at 450 nm using a microplate reader (Biotek-USA). The OD values were then plotted on the standard curve for evaluation of MMP-9 concentrations.

**Statistics**
The data were analyzed using Statistical Package for Social Sciences (SPSS) version 23.0 and Microsoft office 2007. Statistical data including mean and standard deviation were measured to describe the variables. The groups were compared by applying analysis of variance ANOVA (between three groups) and post hoc tukey test (between each 2 groups within ANOVA) and the degree of association between continuous variables was calculated by Pearson’s correlation coefficient (r). The cut off value, sensitivity and specificity were calculated.
by applying Receiver operative characteristics (ROC) curve and the results were considered statistically significant when p value was less than 0.05.

II. RESULTS:

Comparison of demographic features between the study groups

The comparison of the demographic features between control, osteopenia, and osteoporosis groups were illustrated in table 1-1 and figure 1-1. According to the results there were significantly higher mean patient’s age in osteopenia group (p=0.002), there was also significantly higher mean patient’s weight in control group (p=0.018), however there was no significant difference between the study groups regarding patient’s height and BMI.

Table 1-1: Comparison of demographic features between the study groups

<table>
<thead>
<tr>
<th>p value</th>
<th>Osteoporosis group (Mean ± SD)</th>
<th>Osteopenia group (Mean ± SD)</th>
<th>Control group (Mean ± SD)</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.002*</td>
<td>57.53 ± 8.27</td>
<td>59.72 ± 10.53</td>
<td>52.31 ± 4.74</td>
<td>Age (years)</td>
</tr>
<tr>
<td>0.018*</td>
<td>78.2 ± 13.4</td>
<td>79.21 ± 19.02</td>
<td>88.11 ± 16.9</td>
<td>Weight(Kg)</td>
</tr>
<tr>
<td>0.140</td>
<td>157.5 ± 5.76</td>
<td>156.8 ± 5.92</td>
<td>159.80 ± 6.31</td>
<td>Height(cm)</td>
</tr>
<tr>
<td>0.190</td>
<td>31.50 ± 5.13</td>
<td>32.63 ± 7.49</td>
<td>34.54 ± 6.75</td>
<td>BMI (Kg/m²)</td>
</tr>
</tbody>
</table>

SD: Standard deviation; BMI: Body mass index;*:p value less than 0.05(significant)

Comparison of bone mineral density (BMD) and T-score between the study groups

Bone mineral density (BMD) and T-score were evaluated and compared between the study groups with dual energy x-ray absorptiometry of the lumber spines. The results of BMD on the contrary of T-score showed higher levels in healthy control group versus lower levels in women with osteoporosis with highly significant difference between the study groups (p < 0.001) as demonstrated in table 1-2 and figure 1-2. Post hoc test of ANOVA also
demonstrated significant differences in BMD and T-score between (control & osteopenia groups), (control & osteoporosis groups) and (osteopenia & osteoporosis groups) with \( p < 0.001 \) as presented in table 1-3.

Table 1-2: Comparison of BMD & T-score between the study groups

<table>
<thead>
<tr>
<th>p value</th>
<th>Osteoporosis group (Mean ± SD)</th>
<th>Osteopenia group (Mean ± SD)</th>
<th>Control group (Mean ± SD)</th>
<th>Lumber spines BMD (g/cm²)</th>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.001*</td>
<td>0.72 ± 0.08</td>
<td>0.86 ± 0.04</td>
<td>1.05 ± 0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.001*</td>
<td>-2.94 ± 0.68</td>
<td>-1.77 ± 0.35</td>
<td>-0.142 ± 0.48</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD: Standard deviation ;*:p value less than 0.05 (significant).

Table 1-3: Post hoc ANOVA test of BMD & T-score

<table>
<thead>
<tr>
<th>p value</th>
<th>BMD &amp; T-score between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.001*</td>
<td>Osteopenia</td>
</tr>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>&lt; 0.001*</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>&lt; 0.001*</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td></td>
<td>Osteopenia</td>
</tr>
</tbody>
</table>

*:p value less than 0.05 (significant).

