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ORIGINAL ARTICLE

Serum Preptin as a Potential Hormonal Biomarker of Bone Metabolic Abnormalities in Children with Type1 Diabetes Mellitus

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ABSTRACT

Type1 diabetes mellitus (T1DM) is linked to multiple systemic complications, including disruptions in bone metabolism complications, such as disruptions in bone metabolism, especially in children at critical stages of growth. Preptin, a peptide hormone released alongside insulin, has recently been identified as a possible regulator of bone formation possible bone formation regulator. The purpose of the study was to assess the potential of serum preptin as a hormonal biomarker used to detect bone metabolic abnormalities in children with type 1 diabetes mellitus and to determine the relationship between serum preptin and the biochemical parameters and glycemic status. A case-control study was carried out among 50 Iraqi children comprising of 30 T1DM patients and 20 healthy controls. ELISA was used to measure serum preptin levels and by spectrophotometer to measure fasting blood glucose (FBS), alkaline phosphatase (ALP), calcium, and phosphate. The Student's t-test was used for statistical analysis the statistical significance and receiver operating characteristic (ROC) curve was used to assess the diagnostic performance of preptin. The level of serum preptin was considerably lower in T1DM patients than in controls ($p < 0.0001$) whereas the level of ALP and FBS were significantly higher ($p = 0.0003$ and $p < 0.0001$, respectively). The level of calcium was significantly decreased in patients ($p = 0.0249$), but no significant difference was observed in phosphate levels. Correlation analysis showed weak correlations between preptin and FBS, and an inverse correlation between preptin and ALP in the patients. ROC analysis showed that preptin has excellent diagnostic performance (AUC = 0.924, sensitivity = 100% and specificity = 93.3%). Preptin levels are significantly reduced in children with T1DM and can be a potential biomarker to detect bone metabolic abnormalities early. Its diagnostic quality and relating to bone-related variables underscores its possible clinical application in the detection of bone metabolic abnormalities associated with T1DM patients.

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1- INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune disease that involves the destruction of pancreatic β -cells and the complete lack of insulin, which causes persistent hyperglycemia hyperglycemia and systemic complications in the body [1]. Although the microvascular and macrovascular effects of T1DM have been well documented, attention has been on its effects on the bone health especially in children and adolescents at key stages of skeletal growth and development [2]. Growing evidence suggests, T1DM is linked to the impaired bone mineralization, decreased bone mineral density (BMD) and a higher risk of fractures, which means that the disease has adverse effects on bone metabolism beyond the glycemic dysregulation [3]. The pathophysiological processes that cause bone abnormalities in T1DM are complex. The insulin deficiency is a key factor, insulin being an anabolic hormone that enhances the growth and development of osteoblasts and bones [4]. Moreover, chronic hyperglycemia also leads to the increase of advanced glycation end products (AGEs) that adversely affect the quality of bone matrix and decrease the strength of bones [5]. Disturbances in bone remodeling are also worsened by changes in calcium and phosphate homeostasis, as well as vitamin D deficiency and secondary hyperparathyroidism [6]. Additionally, the effects of inflammatory cytokines and oxidative stress related to T1DM can suppress the activity of the osteoblast and increase the activity of osteoclasts that lead to the disruption of the bone formation and breakdown balance [7].

Recently the focus has been on the development of new hormonal biomarkers which can indicate the early alterations in bone metabolism in diabetic patients. One of these is preptin, a 34 amino acid secreted pancreatic β cell co-secreted with insulin that has been identified as a possible regulator of bone physiology [8]. Preptin is demonstrated to stimulate osteoblast activity and bone development, and this implies that it may have involvement in skeletal integrity maintenance [9]. The decreased amount of preptin in T1DM, as a result of the β -cell dysfunction, might contribute to reduced bone formation and increase the risk of bone disorders formation and predisposes bone metabolic abnormalities in children with T1DM [10]. Although preptin is a metabolic and bone-related hormone with increasing interest, there have been few studies on the role of preptin in pediatric T1DM especially in the context of biochemical indicators of bone turnover including alkaline phosphatase (ALP), calcium, and phosphate [11]. Moreover, the evidence of the population in the Middle East, as well as of the Iraqi children, is limited, which indicates a gap in the literature. Thus, the objective of the study was to determine serum preptin levels as a possible hormonal biomarker of bone metabolic disorders in children with type 1 diabetes mellitus and explore its correspondence to biochemical bone turnover and glycemic condition indicators. Also, receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of preptin to ascertain its clinical relevance in detecting bone changes in this population.

