

ORIGINAL PAPER

# The Relation between Parathyroid Hormone with Some Bone Biochemical Markers in Type II Diabetes Mellitus

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## Abstract

**Background:** Diabetes mellitus of type II (T2DM) has a link to bone resorption, as seen by the great level of most osteoclastic activity indicators. As a result, the mineral density of bones is not reduced in individuals with non-insulin-managed T2DM, and this type does not seem to contribute to osteoporosis. This study aims to evaluate the bone metabolism biochemical markers in T2DM patients.

**Materials and Methods:** A total of 120 blood samples were divided into (70) patients (with quite equal numbers of both females and males), and (50) normal cases as controls (also with quite equal numbers of both females and males), the ages were between 30 and 65 years old. During the period between February and August 2020, patients were admitted to Ballad and Salah Aldeen General Hospitals. The samples that were undertaken were (blood sugar, albumin, total calcium, corrected calcium, parathyroid hormone and phosphorus).

**Results:** In male DM patients, there were high significant differences ( $P \leq 0.01$ ) in (blood sugar, parathyroid hormone, total calcium, and corrected calcium), but non-significant differences ( $P \geq 0.05$ ) in phosphorus. On contrary, in female DM patients, there was high noticeable difference ( $P \leq 0.01$ ) in blood sugar, and a considerable difference ( $P \leq 0.05$ ) only in albumin, but non-significant differences ( $P \geq 0.05$ ) in parathyroid hormone, total calcium, and corrected calcium.

**Conclusion:** The current findings concluded that hyperglycemia combined with an insulin deficiency can result in a hypoparathyroid status with PTH downregulation.

**Keywords:** Diabetes mellitus (DM), Bone metabolism, Calcium, Parathyroid hormone.

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## INTRODUCTION

Diabetes Mellitus (DM) is a category of metabolic conditions distinguished by a long-term hyperglycemic state caused by insulin production, insulin activity, or both<sup>1</sup>. In individuals with glucokinase-correlated maturity-onset DM, a total lack of glucokinase activities, which controls insulin secretion, can lead to persistent DM<sup>2</sup>.

T2DM has a link to bone resorption, as seen by the great level of most osteoclastic function indicators. As a result, the mineral density of bones is not reduced in individuals with non-insulin-managed T2DM, and this type of DM does not seem to contribute to osteoporosis<sup>3</sup>. Bone formation and resorption can be indirectly assessed by measuring blood concentrations of several biomarkers, such as enzymes, hormones, and ions required for bone remodeling, as well as bone matrix substances liberated into the bloodstream during formation or resorption<sup>4</sup>.

Diabetes-induced alterations in metabolism have a major impact on the bone metabolic process, increasing the probability of fracture approximately six-times in T1DM and two-times in T2DM<sup>5</sup>. Osteoporosis and DM are two disorders that wreak havoc on the elderly individuals, resulting in medical expenses that are two-time greater than those of healthy elderly individuals<sup>6</sup>. Direct impacts of hyperglycemia, or insulin deficiency or resistance, on the bone structure and bone marrow microenvironments may produce bone or mineral defects in individuals with DM. Advanced glycation end products (AGEs) from proteins of bone matrix, aberrant adipokine and cytokine secretion and their deleterious impacts on bone cellular structure, and altered skeletal/neuromuscular connections are all factors to consider<sup>7</sup>. In those with DM, osteoporosis regards as the commonest principal metabolic bone disorder<sup>8</sup>.

