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The Dual Role of Dickkopf-1 and Other Parameters in Postmenopausal Women with Osteoporosis

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ABSTRACT

Osteoporosis is a silent disease because bone loss occurs without symptoms, this disease is regarded one of the most health problems for women at menopause, it results in rapid loss of bone density. this research included a case-control study to know the prevalence of osteoporosis in Iraqi menopausal women. One hundred women patients visit Al-Sader teaching hospital in AL-Najaf province /Iraq to determine the percentage of bone density using a dual-energy x-ray absorptiometry (DEXA), Blood samples were taken after diagnosis of the disease. In addition, serum calcium, and phosphorous were measured by spectrophotometer, while serum (PTH, and Dkkopf_1) were measured by enzyme-linked immune sorbent assay (ELISA). Data were gathered by direct interviews with the women. The study excluded those who had chronic diseases. This study showed a significant increase ($p < 0.05$) in the concentration of Dkkopf_1 and a reduction in the concentration of serum calcium and phosphorus in osteopenia and osteoporotic menopausal women compared with control group. The current study also showed a significant increase ($p < 0.05$) in the levels of parathyroid hormone in menopausal women with osteoporosis compared with control group. In conclusion, increasing serum (Dkkopf_1) levels in postmenopausal women with osteoporosis play an important role in the development of primary osteoporosis.

INTRODUCTION

Osteoporosis is a systematic bone disease characterized by low bone mass and deterioration of micro architecture of the bone, leading to bone fragility and eventually fractures (Shaki, *et al.*,2018). It may occur in both men and women, but it is more common and begins somewhat earlier in women, Osteoporosis usually remains a completely asymptomatic process until a bone breaks. There are several types of osteoporosis. The most common is postmenopausal osteoporosis, which physicians call type I osteoporosis. Less common is senile osteoporosis, called type II osteoporosis by physicians. In addition, many diseases and drugs can cause osteoporosis, called secondary osteoporosis. Types I and II osteoporosis are diseases of aging (Sodeman, 2005). Bone mineral density (BMD) parameter is used to express the amount of mineral matter per square centimeter at different bone segments, usually forearm, lumber spine and femur (Vezzoli, *et al.*,2017). The most commonly used method of measuring bone density is dual-energy X-ray absorptiometry (DEXA). Dkkopf_1 (DKK_1): is an important secreted inhibitor of Wnt signaling, DKK-1 is expressed in various organs and by several cell types, although osteoprogenitors appear to contribute mostly to systemic DKK-1 levels (Colditz, *et al.*,2019).

It binds to lipoprotein receptor-related protein (LRP) 5/6 receptor blocking the interaction with Wnt proteins and leading to beta-catenin degradation. In bone tissue the lack of translocation of beta-catenin into the nucleus impairs the activation of osteoblast-related genes (Runx2, osteocalcin, and osteoprotegerin), leading to reduced osteoblastogenesis and low bone mass (Lerner & Ohlsson, 2015). Additionally, calcium and phosphate metabolism is tightly bound together hence, an inadequate intake dietary can develop osteoporosis (Al-Azzawi, 2022).

MATERIALS AND METHODS

This study was conducted in Al-Sader teaching hospital in AL-Najaf province from the DEXA unit in the Radiology Department and Fractures and Joints Department. Serum specimens were collected from (n=100) postmenopausal women patients with osteopenia and osteoporosis in addition to control group.

Selection of Patients and Controls Groups:

The medical histories of all the women who participated in the study were evaluated with name, age, body weight, height, as well as history of chronic disease and history of drug use. a selected sample was (n=100) woman, (n=35) who was referred for investigation osteoporosis and (n=35) osteopenia by using DEXA measurement. The age of studied menopausal women patients start from (50) to age (≤ 65) years old.

Collection of Blood Sample:

Five milliliters of blood were taken from a vein using sterile syringes. **Serum:** Samples were placed in a labelled gel tube to enable blood clotting at room temperature for 10 minutes. The samples were centrifuged at 6000 rpm for 15 minutes, and then serum was separated and stored at -80°C until time for performed the laboratory analysis for the study.

Dual Energy X-ray Absorptiometry (DEXA):

Osteoporosis was diagnosed

according to world health organization (WHO) guidelines criteria for the diagnosis of osteoporosis (Kanis, *et al.*, 2008). The test requires only 5 to 15 minutes to complete, the patients' exposition to very lower radiation and is quite accurate. BMD of the patient has contracted, the average peak bone mineral density of healthy young adults of the same race and sex. This score is called the "T-score," and it expresses the bone mineral density in terms of the number of standard deviations (SD) below peak young adult bone mass.

