Original Article

Serum Procollagen Type I N-Terminal Propeptide (PINP) in Adults with Type 2 Diabetes Mellitus in Kalar, Kurdistan Region of Iraq

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is known to be associated with an increased susceptibility of fractures despite normal or high bone mineral density, indicating the poor quality of bones and abnormal collagen turnover. Procollagen type I N-terminal propeptide (PINP) is a sensitive biochemical marker of bone formation and collagenogenesis. **Objectives:** To evaluate serum PINP concentrations and some metabolic parameters in patients with T2DM compared to healthy controls. **Materials and Methods:** This cross-sectional study comprised 42 T2DM and 37 healthy participants between the age of 40 and 70 years. Fasting Blood Samples for measuring fasting plasma glucose (c), A1C, Triglycerides, Total Cholesterol, Albumin Bound-Calcium (AB-Ca), ALP and PINP were drawn after an overnight fast. Biochemical indexes were detected by automated analyzer, and PINP was detected by enzyme linked immunosorbent assay. Statistical analyses unpaired t tests and Chi-square tests were used for statistical comparisons. **Results:** FPG, A1C, and triglyceride were higher in T2DM participants as compared to controls ($P = 0.001$, $P = 0.001$, and $P = 0.032$ respectively). Both hypertension and sedentary life style were more frequent in diabetic subjects ($P = 0.032$ and $P = 0.016$). There were no significant differences in total cholesterol, albumin, calcium level and ALP, or serum concentrations between the two groups (460.7 ± 139.2 pg/mL vs 412.5 ± 127.7 pg/mL; $P = 0.208$). **Conclusion:** Serum PINP, calcium, and ALP shown no significant variation in patients with type 2 diabetes mellitus.

Keyword: Type 2 diabetes; Bone turnover; PINP; Collagen formation; Hypertension; Triglycerides.

Introduction

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disease characterized by insulin resistance, hyperglycemia, and various systemic complications in cardiovascular/renal/skeletal systems. Of these, bone fragility and connective tissue fibrosis have developed as major but less known sequelae. People with T2DM are at increased risk of fractures, even though BMD often is normal or high [1], indicating impaired bone quality in addition to quantity. This dysfunction is associated with low bone turnover and defective collagen synthesis, where Procollagen Type I N-terminal Propeptide (PINP) is a critical marker for bone formation. Persistent hyperglycemia and increased oxidative stress in T2DM negatively affect osteoblast function, and the gene expression of collagen

that leads to decreased levels of bone formation markers (PINP, osteocalcin). Lower levels of PINP 172 has been found in old postmenopausal women with T2DM relative to the healthy controls, suggesting poor osteogenesis and collagen deposition [2]. The same trend has been reported in elderly osteoporotic T2DM subjects, with low PINP levels related to high HbA1c, BMI and TG as an expression of the crosstalk between metabolic disturbances and bone matrix formation [3]. Biochemical factors like glucose, HbA1c, albumin, calcium, ALP, TG, Cholesterol and BMI are very important to evaluate the status of collagen dynamics. Serum albumin and calcium are constituents of the bone matrix mineral, while high ALP meets needs for compensatory remodeling versus pathologic turnover in diabetics with osteopenia [4] .Furthermore, the lipotoxicity and the chronic inflammation of dyslipidemia frequently coexisting with T2DM inhibits osteoblast function and PINP production [5]. Apart from its skeletal implications, PINP is emerging as a systemic marker of insulin sensitivity. In a large Danish population, we found that PINP values were significantly lower in insulin resistant diabetic phenotypes even after adjusting for age, BMI (body mass index), and thus inhibit bone formation as part of the metabolic syndrome [6]. Similarly, among men the biomarker was positively associated with estimated glucose disposal rate (eGDR) an observation that emphasizes its relationship with glucose metabolism [7]. PINP is modified by pharmacologic insults as well. In Japanese patients with T2DM, 6-month use of SGLT2 inhibitors significantly increased PINP levels and improved bone quality with no change in BMD due to enhanced collagen [8]. In contrast, Nordklint et al. found little rise of PINP in patients with metformin and insulin, indicating selective effects of antidiabetic drugs on bone metabolism [9]. Type I procollagen is also the major protein involved in fibrosis, especially in cardiomyocytes. Myocardial fibrosis is a characteristic feature of diabetic cardiomyopathy (DCM) and heart failure with preserved ejection fraction (HFpEF). Increased serum Procollagen Type I C-terminal Propeptide (PICP) has been demonstrated in T2DM patients having HFmrEF suggesting increased type I collagen deposition and myocardial rigidity [10]. This is also consistent with longitudinal studies looking at high baseline PICP predicting future heart failure in individuals treated for SGLT2 inhibitors [11].