Calcium ( $\text{Ca}^{+2}$ ) is just a bivalent mineral cation, which is used as an intermediate messenger in almost all living creatures. It, but from the other side, serves as an integrator, connecting the various body systems. Calcium cannot be manufactured and should be consumed firstly to create and maintain the human skeleton<sup>9</sup>. Calcium, in the crystals form of hydroxyapatite  $\text{Ca}_{10}(\text{OH})_2(\text{PO}_4)_6$  contained in collagen fibers, has a structural function in supplying rigidity (strength and structure) to bony skeleton<sup>10</sup>.  $\text{Ca}^{+2}$  ions on bone surfaces may react with some other ions within

the body fluid, acting as a massive ion exchanger. These characteristics are critical in the aspect of the bone function, since a calcium aid in maintaining a consistent blood calcium level<sup>11</sup>. Reduced mineralization of bone is caused by insufficient calcium intake, inadequate calcium absorption, and high calcium excretion<sup>12</sup>. Because a drop in absorbed calcium leads to a fall in blood ionized calcium level, the PTH is stimulated to operate under one of three pathways to raise and maintain the calcium serum level<sup>13</sup>. The PTH can enhance cholesterol (1.25 dihydroxycholecalciferol) synthesis, which enhances calcium absorption via active transport inside the intestine and glomerular filtration of the kidneys. The bone resorption also may accelerate, causing the bone to release more calcium<sup>14</sup>. The sluggish process in bone density was influenced by a mixture of factors such as reduced vitamin D and calcium consumptions, diminished physical activity, age-related deficiency in bone formation, and the absence of estrogen's potential benefits on calcium homeostasis in the kidney and intestine, and even its influence on bone formation<sup>15</sup>.

The parathyroid gland secretes PTH, which is a protein with 84 amino acids formed following post-translational process. The peptide extracted from human blood plasma that just has 37 N-terminal residues is responsible for the majority of the biological activity<sup>16,17</sup>. PTH might have a function in teleost nervous system development, bone and cartilage growth<sup>18</sup>. According to the manner of administration, PTH induces bone production and can either improve or reduce bone density. Continuous PTH infusions and subcutaneously injectable doses promote bone production in the same way, but have differing influences on the bone density and resorption<sup>19</sup>. PTH inhibits phosphate reabsorption in the renal tubules, resulting in phosphaturia and enhanced calcium reabsorption; this effect causes higher plasma calcium levels and lowering phosphate levels<sup>20</sup>. Through its impact on the production of  $1.25(\text{OH})_2\text{D}$  calcitriol, PTH boosts the gut absorption of both phosphorus and calcium<sup>21</sup>. The amount of the free ionized calcium within the bloodstream that circulates via the parathyroid glands regulates PTH release<sup>22</sup>.

## MATERIALS AND METHODS

The present study was approved by the Medical Ethics Committee of Salah Aldeen Health Directorate with code number (IQ.TIK.REC.7521.2020). According to Helsinki Declaration of World Medical Association,

with its last revision at Edinburgh in 2000; an ethical approval statement was acquired for each participated individual.

The present study was carried out to obtain 120 blood samples taken from 70 patients (35 men and 35 women) with T2DM and 50 healthy people (25 men and 25 women) who considered as control group. Patients in the current study ranged 30-65 years old and they were hospitalized to Ballad and Salah Aldeen General Hospitals in Salah Aldeen province between February and August 2020. A 5 mL blood sample was taken in a plain tube, then left to clot for 20-30 minutes before centrifuged using a microcentrifuge at 4000 rpm for 5 minutes to extract fresh non-hemolysis serum that kept in deep freezer. The serum was separated into two tubes, one for the first set of tests (serum Ca<sup>2+</sup>, blood glucose, serum albumin, PO<sup>4</sup>), which were performed using spectrophotometer enzymatic techniques, and the corrected Ca<sup>2+</sup> which calculated using the following equation:

$$\text{Corrected Ca}^{+2} = \text{Total Ca}^{+2} + 0.8 * (4 - \text{Albumin}).$$

While the second tube was used to determine the PTH using an Enzyme-linked ImmunoSorbent assay (ELIZA).

## STATISTICAL ANALYSIS

T-tests were used in collaboration with ANOVA tables in SPSS version 26 for statistical analysis. To examine the variations between the mean of the tests done on every group of the current study, a program was run, followed by a Duncan's multiple range tests.

