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Original Research

Frequency of Metabolic Syndrome in Paget's Disease of Bone

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Abstract

Objectives: Our aim is to verify the prevalence of metabolic syndrome (MetS) in Paget's disease of bone (PDB) and to reveal the relationship between MetS and bone alkaline phosphatase (ALP) levels.

Methods: Twenty-three patients with PDB and 30 healthy subjects matched with age, sex, and body mass index (BMI) were recruited from the outpatient clinics of endocrinology. The ınternational diabetes federation -2006 MetS criteria were used for the evaluation of all participants. PDB group and control group were compared in terms of MetS and metabolic components of MetS and bone mineral metabolism parameters.

Results: When the two groups were compared in terms of weight, waist circumference, BMI, and systolic blood pressure (p=0.09, p=0.644, p=0.78, and p=0.058, respectively), no statistically significant difference was found. The frequency of impaired fasting glucose (IFG) and diabetes mellitus (DM) was determined as 30% (7/23) in the PDB group. There were no patients in the control group with IFG and DM diagnosis. The frequency of IFG and DM was statistically higher in the PDB group than controls (p=0.002). The frequency of MetS was statistically higher in the PDB group than the controls. (73.91%, (17/23) vs.30% (9/30); p<0.01). There was a correlation between ALP level and hypertension medication (p=0.0045, r=0.27).

Conclusion: Patients with PDB seem to have MetS more frequently, these patients also should be monitored for MetS.

Keywords: Diabetes mellitus, metabolic syndrome, paget's disease of bone

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Paget's disease of bone (PDB) is classified among primary metabolic diseases of bone such as postmenopausal osteoporosis and hyperparathyroidism.[1] Although it is the second most common metabolic bone disease after osteoporosis, its etiopathogenesis has not been fully understood until now.[2,3] Although PDB is seen in approximately 1% of the population over 55 years of age, it occurs more rarely in Asian countries.[3,4]

It has been found that metabolic syndrome (MetS) components such as high blood pressure (HBP) and impaired fasting glucose (IFG) are more common in PDB.[5-7] In fact, one study has suggested that PDB is not only a disease of bone metabolism, but also a systemic disease associated with glucose metabolism.[5] There are also studies in the literature that determined the frequency of diabetes mellitus (DM) in PDB to be lower than in the control group.[8]

In a study conducted in the 50s, it was suggested that the increased concentration of bone alkaline phosphatase (BAP) in PDB might be a factor contributing to glucose tolerance disorders.[9] The results of recent studies also support these

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findings.[6] In addition, in a large-scale study conducted in patients without diabetes, a statistically significant positive correlation was determined between high BAP level, high glucose level, and insulin resistance.[10]

In a study evaluating glucose metabolism and BP data in PDB, Ca level was found to be higher in PDB group compared to the control group and a positive correlation was found between serum Ca level and glucose metabolism disorders. It has subsequently been suggested that Ca may contribute to changes in glucose metabolism. They reported that this result is consistent with the increase in the frequency of insulin resistance, glucose intolerance, and MetS seen in metabolic bone diseases such as primary hyperparathyroidism with high Ca.[6]

In the literature, the number of studies investigating glucose metabolism and comorbid conditions related to glucose metabolism in PDB is few and the current results are conflicting. This study aimed to investigate the frequency of MetS and to determine whether there is a correlation between metabolic parameters and BAP in PDB.

Methods

In this study, 23 patients with PDB followed up in Sisli Hamidiye Etfal Training and Research Hospital Endocrinology Polyclinic between 2009 and 2020 and 30 healthy controls matched in terms of age and gender and body mass index (BMI) were included in the study. PDB's diagnosis was made with high BAP level and monostotic or polyostotic bone involvement in bone scintigraphy. All of our patients with PDB had received IV and/or oral bisphosphonate therapy before the study. Patients with concomitant hyperparathyroidism, thyrotoxicosis, iatrogenic or endogenous hypercortisolemia, and osteosarcoma were excluded from the study. The healthy control group consisted of age and gender-matched individuals who applied to our outpatient clinic for any reason and did not have any disease causing Ca metabolism disorders such as Vitamin D deficiency, familial hypocalciuric hypercalcemia, and primary hyperparathyroidism. The study protocol was approved by the Local Ethics Committee and was performed in accordance with the Declaration of Helsinki (no: 1908, date: 25.05.2021). Oral and written informed consent forms were obtained from all subjects participating in the study.

