

Assessment of Glycemic Markers and Trace Element Imbalance in Type 2 Diabetes Mellitus

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ABSTRACT

Background: Disturbances of trace elements and pancreatic exocrine function are common in type 2 diabetes mellitus (T2DM), but few studies have investigated the glycaemic status, serum trace element levels and pancreatic enzymes simultaneously in patients with T2DM compared to those without pancreatitis, especially for Middle Eastern populations. Objective: This cross-sectional study aims to analyse the levels of HbA1c, FSG, Ca, Zn, Cu, and Fe, and the enzymes amylase and lipase, in three groups: control healthy individuals (Group A), controlled T2DM patients (Group B), and uncontrolled T2DM patients complicated by pancreatitis (Group C). Methods: A sample of 172 patients presenting to the major hospitals in Kirkuk, Iraq were included. Analyses were performed on blood samples using commercially available reagent kits and automated clinical chemistry analyzers. Statistical analyses were conducted using GraphPad Prism 11.0.0, with one-way ANOVA/Tukey's test for parametric data or Kruskal-Wallis/Dunn's test for non-parametric data. Results: HbA1c, and FSG levels were significantly higher in Group B ($P < 0.05$) with a stepwise increase from Group A to C. Although Group B showed a slight increase of calcium, it markedly decreased in Group C reaching hypocalcemic levels, especially females. Zinc decreased consistently, while copper and iron elevated significantly with disease severity. Amylase and lipase showed a biphasic response, with decreased levels in Group B (subclinical exocrine insufficiency) and increased levels in Group C (active pancreatic injury). Conclusion: T2DM with pancreatitis leads to glycemic deterioration, disease-severity-dependent trace-element imbalance, and a biphasic enzymatic trajectory. Composite Evaluation of Glycated, Trace Elemental and Enzymatic Markers Might Allow Early Identify Pancreatic Complications in Type II Diabetes mellitus.

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1. Introduction

Type 2 diabetes mellitus T2DM is one of the most serious global health challenges faced in the given century. According to the International Diabetes Federation (IDF) Diabetes Atlas, 11th Edition, around 589 million adults were living with diabetes in 2025, and the estimate is over 853 million by 2050 (Atlas, 2015). T2DM, with aetiological factors including genetic predisposition to disease, obesity, and physical inactivity, accounts for >90% of all diabetes cases globally and is characterised by peripheral insulin resistance along with progressive β -cell dysfunction, resulting in persistent hyperglycaemia (DeFronzo et al., 2015). In the long-established diagnostic continua of type 2 diabetes (T2DM), glycated hemoglobin (HbA1c) and fasting serum glucose (FSG) are still the most widely used biomarkers, with diagnosis of $\geq 6.5\%$ for HbA1c (Care, 2024) and ≥ 126 mg/dL for FSG (Sherwani et al., 2016). Progressive β -cell loss in T2DM is characterized by glucotoxicity, lipotoxicity and oxidative stress, a net ROS overproduction compared with antioxidant defenses that promote evolution to overt β -cell decompensation when insulin resistance was balanced (Eguchi et al., 2021; Poitout & Robertson, 2008). Trace elements are central modulators in this process: zinc is essential for insulin crystallization and secretion via the ZnT8 transporter (Ahmad et al., 2024); copper contributes to Cu/Zn superoxide dismutase activity but, in excess, drives Fenton-like radical generation (Wu & Li, 2025); iron similarly induces ferroptosis in pancreatic islets (Miao et al., 2023); and calcium functions as a critical intracellular signaler during glucose-stimulated insulin secretion, with pronounced disruptions in both T2DM and pancreatitis (Ahmed et al., 2016). In addition to its endocrine function, the pancreas has a large exocrine component that is increasingly recognised as abnormal in T2DM. Thus, serum amylase and lipase levels remain consistently decreased in T2DM due to the loss of trophic insulin signalling in acinar cells (Chaudhari & Hansen, 2024; Jalal et al., 2024). In contrast, acinar necrosis that occurs with supervening pancreatitis causes stored enzymes to leak into the circulation, causing diagnostic elevations (Steinberg et al., 2017). This biphasic behavior, the