Figure 1-2: Comparison of BMD between the study groups

Comparison of serum matrix metalloproteinase-9 (MMP-9) between the study groups

The comparison of serum matrix metalloproteinase-9 (MMP-9) between the study groups was illustrated in table 1-4. According to the results, there were significantly higher levels in osteoporosis patients versus healthy control group (\( p < 0.001 \)). Post hoc ANOVA test of serum MM-9 was also presented in table 1-5, accordingly, there were also significant differences between each two groups separately (\( p < 0.001 \)).
serum matrix metalloproteinase-9 (MMP-9) as a predictor of osteoporosis diagnosis

Receiver Operative Characteristic curve (ROC curve) has been used to calculate the serum MMP-9 cut-off values as a predictor of diagnosis of osteoporosis with acceptable sensitivity, specificity, and accuracy. The results were demonstrated in table 1-6, table 1-7, figure1-3,figure1-4.

The interpretation of MMP-9 ROC curve results also demonstrated cut off value of osteoporosis was more than 4698 ng/L, normal bone density less than 4065 ng/L, and osteopenia present when MMP-9 levels between 4065 – 4698 ng/L.

<table>
<thead>
<tr>
<th>Cut off value (ng/L)</th>
<th>Accuracy</th>
<th>Area under curve</th>
<th>Specificity</th>
<th>Sensitivity</th>
<th>ROC of MMP9</th>
</tr>
</thead>
<tbody>
<tr>
<td>4065</td>
<td>86%</td>
<td>0.856</td>
<td>86%</td>
<td>86%</td>
<td>Control &amp; Osteopenia</td>
</tr>
<tr>
<td>4698</td>
<td>88%</td>
<td>0.876</td>
<td>93%</td>
<td>83%</td>
<td>Osteopenia &amp; Osteoporosis</td>
</tr>
</tbody>
</table>

Table 1-7: Diagnostic levels of MMP-2 & MMP-9 in control, osteopenia & osteoporosis

<table>
<thead>
<tr>
<th>MMP-9 diagnostic levels (ng/L)</th>
<th>Group of women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 4065</td>
<td>Control</td>
</tr>
<tr>
<td>4065 – 4698</td>
<td>Osteopenia</td>
</tr>
<tr>
<td>More than 4698</td>
<td>Osteoporosis</td>
</tr>
</tbody>
</table>
Correlations between bone mineral density and MMP-9 with patient’s parameters in osteoporosis group

- Significant negative correlation between BMD and MMP-9
  
  \( r = -0.677 \& \ p < 0.001 \).

- Significant positive correlation between BMD and T-score
  
  \( r = 0.998 \& \ p < 0.001 \).

- Significant negative correlation between MMP-9 and T-score
  
  \( r = -0.677 \& \ p < 0.001 \).
Osteoporosis is a significant metabolic disorder of bones manifested by low bone mass, abnormal changes in microstructure of bones, and higher bone fragility. Patients with osteoporosis commonly presented with long-duration pain, higher chance of fractures, low quality of life, and high mortality rates (Mediati et al., 2014; Roth et al., 2010). Although dual energy X-ray absorptiometry is recently the gold standard diagnostic technique for measuring bone mineral density with high accuracy in detection of osteoporosis, most osteoporosis cases, especially at an earlier stage and do not include within the diagnostic definition of osteoporosis regarding bone mineral density value (McCormick, 2007). For that, searching for valid and low-cost markers predicting osteoporosis at an early stage is essential in designing preventive programs of osteoporosis specifically among high-risk groups like postmenopausal women (Wang et al., 2017).

