ISSN: 0067-2904

Assessment of Dickkopf Related Protein1 Levels in Iraqi Women Patients with Osteoporosis

Mawj S. Ibrahim *, Namir I. A. Haddad
Department of chemistry, College of Sciences, University of Baghdad, Baghdad, Iraq

Received: 16/4/2025 Accepted: 6/ 10/2025 Published: 30/ 8/2026

Abstract

Osteopenia and osteoporosis are systemic skeletal disorders characterized by low bone mass and microarchitectural deterioration of bone tissue. Osteoporosis is a silent disease characterized by rapid bone loss, often without noticeable symptoms. A key regulator of this process is Dickkopf-related protein 1 (DKK1), a secreted glycoprotein encoded by the DKK1 gene in humans. It plays a crucial role as an antagonist of the Wnt/β-catenin signaling pathway. DKK1 is a critical regulator in osteoporosis, primarily by inhibiting Wnt signaling, which is essential for osteoblast function and bone formation. This study aims to evaluate DKK1 levels and other biochemical parameters in Iraqi patients with osteoporosis and to investigate whether there is a correlation between these parameters. This study was conducted at Baghdad Teaching Hospital and Al Kadhimain Teaching Hospital, involving 37 participants with osteopenia, 42 with osteoporosis, and 42 healthy controls. Serum concentrations of DKK1, vitamin D3, calcium, magnesium, phosphorus, and lipid profile were measured for all participants. Dkk1 and vitamin D3 were evaluated utilizing an enzyme-linked immunoassay. The results demonstrated that both osteopenic and osteoporotic groups had elevated DKK1 levels compared to controls; however, no significant correlation was observed between Dkk1 levels and bone mineral density (BMD) within these groups ($p > 0.05$). Despite significant differences in bone density markers at ($p<0.01$), no notable differences were found in Mg and Ph levels among control, OP, and OS groups, indicating minimal impact on these groups' bone mineral density (BMD). Regarding other biochemical markers, the study observed lower levels of vitamin D3 and Ca in patients with OP and OS. In addition, the study analyzed lipid profiles, revealing that there was an increase in the values of TG, LDL and VLDL (p-value <0.001) in the OS group than in the control group. Lastly, the receiver operating characteristic (ROC) analysis of Dkk1 for diagnosing osteopenia and osteoporosis yielded an area under the curve (AUC) of 1.000. In conclusion, this study supports DKK1 as a highly promising biomarker for osteopenia and osteoporosis.

Keywords: Osteoporosis, Osteopenia, DKK1

تقييم مستويات الديكويف المرتبط بالبروتين 1 لدى المرضى العراقيات المصابات بهشاشة العظام

موج سعدون ابراهيم *, نمير ابراهيم عباس
قسم كيمياء, كلية العلوم, جامعة بغداد, بغداد, العراق