- Osteoporosis: T-score ≤ -2.5 standard deviations below the mean value of peak bone mass.
- Severe osteoporosis: T-score ≤ -2.5 standard deviations below the mean value of peak bone mass plus the presence of at least one fracture.
- Osteopenia: Is a bone mineral density T-score between -1 and -2.5 standard deviations below the mean value of peak bone mass.
- Normal bone density: a BMD less than -1 standard deviation below the mean value of peak bone mass.

Statistical Analysis:

One way ANOVA test was used to study the correlation between biochemical and the advanced stage of osteoporosis. P-value was considered statistically significant if (<0.05). These data have been analyzed by the use of a statistical (SPSS v. 24).

RESULTS

The comparisons of data from a DEXA scan are reported as age, BMD and T-scores; between the osteoporosis, osteopenia and healthy groups in postmenopausal women: The mean values and the standard deviation of the age and bone mineral density (BMD) are shown in the Table (1) below revealed a significant decrease ($p < 0.05$) in (70) postmenopausal women compared to (30) healthy women. while the mean value and standard deviation of T-score recorded a significant increase ($p < 0.001$) between postmenopausal patients compared to healthy women.

Table 1: Comparisons of age, bone mineral density and T-score between postmenopausal women with osteoporosis, osteopenia and healthy group.

Group Parameter	Mean ±S.D.			P .value
	Osteoporosis n=35	Osteopenia n=35	Control n=30	
Age (Yrs.)	62.9± 6.9	58.53 ± 7.8	54.2 ± 7.25	0.009
BMD(g/cm2)	0.65± 0.43	0.80 ± 0.04	0.97 ± 0.085	< 0.001
T-score	-3.06± 0.69	-1.82±0.23	0.05± 0.82	< 0.001

S.D.: Standered deviation; Significant (p-value ≤ 0.05); Non-significant (p-value ≥ 0.05); BMI: Body mass index; BMD: Bone mineral density.

Study of the Biomarkers for Diagnostic Characteristics of Osteoporosis:

Both osteoporosis and osteopenia are considered dangerous indicators, as they lead to fractures and other complications that may lead to death (Tomasevic -Todorovic, *et al.*, 2018). In addition to the DEXA scan method, osteoporosis is clinically confirmed by several methods including measurement of some parameters such as (Dickkopf 1) and parathyroid hormone (PTH) as well as

biochemical parameters including calcium and phosphorus.

Comparison of Biomarkers in Postmenopausal Women with Osteoporosis, Osteopenia and Control Group:

The results in Table (2) exhibited a significant increase (p<0.001) in serum levels of DKK1, PTH and a significant decrease in serum calcium and phosphorus.

Table 2: Comparison of biomarkers in postmenopausal women with osteoporosis, osteopenia and control group.

Aspect Groups	Mean ±S.D.			P .value
	Osteoporosis n=35	Osteopenia n=35	Control n=30	
DKK-1 (ng/ml)	95.02 ± 47.18	57.71± 3.63	32.16±8.31	< 0.001
PTH (pg/ml)	80.44 ± 2.48	70.02± 2.51	60.08±1.64	< 0.001
Ca++ (mg/dl)	4.4 ± 0.88	7.3± 0.48	9.5±0.64	< 0.001
Po4 (mg/dl)	2.3 ± 0.36	2.9± 0.38	3.5±0.77	< 0.001

Significant (p-value ≤ 0.05); Non-significant (p-value ≥ 0.05) DKK: Dickkopf_1 , PTH :parathyroid hormone ,ca :calcium , po4: phosphorus.

DISCUSSION

Dickkopf-1 (DKK1) is a reliable Wnt inhibitor, which binds to the (LRP5/6) and thereby blocks further interactions with Wnt ligands (Bhat, *et al.*, 2007). DKK1 overexpression in osteoblasts causes osteopenia and inhibits fracture repair (Pinzone, *et al.*,2009). Morvan, *et al.*, (2006) estimated that by blocking Wnt signaling, DKK1 negatively regulates osteoblast differentiation and function, and it stimulates osteoclastogenesis indirectly via the increased production of RANKL and lower production of osteoprotegerin (OPG) in osteoblasts. Thus, DKK1 is a potent negative

according to (Tariq, *et al.*,2019). We found a better negative correlation (r= -0.368) between serum DKK1 and lumbar BMD due to age in postmenopausal women. We also recorded a positive correlation (r= 0.499) between age and DKK1.