Our study was designated as a cross-sectional and case–controlled study. All participants underwent a thorough medical evaluation and physical examination. The presence of hypertension/antihypertensive treatment, abnormal glucose intolerance/DM/antihyperglycemic treatment, hyperlipidemia/antihyperlipidemic treatment, and measurement of waist circumference were assessed for the evaluation of MetS criteria. After an overnight fasting, blood samples were taken early in the morning for serum Ca, phosphorus (PO4), total alkaline phosphatase (ALP), PTH, albumin, creatinine, glucose, HbA1c, triglyceride (TG), total cholesterol, low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL). BAP level was also studied in the PDB group. BP was measured twice after 5 min rest in sitting position using a manual sphygmomanometer and the average of the two measurements was taken. Height (cm), weight (kg), waist circumference (cm) were measured. The formula weight (kg) divided by height squared (m^2) was used to calculate BMI kg/m^2. Waist circumferences were measured from the midway between the lower rib margin and the iliac crest while the patients were naked. The MetS was defined according to the ınternational diabetes federation-2006 criteria.[11] The diagnosis of MetS was made when a waist circumference of ≥80 cm in women and 94 cm in men, or BMI of >30 regardless of waist circumference, was accompanied by at least two of the followings: BP ≥130/85 mmHg, glucose ≥100 mg/dl or a history of type 2 DM, TG ≥150 mg/dl, HDL-C <40 mg/dl in men, and <50 mg/dl in women.

Biochemical Evaluation

Serum Ca level (normal range: 8.6–10.2 mg/dL) was evaluated by the orthosolphthalein dye binding method in Cobas c 701/702 (Roche Diagnostics, Mannheim, Germany). The intra-assay and inter-assay coefficient variants for Ca were 0.9–1.2% and 1.2–1.4%, respectively. Serum PTH (normal range: 15–65 pg/mL) was evaluated by electrochemiluminescence immunoassay (ECLIA) in Cobas e-601 (Roche Diagnostics, Mannheim, Germany). The inter-assay coefficients for PTH were 1.1–2% and intra-assay coefficients for PTH were 2.8–3.4%. Plasma glucose (normal range: 74–106 mg/dL) was analyzed by the hexokinase enzymatic method (Olympus AU 2700), HbA1c (normal range: 4–6%) in TOSOH G8 (Tosoh Bioscience, San. Francisco, CA, USA). Serum total cholesterol, TG, and lipoprotein fractions were determined by colorimetric method in Cobas c 701 (Roche Diagnostics, Mannheim, Germany). LDL-C was defined by the Friedwald Formula: (total cholesterol – [HDL-C] – [TG × 0.45]) in mg/dL.

Statistical Analysis

The absolute data and percentage distributions were analyzed using descriptive statistics and presented as mean, standard deviation, percentage, and frequency. The distribution of the variables was confirmed by the Kolmogorov–Smirnov test. Quantitative values were analyzed by ANOVA (Tukey test), Kruskal–Wallis, and Mann–Whitney U test. Qualitative values were analyzed by Chi-square and Fisher's test. Correlation between parametric data, Pearson's

linear regression analysis, and Spearman correlation test was used for non-parametric data. P<0.05 was accepted as statistically significant. SPSS 21.0 was used for statistical analysis.

Results

No significant difference was found between PDB group and controls when evaluated for age, gender, and PTH. As expected, the ALP level was shown to be significantly higher in the PDB group than in the control group (p<0.001). Ca, PO4, and albumin levels were found to be significantly lower in the patient group than the control group (p=0.02, p=0.002, and p<0.001, respectively). Demographic and biochemical data are summarized in Table 1.

The two groups did not differ in terms of weight, waist circumference, BMI, and systolic BP (SBP) (p=0.09, p=0.644, p=0.78, and P = 0.058, respectively) The diastolic BP (DBP) of the PDB group was statistically higher than the control group (p=0.042). When the PDB group was compared with the control group concerning fasting blood glucose and HDL cholesterol values, which are metabolic parameters, it was observed that fasting blood glucose was higher and HDL cholesterol value was lower in the PDB group compared to the control group (p=0.07 and p<0.01, respectively). The groups did not show significant difference between for the LDL cholesterol and TG values of both groups (p=0.938 and p=0.33, respectively). The biochemical parameters which are showing the anthropometric and metabolic status of the PDB and control groups are shown in Table 2.