*Email: mawj.saadoun2305@sc.uobaghdad.edu.iq

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الخلاصة

لين العظام وهشاشة العظام هما اضطرابان هيكليان جهازيان يتميزان بانخفاض كتلة العظام وتدهور البنية الدقيقة لأنسجتها. هشاشة العظام مرض صامت يتميز بفقدان سريع للعظام، وغالبًا ما يكون دون أعراض ملحوظة. يُعد الديكوف المرتبط البروتين1 DKK1 منظمًا رئيسيًا لهذه العملية، وهو بروتين سكري مُفرز يُشفره جين DKK1 لدى البشر. يلعب دورًا حاسمًا كمضاد لمسار إشارات .Wnt/β−catenin يُعد DKK1 منظمًا أساسيًا في هشاشة العظام، وذلك بشكل أساسي عن طريق تثبيط إشارات Wnt، وهي ضرورية لوظيفة الخلايا العظمية وتكوين العظام. تهدف هذه الدراسة إلى تقييم مستويات DKK1 وغيرها من المعايير الكيميائية الحيوية لدى المرضى العراقيين المصابين بهشاشة العظام، والتحقق من وجود علاقة بين هذه المعايير. أجريت هذه الدراسة في مستشفى بغداد التعليمي ومستشفى الكاظمية التعليمي، وشارك فيها 37 مشاركًا يعانون من لين العظام، و42 يعانون من هشاشة العظام، و42 من الضوابط الأصحاء. تم قياس تركيزات مصل DKK1 وفيتامين D_3 والكالسيوم والمغنيسيوم والفوسفور ومستوى الدهون لجميع المشاركين. تم تقييم DKK1 وفيتامين D_3 باستخدام مقايسة مناعية مرتبطة بالإنزيم. أظهرت النتائج أن كل من مجموعات هشاشة العظام وهشاشة العظام كان لديها مستويات مرتفعة من DKK1 مقارنة بالضوابط؛ ومع ذلك، لم يلاحظ أي ارتباط كبير بين مستويات Dkk1 وكثافة المعادن في العظام BMD داخل هذه المجموعات ($p> 0.05$). وعلى الرغم من الاختلافات الكبيرة في علامات كثافة العظام عند ($p < 0.01$)، لم يتم العثور على اختلافات ملحوظة في مستويات المغنيسيوم والأس الهيدروجيني بين مجموعات الضبط وOP وOS، مما يشير إلى تأثير ضئيل على كثافة المعادن في العظام BMD لهذه المجموعات. وفيما يتعلق بالعلامات البيوكيميائية الأخرى، لاحظت الدراسة مستويات أقل من فيتامين D_3 والكالسيوم في المرضى الذين يعانون من OP و .OS بالإضافة إلى ذلك، حللت الدراسة مستويات الدهون، وكشفت عن زيادة في قيم الدهون الثلاثية TGوالكوليسترول الضار LDL والكوليسترول الضار جدًا VLDL ($P<0.001$) في مجموعة OS مقارنةً بالمجموعة الضابطة. وأخيرًا، أظهر تحليل خاصية تشغيل المُستقبِل (ROC) لـ DKK1 لتشخيص هشاشة العظام وهشاشة العظام مساحةً تحت المنحنى (AUC) قدرها 1000. ختامًا، تدعم هذه الدراسة DKK1 كمؤشر حيوي واعد للغاية للين العظام وهشاشة العظام.

1. Introduction

Both osteopenia (OP) and osteoporosis (OS) are systemic disorders of the skeleton in which bone gradually weakens. The loss of bone mass together with the breakdown of its microarchitecture are key characteristics of these conditions, ultimately predisposing affected individuals to fractures[1]. OS can affect both men and women, , but it is more common in younger women and typically develops slightly earlier in life [2]. OS often remains asymptomatic until a bone breaks, and different forms of OS exist. Physicians refer to postmenopausal OS as type I OS, which is the most prevalent, while senile OS, known as type II, is less frequent [3]. Furthermore, OS, also known as secondary OS, can be caused by various illnesses and medications. Ageing diseases include types I and II OS [4]. A clinical condition known as OP occurs when bone mineral density (BMD) falls below normal reference levels but not sufficiently to satisfy the diagnostic requirements to be classified as osteoporotic [5] . While decreased bone density is a common feature of both OS and OP, their severity varies. Whereas OS has a T-score below -2.5, indicating a more substantial loss of bone density and an increased risk of fractures, OP is defined by a T-score between -1 and -2.5, indicating lower-than-normal bone density [6]. BMD, or bone mineral density, provides an indication of the mineral concentration in specific regions of the skeleton, such as the femur, lumbar spine, and forearm [7]. The most frequently applied tool for this measurement is dual-energy X-ray absorptiometry (DEXA), which is considered the gold standard for evaluating bone density and determining the extent of OP and OS[8].