## RESULTS

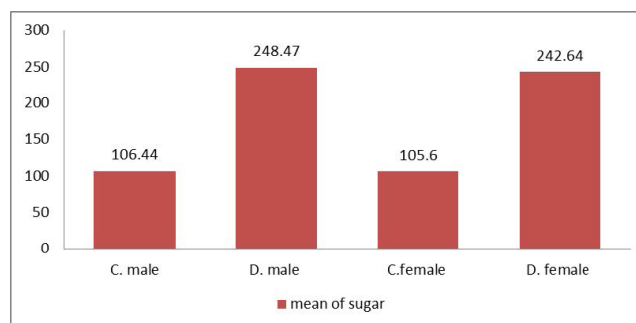
### Blood sugar levels in control and DM patients

As indicated in Table 1 and Figure 1, the mean±SD of blood glucose in males DM individual cases and control was (248.47±103.86) and (106.44±12.98) with ranges of (130.3-498.6) and (85-130) mg/dl respectively. The findings revealed a rather high significant difference (P≤0.01) between males' DM patients and controls. As indicated in Table 1 and Figure 1, the mean±SD of blood glucose in females' DM individual cases and control was (242.64±88.94) and (105.60±12.24) with ranges of (108.2-460) and (80-123) mg/dl respectively. The results revealed a quite significant difference (P≤0.01) between females' DM patients and control.

**Table 1.** Blood glucose (mg/dl) levels in control and DM patients

Group	Individual No.	S.D.±Mean	Reference range	P. value
Control males	25	106.44±12.98	85-130	P≤0.01*
Diabetic males	35	248.47±103.86	130.3-498.6	
Control females	25	105.60±12.24	80-123	P≤0.01*
Diabetic females	35	242.64±88.94	108.2-460	

\*Highly significant, \*\* non-significant



**Figure 1.** Blood glucose levels in control and DM patients

### Serum albumin (g/dl) levels in control and DM patients

As mentioned in Table 2 and Figure 2, the mean±SD for serum albumin in males' DM patient cases and control was (4.48±0.29) and (4.63±0.67) ranging from (2.92-6.2) and (3.96-5.12) g/dl respectively. There would be no significant difference between males' DM patient cases and control (P≥0.05), according to the findings. As indicated in Table 2 and Figure 2, the mean±SD for serum albumin in females' DM patient cases and control was (4.23±0.36) and (4.42±0.29) ranging from (4.0-5.0) and (3.24-4.98) g/dl respectively. The findings revealed a significant difference (P≤0.05) between females' DM patients and control.

**Table 2.** Serum albumin (mg/dl) levels in control and DM patients

Group	Individual No.	S.D.±Mean	Reference range	P. value
Control males	25	4.63±0.67	3.96-5.12	P≥0.05**
Diabetic males	3	4.48±0.29	2.92-6.2	
Control females	25	4.42±0.29	3.24-4.98	P≥0.01*
Diabetic females	35	4.23±0.36	4.0-5.0	

\*Highly significant, \*\* non-significant.

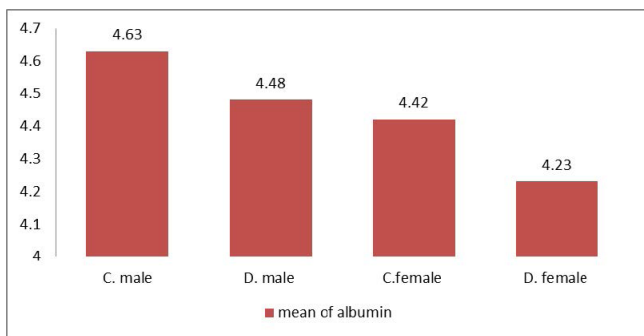


Figure 2. Serum albumin levels in control and DM patients

**Serum calcium levels in control and DM patients**

As indicated in Table 3 and Figure 3, the mean±SD of calcium in males’ DM patient cases and control was (7.80±1.45) and (9.29±0.54) ranging from (4.8-10.5) and (8.5-10.3) mg/dl respectively. The results revealed a highly significant difference between the males’ DM patient cases and control group (P≤0.01). As indicated in Table 3 and Figure 3, the mean±SD of calcium in female DM patient cases and control was (9.08±0.955) and (9.16±0.48) ranging from (6.3-10.7) mg/dl and (8.3-10.2) mg/dl respectively. There was also no significant difference between females’ DM patient cases and control (P≥0.05), according to the findings.