The frequency of IFG and DM was determined as 30% (7/23) in the PDB group. There were no patients in the control group with IFG and DM diagnosis. When both groups were compared in terms of the frequency of IFG and DM, it was found that the frequency of IFG and DM was statistically higher in the PDB group (p=0.002). The frequency of HT was 47% (11/23) in the PDB group and 20% (6/30) in the control group. When both groups were compared, the frequency of HT was statistically higher in the PDB group (p=0.04). While the frequency of taking antihypertensive treatment in the PDB group was 47% (11/23), the frequency of taking antihypertensive treatment in the control group was 13% (4/30). When both groups were compared in terms of the frequency of taking antihypertensive treatment, it was determined that the frequency of taking antihypertensive treatment was statistically higher in the PDB group than in the control group (p=0.01). While the frequency of MetS was 73.91% (17/23) in the PDB group, the frequency of MetS was found to be 30% (9/30) in the control group. When both groups were compared, the frequency of MetS was statistically higher in the PDB group than in the control group (p<0.01). The incidence of MetS components in the PDB group and control group is summarized in Table 3.

Table 1. Demographic and biochemical characteristics of Paget's patient and control groups

	Patient (Mean±SD)	Control (Mean±SD)	p
Age (years)	57.65±9.67	53.89±7.41	0.11
Total ALP	242.73±208.44	69.66±21.70	<0.001
PTH	44.6±15.70	47.80±9.66	0.37
Ca	9.30±0.52	9.55±0.30	0.02
PO4	3.25±0.69	3.65±0.50	0.002
Albumin	4.09±0.36	4.52±0.27	<0.001
	n (%)	**n (%)**	
Gender			
Female	13 (56.53)	21 (70)	0.234
Male	10 (43.47)	9 (30)	

Table 2. Biochemical data showing the anthropometric and metabolic profile of Paget's patient and control groups

	Patient (Mean±SD)	Control (Mean±SD)	p
Weight (kg)	75.47±10.04	77.23±12.36	0.09
BMI (kg/m^2)	29.93±5.98	29.50±5.35	0.78
WC (cm)	98.34±10.89	97.00±10.09	0.644
Systolic BP (mmHg)	120.17±23.87	117.17±11.46	0.058
Diastolic BP (mmHg)	78.5±12.04	72.83±7.66	0.042
Glucose (mg/dl)	100.04±23.01	91.90±7.42	0.07
Triglyceride (mg/dl)	136.63±48.36	125±20	0.33
HDL-C (mg/dl)	45.74±10.64	61.75±19.19	<0.001
LDL-C (mg/dl)	139.86±25.97	140.51±32.48	0.938

BMI: Body mass index; WC: Waist circumference; BP: Blood pressure.

Table 3. Frequency of metabolic syndrome components in Paget's patient and control groups

	Patient, n %	Control, n %	p
DM/BAG	7/23, 30	0/30, 0	0.002
Anti-HG Tx	3/23, 13	0/30, 0	0.07
HT	11/23, 47	6/30, 20	0.04
Anti-HT Tx	11/23, 47	4/30, 13	0.01
HL	10/23, 43	19/30, 63	0.17
Anti-HL Tx	3/23, 13	1/30, 0.3	0.3
MetS	17/23, 73.91	9/30, 30	<0.01

DM: diabetes mellitus; IFG: impaired fasting glucose; Anti-HG Tx: antihyperglycemic therapy; HBP: hypertension; Anti-HBP Tx: antihypertensive therapy; HL: hyperlipidemia; Anti-HL Tx: antihyperlipidemic therapy; MetS: metabolic syndrome.

A correlation was found between total ALP (both in PDB and control groups) and those receiving antihypertensive treatment (p=0.045, r=0.27). A significant positive correlation was also found between total ALP and age (p=0.01, r=0.485). No correlation was found between BAP and DM, IFG and MetS.

Discussion

In our study, we found that DM, IFG, and MetS were more common in PDB group, DBP and SBP were higher than the control group, but SBP value did not create a statistically significant difference between the two groups. We also found that HDL levels were lower in PDB group than in the control group.