Dickkopf related protien1 (Dkk1) is a protein that frustrates the Wnt signaling pathway by binding to lipoprotein receptor-related protein (LRP5/6), thereby inhibiting osteoblast development and osteogenesis [9]. This could be a crucial factor in identifying OS, as the canonical Wnt pathway influences mesenchymal stem cell fate[10]. The DKK1, a secretory glycoprotein, was discovered in 1998. It is a 170-kb long human gene with two cysteine-rich domains and a connecting region. It is a member of the Dickkopf protein family in vertebrates, encoded by the gene DKK [11]. The Dkk1's molecular weight is around 29 kDa [12]. Additionally, Dkk1 is an innovative target for statins and a potential biomarker for high-risk patients, both of which are essential for the prevention and management of cardiovascular disease[13]. Dkks, particularly Dkk-1, have been found to significantly contribute to the development of atherosclerosis, although their role in arterial wall pathophysiology remains poorly understood[14].

The Dkk2 and Dkk4 are similar in vertebrates, but their inhibitory effects are weaker than Dkk1. Osteoporosis-pseudoglioma, a disorder characterized by poor bone density, early OS, fractures, and abnormalities, is brought on by this LRP5/6 loss-of-function mutation[13]. The Dkk family proteins regulate the Wnt/β-catenin signalling pathway, impacting various biological processes and illnesses. In addition to controlling the canonical Wnt pathway, Dkks exhibit context-dependent effects, engaging in Wnt-independent activities and interfering with noncanonical Wnt signalling.

Dkk1, which is released by activated platelets, has been linked to many diseases, as well as OS, OP and direct regulation of atherosclerosis-related protein synthesis[15]. The DKK-1 plays a vital role in Osteoporosis. It is hypothesized that elevated DKK1 levels are associated with alterations in biochemical parameters in Iraqi patients with OP and OS, suggesting a possible role of DKK1 in the metabolic pathways involved in bone density reduction. This study aims to evaluate DKK1 levels and other biochemical parameters in Iraqi patients with OP and OS, and explore whether there is a correlation between them. The study highlights the need to understand the role of DKK1 and the metabolic changes associated with these diseases to improve diagnosis and treatment strategies.

2. Materials and Methods

2.1. Study Subjects

This study collected 121 serum samples from Iraqi females aged 30 to 70 years. Forty-two healthy with an average age of (52±12) were compared to 37 samples of patients who had OP age mean (57±10), and 42 OS patients who had age mean (58±8). The samples were gathered over a two-month period from December 2023 to February 2024, in the governorate of Baghdad. The specimens were chosen from Baghdad Teaching Hospital and Al Kadhimain Teaching Hospital. The hospital's consultant medical staff confirms the patients' diagnoses based on a DEXA scan.

2.2. Collection of Blood Samples:

Approximately 5 milliliters of fasting blood were collected and placed in gel tubes, then were then centrifuged at 3000 × g for 10 minutes to separate the blood and obtain the serum. The serum was stored in Eppendorf tubes at -20℃.

Dual Energy X-ray Absorptiometry (DEXA):

Osteopenia and osteoporosis were diagnosed according to the World Health Organization's (WHO) established criteria for diagnosing osteoporosis[16]. The test is highly accurate, takes only five to fifteen minutes to complete, and exposes patients to very little radiation. The patient's BMD is lower than the mean peak BMD of young, healthy adults of the same sex. This score, known as the "T-score", is the number of standard deviations (SD) below the peak

young adult bone mass, which represents the bone mineral density. The T-score for osteoporosis is less than -2.5 standard deviations from the mean value of peak bone mass.
• At least one fracture and a T-score ≤ -2.5 standard deviations below the mean value of peak bone mass indicate severe osteoporosis.
A bone mineral density T-score of -1 to -2.5 standard deviations below the mean value of peak bone mass is indicative of osteopenia.
• A BMD more than -1 standard deviation below the mean value of peak bone mass is considered normal bone density.