decline in risk in uncomplicated diabetes and the surge seen with pancreatitis, has important implications for the early detection of pancreatic complications among people with diabetes. Due to distinct genetic and dietary patterns, glycemic dysregulation (Miao et al., 2023), trace element imbalance (Ahmed et al., 2016; Jalal et al., 2024) and pancreatic enzyme alterations (Chaudhari & Hansen, 2024; Zibara et al., 2021), have been investigated in T2DM in the Middle Eastern population; however, studies have focused mainly on each of these parameters in isolation rather than their interactions with each other. This study thus aimed to evaluate glycemic markers (HbA1c and FSG), serum trace elements (Ca, Zn, Cu, and Fe) and pancreatic enzymes (amylase and lipase) simultaneously in healthy controls as well as controlled T2DM patients and uncontrolled T2DM patients complicated by pancreatitis residing in the Kirkuk region of Iraq to deliver integrated assessment of disorder among metabolic and enzymatic derangements related to progression of disease (Rattanakorn & Putri, 2026).

2. Materials and Methods

2.1 Study Design and Population

In this cross-sectional study at major hospitals in Kirkuk, Iraq, we included a total of 172 participants divided into three groups; Group A (44 healthy controls: 22 males and 22 females), Group B (86 controlled patients with T2DM; 43 males and 43 females), and Group C (42 uncontrolled patients with T2DM complicated by pancreatitis; hence. T2DM was diagnosed according to the ADA criteria (FSG $\geq$ 126 mg/dL and/or HbA1c $\geq$ 6.5%) (Care, 2024). Group C pancreatitis was confirmed by clinical presentation, elevated amylase/lipase and imaging. Participants who have type 1 diabetes, are pregnant, had chronic kidney diseases (stages 4 and 5), hepatic cirrhosis, malignancy and took trace element supplements in the past 3 months were excluded. All subjects gave written informed consent, and Institutional Review Board approved the study.

2.2 Blood Sample Collection

Blood samples were taken from the vein after 10-12 hours of fasting. Approximately 10 mL was collected from the antecubital vein and separated into plain serum separator tubes (for FSG, Ca, Fe, Cu, Zn, amylase and lipase) and EDTA tubes (for HbA1c). Following application of RPMI medium, serum was collected by centrifugation (3000 rpm for 10 min) and stored at -20 °C until analysis. Hemolyzed samples were excluded, and polypropylene tubes free of trace elements were used to minimize contamination (Lippi et al., 2006).

2.3 Biochemical Analysis

Biochemical parameters were assessed using automated clinical chemistry analyzers and reagents kits from a variety of suppliers. FSG was measured by glucose oxidase-peroxidase (GOD-PAP) method at 505 nm (Bio Research, Amman, Jordan) (Trinder, 1969). HbA1c was measured by turbidimetric immunoassay at 600 nm (BioLabo SAS, Maizy, France; Ref. 22010) (Fagnani et al., 2025). Serum calcium was measured by the cresolphthalein complexone (CPC) method (BioLabo; Ref. 80004). The iron was measured using the Ferene direct method at 600 nm, with thiourea added to avoid copper interference (BioLabo; Ref. 92108). Copper was assessed at 580 nm through a direct method using 3,5-DiBr-PAESA (LTA S.r.l., Milan, Italy; Cat. CC02150). For quantification of Zn, 5-Br-PAPS was used at 560 nm (AFCO Diagnostic Reagent). The alpha amylase activity was measured using the kinetic method of CNPG3 (at 405 nm; BioLabo; Ref. 99523/99123), while lipase activity was measured by the Imamura enzymatic method (Biolabo; Ref. 99881).

2.4 Quality Control

Daily internal quality control was performed using normal and pathological control sera (BioLabo, Levels I and II) on the same batch of the UV-Visible spectrophotometer; recalibration occurred whenever a control value was greater than ± 2 % SD from the target mean. External quality assessment was conducted through proficiency testing program.

2.5 Statistical Analysis

Statistical analysis was performed using GraphPad Prism version 11.0.0. Data are shown as mean $\pm$ SD. Shapiro-Wilk test was used to assess normality. One-way (ANOVA) followed by Tukey's HSD was used for normally distributed data, Kruskal-Wallis with Dunn's post hoc test for non-parametric data. The Tukey-Kramer modification was used to correct for unequal group sizes. Results were stratified by gender ($P < 0.05$ defined as significant).

