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Clinical Study of Dickkopf-Related Protein 1 and its Relation with Biomarkers of Bone Resorption in Patients with Metabolic Syndrome

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Abstract

Metabolic syndrome (MetS) is a global health concern, with potential complications affecting bone health. Dickkopf-1 (DKK1) may serve as a marker for MetS progression, particularly when analyzed alongside other bone metabolism markers such as Bone Gamma Osteocalcin (BGP-OST), calcitonin, and intact parathyroid hormone (I-PTH). To evaluate the correlations between DKK1 levels and bone metabolism markers (BGP-OST, calcitonin, and I-PTH) in patients with MetS, this case-control study included 88 participants (60 MetS patients and 28 healthy controls). Based on data distribution, biomarker levels were analyzed using one-way ANOVA or Kruskal-Wallis H tests. Correlations were assessed using Spearman's test, with $p < 0.05$ considered statistically significant. The diagnostic utility of DKK1 was evaluated using ROC curve analysis. No significant differences were observed between MetS patients and controls for DKK1, I-PTH, or calcitonin levels, whereas BGP-OST levels were significantly higher in MetS patients ($p < 0.05$). In MetS patients, DKK1 showed a significant negative correlation with calcitonin, while BGP-OST had a significant positive correlation with calcitonin. DKK1 demonstrated diagnostic potential with an AUC of 0.758 and a 4.11 ng/mL cut-off value. DKK1 is significantly correlated with calcitonin and shows diagnostic utility for MetS. Elevated BG-OST levels in MetS patients further suggest its potential role in bone metabolism alterations associated with MetS progression.

Keywords*: Bone Metabolism, Calcitonin, DKK1, Intact Parathyroid Hormone (I-PTH), Metabolic Syndrome, Osteocalcin.*

Introduction

A cluster of abdominal obesity, hyperglycemia, hypertension, and dyslipidemia characterizes metabolic syndrome (MetS). The global prevalence of MetS is approximately 31%, associated with a two-fold increase in the risk of coronary heart disease and cerebrovascular disorders, as well as a 1.5-fold increase in all-cause mortality [1-2] Central to MetS is insulin resistance, which is linked to the accumulation of body fat, dyslipidemia, diabetes, and hypertension. Conversely, peripheral fat distribution is metabolically less impactful.

MetS negatively influences bone mineral density (BMD), which correlates positively with physical activity. Individuals with MetS often exhibit reduced physical activity, leading to early signs of decreased BMD at the hip and a higher incidence of osteoporosis [3]. Bone is a metabolically active tissue undergoing continuous remodeling, driven by circulating cytokines and hormones. Abnormalities in this process can weaken bone structure, impair mechanical strength, and manifest as clinical symptoms, including deformities and disrupted homeostasis [4].

Studies suggest MetS contributes to inflammation and osteoarthritis, with obesity,

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dyslipidemia, insulin resistance, and hypertension recognized as primary metabolic risk factors. This "deadly quartet" disrupts physiological processes, causing detrimental bone and cartilage changes and perpetuating a pro-inflammatory joint microenvironment [5].

Dickkopf-related protein 1 (DKK1) is a key regulator of embryogenesis and bone remodeling. It is a potent natural inhibitor of the Wingless (Wnt) signaling pathway, crucial for osteoblastogenesis and bone formation. Overexpression of DKK1, particularly in osteoblasts, is implicated in metabolic bone diseases and arthritis [6]. The Wnt pathway governs the differentiation of mesenchymal stem cells into osteoblasts or fibroblasts. DKK1 activation inhibits Wnt signaling, reduces β-catenin translocation to the nucleus, and ultimately downregulates osteoblast activity [7-8]. Bone-related proteins, such as osteocalcin, parathyroid hormone (PTH), and calcitonin, also play pivotal roles in bone and energy metabolism. Osteocalcin, secreted by osteoblasts, extends its influence beyond bone mineralization to regulate reproduction, metabolism, and cognition [9]. PTH, traditionally known for calcium homeostasis, is now recognized as a multifunctional hormone affecting adipocyte browning and lipolysis [10]. Calcitonin, produced by thyroid parafollicular cells, suppresses bone resorption by inhibiting osteoclast activity and is a clinical marker for medullary thyroid carcinoma [11].