2.3. Anthropometric Measurements:

Weight (Kg) and height (cm) were measured for all the participants. The body mass index (BMI) was computed by dividing the weight (Kg) by the square of height

2.4. Laboratory Tests:

The DKK1 and vitamin D3 were evaluated utilizing an enzyme-linked immunoassay (My Bio Source, U.S.A., AFIAS Vitamin D Neo), respectively. Serum total cholesterol (TC) was estimated by enzymatic colorimetric tests with cholesterol oxidase and cholesterol esterase, while serum triglyceride (TG) was evaluated by the enzymatic colorimetric tests with glycerol phosphate oxidase. High-density lipoprotein cholesterol (HDL-C) was evaluated after precipitation of the Apo lipoprotein B-containing lipoproteins Serum levels of LDL, VLDL, $Ca^{2+,}$ Mg^{2+} and P were estimated using enzymatic colorimetric techniques, with phosphotungstic acid utilized in the analytical process. The LDL and VLDL were also calculated using the equation:
VLDL = Triglyceride \5
LDL= (Total Cholesterol) - (VLDL+HDL) [17]

2.5. Analytical Statistics

The statistical analysis was carried out using the SPSS Statistical package (Version 27: SPSS). The one-way ANOVA was used to compare the quantitative variables between the research groups, and Pearson's analysis was used to find the correlations between parameters. Additionally, the Receiver Operating Characteristic (ROC) analysis was employed in this study. Statistics with a p-value of less than 0.05 and 0.001 were considered significant and highly significant, respectively.

3. Results

The general anthropometric data of the participants are represented in Table 1. Statistical analysis using ANOVA revealed a highly significant difference in BMD between the control and OP groups, as well as OP and OS groups ($P < 0.001$), but there was no significant difference in height, weight and BMI between the control and OP, OS groups.

Table 1: Anthropometric analysis of the studied groups.

Parameters	Control group(No.=42) (Mean ±SD)	Osteopenia group(No.=37) (Mean ±SD)	Osteoporosis group(No.=42) (Mean ±SD)	P-value		
				*P*a	*P*b	*P*c
Height (cm)	160.09 ± 5.32	159.54 ± 5.53	157.6429 ± 6.15	0.902	0.123	0.305
Weight (kg)	78.3 ± 14.96	79.67 ± 11.51	74.5 ± 14.12	0.898	0.412	0.219
BMI (Kg/m^2)	30.53 ± 5.66	31.4 ± 4.95	29.9 ± 5.32	0.746	0.874	0.450
BMD(g/cm^2)	1.14 ± 0.13	0 .83 ± 0.08	0.69 ± 0.08	0.0001	0.0001	0.0001

***P*a** = the osteopenia group compared with the control group, ***P*b** =the osteoporosis group compared with the control group, ***P*c** = the osteoporosis group compared with the osteopenia group.

Table 2 shows a highly significant difference in vitamin D3 and Ca levels between the control group and OP group, as well as the control and OS group ($P < 0.001$), but there was no significant difference in vitamin D3 levels between the OP and OS groups. The Ca levels showed significant differences between OP and OS groups. Regarding the lipid profile, levels of TC, TG, LDL and VLDL were significantly higher in both the OS and OP groups compared to the control group, with no significant differences between the OS and OP groups. In contrast, HDL levels showed a significant difference between the OS and OP groups, but there was no significant difference between the control group and either of the patient groups. Phosphorus levels showed no significant differences among the groups. However, Mg^{2+} levels differed significantly between the OS and OP groups ($p < 0.05$). Finally, DKK1 levels were significantly elevated in both OS and OP groups compared to the control group ($p < 0.001$), as shown in Table 2.

Table2: Statistical analysis of the studied groups according to biomarker and diagnostic parameters