Metalloproteinase-9 and osteopenia

The current study found that mean serum matrix metalloproteinase-9 (MMP-9) of postmenopausal women with osteopenia was significantly higher in comparison to controls (p<0.001). This finding is consistent with results of Khalil et al (2019) study in Egypt which reported that serum MMP-9 could be a significant marker for osteopenia among patients with obstructive pulmonary diseases. The matrix metalloproteinase-9 has ability in degradation activity of abnormal collagens in the extracellular matrix. It also divided the elastin and native type IV, V, XI collagens, but not non-native type I collagen, proteoglycan, or laminins (Shimokawa et al., 2002). Despite the important role of MMP-9 in different biological and physiological activities regarding development and remodeling of bones, there was also higher interest in its role in other pathological abnormalities like chronic inflammatory disorders and cancers (Breuer et al., 2005).

Metalloproteinase-9 and osteoporosis

In present study, the mean serum matrix metalloproteinase-9 of postmenopausal women with osteoporosis was significantly higher in comparison to controls (p<0.001). This finding is in agreement with many literatures such as Paiva and Grigoryan (2017) study in Brazil and Liang et al (2016) study in Australia which all documented that serum MMP-9 is increased among postmenopausal women with osteoporosis. In animal study on rats carried out by Grigoryan et al (2017) in Bulgaria found a significantly higher level of matrix metalloproteinase-9 among animals with bone osteoporosis that could help in predicting osteoclast activity. Although different researches detecting higher levels of serum metalloproteinase-9 in atherosclerotic disorders (Silvello et al., 2014) or in osteoclastogenesis and osteoporosis (Kim et al., 2016), some researchers few studies documented that MMP-9 level could be predictive for abnormal pathology of both two diseases (Azevedo et al., 2018).

Metalloproteinase-9 between osteopenia and osteoporosis

III. DISCUSSION:

Osteoporosis is a significant metabolic disorder of bones manifested by low bone mass, abnormal changes in microstructure of bones, and higher bone fragility. Patients with osteoporosis commonly presented with long-duration pain, higher chance of fractures, low quality of life, and high mortality rates (Mediati et al., 2014; Roth et al., 2010). Although dual energy X-ray absorptiometry is recently the gold standard diagnostic technique for measuring bone mineral density with high accuracy in detection of osteoporosis, most osteoporosis cases, especially at an earlier stage and do not include within the diagnostic definition of osteoporosis regarding bone mineral density value (McCormick, 2007). For that, searching for valid and low-cost markers predicting osteoporosis at an early stage is essential in designing preventive programs of osteoporosis specifically among high-risk groups like postmenopausal women (Wang et al., 2017).
The present study revealed that mean serum matrix metalloproteinase-9 of postmenopausal women with osteoporosis was significantly higher in comparison to osteopenia (p<0.001). This finding is similar to results of Bolton et al (2009) study in UK which reported higher mean of serum matrix metalloproteinase-9 among patients with osteoporosis as compared to osteopenia. The osteoporosis is acquired during postmenopausal period gradually after menopause without definite cutoff value detecting early stage of osteoporosis. The World Health Organization (WHO) classification of osteoporosis by bone mineral density T score is helpful in clinical diagnosis and evaluation of treatment response for osteoporotic patients (McCormick, 2007). Despite that, the bone mineral density T score is not sensitive for detecting patients at high risk of osteoporosis, or patients at early stages (Wang et al., 2017). Our study also revealed that levels of serum matrix metalloproteinase-9 are helpful in differentiation between postmenopausal women with osteopenia and women with osteoporosis.

Validity of MMP-9 in diagnosis of osteopenia and osteoporosis

Current study showed that an appropriate cutoff value of serum MMP-9 in diagnosis of osteopenia was (4065 ng/L; AUC=0.85) with accuracy of (86%), while the appropriate cutoff value of serum MMP-9 in diagnosis of osteoporosis was (4698 ng/L; AUC=0.87) with accuracy of (88%). These findings are close to results of Bolton et al (2009) study in UK and Kochetkova et al (2012) study in Russia. The explanation in relationship between MMP-9 and osteoporosis might be due to fact that MMP-9 is important in osteoblast differentiation in the initial phase of osteogenesis and its level increased at earlier stages of osteoporosis and negatively correlated with BMD (Filanti, et al., 2000).