Calcium and phosphorus are the strongest predictors of T-score in postmenopausal normal women.

Correlation Study:

• Figure (1), indicated that there was a significant negative correlation(r= -0.805) between calcium and PTH concentrations in postmenopausal women.

- Figure (2), indicated that there was a significant negative correlation($r= -0.368$) between BMD and DKK1 concentrations in postmenopausal women.
- Figure (3) indicated that there was a significant positive correlation($r=0.499$) between age and DKK1 concentrations in postmenopausal women.
- Figure (3) indicated that there was a significant negative correlation($r= -0.363$) between BMD and age in postmenopausal women.

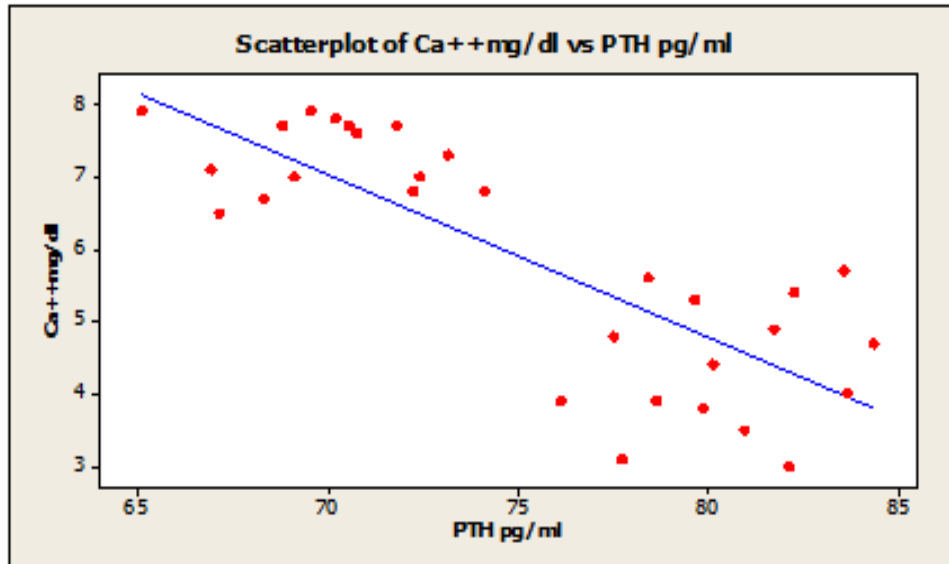


Fig.1: Correlation between serum calcium and PTH levels in (osteopenia, osteoporosis) postmenopausal women.

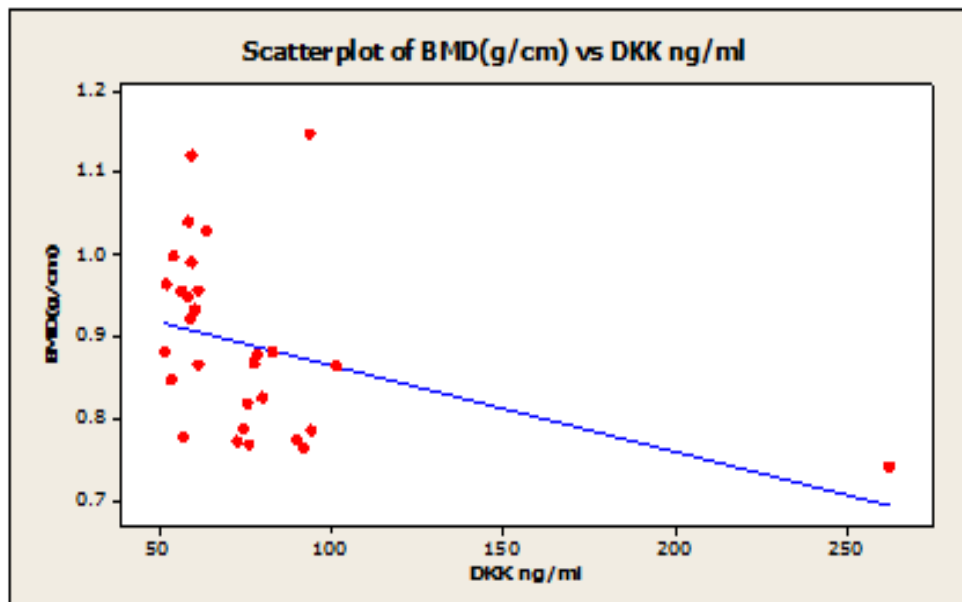


Fig. 2: Correlation between BMD and DKK1 in (osteopenia, osteoporosis) postmenopausal women.