Parameters	Control group(No.=42) (Mean ±SD)	Osteopenia group(No.=37) (Mean ±SD)	Osteoporosis group(No.=42) (Mean ±SD)	P-value		
				*P*a	*P*b	*P*c
DKK1(pg/mL)	124.53 ± 23.98	637.29 ± 75.83	635.94 ± 106.24	<0.001	<0.001	0.997
V.D3(ng/mL)	33.24 ± 1.04	9.33 ± 3.28	8.98 ± 3.82	<0.001	<0.001	0.860
Ca (mg/dL)	9.32 ± 0.50	5.45 ± 1.77	6.4 ± 1.68	<0.001	<0.001	0.010
Mg (mg/dL)	1.96 ± 0.08	2.00 ± 0.37	1.84 ± 0.19	0.716	0.90	0.015
Ph (mg/dL)	3.56 ± 0.1	3.48 ± 0.76	3.76 ± 0.68	0.824	0.245	0.084
TG (mg/dL)	185.63 ± 15.78	206.13 ± 34.97	216.59 ± 13.99	<0.001	<0.001	0.112
LDL (mg/dL)	95.94 ± 6.13	114.49 ± 10.5	109.13 ± 12.68	<0.001	<0.001	0. 053
VLDL (mg/dL)	37.12 ± 3.15	41.22 ± 6.99	43.31 ± 2.79	<0.001	<0.001	0.112
HDL (mg/dL)	35.44 ± 2.79	30.84 ± 8.93	38.93 ± 11.04	.042	0.137	<0.001
Cholesterol(mg/dL)	168.51 ± 6.84	186.56 ± 8.15	191.38 ± 11.58	<0.001	<0.001	0.054

***P*a** = the osteopenia group compared with the control group, ***P*b** =the osteoporosis group compared with the control group, ***P*c** = the osteoporosis group compared with the osteopenia group. DKK1= Dickkopf Related Protein1 V. D3=vitamin D3, Ca=calcium, Mg=magnesium, Ph=phosphorus, TG=Triglycerides, LDL= low-density lipoprotein, VLDL=very low-density lipoprotein, HDL= high-density lipoprotein.

The correlation between DKK1 and other biochemical parameters in the osteopenia and osteoporosis groups,

As observed in Table 3, there appears to be no significance correlation between DKK1 with any of the studied parameters in osteopenia as well as in osteoporosis groups.

Table 3: Correlation the DKK1 and other parameters for the osteopenia group and osteoporosis groups.

	Osteopenia		Osteoporosis	
Parameters	r	P-value	r	P-value
DKK1(pg/mL)	1	-	1	-
V.D3(ng/mL)	-0.282	0.091	-0.087	0.586
Ca (mg/dL)	0.226	0. .178	0.071	0.657
Mg(mg/dL)	0.204	0.225	-0.088	0.579
Ph (mg/dL)	-0.220	0. .190	0.059	0.710
TG (mg/dL)	-0.254	0. .129	0.026	0.870
LDL (mg/dL)	-0.252	0. .132	0.198	0.208
VLDL (mg/dL)	-0.254	0.129	0.026	0.870
HDL (mg/dL)	0.260	0. .120	-0.182	0.249
Cholesterol(mg/dL)	-0.258	0.123	0.050	0.753

r =Pearson coefficient. p>0.05= statistically non-significant correlation, * Statistically significant correlation at p< 0.05, ** Statistically significant correlation at p≤0. 01.V.D3=vitamin D3, Ca=calcium, Mg=magnesium, Ph=phosphorus, TG=Triglycerides, LDL= low-density lipoprotein, VLDL=very low-density lipoprotein, HDL= high-density lipoprotein.

Receiver operating characteristic (ROC) curve of DKK1

The (ROC) curve of DKK1 showed an area under the curve (AUC) of 1.000 for both osteopenia and osteoporosis, indicating DKK1 as a strong potential marker for these conditions, with cutoff values of 326.0870 for osteopenia and 317.6087 for osteoporosis, as explained in Table 4 and shown in the following Figures

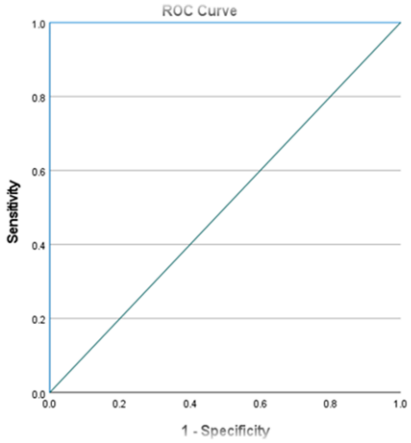

Figure 1: Receiver operator curve(ROC) analysis for the predictive value of DKK1 levels for the people who suffer from osteopenia group (n=37) versus the healthy group (n=42), AUC= area under the curve, SE= standard error, CI= confidence interval.

