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Effects of Chronic Ghrelin Administration On Metabolic Profile, S100A4 Levels, and Cardiohepatic Histopathology In Type 2 Diabetic Rats

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ABSTRACT

Each year, nearly 18 million deaths occur due to cardiovascular diseases, and diabetes mellitus (DM) as well as hypertension are recognized as major underlying risk factors. The present study was designed to evaluate the impact of ghrelin on the blood lipid profile, LDH, serum and hepatic S100A4 levels, and liver and cardiac histology in a high-fat diet-HFD/ streptozotocin-induced animal model of type 2 DM (T2DM). HbA1c, LDL, cholesterol and triglyceride levels were significantly increased in the untreated T2DM group compared to controls, whereas HDL and LDH levels were decreased. In the T2DM+Metformin group, LDL, cholesterol, triglyceride and HbA1c levels were reduced, while HDL and LDH levels were increased compared to the T2DM group. In the T2DM+Ghrelin group, LDL levels were significantly increased whereas HDL, cholesterol, triglyceride and HbA1c levels were decreased relative to untreated diabetic animals. Serum and hepatic S100A4 levels were significantly increased in T2DM group, however ghrelin treatment significantly reduced hepatic S100A4 levels. Histological evaluation of cardiac tissue in untreated diabetic rats revealed structural irregularities, cardiomyocyte degeneration, reduced cell size, myocardial damage, and lymphatic infiltration. These diabetes-induced myocardial alterations were markedly improved by ghrelin or metformin treatment. In liver tissue, extensive hepatocyte damage, necrosis, and cellular degeneration were observed in the T2DM group, whereas both treatments reduced lymphocytic infiltration and hepatocellular damage. In conclusion, the results indicate that ghrelin may represent a potential therapeutic candidate for attenuating T2DM-related structural cardiac and hepatic damage; however, additional investigations are required to confirm these effects.

Keywords: Diabetes, ghrelin, lipid profile, metformin, neuropeptide, S100A4.

Introduction

Diabetes is a serious, chronic disease in which high glucose levels occur when the body cannot produce an adequate amount of insulin or is unable to utilize insulin effectively (1). The global burden of diabetes reached approximately 589 million adults in 2024, with this number expected to rise to 853 million by 2050 (1). Diabetes is associated with a range of severe complications, including blindness, kidney failure, cardiovascular events such as heart attacks and strokes, as well as the risk of lower limb amputations (2). More than 90% of all diabetes cases worldwide are Type 2 diabetes mellitus (T2DM) (1). Although the exact pathogenesis of T2DM remains incompletely understood, it is recognized that hyperglycemia, dyslipidemia, and other metabolic abnormalities promote insulin resistance (IR) and/or β-cell dysfunction via shared mechanisms, including inflammation, oxidative stress (OS), and ectopic lipid deposition (3).

Elevated glycated hemoglobin (HbA1c), which reflects peripheral IR and the average blood glucose level within the last 2–3 months (4), is closely linked to an increased risk of diabetes-related complications and death (4, 5). These complications affect multiple organ systems, including the cardiovascular and hepatic systems (6). Alterations in liver enzyme levels have also been reported in association with diabetes-related pathophysiological processes (7). A previous study reported significantly increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in individuals with T2DM compared to controls (8).

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In T2DM, cardiovascular diseases constitute the primary cause of both premature mortality and increased risk of death (9). In this context, insulin resistance and hyperglycemia disrupt triglyceride lipolysis and impair the uptake of low-density lipoprotein (LDL), ultimately resulting in elevated triglyceride and LDL levels accompanied by decreased levels of high-density lipoprotein (HDL) (10). Consistent with these metabolic abnormalities, experimental animal models of T2DM have demonstrated diabetes-related histopathological changes in the heart (11) and liver (12).