3. Results

All biochemical parameters across the three study groups are summarised in Tables 1-3 and show significant

differences ($P < 0.05$).

Table 1: Glycemic Parameters (Mean $\pm$ SD) Across Study Groups, Stratified by Gender.

Parameter	Males A (n=22)	Males B (n=43)	Males C (n=21)	P Value	Females A (n=22)	Females B (n=43)	Females C (n=21)	P Value
HbA1c (%)	5.109 $\pm$ 0.341	7.270 $\pm$ 0.673	9.376 $\pm$ 0.729	<0.05	5.170 $\pm$ 0.381	7.168 $\pm$ 0.676	9.492 $\pm$ 0.946	<0.05
FSG (mg/dL)	91.55 $\pm$ 10.41	120.0 $\pm$ 16.47	203.1 $\pm$ 15.61	<0.05	89.91 $\pm$ 9.57	117.3 $\pm$ 16.10	203.9 $\pm$ 12.00	<0.05

Group A = Healthy Controls; Group B = Controlled T2DM; Group C = Uncontrolled T2DM with Pancreatitis.

Table 2: Serum Calcium and Trace Elements (Mean $\pm$ SD) Across Study Groups, Stratified by Gender.

Parameter	Males A (n=22)	Males B (n=43)	Males C (n=21)	P Value	Females A (n=22)	Females B (n=43)	Females C (n=21)	P Value
Ca (mg/dL)	9.295 $\pm$ 0.981	9.691 $\pm$ 0.951	8.095 $\pm$ 0.784	<0.05	9.322 $\pm$ 0.975	9.532 $\pm$ 0.974	7.733 $\pm$ 1.019	<0.05
Fe (μ g/dL)	99.09 $\pm$ 10.64	117.2 $\pm$ 15.07	129.7 $\pm$ 14.93	<0.05	98.91 $\pm$ 12.08	116.3 $\pm$ 15.36	127.5 $\pm$ 20.01	<0.05
Cu (μ g/dL)	104.0 $\pm$ 9.90	111.1 $\pm$ 14.14	130.5 $\pm$ 15.62	<0.05	103.3 $\pm$ 11.08	119.0 $\pm$ 13.96	127.8 $\pm$ 11.08	<0.05
Zn (μ g/dL)	87.73 $\pm$ 9.28	72.16 $\pm$ 9.53	65.38 $\pm$ 10.51	<0.05	86.30 $\pm$ 8.06	72.30 $\pm$ 11.23	64.75 $\pm$ 6.98	<0.05

Group A = Healthy Controls; Group B = Controlled T2DM; Group C = Uncontrolled T2DM with Pancreatitis.

Table 3: Pancreatic enzyme levels (Mean $\pm$ SD) across study groups, stratified by gender.

Parameter	Males A (n=22)	Males B (n=43)	Males C (n=21)	P Value	Females A (n=22)	Females B (n=43)	Females C (n=21)	P Value
Amylase (IU/L)	67.59 $\pm$ 7.80	55.65 $\pm$ 9.80	177.1 $\pm$ 15.88	<0.05	63.65 $\pm$ 11.97	53.21 $\pm$ 7.76	177.3 $\pm$ 17.30	<0.05
Lipase (IU/L)	38.23 $\pm$ 10.41	30.21 $\pm$ 8.76	157.5 $\pm$ 11.69	<0.05	35.61 $\pm$ 9.68	29.49 $\pm$ 8.15	159.7 $\pm$ 14.00	<0.05

Group A = Healthy Controls; Group B = Controlled T2DM; Group C = Uncontrolled T2DM with Pancreatitis.

Both HbA1c and FSG progressively increased from Group A to Group C. At the same time, Group C values were nearly twice those of Group A. Serum calcium was slightly elevated in Group B but significantly lower in Group C, where females approached a hypocalcemic state (7.733 ± 1.019 mg/dL). With increasing disease severity, zinc decreased, while copper and iron increased in all groups. Group B exhibited lower levels of amylase and lipase relative to Group A, yet amylase and lipase were significantly elevated in Group C to approximately 3-fold (amylase) and 4-fold (lipase) of the comparison group values, respectively.