2- MATERIALS AND METHODS

2.1 Study Design and Population

The study was a case–control study, and it was carried out at the Children's Welfare Teaching Hospital, Medical City Complex, Baghdad, Iraq, between the first of January 2024, and the first of July 2024. The sample size was estimated using G*Power software (version 3.1). Assuming a two-tailed significance level ($\alpha = 0.05$), a statistical power of 80%, and a large anticipated effect size based on previous studies evaluating serum preptin levels in children with type 1 diabetes mellitus, a minimum sample size of 44 participants was required. To compensate for possible missing data, 50 participants were enrolled, including 30 patients and 20 healthy controls. The age of participants ranged from 6 to 12 years. The average years of diabetes in patients was 3.6 years. The healthy controls were chosen among family members of hospital employees to make them similar in terms of environmental and socioeconomic factors. Parents or legal guardians of all participants were informed about the study and gave informed consent before participating. Before sample collection all subjects were asked to fast overnight.

2.2 Blood Sample Collection

Sterile disposable syringes were used to collect 5 mL of venous blood under aseptic conditions. The blood samples were collected in the morning (9:00 AM to 12:00 PM), which reduced the diurnal variation. The blood was transferred into plain tubes in about 2 mL of blood, and left to clot at room temperature (30 minutes). Serum was centrifuged at 3000 rpm and 10min and kept in clean plastic tubes at -20 °C till preptin hormone levels were analyzed. The rest 3 mL of blood was handled instantly and the serum separated was utilized to determine the biochemical parameters such as fasting blood glucose (FBS), alkaline phosphatase (ALP), calcium, and phosphate.

2.3 Measurement of Studied Parameters

2.3.1 Serum Preptin Assay

The preptin level in the serum was measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (MyBioSource, USA), which is designed to determine the level of preptin in the serum and plasma samples quantitatively. The principle of the assay is the biotin double-antibody sandwich method, where serum samples are incubated in the pre-coated microplate wells with monoclonal anti-preptin antibodies. Biotin-labeled antibodies against preptin are added after incubation followed by streptavidin–horseradish peroxidase (HRP), which constitute an immune complex. Washing eliminates unbound components and color development is carried out by the addition of chromogenic substrates (solutions A and B). The color intensity is directly proportional to the preptin concentration in the sample, and is spectrophotometrically measured [11].

2.3.2 Measurement of Fasting Blood Glucose (FBS)

Serum glucose levels were determined spectrophotometrically using the glucose oxidase–peroxidase method, based on the following reactions:

$$\text{Glucose} + O_2 + H_2O \rightarrow \text{gluconic acid} + H_2O_2$$
$$H_2O_2 + \text{4-aminophenazone} + \text{phenol} \rightarrow \text{quinoneimine} + H_2O$$

The absorbance of the colored product is directly proportional to glucose concentration.

2.3.3 Measurement of Alkaline Phosphatase (ALP)

Serum alkaline phosphatase activity was measured spectrophotometrically at a wavelength of 405 nm using the p-nitrophenyl phosphate method. In this reaction:

$$\text{p-nitrophenyl phosphate} + H_2O \rightarrow \text{phosphate} + \text{p-nitrophenol}$$

The rate of formation of p-nitrophenol is proportional to ALP activity [12].

Serum alkaline phosphatase activity was measured according to the routine laboratory protocol and reported in King–Armstrong Units (K.A.U.), which remain the standard reporting unit used by the participating clinical laboratory. Consequently, ALP values are presented in K.A.U. throughout the study.

2.3.4 Measurement of Serum Calcium

The levels of serum calcium were identified spectrophotometrically at 570 nm through o-cresolphthalein complexone method. In the presence of an alkaline solution the calcium ions react with o-cresolphthalein to produce a violet complex. The color strength directly depends on the concentration of calcium. Normal range of serum calcium is 8.1-10.4 mg/dL [13].

2.3.5 Measurement of Serum Phosphate

The phosphate levels in serum were determined spectrophotometrically at 690 nm. The inorganic phosphate reacts with molybdic acid to produce phosphomolybdic acid which is later reduced to molybdenum blue. Phosphate concentration is proportional to the absorbance of the blue complex. The normal reference range is 2.5–4.9 mg/dL [14].

2.4 Statistical Analysis

The statistical package of social sciences (SPSS), version 23 was used to analyze the data. Descriptive statistics were presented as a mean with a standard deviation (SD). Student t-test was used to compare the groups. A p-value < 0.05 was considered to be significant. The receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic performance of preptin hormone levels, such as sensitivity, specificity and area under the curve (AUC).