Our study is the first national study discussing the cutoff values of serum MMP-9 in differentiation between normal and osteoporotic.

postmenopausal women and in differentiation between osteopenia and osteoporosis with lack of published national articles on these subjects. Generally, the osteopenia is considered with low bone density, while osteoporosis is considered with low bone density and destructed bone tissue architecture (Coleman et al., 2014). Many authors reported some serum biomarkers of bone formation or resorption used for diagnosis of osteoporosis and differentiation from osteopenia which are characterized by simplicity and cost-effectiveness as compared to bone mineral density measurement (Vasikaran et al., 2011; Vasikaran et al., 2014; Chubb et al., 2015). Our study findings are also close to results of Zheng et al (2018) animal study in China which revealed that serum matrix metalloproteinase-2, 9 and 13 levels are responsible in regulation of osteoporosis and the serum matrix metalloproteinase-9 level is an important predictor of osteoporosis diagnosis and in differentiation between osteopenia and osteoporosis.

Patients characteristics and bone mineral density

This study showed that postmenopausal women with osteopenia were significantly older in age (p=0.002). This finding is consistent with results of Demontiero et al (2012) study in Australia which reported that the bone loss is related to aging of both men and women. Inconsistently, a recent Iraqi study carried out by Al-Rukabi et al (2020) found that aging the common risk factor for osteopenia and osteoporosis among postmenopausal women and the women with osteoporosis were significantly older in age than women with osteopenia. This inconsistency might be attributed to differences in study methodology and inclusion criteria between different studies. Our study also found that weight of postmenopausal women with osteoporosis was significantly lower than controls (p=0.01), while no significant differences were observed regarding height and BMI. These findings are in agreement with results of Riedt et al (2005) study in USA which found a significant association between weight loss and bone loss among postmenopausal women in some sites. However, Saarelainen et al (2012) study in Finland found no significant differences in BMI between normal and osteoporotic postmenopausal women and they just detected a delay in bone loss among obese women that is related to delayed x-ray response caused by fat.

Bone mineral density in study groups

This study revealed a significantly decline in means of bone mineral density of lumbar spine and T-score among postmenopausal women with osteoporosis as compared to women with osteopenia and healthy women (p<0.001). This finding is consistent with many literatures such as Almajeed and Hamdan study in Iraq and Cranney et al (2007) cohort study in Canada which all reported that according to WHO criteria, the bone mineral density of lumbar spine and T-score was significantly decreased among postmenopausal women.
IV. CONCLUSIONS

According to the findings reported in the present study, the following can be concluded:

1. The matrix metalloproteinase-9 are increased and significant predictors of osteopenia and osteoporosis at early stage in postmenopausal women.

2. The matrix metalloproteinase-9 are helpful in differentiation between osteopenia and osteoporosis in postmenopausal women.

3. The matrix metalloproteinase-9 are negatively correlated with bone mineral density.

Recommendations:

1. We recommend another Study on the enzyme MMP-9 level with Tissue Inhibitor of Metalloproteinase-1 (TIMP-1) level in post-menopausal women with osteoporosis for diagnosis and follow-up of osteoporosis.

2. Make future intervention study on women with osteoporosis taking medical treatment to access if these markers can be used for follow up of patient response to medical treatment and by this we can decrease the use of DEXA and measure the effectiveness of a drug on osteoporotic postmenopausal women by making follow up based on a careful evaluation of serum MMP-9 levels after taking the drug.

3. Study the enzyme MMP9 for patients with other diseases such as breast cancer.

4. Emphasis on screening programs for postmenopausal women at high risk such as elderly age women.

5. Further national large sized multi-centers studies on role of matrix metalloproteinase in prediction of osteoporosis.

6. Encouraging physicians to adopt the matrix metalloproteinase in screening and diagnosis of osteopenia, osteoporosis in postmenopausal women at earlier stages to adopt protocols of treatment and decrease fracture risk.

REFERENCES