Table 3. Serum calcium (mg/dl) levels in control and DM patients

Group	Individual No.	S.D.±Mean	Reference range	P. value
Control males	25	9.29 ±0.54	8.5-10.3	P≤0.01*
Diabetic males	35	7.80 ±1.45	4.8-10.5	
Control females	25	9.16±0.48	8.3-10.2	P ≥ 0.05**
Diabetic females	35	9.08±0.955	6.3-10.7	

\*Highly significant, \*\* non-significant

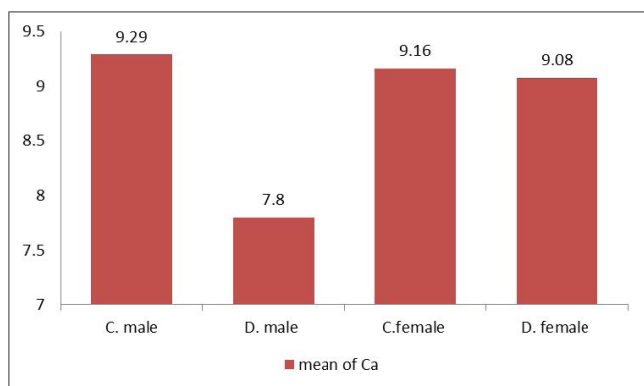


Figure 3. Serum Calcium levels in control and DM patients

**Corrected calcium (mg/dl) levels in control and diabetic patients**

As described in Table 4 and Figure 4, the mean±SD for corrected calcium in males’ DM patient cases and control was (6.51±1.27) and (7.86±0.59) ranging from (4.34-9.77) and (6.87-9.09) mg/dl respectively. There was a high significant difference comparing males’ DM patient cases with control (P≤0.01), according to the findings. As described in Table 4 and Figure 4, the mean±SD of corrected calcium in females’ DM patient cases and control was (8.04±0.96) and (7.93±0.57) with values ranging from (6.21-9.75) and (6.6-8.91)mg/dl respectively. There was no significant difference between females’ DM patient cases and control (P≥0.05), according to the findings. Because it is dependent on serum Ca<sup>2+</sup> and serum albumin concentrations, which reduced in males DM patient cases when compared to control and slightly elevated in females DM patient cases when compared to control, corrected calcium lowered in males DM patient cases rather than control in the current study. Because calcium levels were lower, corrected calcium levels were lower in males DM patient cases than female DM individuals.

Table 4. Corrected calcium (mg/dl) levels in control and DM patients

Group	Individual No.	S.D.±Mean	Reference range	P. value
Control males	25	7.86±0.59	6.87-9.09	P≤0.01*
Diabetic males	35	6.51±1.27	4.34-9.77	
Control females	25	7.93±0.57	6.6-8.91	P≥0.05**
Diabetic females	35	8.04±0.96	6.21-9.75	

\*Highly significant, \*\* non-significant.