The bone-specific isoform of osteocalcin, Bone gamma osteocalcin (BGP-OST), has been identified as a critical factor in regulating bone metabolism and systemic glucose homeostasis. BGP-OST enhances insulin production and reduces insulin resistance, further establishing its role in metabolic regulation. In a cross-sectional study of patients 18 years and older who met the NCEP-ATP III criteria for metabolic syndrome, serum osteocalcin levels, including BGP-OST, were positively associated with lower fasting blood glucose and higher serum HDL cholesterol levels. Additionally, individuals with fewer components of metabolic syndrome exhibited higher serum osteocalcin levels, including BGP-OST, compared to those with more components [12].

Patients with metabolic syndrome tend to have lower serum osteocalcin and BG-OST levels, highlighting their significant association with glucose metabolism and adipose tissue regulation. Furthermore, BG-OST plays a regulatory role in systemic inflammation, contributing to its broader impact on metabolic health [13].

The aim of this study is to investigate the relationship between metabolic syndrome (MetS) and bone disorders, especially focusing on the role of Dickkopf-related protein 1 (DKK1) as a key representative in future diagnostic and therapeutic strategies. To analyze the correlation between DKK1 levels and bone resorption markers (such as Bone gamma osteocalcin (BGP-OST), calcitonin, and parathyroid hormone) in patients with MetS, aiming to determine its role in bone metabolism disruption related to MetS.

Materials and Methods

Participants and Study Design

This case-control study included 88 participants (60 with Metabolic Syndrome [MetS] and 28 healthy controls) recruited from Kirkuk and Azadi Teaching Hospitals, Kirkuk City, Iraq, between June and September 2024. Participants were selected through a systematic random sampling method to minimize selection bias. MetS was diagnosed based on the NCEP ATP III criteria, requiring the presence of at least three of the following components [14]:

1. Abdominal obesity: Waist circumference >102 cm (male), >88 cm (female).
2. Reduced HDL cholesterol: <40 mg/dL (male), <50 mg/dL (female).
3. Elevated fasting triglycerides: >150 mg/dL.
4. Elevated fasting glucose: >100 mg/dL.
5. High blood pressure: ≥130/85 mmHg.

Exclusion Criteria

Participants were excluded if they had:

1. Endocrine disorders, rheumatoid arthritis, liver disease, chronic kidney disease (eGFR <60 mL•min^{1}•1.73 m^{2}), malignancy, or cerebrovascular diseases.
2. Use of medications affecting bone metabolism, such as vitamin D, alfacalcidol, calcitonin, calcium, bisphosphonates, estrogen, thiazolidinediones, glucocorticoids, or SGLT-2 inhibitors.

Data Collection and Anthropometric Measurements

Participants were interviewed using a structured and pretested questionnaire to gather demographic and clinical data, including age, weight, height, and waist circumference. Waist circumference was measured at the midpoint between the lower rib margin and the iliac crest using a flexible, non-stretchable tape, ensuring snug but non-compressive placement. Body mass index (BMI) was calculated as weight (kg) divided by height (m^{2}).

Laboratory Analysis

Fasting blood samples (6 mL) were collected via venipuncture, allowed to clot at room temperature, and processed as follows:

1. 3 mL in plain gel tubes for serum separation to measure fasting blood glucose, HDL cholesterol, and triglycerides using the colorimetric method (BIOLABO Kit, France).
2. 3 mL in plain gel tubes stored at -80°C and thawed only once before analysis for biomarkers:
    - DKK1 (Cat. No. ELK2097, Lot No. 27426701) and I-PTH (Cat. No. ELK2427, Lot No. 27427413) via ELISA kits from ELK Biotechnology.
    - BGP-OST (Cat. No. QS1308Hu, Lot No. 20240826) and Calcitonin (CT) (Cat. No. QS0391Hu, Lot No. 20240826) via ELISA kits from SunLong Biotech.

Statistical Analysis

Data were analyzed using SPSS software (version 25, IBM, USA). Descriptive statistics were presented as mean ± standard deviation (SD) for continuous variables. The Kolmogorov-Smirnov/Shapiro-Wilk tests assessed normality. Statistical methods included:

1. One-way ANOVA for normally distributed data.
2. Kruskal-Wallis H tests with post hoc Dunn test for non-normally distributed data.
3. Pearson's or Spearman's correlation analyses based on data distribution.
4. ROC analysis will evaluate the predictive power of DKK1 and BGP-OST, with cut-off values determined using the Youden index.
5. Statistical significance was set at $P < 0.05$.