MetS is an endocrinopathy consisting of heart attack risk factors such as DM, IFG, abdominal obesity, HL, and HT.[11,12] It is estimated that approximately 20–25% of the adult population in the world has MetS. It is one of the most common chronic diseases and is the fourth or fifth cause of death worldwide.[11] Although the etiopathogenesis of the MetS is not fully understood, the most of the evidence suggests that insulin resistance and low-grade inflammation play a major role in the development of MetS.[13,14] Although there are a few studies investigating the frequency of glucose metabolism and HT in patients with PDB in the literature, there is no study investigating the frequency of MetS.

Moehlig and Abbott. examined patients with PDB by performing a glucose tolerance test and showed that 27–31 patients had impaired glucose tolerance. They even found that the prevalence of obesity and DM increased in the family anamnesis of patients with PDB and proposed that PDB is a systemic disease that affects not only bone metabolism but also carbohydrate metabolism.[5] In a recent study, it was determined that the prevalence of IFG was more common in patients with PDB than in the control group and that fasting blood glucose was higher in patients with PDB than in the control group. They based their results on the previously proposed hypothesis that it could be achieved by increasing intestinal glucose absorption and dephosphorylation of glucose phosphatase through serum BAP. Again, they hypothesized that nephrocalcinosis may occur through the elevation of BAP, and HT may occur as a result of loss of elasticity of calcified vessels.[6,7,9] In our study, we found that the frequency of IFG, DM, and MetS, DBP, and SBP was higher in patients with PDB than in the control group, although there was no statistically significant difference in support of other studies and hypotheses.

ALP, a metalloenzyme that catalyzes the hydrolysis of monophosphate esters in an alkaline pH environment, is a widely used marker in the diagnosis of PDB and in the evaluation of treatment response.[15] In recent studies, it has been found that ALP is associated with cardiometabolic diseases such as HT, Type 2 DM, and HL.[16,17] Moreover, in a study conducted on 3773 people without DM, a correlation was found between mean BP, HDL, MetS, and BAP.[10] Again, in a population-based study, it was shown that the total ALP value was independently and positively associated with MetS in both male and female gender.[18] In another study, they found that the prevalence of IFG was more common in patients with PDB than the control group, that fasting blood glucose was higher in patients with PDB than in the control group, and that there was a correlation between glucose values and serum BAP levels.[6] In our study, we found that the prevalence of MetS was common in patients with PDB, which was statistically significant compared to the control group, but we could not find a correlation between BAP value and MetS. This may be due to the small number of patients included in this study and the fact that our patients had previously received bisphosphonate therapy.

It has been reported that 12–18% of PDB may have secondary normocalcemic hyperparathyroidism. It has been reported that the underlying mechanism may occur as a result of the increased Ca requirement during the active new bone formation periods specific to Pagetic bone.[19,20] Ozturk et al. compared normocalcemic primary hyperparathyroidism (NC-PHPT), primary hyperparathyroidism with hypercalcemia (HC-PHPT), and healthy control group in terms of MetS prevalence. They found that the frequency of MetS in NC-PHPT was similar with HC-PHPT and more common than control group.[21] In our study, we determined that the frequency of MetS was more common in patients with PDB than the control group, similar to NC-PHPT patients. In their study, some authors found that the serum Ca value was higher in the patients with PDB compared to the control group, and the Ca value showed a positive correlation with the glucose level.[6] It has been shown that glucose metabolism disorders such as insulin resistance, IFG, and MetS are increased in clinical conditions such as hypercalcemic primary hyperparathyroidism with high serum Ca levels.[22] In our study, we found that the Ca value in PDB was lower than in the control group. The lower Ca value in PDB compared to the control group may be due to the fact that they received bisphosphonate therapy.

Since the frequency of the disease is generally low, and it is seen at an even lower rate in our country, a small number of cases were recruited to the study. This may be a limitation for the study. Second, the patients had previously received bisphosphonate therapy. Third, insulin resistance, which is thought to play an important role in the etiopathogenesis of MetS, has not been evaluated.

In the light of our results, which are consistent with the studies in the literature, we think that patients with PDB have an effect not only on bone metabolism but also on glucose metabolism, and the patients with PDB should be evaluated in terms of MetS and cardiovascular diseases caused by it. However, relatively large-scale studies are needed to support our findings in our country where the prevalence is low.

Disclosures

Ethics Committee Approval: The study was approved by the Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee (Date: 25/05/2021, no: 1908).

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Conflict of Interest: None declared.

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