3- RESULTS AND DISCUSSION

3.1 Comparison of Hormonal and Biochemical parameters

Children with T1DM showed statistically significant differences in several parameters compared to healthy controls (Table 1). Table.1 indicates that Serum preptin hormone level was significantly lower in the patient group (307.50 ± 26.42 ng/ml) than in control group (1214.00 ± 159.40 ng/ml), which shows a highly significant difference indicating hyperglycemia ($p < 0.0001$) (Figure 1). In contrast, alkaline phosphatase (ALP) levels were significantly elevated in T1DM patients (26.33 ± 1.79 K.A.U) compared to controls (17.02 ± 0.73 K.A.U), ($p = 0.0003$) (Figure 2). The level of fasting blood sugar (FBS) showed a significant difference between the patient group (238.7 + 22.09 mg/dl) and controls (86.20 + 1.96 mg/dl) with the patient group showing hyperglycemic status ($p = 0.0001$). The calcium level in the serum of patients (8.492 ± 0.13 mg/dl) compared to controls (8.927 ± 0.10mg/dl), ($p = 0.0249$) (Figure 3) showed that calcium homeostasis is disturbed.

Figure 4 however, did not show a statistically significant difference between the two groups in serum phosphate levels (3.721 + 0.13 vs. 3.860 + 0.12 mg/dl, $p = 0.4850$).

The mean of serum calcium concentrations in the children with T1DM (8.492 ± 0.13 mg/dL) was not significantly different from that of the accepted pediatric reference range (8.1–10.4 mg/dL) but was significantly lower than that of the control group, indicating slight disturbance in calcium homeostasis. Similarly, serum phosphate levels in both groups were normal for children (2.5–4.9 mg/dL), and no significant difference was found between patients and controls. The level of serum alkaline phosphatase was higher in children with T1DM than in healthy controls. The higher ALP levels in the patient group could be due to pathological liver disease, but the elevated levels should be taken into account when considering skeletal growth and comparing to ALP reference values, which vary with age, sex, and pubertal status.

Table (1): Comparison of biochemical and hormonal parameters T1DM vs control

Parameter	Control Group (Mean ± SD)	T1DM Patients (Mean ± SD)	p-value
Preptin (ng/mL)	1214.00 ± 159.40	307.50 ± 26.42	< 0.0001
Alkaline phosphatase (K.A.U)	17.02 ± 0.73	26.33 ± 1.79	< 0.0001
Fasting blood glucose (mg/dL)	86.20 ± 1.96	238.7 ± 22.09	< 0.0001
Calcium (mg/dL)	8.927 ± 0.10	8.492 ± 0.13	0.0249
Phosphate (mg/dL)	3.860 ± 0.12	3.721 ± 0.13	0.4850