Non-pharmacologic strategies, such as lifestyle interventions, also impact PINP levels. In a randomized trial, increased PINP following intensive aerobic and resistance training was associated with improved metabolic profiles in T2DM patients, despite no changes in BMD, suggesting functional gains in bone metabolism [12]. Given the complex interplay of glycemic control, lipid metabolism, body composition, nutrient status, and therapy in modulating PINP expression, comprehensive clinical evaluation is essential. Markers such as glucose, HbA1c, ALP, calcium, albumin, TG, and cholesterol provide essential context for interpreting changes in PINP and identifying patients at risk for diabetic bone disease and fibrosis. In reference to our hypothesis about T2DM as a complex metabolic disease, we hypothesize that bone metabolism should fall indeed. The objective of this study was to investigate the correlation between serum PINP levels and some important metabolic markers in T2DM patients, to determine the pattern of collagen turnover that might reflect early skeletal and fibrotic complications. Further insight into these relationships might help to improve the early detection and treatment of diabetic-induced tissue damage.

Materials and Methods

Selection of Patients and Formation of Study Groups:

All participants visited the polyclinics of Baxshin Private Hospital from March 2025 to April 2025. A total of 79 Kurdish participants, comprising 36 females and 43 males, aged between 40 and 70 years, were included; 37 were healthy and 42 had type 2 diabetes mellitus. In accordance with the criteria established by the American Diabetes Association, we identified 42 patients and classified them as having type 2 diabetes mellitus (13). .The eligibility requirements required a diagnosis of Type 2 Diabetes Mellitus (T2DM) and ongoing use of antidiabetic medicines. Patients excluded from the study were those with cancer, pregnancy, or acute or chronic illnesses. The questionnaire component of the study included Age, Sex, Smoking history, Lifestyle, duration of Type 2 Diabetes Mellitus (T2DM), and Hypertension. Clinical data, including stomach pain and fever, were gathered regarding the patient groups. The research complied with the tenets established in the Helsinki Declaration. All participants granted informed consent before their participation in the investigation. The Ethics Committee for Clinical Research at Garmian Polytechnic University approved the current inquiry, under decision number GPUREC04924.

Laboratory analysis:

Blood was sampled by vein puncture of antecubital veins. After 12-h dating (overnight fasting) in the morning, venous blood was taken via a straight needle attached to a tube holder loaded with the plastic 10ml Serum gel and clot activator tube, filled 5ml HbA1c tube with EDTA additive respectively. First, the samples were kept at room temperature for five minutes, then centrifuged at 3000 rpm for 20 minutes. The supernatant was divided into two parts. One part was used to measure Serum Glucose, HbA1c, TG, T. Ch, concentrations, following the Cobas c 311 manufacturer's guidelines. Concentration of GLUC3, Cobas integra/cobas c systems REF. 04404483190, ID. 0768316, LOT. (10)040156309920297 cobas c kit, Germany. Concentration of A1C-3, Cobas integra/cobas c systems REF . 05336163190, ID . 0774553, LOT .79012301 cobas c kit , Germany. Concentration of TRIGL, Cobas integra/cobas c systems REF) . 240)20767107322, ID . 0767107, LOT . (10)82371001 cobas c kit, Germany. Concentration of CHOL 2, Cobas integra/cobas c systems REF . (240)03039773190, ID . 07 6726 3, LOT . (10)83648901 cobas c kit, Germany.