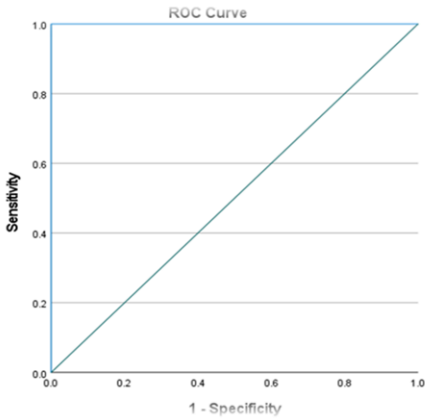

Figure 2: The Receiver operator curve (ROC) analysis for the predictive value of DKK1 levels for the people who suffer from osteoporosis group (n=42) versus the healthy group, AUC= area under the curve, SE= standard error, CI= confidence interval.

Table 4: The Receiver operator curve (ROC) data for DKK1 as biomarker parameter for the osteopenia and osteoporosis disease.

Parameter	AUC	SE	95% CI	Specificity (%)	Sensitivity (%)	Cut-off value	P-value
DKK1 for OP(pg/mL)	1.000	0.0001	1.000	0.000	1.000	326.0870	<0.0001*
DKK1 for OS(pg/mL)	1.000	0.0001	1.000	0.000	1.000	317.6087	<0.0001*

AUC= area under the curve, SE= standard error, CI= confidence interval, OP=osteopenia, OS=osteoporosis, DKK1=Dickkopf related protein1. * highly Significant at p > 0.001.

The ROC curve for DKK1 showed AUC of 1.000 for both osteopenia and osteoporosis, indicating perfect sensitivity and specificity. The cutoff values were identified as 326.0870 pg/mL for OP and 317.6087 pg/mL for OS.

These values strongly suggest that DKK1 is an excellent biomarker for distinguishing osteopenia and osteoporosis from normal bone health. In summary, these results demonstrate that elevated DKK1, along with lower levels of vitamin D3, Ca^{+2}, and BMD, as well as an altered lipid profile, are characteristic markers of OP and OS. The ROC analysis confirms DKK1's high diagnostic potential.

4. Discussion

OS is primarily defined by a reduction in bone mass, which results from both excessive bone loss and insufficient bone formation. This leads to increased bone brittleness, raising the risk of fractures, especially in the shoulder, wrist, hip, and spine areas[18]. The decrease in bone marrow and osteoblasts observed in several diseases, particularly osteoporosis (OP), is associated with age-related changes in the production and differentiation of osteoblasts and other bone-forming cells [19]. This research is unique in Iraq, as it is the first study conducted on Iraqi patients, and it linked osteoporosis with the biomarker DKK1. This study investigated the interrelationships between bone health, osteoporosis, osteopenia and various biochemical parameters. The findings contribute to the growing body of evidence on the multifactorial etiology of bone diseases and their potential diagnostic biomarkers**.** Bone health and anthropometric parameters, the observed reduction in BMD across the control,

osteopenia, and osteoporosis groups aligns with the well-established role of ageing as a major risk factor for bone loss[20]. Height, weight, and BMI did not show significant differences between the groups ($p > 0.05$). Body mass index is not significantly affected in the groups studied (osteopenia and osteoporosis) because, unlike bone mineral density (BMD), BMI primarily reflects overall body weight relative to height and does not directly measure bone health or density. In the provided data, the BMI values across the control, osteopenia, and osteoporosis groups were relatively similar, with no statistically significant differences (p-values: 0.746, 0.874, 0.450 for respective comparisons). This suggests that patients with osteopenia and osteoporosis exhibit changes in bone density and composition, which do not necessarily affect overall body mass or the fat-to-height ratio, as measured by BMI. This is in contrast to what previous studies have shown (although the BMI values did not differ significantly among the control, osteopenic, and osteoporotic groups); this finding might be influenced by several factors. One possible explanation is the limited sample size, which may not have been sufficient to detect subtle differences. Additionally, variations in physical activity levels, nutritional status, or genetic predispositions among the participants may have acted as confounding variables, masking any potential association between BMI and BMD. Furthermore, population-specific characteristics such as lifestyle, dietary habits, or cultural practices could have contributed to the observed discrepancy [21-24].