Ethical Approval

The ethical committees of Azadi Teaching Hospital, Kirkuk Teaching Hospital, and the Kirkuk Health Directorate approved the study. In compliance with the Declaration of Helsinki, written and verbal informed consent was obtained from all participants.

Results

Demographics and Baseline Characteristics

The study included 88 participants (60 with MetS and 28 healthy controls). The mean age of participants was comparable between groups, with a higher prevalence of overweight and obesity among MetS patients (Table 1). It was observed that 30.7 % and 1.1% of the controls were normal and overweight, respectively (Table 2).

Table 1. Age Distribution by Group and Sex

Group	N (Total)	Sex	N	% within total	Mean Age ± SD	Range
MetS Patients	60	Male	28	31.8%	50.93 ± 9.53	29–60
MetS Patients	60	Female	32	36.3%	48.09 ± 10.95	18–60
Control Group	28	Male	18	20.5%	45.61 ± 8.76	26–59
Control Group	28	Female	10	11.4%	43.20 ± 6.30	35–54
Overall Total	88	–	–	–	48.85 ± 9.50	18–60

Table 2. BMI Distribution in Metabolic Syndrome Patients

BMI Category	Male (n)	Female (n)	Total (n)	% of Total (n=60)
Normal (18.5–24.9)	4	3	7	8.0%
Overweight (25–29.9)	11	10	21	23.9%
Obese Class I (30–34.9)	9	7	16	18.2%
Obese Class II (35–39.9)	3	5	8	9.1%
Obese Class III (>40)	1	7	8	9.1%
Total	28	32	60	100%

Metabolic Parameters

Patients with MetS exhibited significantly elevated fasting glucose and triglyceride levels, alongside reduced HDL-C levels, compared to controls (Figure 1). These findings align with the diagnostic criteria for MetS.

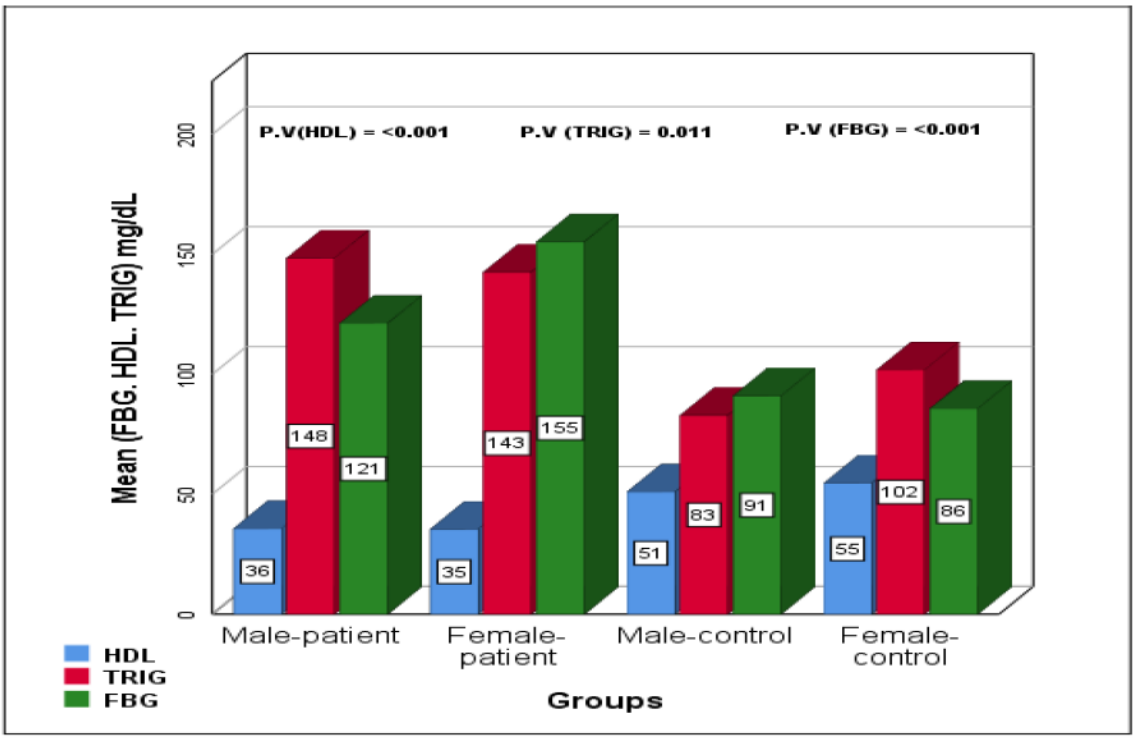

Figure 1. Comparison Between Patients with MetS and Control Groups with Both Genders Regarding Mean ± Standard Deviation (SD) of Serum Fasting Blood Glucose (FBG), Triglyceride (TRIG), and HDL