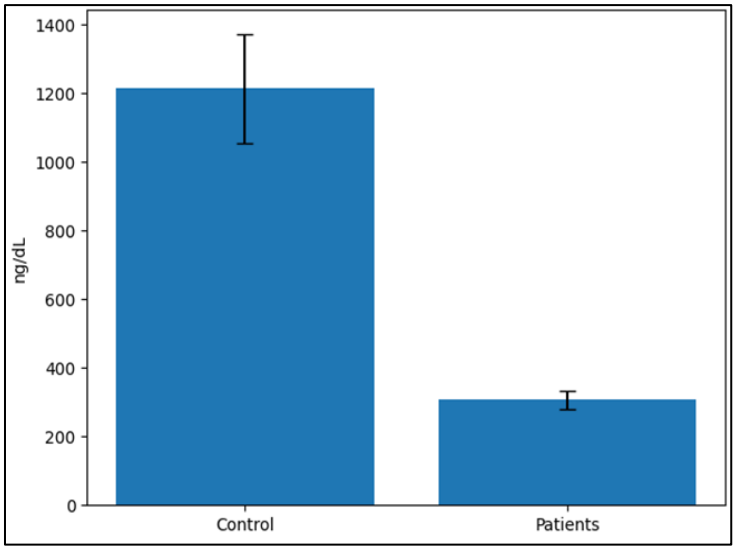

Fig (1): preptin level in serum in T1DM patients and control

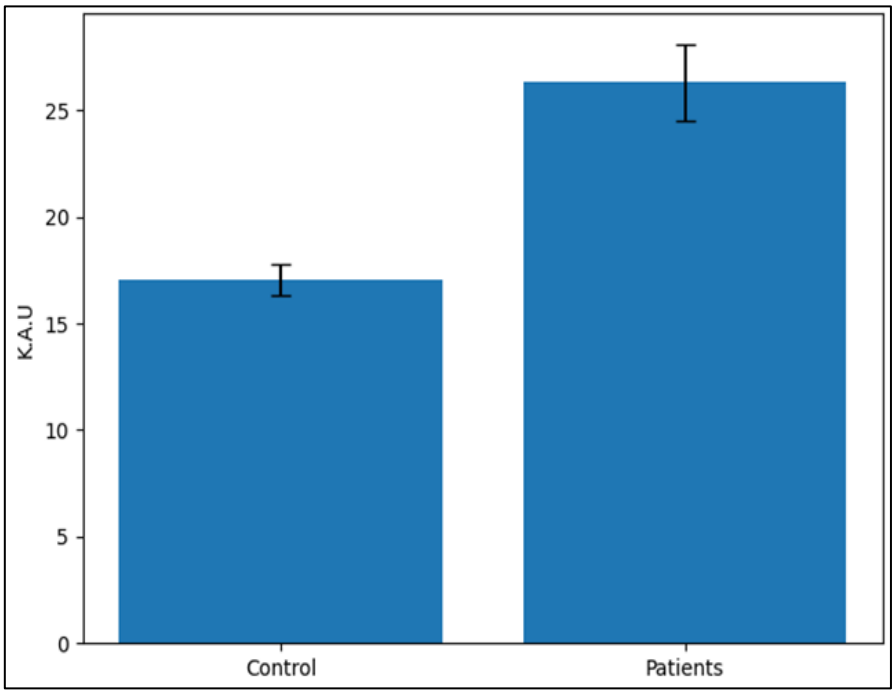

Fig (2): alkaline phosphatase (ALP) level in serum in T1DM patients and control

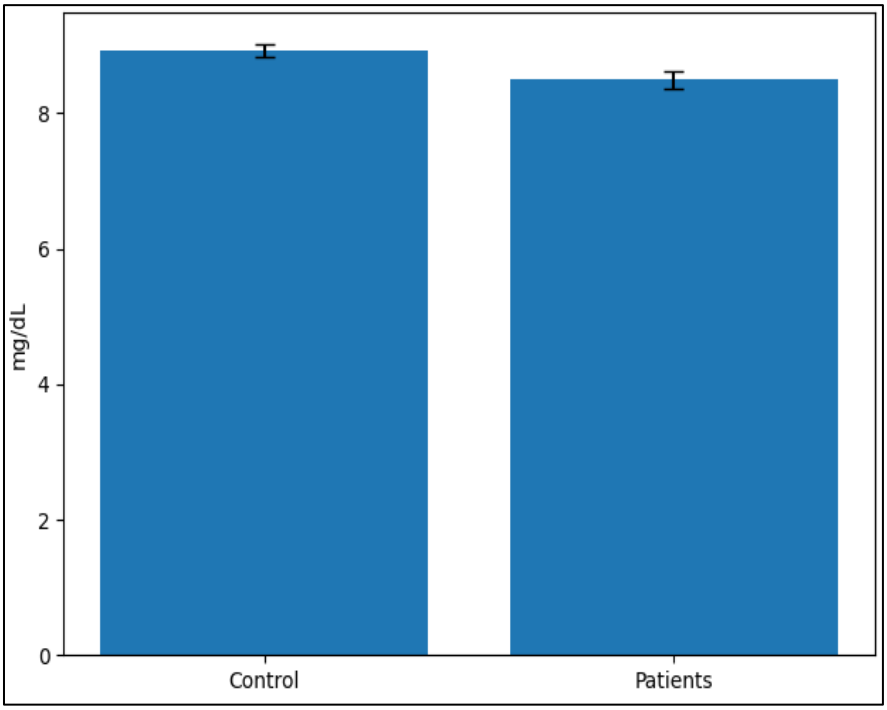

Fig (3): calcium level in serum in T1DM patients and control

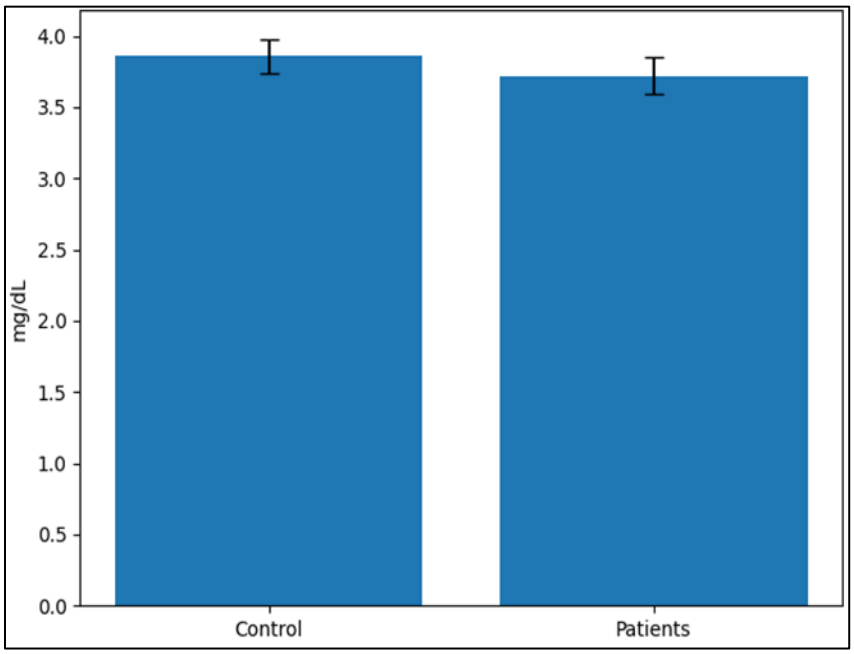

Fig (4): Phosphate level in serum in T1DM patients and control

3.2 Correlation Analysis

The relationships of serum preptin to metabolic parameters were assessed by correlation analysis in both study groups. In the control group, no significant relation was found between serum preptin and Fasting Blood Glucose (FBS), suggesting that the level of preptin remained relatively stable in the normal physiological range of