The trend of declining BMD was statistically significant ($p < 0.001$). This reaffirms the importance of BMD as a gold standard for assessing bone health. A low BMD reflects the severity of bone density loss. The lower BMD values in the OP and OS groups align with other biochemical abnormalities, such as reduced vitamin D3 and calcium, potentially indicating underlying mechanisms of bone loss. This has also been proven by previous studies [25-28]. Additionally, the findings imply a limited reliability of traditional anthropometric measures relative to biochemical and molecular markers in the context of predicting bone health. Vitamin D3 and Ca^{2+} levels were significantly lower in OP and OS groups compared to controls ($p < 0.001$). The decline in vitamin D3 levels in osteopenia and osteoporosis is a complex process influenced by multiple physiological, lifestyle, and pathological factors. Vitamin D3 (cholecalciferol) is vital for maintaining bone health because it facilitates Ca^{2+} and P absorption in the intestines and regulates bone remodeling by osteoblasts (bone-forming cells) and osteoclasts (bone-resorbing cells). Promotes mineralization of bone matrix to maintain BMD. Without adequate Vitamin D3, calcium absorption decreases, resulting in a negative calcium balance that can lead to secondary hyperparathyroidism and bone resorption. This is consistent with existing literature suggesting their pivotal role in maintaining bone integrity through regulation of Ca^{+2}-P metabolism and osteoblast function [29-31] .

Interestingly, Mg^{2+} levels, although slightly altered, exhibited a significant reduction only in the osteoporosis group. The involvement of Mg^{2+} in bone mineralization is essential, as it contributes to the structural development and strength of bone tissue. This is consistent with previous studies [32, 33]. Additionally, another study reported a lower serum Mg^{2+} value; moreover, the Mg^{2+} concentration was strongly associated with a high risk of fractures [34, 35]. These findings highlight the necessity of maintaining optimal levels of these nutrients to mitigate the risk of bone disorders. This study suggests that Mg^{2+} may be a secondary but important factor in the progression of OS, warranting closer investigation. As for P, it is essential for forming hydroxyapatite, the mineralized component of bones, working in concert with calcium. It supports structural integrity and metabolic functions, including energy transfer (via ATP) and cell signaling [36].

Both excessive and deficient P levels can disrupt bone metabolism. However, phosphorus is typically less emphasized compared to Ca^{2+} in bone-related diseases. In both osteopenia and OS groups, there were no correlations between DKK1 (a biomarker for bone turnover) and P ($r = -0.220$ and 0.059, respectively; $p > 0.05$). This implies that P does not have a direct

relationship with DKK1, distinguishing it from other parameters like Ca^{2+} and vitamin D, which play more dynamic roles in bone health.

Lipid profile is a diagnostic tool used to evaluate the levels of various lipids in the blood, including TC and TG. It serves as a marker for cardiovascular health and is increasingly being studied for its association with other systemic conditions, such as OS and OP. The study revealed significant dyslipidemia in the osteopenia and osteoporosis groups, characterized by increased levels of TG, LDL, VLDL, and TC ($p < 0.001$). These findings align with emerging evidence that links lipid metabolism to bone turnover. Excess lipids, particularly LDL, are hypothesized to induce oxidative stress and inflammation, which may impair osteoblast activity and promote bone resorption. Interestingly, HDL levels demonstrated a non-linear trend, decreasing significantly in the osteopenia group but showing a modest increase in the osteoporosis group. This paradoxical pattern (this unexpected pattern warrants further investigation, as the underlying mechanisms remain unclear). Warrants further research, as it may indicate compensatory mechanisms or metabolic shifts investigation. These results are also in line with the findings reported by [36]. This study concludes that the lipids, particularly TC and TG, are thought to influence bone health through inflammatory pathways. Chronic inflammation caused by dyslipidemia can disrupt bone remodeling processes, resulting in decreased BMD. This study highlights that individuals with osteopenia and osteoporosis have both elevated lipid levels and reduced BMD, suggesting a shared pathophysiological mechanism.