Biomarker Analysis: DKK1 Levels: No significant difference between groups, though a trend of higher levels in MetS patients was observed (P = 0.361). Also, Calcitonin and I-PTH have shown no significant difference between groups (P > 0.05; See Table 3)**.** BGP-OST Levels: Significantly lower in MetS patients than controls (P < 0.001; Table 4), indicating potential disruptions in bone metabolism.

Table 3. Comparison Between Patients with Metabolic Syndrome and Control Groups with Both Sexes Regarding the Mean ± Standard Deviation (SD) of DKK1, CT, and I-PTH

Studied groups	**N**	**Markers**	**Total (Mean ± SD)**	**Male (Mean ± SD)**	**Female (Mean ± SD)**
Patients with MetS	60	DKK1(ng/mL)	4.96 ± 1.24	4.73 ± 1.19	5.17 ± 1.26
Patients with MetS		CT(pg/mL)	10.37±14.73	10.65±11.27	10.13±17.38
Patients with MetS		I-PTH(pg/mL)	41.30 ± 18.70	41.49 ± 18.14	41.15 ± 19.48
Control group	28	DKK1(ng/mL)	4.65 ± 1.46	4.53 ± 1.57	4.88 ± 1.27
Control group		CT(pg/mL)	10.37 ± 7.80	10.52 ± 8.61	10.11 ± 6.51
Control group		I-PTH(pg/mL)	40.39 ± 17.67	46.13 ± 14.70	30.07 ± 18.55
P-Value within subgroups			DKK1= 0.361	CT=0.805	I-PTH=0.256
DKK1 (One- way ANOVA), CT, and I-PTH ((Kruskalls- wallis H)					

Table 4. Comparison Between Patients with Metabolic Syndrome and Control Groups with Both Sexes Regarding the Mean ± Standard Deviation (SD) of BGP-OST

Studied groups	**N**	**BGP-OST Mean ± SD**		
		Total	**Male**	**Female**
Patients with MetS	60	**P** 1.44 ± 1.47	**M-P** 1.52 ± 1.11	**F-P** 1.38 ± 0.73
Control group	28	**C** 2.54 ± 1.03	**M-C** 2.64 ± 1.03	**F-C** 2.39 ± 1.07
P-value between the two groups	**P * C** **M-P * F-C** **M-C * F-P** **M-P * F-P** **M-C * F-C**	< 0.001 0.017 < 0.001 0.230 0.579	0.001	0.001
P-Value (Kruskalls- wallis H)	88	< 0.001		
Male-Patient (M-P), Male-Control (M-C), Female-Patient (F-P), Female-Control (F-C)				

Correlation and Predictive Value: In the MetS group, DKK1 negatively correlated with CT (r = -0.332, P = 0.009), while BGP-OST positively correlated with CT (r = 0.432, P = 0.001). See Figures 2 and 3.