glucose concentration (Figure 5A). Similarly, in children with type 1 diabetes mellitus, the correlation between the serum preptin and the FBS was weak and statistically non-significant (Figure 5B), indicating that the FBS does not directly influence the serum preptin level. In the control group, no significant correlation was found between preptin and alkaline phosphatase (ALP) in the serum (Figure 6A). In the T1DM group, the preptin level was inversely correlated with ALP with a weak correlation (Figure 6B) indicating possible association of decreased preptin level with changes in bone turnover activity in diabetic children.

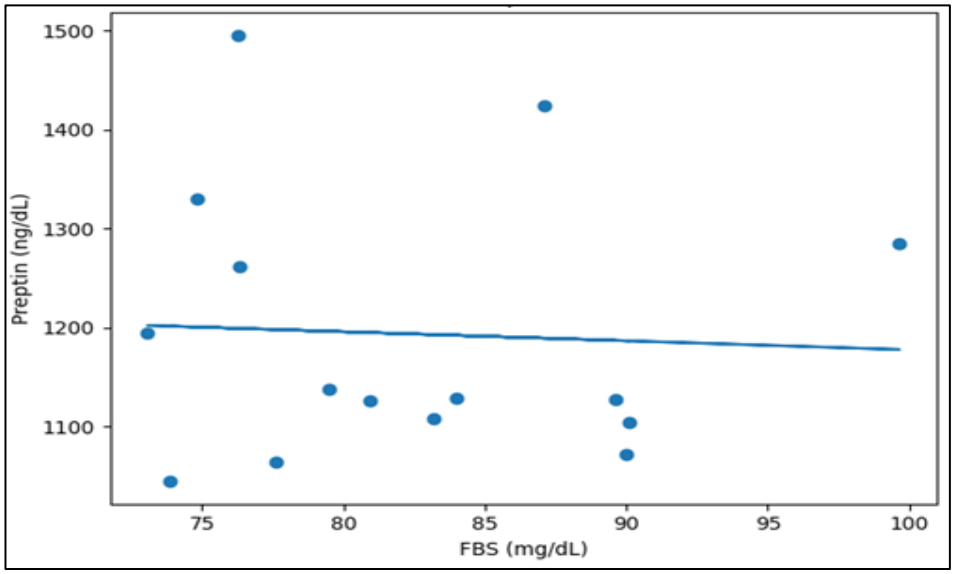

Fig (5A): Scatter plot showing the relationship between fasting blood glucose and serum preptin levels in healthy controls