4. Discussion

4.1 Glycemic Parameters

In Group A, mean HbA1c in males was $5.109 \pm 0.341\%$, females were $5.170 \pm 0.381\%$ were in the normoglycemic range of <4.0 – $<5.6\%$. Hypoglycaemia was most common in Group C, with a prevalence of 11%, compared to 3% and $<1\%$ in Group B and Group A respectively, over the entire study period. HbA1c was used as a glycaemic marker and significantly increased in Groups A to B ($7.270 \pm 0.673\%$ vs. $6.706 \pm 0.640\%$) ($P < 0.05$), beyond the diagnostic criterion of $\geq 6.5\%$, previously applicable. An alarming increase in Group C HbA1c to $9.376 \pm 0.729\%$ (males) and $9.492 \pm 0.946\%$ (females); values that were approaching double those of the Group A individuals, a stark contrast to the other groups observed; GBC $\times$ GGB remain low ~ 40 mL/min/m². Han et al. (2023) highlighted that HbA1c $\geq 6.5\%$ was an independent predictor for organ failure in acute pancreatitis and Ainger et al. (2025) found 2.14-fold increased odds of SA with elevated HbA1c. Davidsen et al. (2025) also shown that glycemic variability is greater in pancreatitis-associated diabetes than T2DM itself.

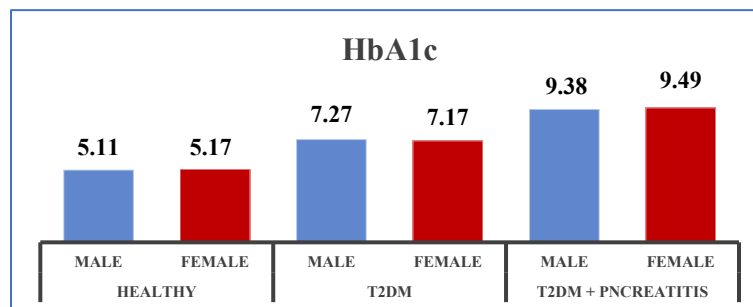


Figure 1: Serum HbA1c Across Study Groups.

Fast serum glucose FSG tracked with deterioration of HbA1c. Group A VLDL values (91.55 ± 10.41 and 89.91 ± 9.57 mg/dL) were within the normoglycemic range of 70–99 mg/dL. In group B, FSG significantly increased to 120.0 ± 16.47 and 117.3 ± 16.10 mg/dL ($P < 0.05$), as evidence of partially controlled diabetes (Care, 2024). Group C had an even more pronounced rise (203.1 ± 15.61 and 203.9 ± 12.00 mg/dL) as observed by Balaban et al. (2024), which reported for acute pancreatitis an admission glucose of 138–244 mg/dL. Moreover, in Group C as pancreatic dysfunction takes precedence over gender effects on FSG values are comparable between genders. This deterioration of glycemia is caused by β -cell glucotoxicity, destruction of islet entrapped due to pancreatitis and altered incretin signaling (Davidsen et al., 2025; Eguchi et al., 2021).