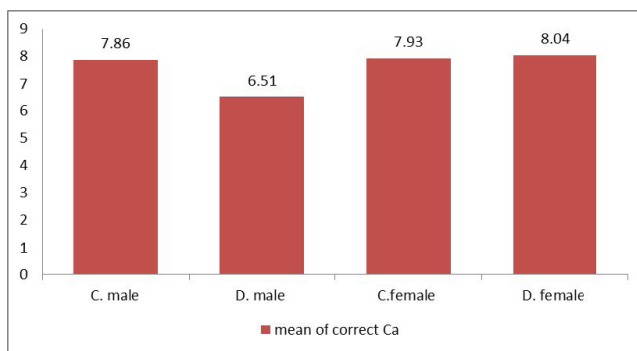


Figure 4. Corrected calcium levels in control and DM patients

**Serum phosphorus levels in control and DM patients**

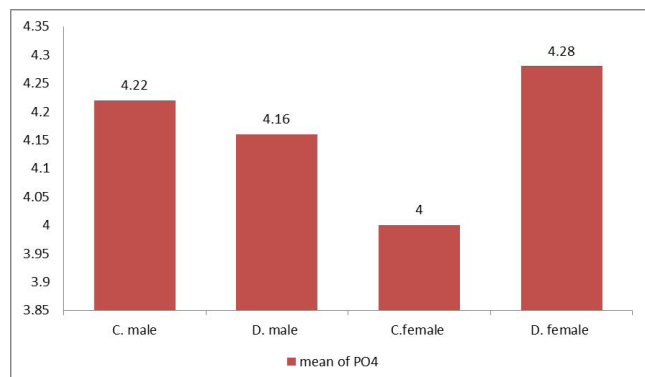
As reported in Table 5 and Figure 5, the mean±SD for phosphorus in males’ DM patient cases and

control was (4.16±0.93) and (4.22±0.38) with levels ranging from mg/dl (2.6-6.5) and (3.5-5.0) mg/dl respectively. There was no significant difference comparing females' DM patient cases with control (P≥0.05), according to the findings. As reported in Table 5 and Figure 5, the mean±SD for phosphorus in females' DM patient cases and control was (4.28±0.79) and (4.00±0.46) with values ranging from (3.0-5.8) and (3.0-4.7) mg/dl respectively. There was no significant difference between females' DM patient cases and control (P≥0.05), according to the findings.

**Table 5.** Serum Phosphorus levels (mg/dl) in control and DM patients

Group	Individual No.	S.D.±Mean	Reference range	P. value
Control males	25	4.22±0.38	3.5-5.0	P≥0.05*
Diabetic males	35	4.16±0.93	2.6-6.5	
Control females	25	4.00±0.46	3.0-4.7	P≥0.05*
Diabetic females	35	4.28±0.79	3.0-5.8	

\* non-significant.



**Figure 5.** Serum Phosphorus levels in control and DM patients

### Serum parathyroid hormone (PTH) levels in control and DM patient

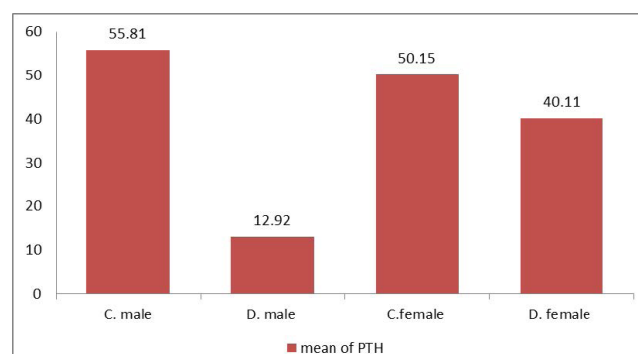
As seen in Table 6 and Figure 6, the mean±SD for serum PTH in males' DM patient cases and control was (12.92±18.73) and (55.81±16.07) ranging from (3.8-108.3) and (25.3-85.3) pg/ml respectively. There was a highly significant difference comparing males' DM patient cases with control (P≤0.01), according to the findings. As seen in Table and Figure 6, the mean±SD for serum PTH in females' DM patient cases and control was (40.11±32.958) and (50.15±13.06) with values ranging from (3.8-134.2) and (25.6-74.1) pg/ml respectively. There was no significant difference

between females' DM patient cases and control (P≥0.05), according to the findings.

**Table 6.** Serum parathyroid hormone levels (pg/ml) in control and DM patients

Group	Individual No.	S.D.±Mean	Reference value	P. value
Control males	25	55.81±16.07	25.3-85.3	P≤0.01*
Diabetic males	35	12.92±18.73	3.8-108.3	
Control females	25	50.15±13.06	25.6-74.1	P≥ 0.05**
Diabetic females	35	40.11±32.958	3.8-134.2	

\*Highly significant, \*\* non-significant.