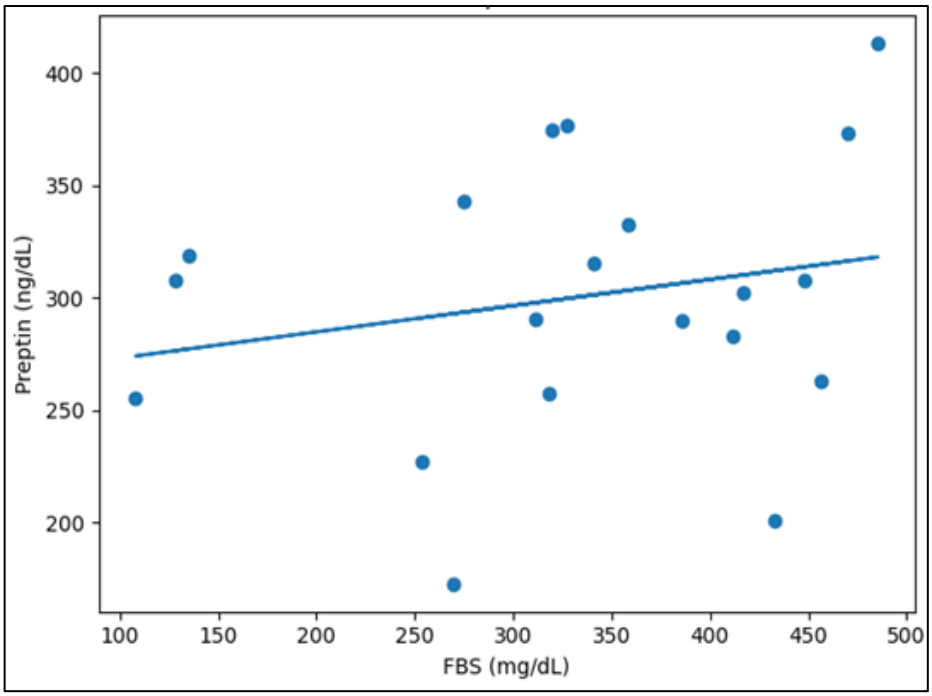

Fig (5B): Scatter plot showing the relationship between fasting blood glucose and serum preptin levels in children with type 1 diabetes mellitus

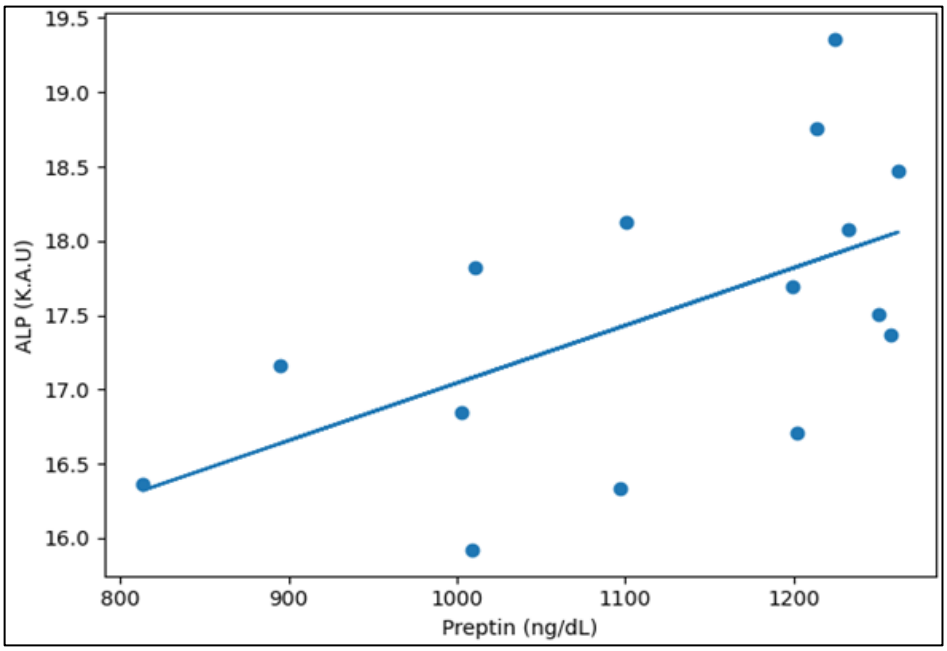

Fig (6A): Scatter plot showing the relationship between alkaline phosphatase and serum preptin levels in healthy controls