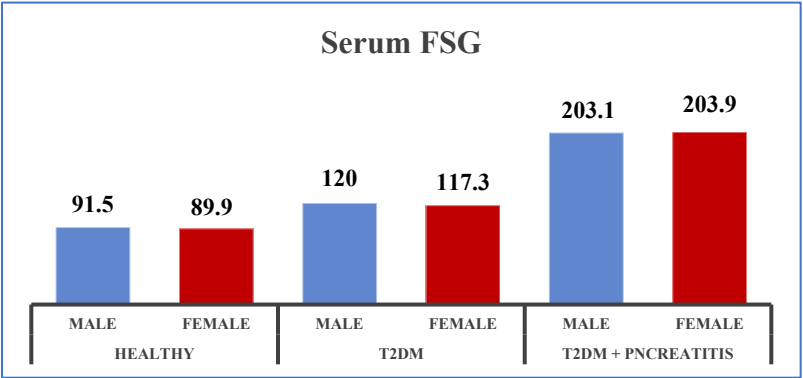


Figure 2: Serum FSG Levels Across Study Groups

4.2 Calcium and Trace Elements

4.2.1 Serum Calcium

In Group A, serum calcium in males was 9.295 ± 0.981 mg/dL and in females, 9.322 ± 0.975 mg/dL; both values were within normal limits (8.5–10.5 mg/dL), as reported by Zibara et al. (2021). Calcium levels were only moderately high (9.691 ± 0.951 and 9.532 ± 0.974 mg/dL) in Group B, as reported by Becerra-Tomas et al. (2014) reported that, compared with calcium < 9.6 mg/dL, excess calcium (9.6–10.2 mg/dL) increased T2DM risk. In Group C, calcium was considerably decreased to 8.095 ± 0.784 and 7.733 ± 1.019 mg/dL ($P < 0.05$), approaching hypocalcemia in females. Faysal et al. (2023) found hypocalcemia in 15–88% of acute pancreatitis patients owing to saponification, transient hypoparathyroidism and inflammatory calcium redistribution.

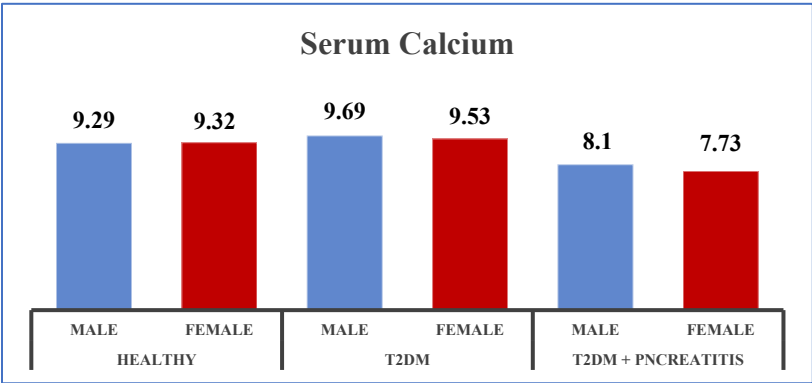


Figure 3: Serum Calcium Across Study Groups.

4.2.2 Serum Zinc

Zinc appeared to be inversely correlated with disease severity. For Group A, the levels (87.73 ± 9.28 and 86.30 ± 8.06 μ g/dL) were below (Singh et al., 2025). In Group B, zinc was reduced to 72.16 ± 9.53 and 72.30 ± 11.23 μ g/dL (~18%) ($P < 0.05$), similar to those reported by Klein et al. (2025), where it was reported that zinc levels were lowered by 10–25% in T2DM. This is attributed to urinary losses due to hyperglycemia, impaired intestinal absorption, and hepatic sequestration of zinc (Ahmad et al., 2024). In Group C, zinc levels were 65.38 ± 10.51 and 64.75 ± 6.98 μ g/dL; therefore were near the normal lower limit. Quilliot et al. (2001) reported that renal losses and malabsorption cause major loss of zinc in diabetes

associated with pancreatitis.

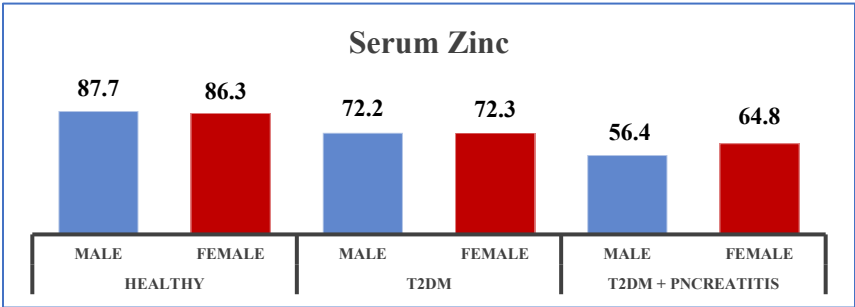


Figure 4: Serum Zinc Across Study Groups.