**Figure 6.** Serum parathyroid hormone levels in control and DM patients

## DISCUSSION

Males and females DM patient individuals had higher blood glucose levels than the control group. Also, male DM patients had higher blood glucose levels than female DM patients. Patients with T2DM may still secrete insulin, but it is insufficient to meet their body's requirements. In many situations, this indicates that the pancreas is releasing more insulin than usual. Insulin resistance (lack of insulin sensitivity) is the main characteristic of T2DM by the body cells (especially muscle and fat cells). Besides to the issues associated with great resistance, the pancreas' insulin release can be faulty and inefficient. These findings were backed up by studies from throughout the world.

Serum albumin reduced in DM patients compared to controls of both males and females cases, although it reduced more in females DM patients than in males DM patients. Bhonsle HS<sup>23</sup>, Hemangi et al<sup>24</sup>, Ali SJ<sup>25</sup>, Kielmas M<sup>26</sup> concurred with these findings. Diet, inflammation, lifestyle, illness, medicines, and other variables all have an impact on albumin serum level. Albumin biosynthesis and secretion are

reduced in diabetics owing to insulin insufficiency. As a result, it was predicted that albumin serum levels would drop in individuals with DM, affecting glycosylated haemoglobin (HbA1c) and plasma protein glycation, is an indicator of high sugar levels<sup>25</sup>.

Men and women DM patients had reduced serum calcium levels than controls; however male DM patients had lower levels than female DM patients because PTH, which raises calcium levels, was lower in male DM patients than female DM patients. Wasan AA<sup>27</sup>, Ehsaneh T<sup>28</sup>, Ali SJ<sup>29</sup>, Hussein RM<sup>30</sup> were agreed with the above results. However, Masahiro Y<sup>31</sup>, Pratheesh GM<sup>32</sup>, Fu XM<sup>33</sup> disagreed with these findings. Calcium is required for insulin secretion. GLUT-4 transporters transfer glucose inside the body as blood glucose concentrations rise. With the help of glucokinase, this glucose is transformed to glucose-6-phosphate, which is subsequently oxidized to produce more ATP, resulting in potassium channel closure and cell membrane depolarization. Depolarization increases calcium flow through calcium channels, causing insulin-filled vesicles to attach to the cell membrane. After that, exocytosis secretes insulin<sup>34</sup>.

When male and female DM patients were compared to controls, phosphorus levels were somewhat lower in males and slightly higher in females. As a result, the phosphorus concentration in DM individuals did not alter much. Nyman JS<sup>35</sup>, Deng X<sup>36</sup>, Marwa AT<sup>37</sup> agreed with these findings, however Romero-Daz C<sup>38</sup>, Ali SJ<sup>29</sup> disagreed.

Insulin affects phosphorus excretion; the greater the amount of plasma sugar, the greater the concentration

of the phosphorus; it has also been proven that insulin affects bone metabolism; hence, phosphorous levels are influenced by insulin levels<sup>38</sup>.

When compared to control and DM females, serum PTH was reduced in males and females DM patients and raised in female DM patients, explaining the reduced calcium levels in male DM patients. These findings were corroborated by Ehsaneh T<sup>28</sup>, Masahiro Y<sup>31</sup>, Wasan AA<sup>27</sup> and Al-Jebawi AF et al<sup>22</sup> but opposed by Gulcelik NE<sup>15</sup>. The negative relationship between blood sugar and PTH suggests that hyperglycemia inhibits PTH production and secretion, and it's tempting to think that hyperglycemia combined with the insulin deficiency might result in hypoparathyroidism and PTH down-regulation<sup>22</sup>.

## CONCLUSIONS

The current findings showed that DM with insulin resistance might cause hypoparathyroidism, which is characterized by a decrease in PTH levels that has an influence on phosphorus and calcium levels.

**Compliance with ethics requirements:** The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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