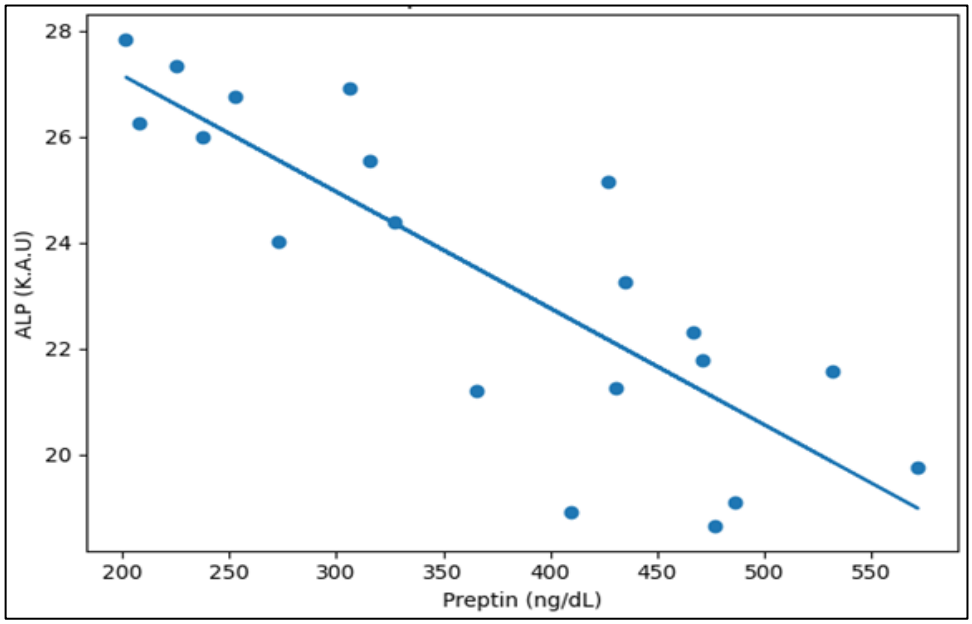

Fig (6B): Scatter plot showing the relationship between alkaline phosphatase and serum preptin levels in children with type 1 diabetes mellitus

3.3 Diagnostic Performance of Preptin Hormone

The area under the receiver operating characteristic (ROC) curve for serum preptin in differentiating type 1 diabetes mellitus from healthy controls was 0.924 ($p < 0.0001$). The final analysis showed a sensitivity of 100% and a specificity of 93.3%, which means that the test has a very high discriminatory ability. The optimal diagnostic threshold was calculated by the Youden index and defined as the serum preptin concentration (ng/mL) where the sensitivity and specificity were maximized (Figure 7).

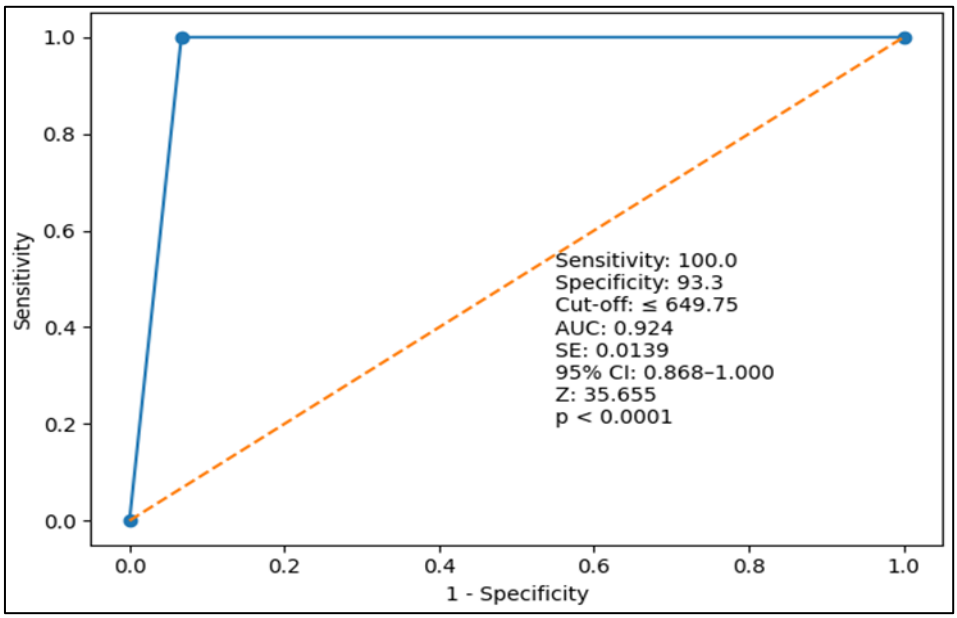

Fig (7): Receiver operating characteristic (ROC) curve analysis of serum preptin for distinguishing children with type 1 diabetes mellitus from healthy controls (AUC = 0.924, $p < 0.0001$). The optimal cut-off value was determined using the Youden index and expressed as serum preptin concentration (ng/mL)

The analysis showed good diagnostic performance of preptin hormone, area under the curve (AUC) of 0.924, sensitivity of 100, specificity of 93.3 as well as an optimal cut-off value of 0.924 (P< 0.0001). These results suggest that preptin is a highly sensitive and specific biomarker and can be effectively used to differentiate children with type 1 diabetes mellitus and healthy controls as well as can be used as an early predictor of bone metabolic changes related to the disease.