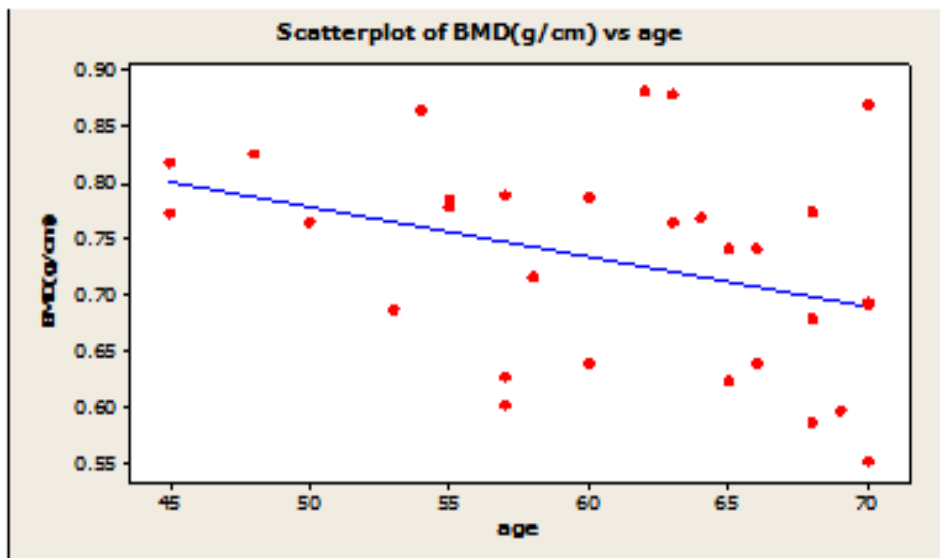


Fig. 3: Correlation between BMD and age in (osteopenia, osteoporosis) postmenopausal women.

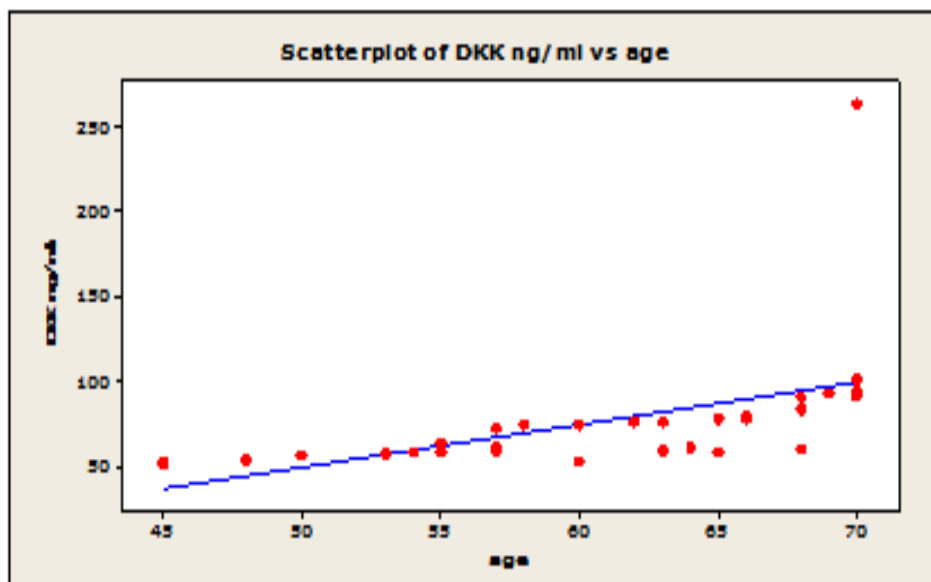


Fig. 4: Correlation between DKK1 and age in (osteopenia, osteoporosis) postmenopausal women.

CONCLUSION

Postmenopausal women with significantly increased serum DKK1 had more significant osteoporosis in the lumbar spine as detected by DEXA scan, Prolonged duration of menopause and increased serum DKK1 are important risk factors for the development and severity of osteoporosis.

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