4.2.3 Serum Copper

Copper was elevated in a dose-dependent manner versus zinc. Group A levels were within the reference range of 62-140 µg/dL, with values of 104.0 ± 9.90 and 103.3 ± 11.08 µg/dL, respectively. In Group B, the copper increased to 111.1 ± 14.14 and 119.0 ± 13.96 µg/dL (P < 0.05), through estrogen-mediated ceruloplasmin synthesis. Li et al. (2026) reported markedly increased copper levels in older T2DM patients, and Nataraj et al. (2022) reported even much higher levels in uncontrolled T2DM. Elevated levels of copper facilitate Fenton-like reactions, wherein hydroxyl radicals are produced, leading to the destruction of β-cells (Wu & Li, 2025). Group C exhibited the highest concentrations (130.5 ± 15.62 and 127.8 ± 11.08 µg/dL), consistent with that noted by Braganza et al. (1981) altered copper metabolism in chronic pancreatitis. In T2DM, the increased copper and reduced zinc yield an unfavorable Cu/Zn ratio that correlates with oxidative stress severity (Nataraj et al., 2022).

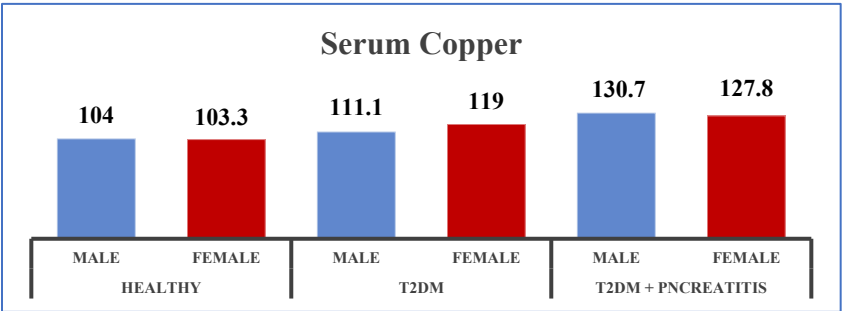


Figure 5: Serum Copper Across Study Groups.

4.2.4 Serum Iron

Iron levels mirrored copper. (males: 75-150; females: 60-140 µg/dL), Group A values (99.09 ± 10.64 and 98.91 ± 12.08 µg/dL) were normal. The amount of iron in Group B being raised to 117.2 ± 15.07 and 116.3 ± 15.36 µg/dL (P < 0.05) (Bayih et al., 2024). This connection includes iron-catalyzed Fenton reactions inducing ferroptosis in β-cells through the ASK1/P-38/CHOP pathway (Deng et al., 2023). Iron in Group C was 129.7 ± 14.93 and 127.5 ± 20.01 µg/dL Yu et al. (2025) showed that disturbed iron homeostasis is associated with over 4-fold increased 30-day mortality of acute pancreatitis while Pepe et al. (2020) reported a direct correlation between pancreatic iron deposition and impaired β-cell function.

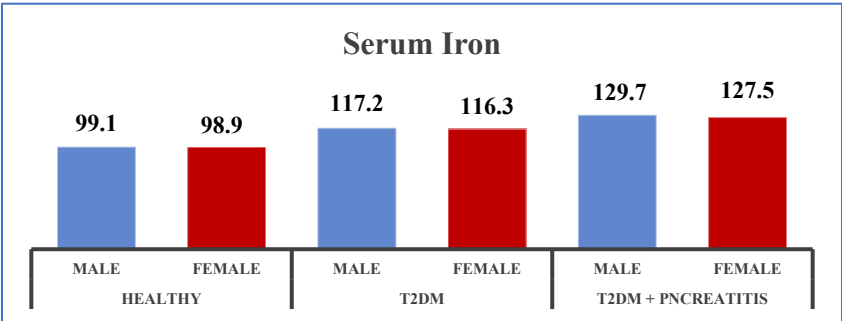


Figure 6: Serum Iron Across Study Groups.