Ghrelin is a peptide predominantly synthesized in the stomach that functions as a regulator of appetite and growth hormone secretion (13). Ghrelin has been suggested to modulate pancreatic β-cell activity and glucose homeostasis (13). It has been reported that ghrelin plays a role in T2DM, metabolic syndrome, as well as the cardiovascular system (14). In a previous study, low plasma ghrelin levels were reported to be independently associated with T2DM and insulin resistance (15). Acute ghrelin administration was reported to increase blood glucose levels in healthy human subjects (16). It has been suggested that ghrelin decreases glucose-stimulated insulin secretion in healthy individuals (17). In a previous study, although acute ghrelin administration was reported to induce hyperglycemia and hyperinsulinemia, a 21-day chronic ghrelin treatment was reported to normalize insulin levels and regulate blood glucose in healthy rats (18). Moreover, chronic ghrelin treatment was shown to exert antioxidative, anti-inflammatory, and tissue protective effects on pancreatic and brain tissues in a fat-fed streptozotocin-induced rat model (19). Considering the association of S100A4 with inflammatory responses, and diabetes (20), its serum and liver levels were evaluated to investigate its possible connection with the anti-inflammatory effects of ghrelin. To our knowledge, no studies have evaluated the impact of chronic ghrelin administration on metabolic and structural parameters in T2DM. Accordingly, this study aimed to assess the effects of ghrelin treatment on blood lipid profile, hepatic enzyme levels, serum and hepatic S100A4 levels, and histopathological alterations in the heart and liver in a STZ and high-fat diet (HFD)-induced rat model of T2DM. Metformin is a widely used antidiabetic agent that is recommended as first-line therapy for T2DM (21). Therefore, the effects of ghrelin on T2DM were compared to a metformin-treated group.

Materials and methods

Drugs: For diabetes induction, streptozotocin (STZ; Sigma-Aldrich, S130) was freshly prepared in 0.1 mol citrate buffer (pH 4.5) and administered as a single injection (40 mg/kg) (19). Ghrelin (GenScript, Cat. No. RP10781) was dissolved in distilled water and stored at −20°C until administration. On the day of administration, it was freshly diluted in physiological saline (PS) and administered i.p. at a dose of 100 µg/kg. Metformin was dissolved in PS and administered orally (100 mg/kg) (19).

Animals: 38 Wistar albino rats (100-150 g, male) were maintained in the Experimental Animals Unit of Van Yuzuncu Yil University under controlled standard conditions (light-dark cycle: 12-12 h, 21°C, 40–60% humidity) and ad libitum access to food and water (19).

Experimental Procedure: This study was conducted using blood, serum, liver, and heart tissues obtained from rats in which a fat-fed streptozotocin (STZ) model had been previously established (19). The research protocol was approved by the Van Yuzuncu Yil University Ethical Committee (2023/13-01). In the previous study, rats were assigned to 4 experimental groups: Control (n = 8), T2DM (n = 10), T2DM + Ghrelin (T2DM+G, n = 10), and T2DM + Metformin (T2DM+M, n = 10). Control animals received standard chow, whereas all other groups were exposed to a HFD (60 % kcal from fat) throughout the experimental period to promote insulin resistance (22). On day 22, streptozotocin (40 mg/kg, i.p.) was administered to induce diabetes in 30 rats, while control animals (n = 8) received citrate buffer (1 mL/kg, i.p.) (19). Blood glucose levels were measured prior to STZ administration and measured again 10 days after the injection. Animals exhibiting blood glucose levels above 270 mg/dL were considered diabetic and enrolled in the experimental groups (22). From day 32 onwards, ghrelin (100 µg/kg/day, i.p.) or metformin (100 mg/kg/day, orally) was administered to the animals in the T2DM+Ghrelin and T2DM+Metformin groups, respectively, for 3 weeks.

Biochemical Analysis: Blood samples were collected under ketamine–xylazine anesthesia (50/15 mg/kg), and serum was analyzed for AST, lactate dehydrogenase (LDH), HbA1c, ALT, triglycerides, LDL, HDL, and total cholesterol using the Abbott Architect i1000 chemiluminescent microparticle immunoassay system.

ELISA Studies: Serum S100A4 levels were analyzed using a commercially available enzyme-

linked immunosorbent assay (ELISA) kit with a Bio-Tek ELX800 microplate reader.

Tissue Collection: Heart and liver tissues were collected from rats and immersed in 10 % neutral-buffered formalin for 48 h. Following fixation, the tissues were rinsed under running tap water to eliminate residual fixative. The tissues were dehydrated through a graded alcohol series (70%, 80%, 96%, and three changes of 100%), followed by clearing in xylene (I, II, and III). The samples were subsequently embedded in paraffin. Paraffin-embedded tissues were cut into 5-µm-thick sections using a rotary microtome, and all sections were mounted onto coated slides and left to dry at room temperature.