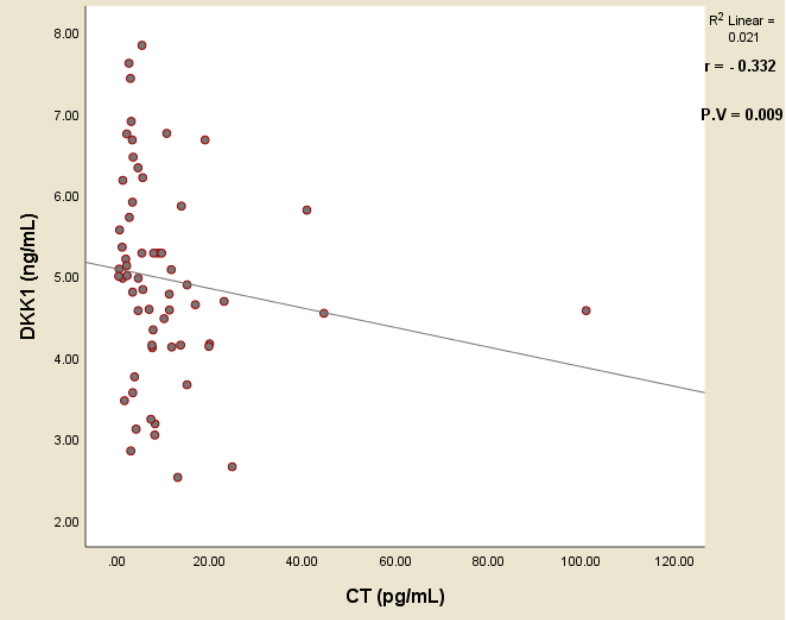

Figure 2. Correlation between Serum BGP-OST Levels and Serum CT Levels in Patients with Metabolic Syndrome

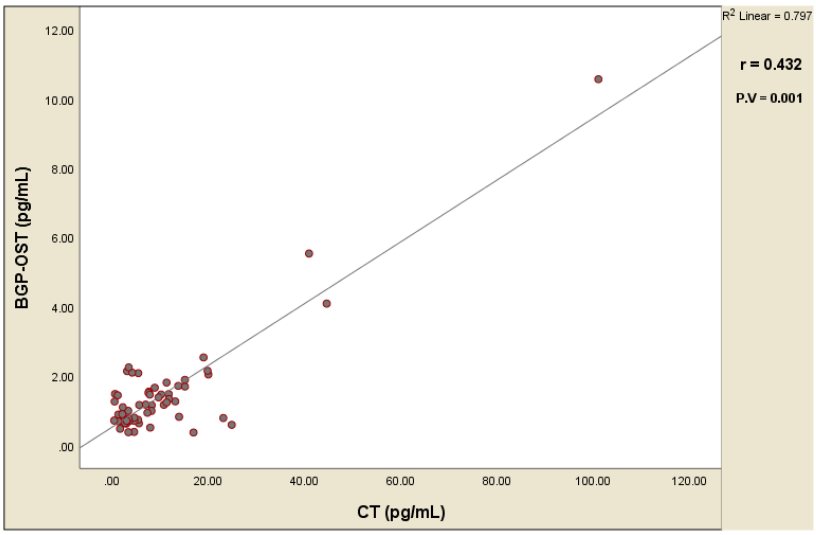

Figure 3. Correlation between Serum DKK1 Levels and Serum I-PTH Levels in Patients with Metabolic Syndrome

The ROC analysis (Table 5) demonstrated moderate diagnostic utility for DKK1 (AUC = 0.758, P = 0.014; Figure 4), while BGP-OST showed limited predictive value (AUC = 0.612, P = 0.140; Figure 5).

Table 5. The Data of the ROC Curve for the Following Biomarker (Patient Group)

Biomarker (patient group)	**AUC**	**S.E**	**Confidence Intervals (CI)**	**Sen %**	**Spe %**	**Acc%**	**PPV%**	**NPV%**
DKK1	0.758	0.102	0.558-0.958	76.56	54.17	70.45	81.67	46.43
BGP-OST	0.612	0.074	0.467-0.757	91.30	57.14	75	70	85.71
Sen = Sensitivity, Spe = Specifity, Acc = Accuracy								