Moreover, 1ml of serum was placed in an Eppendorf tube for further study and stored in a deep freezer at -20°C until the day of the experiment. After blood collection, levels of Ca, Albumin, and ALP in the serum samples will be analyzed using commercially available Mindray kits. Concentration of ALB, SHENZHEN MINDRAY BIO-MEDICAL ELECTRONICS CO., LTD. REF . 105-000822-00, LOT . 148324017 mindray kit, Germany. Concentration of Ca, SHENZHEN MINDRAY BIO-MEDICAL ELECTRONICS CO., LTD. REF . 105-000825-00, LOT . 142224012 mindray kit, Germany. Concentration of ALP, SHENZHEN MINDRAY BIO-MEDICAL ELECTRONICS CO., LTD. REF . 105-000816-00, LOT . 140324018 mindray kit, Germany. Additionally, 0.5ml of serum was placed in an Eppendorf tube for further study and stored in a deep freezer at -20°C until the day of the experiment. After blood collection, levels of PINP in the serum samples was measured manually via a sandwich enzyme-linked immunosorbent assay (ELISA), Procollagen type I N-terminal propeptide, PINP; ELISA Kit; Sunlong Biotech. REF. SL1448Hu,

LOT:20250522, Zhejiang, China. Results are reported in SI units (mmol/L, g/L, IU/L, pg/mL).

Statistical analysis

SPSS version 23.0 software used to perform the analysis of the collected data. Unpaired t-test was conducted to assess whether the differences between groups were statistically significant. All analyses were conducted twice, and the data are presented as mean values ± standard deviation. A p-value of less than 0.05 was considered statistically significant.

Ethical Approval and Consent to Participation

The experimental methodology complied with the ethical principles outlined in the Helsinki Declaration and received approval from the Human Ethics Committee of the Affiliated Garmian Polytechnic University, under license number GPUREC04924. We comprehensively briefed each participant and obtained explicit consent to conduct the study.

Results

Participant characteristics

Study group consisted of 42 patients with type 2 diabetes mellitus (T2DM) and control group included the 37 healthy individuals. The average age of participants with T2DM was significantly higher than that of control group (55.7 ± 1.4 years vs 49.0 ± 1.4 years; p = 0.001). Mean body mass index (BMI) was not significantly different between both groups (28.6 ± 0.7 kg/m² vs 28.8 ± 1.3 kg/m², p = 0.898). Sex distribution did not differ between groups (p = 0.124).

Participants with T2DM had a mean duration of disease 5.7 ± 0.8 years. The proportion of sedentary participants was higher in T2DM subjects vs controls (59.5% vs 32.4%; p = 0.016). Hypertension was significantly more common in diabetes group (47.6% vs 24.3%; p = 0.032). There was also more frequent fever among those with T2DM (26.2% vs 8.1%; p = 0.036). There was no abyss between groups with respect to smoking history or abdominal pain (Table 1).

Table 1: Demographic and clinical characteristics of study participants

Parameters	T2DM	Control	P value
Age (Year)	55.74 ± 1.352	49.03 ± 1.416	0.001*
BMI (Kg/m^2)	28.61 ± 0.662	28.79 ± 1.296	0.898*
Gender (Female/Male)	[22 (52.4 %) / 20 (47.6%)]	[13 (35.1%) / 24 (64.9%)]	0.124 **
Duration of T2DM (Year)	5.7024 ± .754	-	<0.001*
Fever N (%)	11 (26.2%)	3 (8.1%)	0.036 **
Abdominal Pain N (%)	11 (26.2%)	7 (18.9%)	0.442**
Life style (Active\Sedentary) N (%)	17\25 (40.5%\59.5%)	25\12 (67.6% \32.4%)	0.016**
Smoking N (%)	3 (7%)	-	0.097**
Restrict Carbohydrate N (%)	13 (31%)	-	<0.001**
Hypertension N (%)	20 (47.6%)	9 (24.3%)	0.032**

Notes: Data are expressed as mean ± standard error or number (percentage). BMI = body-mass index.

* Unpaired t-test; ** Pearson Chi-square test.

Biochemical findings

Fasting plasma glucose (FPG) and glycated hemoglobin (A1C) levels were markedly elevated in the T2DM cohort compared to the control group (153.13 ± 65.27 mg/dL vs 97.32 ± 8.3 mg/dL, $p < 0.001$; and 7.7 ± 1.6% vs 5.2 ± 0.4%, $p < 0.001$, respectively). Participants with T2DM had elevated serum triglyceride concentrations (161.90 ± 113.74 mg/dL vs 116.68 ± 57.23 mg/dL; $p = 0.032$). No statistically significant changes were detected between the two groups regarding total cholesterol, albumin, calcium, adjusted calcium, alkaline phosphatase (ALP), or serum PINP concentrations (all $p > 0.05$). The mean serum PINP levels were 460.7 ± 139.2 pg/mL in the T2DM group and 412.5 ± 127.7 pg/mL in the control group ($p = 0.208$) (Table 2).