Hematoxylin-Eosin Staining: For histological examination, the tissue sections were initially dried in a 60°C oven for approximately 1 h. The sections were deparaffinized in xylene and rehydrated through a graded alcohol series. Sections were rinsed in distilled water and stained with hematoxylin for 1 min, followed by washing under running tap water. Counterstaining was performed with eosin for 30–45 s. Subsequently, sections were dehydrated through ascending alcohol concentrations, cleared in xylene, and mounted with Entellan. Stained slides were examined using an Olympus BX53 microscope equipped with a DP74 digital camera.

Statistical Analysis: Descriptive statistics were reported as mean±standard deviation (SD). Data normality was assessed using the Shapiro–Wilk test. The homogeneity of variances was assessed using Levene's test. Since all parameters met the assumptions of parametric tests for intergroup comparisons, one-way ANOVA analysis was applied for comparisons between independent groups. Post-hoc pairwise comparisons following one-way ANOVA were conducted using Games–Howell test (for heterogeneous variances) or Bonferroni's test (for homogeneous variances). Statistical analyses were conducted using SPSS software (version 26.0; SPSS Inc., Chicago, IL), and a p-value < 0.05 was accepted as significant.

Results

As previously documented (19) by the end of the experiment, blood glucose levels were significantly reduced in the T2DM+G and T2DM+M groups compared to the T2DM group, with the T2DM+G group showing the most marked improvement.

Hemoglobin A1c Levels In Experimental Groups: HbA1c levels were significantly higher in the T2DM group compared to all other groups ($p \leq 0.001$). Although the HbA1c levels in the T2DM+M and T2DM+G groups were elevated relative to the control group, they were significantly lower than those in the T2DM group ($p \leq 0.001$). No significant difference was observed between the T2DM+M and T2DM+G ($p > 0.05$, Fig. 1).

Lipid Profile and Liver Enzyme Parameters: LDL levels were significantly greater in the T2DM group compared with controls ($p \leq 0.001$). Metformin treatment significantly decreased LDL levels compared to the untreated T2DM group, while ghrelin administration resulted in significantly higher LDL levels compared to all other groups ($p \leq 0.001$). HDL levels were significantly lower in the T2DM group relative to the control ($p \leq 0.001$). Metformin reversed this reduction, whereas ghrelin treatment further decreased HDL levels compared with other groups ($p \leq 0.001$). Total cholesterol levels were significantly increased in the T2DM group compared with controls ($p \leq 0.001$). Both metformin and ghrelin significantly reduced cholesterol levels compared with the T2DM group, with metformin causing a more pronounced reduction ($p \leq 0.001$). Triglyceride levels were significantly higher in the T2DM group than in the control group ($p \leq 0.001$). Both treatments significantly lowered triglyceride levels compared with the T2DM, with a greater reduction observed in the metformin group ($p \leq 0.001$, Table 1). AST levels were significantly higher in the T2DM group than in the control group ($p \leq 0.001$). In the metformin- and ghrelin-treated groups, AST levels were further elevated compared to the T2DM group ($p \leq 0.001$). ALT levels were likewise significantly elevated in the T2DM group ($p \leq 0.001$), and treatment with either metformin or ghrelin led to an additional increase, with the ghrelin group demonstrating significantly higher levels than the metformin group ($p \leq 0.001$). LDH levels were significantly lower in the T2DM group compared with controls ($p \leq 0.001$). While metformin treatment significantly increased LDH levels, ghrelin-treated rats exhibited levels comparable to those in the T2DM group (Table 1).