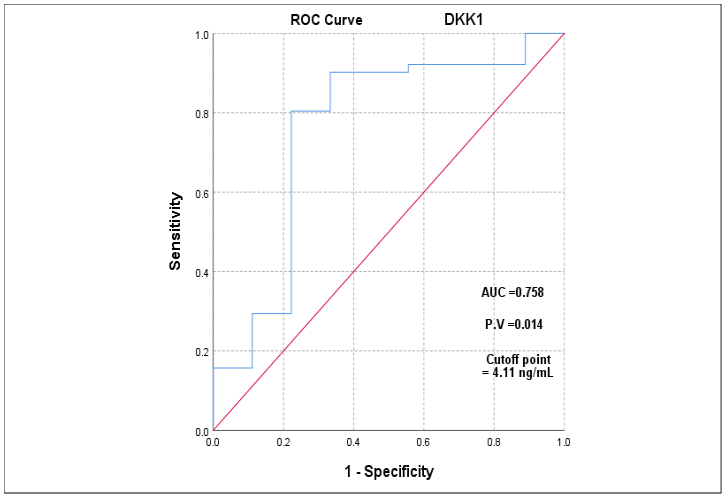

Figure 4. The ROC Curve of DKK1

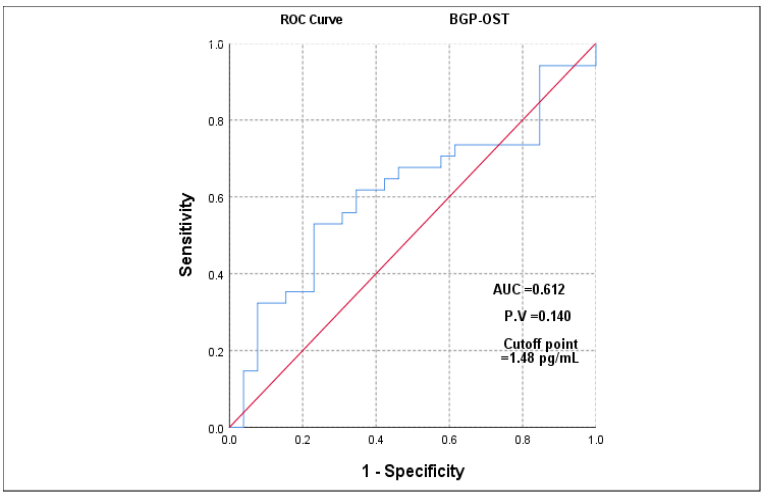

Figure 5. The ROC Curve of BG-OST

Discussion

It is important to estimate the incidence of MetS in our country because of the global increase in MetS prevalence, especially MetS risk factors, abdominal obesity, hyperglycemia, and hypertension, which have increased among the population, leading to an increased incidence of untreated MetS among Mediterranean countries. This study concluded that a higher incidence of MetS was in females (36.3%) than males (31.8%). This distribution agrees with a study in Iraq and another that suggested a higher incidence of MetS among females than males [15-16] (Table 1).

This study showed that the percentage proportion of BMI among most study participants was overweight and obese 1. It has been observed that obesity and abdominal obesity increased in the Middle East and North Africa (MENA) region involving (18) countries at different economic levels, classified (Jordan, and Iraq) as upper-middle-income level, and about one-fifth of the adults considered as obese, increasing, with age increase, gender, income, nutrition patterns, education, and urbanization. [17]. The relation of BMI with insulin resistance and Type 2 diabetes mellitus, a complication of MetS, was confirmed by Ilyas et al in Iraqi overweight and obese adults [18] (Table 2).

Dickkopf 1 (DKK1) is a protein linked with metabolic diseases, including insulin resistance (IR). In this study, we found that there is no statistical difference in the mean of the patient group with MetS and control subgroups by one-way ANOVA (P.Value = 0.361) Table 3, even

studies found that had a relation with insulin resistance but more of these studies found DKK1 had a relation with complications of MetS as diabetes mellitus (DM) and congenital heart disease (CHD), maybe as the MetS become more complicated and progress to diseases with years to DM and CHD, the DKK1 become more obvious. The studies about DKK1 in MetS were not found; rather, they were related to MetS complications. The following studies explain the complications of MetS, such as DM and CHD. A study found that serum DKK1 levels were elevated in patients with Insulin resistance than in controls and positively correlated with BMI, systolic blood pressure, Triglycerides, blood glucose, and glycosylated hemoglobin HbA1c [19]. Also, a study in Egypt found that serum DKK1 was elevated in type 2 DM patients with prolonged duration and inadequate glycemic control compared to controls [20].

The study found that patients with MetS had significantly lower serum BGP-OST levels than controls (Table 4). A study done by Liu X et al. demonstrated that both forms of osteocalcin (carboxylated **cOST** and uncarboxylated **ucOST**) at lower levels were related to metabolic health (e.g., higher glucose, triglycerides, and lower HDL) [21]. Osteocalcin has been linked to reducing insulin resistance. A study by Viswanath et al. indicated that higher total osteocalcin levels are associated with lowering blood glucose and elevated HDL cholesterol, suggesting its protective effect [22].

Calcitonin levels in this study were not significantly different between patients and control subgroups (Table 3). Because the research about calcitonin in MetS was limited, other studies showed significant differences between patients and control groups compared to this study; a study found that serum calcitonin levels in Type 2 DM patients were lower than those in the control group [23].