4.3 Pancreatic Enzymes

4.3.1 Serum Amylase

Amylase displayed a biphasic response. Group A values (67.59 ± 7.80 and 63.65 ± 11.97 IU/L) were in the range of the reference interval (25-125 IU/L). In contrast, amylase decreased to about ~17% to each Group B measures of 55.65 ± 9.80 and then, respectively, a second Group B measure of levels at 53.21 ± 7.76 IU/L that is significant when compared for significance ($P < 0.05$) in line with [Jalal et al. \(2024\)](#) which had observed low amylase as characteristic for T2DM. [Chaudhari and Hansen \(2024\)](#) demonstrated the decline of amylase from normal to T2DM. This negative effect is attributed to impaired insulin signaling in acinar cells, leading to atrophy of the acinar tissue ([Jalal et al., 2024](#); [Madole et al., 2016](#)). Amylase also increased to 177.1 ± 15.88 and 177.3 ± 17.30 IU/L in Group C, approximately threefold higher than that of Group A ([Ibrahim et al., 2024](#)), which indicates active pancreatic injury.

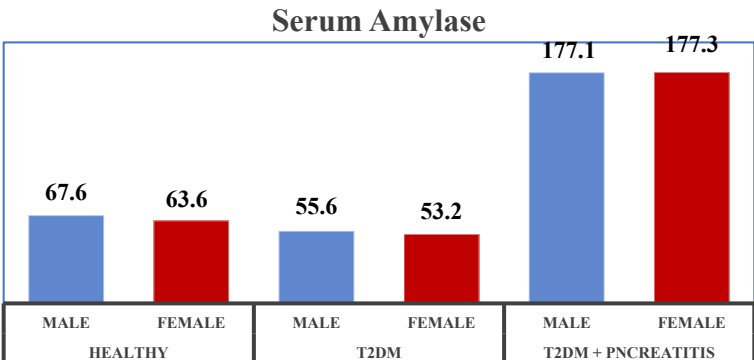


Figure 7: Serum Amylase Across Study Groups.

4.3.2 Serum Lipase

Lipase exhibited a biphasic pattern. Group A values (38.23 ± 10.41 and 35.61 ± 9.68 IU/L) were in the reference range of 13-60 IU/L. In Group B, lipase further decreased by ~20% at 30.21 ± 8.76 and 29.49 ± 8.15 IU/L, corroborating the retention of exocrine insufficiency ([Chaudhari & Hansen, 2024](#); [Jalal et al., 2024](#)). [Oh et al. \(2017\)](#): low amylase and lipase predicts chronic pancreatitis. In Group C, lipase was found to be 157.5 ± 11.69 and 159.7 ± 14.00 IU/L in concentration, almost four folds higher than that of Group A ($P < 0.001$). Lipase is the marker of choice for pancreatitis as it has greater sensitivity and specificity compared to amylase ([Hu et al., 2026](#)). The biphasic behavior of both enzymes suggest that early detection for monitoring of pancreatic complications must be monitored in diabetic patients ([Chaudhari & Hansen, 2024](#); [Oh et al., 2017](#)).

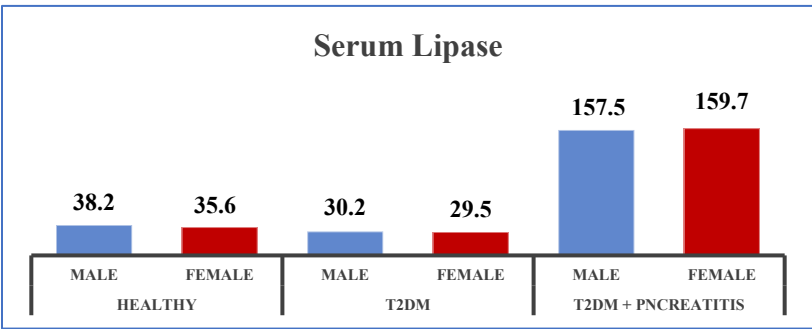


Figure 8: Serum Lipase Across Study Groups.

5. Conclusions

This study shows that T2DM with pancreatitis has exacerbated glycemic control, elemental imbalance, including zinc depletion and copper and iron accumulation, toxic onset of β -cell injury, and a decreasing trajectory in calcium levels, especially in females. The pattern of changes in pancreatic enzymes is biphasic: levels are decreased in controlled T2DM and elevated in pancreatitis. These findings support evaluating a constellation of glycemic, trace element, and enzymatic

biomarkers as potential tools for monitoring pancreatic injury in T2DM and warrant additional studies to validate the prognostic significance of these profiles.

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