Regarding DKK1, the study identified it as a highly discriminatory biomarker for both osteopenia and osteoporosis, with $p<0.001$. The ROC analysis (AUC = 1.000 for markers) underscores their diagnostic precision. Elevated DKK1 levels suggest enhanced Wnt signaling inhibition, which is critical in the pathophysiology of bone loss. Further emphasizing their potential as early indicators of bone disease. This finding is consistent with a previous study. The significant diagnostic value of this biomarker supports its inclusion in future diagnostic protocols for early detection and risk stratification in patients with compromised bone health. In correlation analysis, correlation studies revealed minimal significant associations between DKK1 and other measured parameters in both osteopenia and osteoporosis groups. However, in the osteopenia group, DKK1 showed a non-correlation with TG, VLDL, LDL and TC ($p > 0.05$), and a positive correlation with HDL. In the osteoporosis group, DKK1 demonstrated a non-correlation with HDL and a positive correlation with LDL, TG, LDL, VLDL and TC ($p > 0.05$), that's led to the correlations between DKK1 and lipid profile parameters (HDL, TG, TC) in both osteopenia and osteoporosis groups being non-correlated. This weak association may indicate that while DKK1 is elevated in disorders associated with bone density loss conditions, its levels do not directly correlate with lipid metabolism markers.

On the other hand, the ROC curve analysis for DKK1 shows an AUC of 1.000 for both osteopenia and osteoporosis, which strongly indicates DKK1's potential as a diagnostic marker. The cutoff values for DKK1 are 326.0870 for osteopenia and 317.6087 for osteoporosis, with $p< 0.0001$. These high AUC values highlight DKK1's specificity and sensitivity, suggesting that it could be a powerful diagnostic tool for identifying individuals at risk for or suffering from these conditions. The findings presented here stress the multifactorial basis of OP and OS. The association of dyslipidemia with deficiencies in vitamin D3 and Ca^{+2} suggests that management approaches should extend beyond bone density to encompass broader aspects of metabolic health. Importantly, DKK1 demonstrated strong diagnostic potential, offering opportunities for earlier detection and more personalized treatment plans. Further longitudinal research is needed to establish causal links and to strengthen the evidence for DKK1 as a clinical biomarker. At the same time, studying how lipid metabolism interacts with bone, and how Mg^{+2} contributes to bone turnover, could provide valuable insights for developing new therapeutic strategies.

Conclusion

In conclusion, this study provides that DKK1 as a promising diagnostic biomarker for OP and OS. Elevated DKK1 levels showed a strong associated with bone density loss, and ROC analysis confirmed its high diagnostic accuracy. The results also indicated frequent disturbances in vitamin D3, calcium, and lipid profiles among affected individuals. While DKK1 levels appear more closely linked to bone density than to lipid alterations, its potential therapeutic relevance should be explored in future research.

6. Ethical Clearance

The Iraqi Ministries of Environment, Health, Higher Education, and Scientific Research have approved this study. The Research Ethics Committee for Scientific Research has been approved by the College of Science Ethics Committee at the University of Baghdad (Ref.CSEC/1123/0125 on November 26,2023).

7. Acknowledgment

The authors would like to thank every member of the staff at Kadhimain Teaching Hospital and Baghdad Teaching Hospital, located in the Medical City. They are also very grateful to the patients and healthy individuals who provided us with blood samples.

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