Table 2: Biochemical characteristics of study participants

Parameters	T2DM	Control	P value
FBS (mg/dL)	153.13 ± 65.27	97.32 ± 8.3	<0.001
A1C (%)	7.68 ± 1.61	5.22 ± 0.354	<0.001
TG (mg/dL)	161.90 ± 113.74	116.68 ± 57.23	0.032
T.CH (mg/dL)	183.94 ± 46.98	189.14 ± 34.97	0.583
ALB (g/dL)	4.45 ± 0.26	4.53 ± 0.25	0.151
Ca^{++} (mg/dL)	9.24 ± 0.37	9.21 ± 0.32	0.634
ALP (IU/L)	77.73 ± 22.8	84.80 ± 27.30	0.214
Correct Ca^{++} (mg/dL)	8.89 ± 0.32	8.78 ± 0 .261	0.118
PINP (pg/mL)	460.71 ± 139.157	412.521 ± 127.677	0.208

Notes: Data are presented as mean ± standard deviation. Unpaired t-test. FPG = fasting plasma glucose; A1C = glycated hemoglobin; TG = triglycerides; T.CH = total cholesterol; ALP = alkaline phosphatase; ALB = albumin; Ca = calcium; PINP = procollagen type I N-terminal propeptide.

Discussion

Our results that individuals with T2DM were significantly older compared to controls are consistent with abundant literature of aging as a major risk factor for T2DM due to age-dependent decreases in insulin secretion and sensitivity. Older groups also have an increasing number of comorbidities, thus predisposing them to this risk [14]. Higher rates of sedentary life-style in diabetic subjects confirmed the significance of physical inactivity for metabolic dysfunction. Extended periods of inactivity deteriorate glucose tolerance and increase the circulating concentration of triglycerides mechanisms directly conducive to the development of insulin resistance and T2DM [15]. The elevated FBS and A1C in the T2DM group adequately represent chronic hyperglycemia and its metabolic stress. Particularly, A1C is a measure of long-term glycemic control that correlates well with risk of complications such as heart disease and stroke [16]. The higher TG concentrations in diabetics reveal one of the most relevant features of diabetic dyslipidemia. Increased TG levels are associated with increased cardiovascular risk [13], even in patients treated with statins [14], and an actionable factor that contributes to the residual vascular risk indeed [17]. With the synergism of aging, sedentary behavior and hypertension, increase in glycemia and hypertriglyceridemia that occur similarly to ours, there is emphasis on lifestyle measures (with relevant need for increased physical activity and changes in diet) as highly effective. Exercise enhances insulin sensitivity, lowers blood pressure and lipids as well as HbA1C, and improves metabolic health in general [18]. The T2DM group was significantly older than the control group, but had similar BMI and gender distribution. Lifestyle and comorbidity: Diabetic patients were more often sedentary, more frequently reported fever episodes, and had higher rates of hypertension (all $P < 0.05$). Smoking and abdominal pain did not differ significantly.

T2DM subjects had markedly higher FBS and A1C levels and elevated TG (all $P < 0.05$). Other biochemical markers (T.CH, albumin, Ca^{++}, ALP, PINP) showed no significant differences. According to the literature, metabolic bone is impaired in T2DM patients [19, 20]. In contrast to our finding, it was unchanged as we analyzed and compared the serum Ca^{++}, ALP, and PINP).

In agreement with studies founded by [21, 22] serum PINP showed no significant variation in people with T2DM, potentially attributable to the limited sample size, medication influences, or metabolic regulation of bone production.

Conclusion

Serum PINP, Ca^{++}, and ALP showed no significant variation in patients with T2DM, which may be due to the limited sample size, medication influences, or metabolic regulation of bone production. Consequently, we advocate for further experiments to validate the correlation between bone processes and T2DM.

Disclosure statement

The authors report there are no competing interests to declare.

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Data availability

Data will be made available on request.

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