The current study indicated that the concentration of preptin in the serum was significantly lower in the T1DM group than in healthy controls but not significantly different between groups for alkaline phosphatase (ALP) activity, fasting blood glucose (FBG) levels or serum calcium levels, with levels being significantly higher in the T1DM group than in healthy controls. These results suggest that T1DM is also linked to an increased bone metabolism and disruption of the bone's normal turnover and remodeling, probably due to insulin lack, chronic hyperglycemia, oxidative stress and altered bone remodeling. Previous reviews and meta-analyses also have shown a reduction in BMD and deterioration in bone quality in children and adolescents with T1DM [15–18]. The significantly lower levels of serum preptin found in the diabetic group is biologically relevant, as preptin is also secreted together with insulin from the pancreatic β-cells, and has been shown to promote osteoblast proliferation and bone formation. Thus, it is possible that the autoimmune destruction of the β-cells in T1DM may result in a decrease in insulin and preptin secretion, which can impair bone formation. Children with T1DM also have similar serum preptin reductions reported [19–21]. In contrast, raised levels of preptin in insulin-resistant conditions like type 2 Diabetes mellitus may be due to intact or enhanced insulin production only, and not reflecting opposing biological mechanisms.

The level of serum ALP was significantly higher in T1DM, indicating that there is increased bone turnover or compensation bone remodeling while growing. The changes in bone turnover markers in children with T1DM have been previously reported but results are conflicting due to differences in age, pubertal stage, glycemic control, nutritional status, vitamin D status, and the type of ALP measured (total versus bone specific) [22-24]. Therefore, the physiological rise in children as a result of the skeletal growth needs to be taken into account when interpreting ALP, and the high levels recorded in this study should not be attributed to a single biochemical defect [23]. The serum calcium level was significantly decreased in children with diabetes supporting the hypothesis of disturbed mineral metabolism. Comparable findings have been linked to vitamin D deficiency and calcium imbalance in T1DM children, which could affect bone mineralisation and bone quality [25–27]. However, the serum phosphate levels were maintained within the normal range and did not differ between groups and thus may not be a sensitive early marker for diabetes-associated bone metabolic abnormalities in children without renal insufficiency [28–30].
The very high fasting blood glucose levels confirmed the hyperglycemic status of the patient group. The simultaneous decrease in preptin and calcium with increase in ALP as seen in the present study may be explained by the involvement of chronic hyperglycemia-induced mechanisms that may decrease the quality of bone such as the accumulation of advanced glycation end products, oxidative stress, and inhibition of osteoblast activity [31–33].
The correlation analysis revealed only weak correlations between preptin levels in the serum and fasting blood glucose levels in both groups, indicating that the fasting blood glucose level does not directly regulate preptin in serum. Preptin, on the contrary, seems to be more closely related with the secretory function of β-cells and insulin physiology than with glycemic control. This observation is in line with earlier reports of diabetic bone disease being caused by a complex interaction of insulin deficiency, duration of the disease, mineral homeostasis and metabolic control, rather than by fasting glucose per se [34–40]. Likewise, the poorly correlated association between preptin and ALP in the T1DM children could reflect that bone remodeling may be altered in the presence of decreased preptin levels. The presence of preptin's osteogenic effect makes it possible that low circulating levels and high ALP could be a sign of dysregulated bone turnover, rather than an efficient bone formation. Similar changes in bone turnover markers and bone quality have been reported in children with T1DM, but results have varied significantly from one study to another, likely due to differences in their study populations and metabolic profile [41–45].
Overall, the present results highlight that, in children with T1DM, preptin levels in serum could be a promising hormonal marker of bone metabolic abnormalities, especially in combination with the common serum biochemical markers of bone health, ALP and calcium. The small sample size and lack of bone-specific turnover markers, vitamin D, PTH and bone mineral density measurements, however, suggest that larger prospective studies are needed to confirm the clinical value of preptin as an early marker of skeletal changes in children with T1DM [46].

4- CONCLUSION

Children with type 1 diabetes mellitus demonstrate significant disruption in bone metabolism which is in the form of low preptin levels, elevated alkaline phosphatase activity, and decreased calcium concentrations. Preptin showed good diagnostic performance, which suggests that it could be a good biomarker to detect bone metabolic changes in this population at an early stage. Its poor correlation with glycemic status indicates that it is a measure of β -cell dysfunction and skeletal imbalance instead of glucose levels per se. Despite limitations including the small sample size, preptin has the potential to be used as an effective instrument in early detection and treatment of bone complications in children with T1DM and this should be investigated further.

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