I-PTH levels in this study were not significantly different between patient and control subgroups (Table 3). Given the limited research on calcitonin and PTH in MetS, measuring these levels was crucial to confirm that participants did not have bone metabolic diseases. The lack of significant differences supported the accuracy of our findings. A study reported higher serum I-PTH -Vitamin D3 ratio levels in individuals with MetS than those without it. It suggested that it could predict chronic inflammation and dyslipidemia, which aligns with our observations [24]. Similarly, a study found elevated serum I-PTH levels in patients with diabetic mellitus and chronic kidney disease [25]. In contrast, another study indicated that reduced I-PTH levels were associated with decreases in BMI and diastolic blood pressure [26].

Results on Novel Correlations Between DKK1, BGP-OST, and calcitonin in Bone Metabolism

The roles of DKK1, BGP-OST, and calcitonin in bone metabolism are well-recognized, yet their interrelationships remain underexplored. This study investigates the correlations between serum DKK1 and calcitonin levels ($r = -0.332$, $p = 0.009$) and between BGP-OST and calcitonin levels ($r = 0.432$, $p = 0.001$). The findings supply new insights into the potential interplay of these biomarkers in regulating bone homeostasis and may inspire future research directions in bone disease diagnostics and therapeutics. Bone metabolism is a dynamic process regulated by several factors, involving hormones, signaling molecules, and bone-specific proteins. DKK1, a key modulator of the Wnt/β-catenin signaling pathway, has been implicated in bone density regulation and osteoporosis. Calcitonin, a hormone secreted by parafollicular cells of the thyroid gland, inhibits osteoclast activity, thus reducing bone resorption. BGP-OST, a marker of bone formation, reflects osteoblastic activity and overall bone turnover. Despite their roles in an individual's bone health, limited data exist on the direct correlations between these

biomarkers. This study fills this gap by investigating the relationships between DKK1, BGP-OST, and calcitonin levels.

1. Correlation between DKK1 and Calcitonin: A statistically significant negative correlation ($r = -0.332$, $p = 0.009$) was identified, suggesting an inverse relationship between DKK1 and calcitonin levels (Figure 2).
2. Correlation between BGP-OST and Calcitonin: A statistically significant positive correlation ($\gamma = 0.432$, $p = 0.001$) was observed, indicating a potential link between osteoblastic activity and calcitonin (Figure 3).

The inverse correlation between DKK1 and calcitonin supports the hypothesis that these biomarkers may have opposing roles in bone metabolism. While DKK1 is recognized to prevent bone formation through Wnt signaling, calcitonin's inhibitory effect on osteoclasts could counteract DKK1's impact on bone resorption.

The positive correlation between BGP-OST and calcitonin emphasizes a potential feedback mechanism in which calcitonin may support bone formation by promoting osteoblastic activity. These findings relate to understanding the complex interplay of molecular and hormonal factors in bone homeostasis. The ROC curve analysis highlights the diagnostic potential of DKK1 and BGP-OST in metabolic syndrome. DKK1 showed a moderate diagnostic performance with an AUC of 0.758, suggesting its utility as a biomarker for characterizing metabolic syndrome (Figure 4). Conversely, BGP-OST showed lower diagnostic differentiation (AUC = 0.612) but displayed high sensitivity (91.30%), suggesting its potential role in early detection (Table 5, Figure 5). This study provides novel evidence of significant correlations between DKK1, BGP-OST, and calcitonin levels, and insights into their possible roles in bone metabolism. Additionally, the ROC analysis suggests that DKK1 and BGP-OST may be useful biomarkers for metabolic syndrome, with distinct diagnostic characteristics [27-30]. Further research, including mechanistic and longitudinal studies, is needed to support these findings and search for their clinical implications in bone diseases.

Conclusion

Although serum DKK1 levels were not significantly different between patients and control subgroups, DKK1 demonstrated a significant relationship with calcitonin. It displayed diagnostic potential (significant ROC) for identifying patients with metabolic syndrome (MetS). This suggests a possible role of DKK1 in the progression of MetS into more complex diseases involving bone health. Furthermore, the significant difference in serum BGP-OST levels between patients with MetS and controls suggests the potential impact of MetS on bone metabolism. These findings emphasize the importance of further research into the reciprocal action between metabolic syndrome and bone health to better understand and alleviate disease progression.

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This research did not receive funds.

Conflict of Interest

The authors declare no conflict of interest.

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