S100A4 Levels In Serum and Liver Tissues: Serum S100A4 levels were significantly increased in the T2DM group compared with controls ($p \leq 0.001$). Although ghrelin treatment tended to reduce S100A4 levels relative to the T2DM group,

Table 1: Comparison of Lipid Profile and Liver Enzyme Parameters Among Experimental Groups (mean ± SD)

	Control	T2DM	T2DM+M	T2DM+G	p value
LDL (mg/dL)	12.25±0.27d	28.74±0.67c	22.60±0.96b	33.63±0.99a	≤0.001
HDL (mg/dL)	40.14±0.42b	37.00±1.22c	41.35±1.16a	33.86±0.87d	≤0.001
Cholesterol (mg/dL)	63.88±0.99d	97.00±1.22a	83.38±1.30c	91.57±2.37b	≤0.001
Triglyceride (mg/dL)	90.25+1.49d	459.80±9.98a	297.75±15.81c	384.43±22.77b	≤0.001
AST (U/L)	101.96±1.93d	107.52±1.17c	132.99±3.27a	122.23±4.59b	≤0.001
ALT (U/L)	30.13±0.64d	81.20±1.30c	92.63±2.00b	100.00±4.55a	≤0.001
LDH (U/L)	1464.63±20.78a	642.60±7.16c	879.63±48.25b	657.86±17.58c	≤0.001

Data are expressed as mean±SD. p values show the results of the one-way ANOVA analysis. Post-hoc analysis results are summarized in lowercase letters. Superscript letters denote significant differences among groups in the same row ($p \leq 0.001$). Groups sharing an identical letter do not differ significantly from one another.

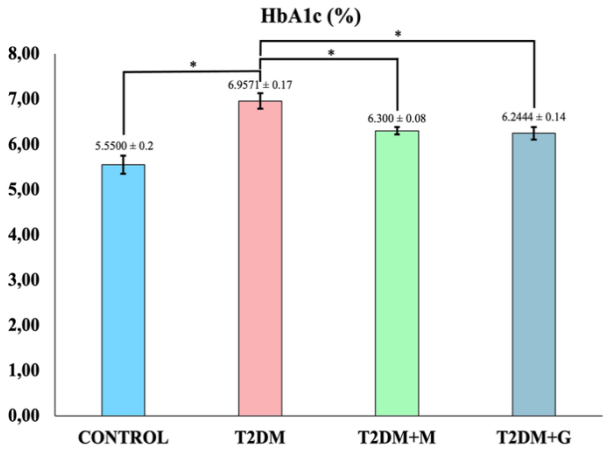

Fig. 1. Comparison of HbA1c Levels Among Groups. Data are expressed as mean±SD. Asterisks (*) denote statistically significant differences between the groups (p≤0.001). (The results of the Games-Howell post-hoc test, used for multiple comparisons of group means after one-way ANOVA analysis, are indicated with "*". *p <0.05 was considered significant,
G: ghrelin, HbA1c: glycated hemoglobin, M: metformin, SD: standard deviation, T2DM: Type 2 diabetes mellitus)

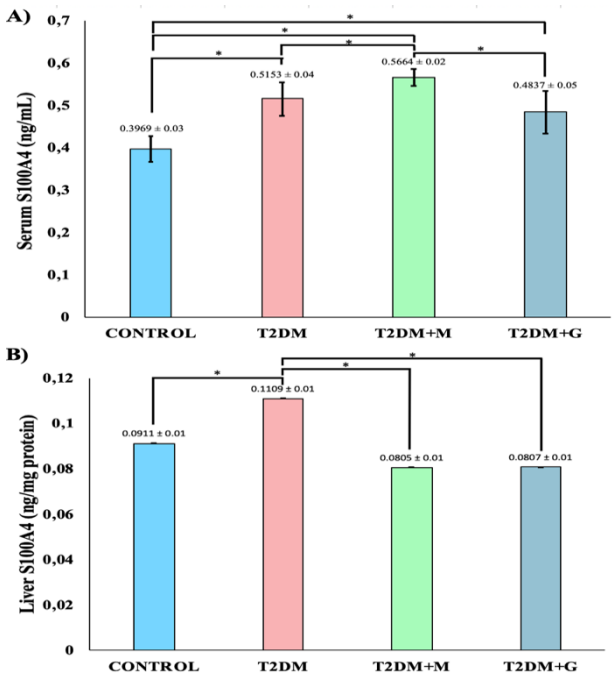

Fig. 2. Comparison of S100A4 Levels in Serum and Liver Tissues Among Groups. (A) Serum S100A4 levels in Control, T2DM, T2DM+M, and T2DM+G groups. **(B)** Liver S100A4 levels among the same groups. Data are expressed as mean±SD. Asterisks (*) denote significant differences among groups ($p \leq 0.001$). (The Bonferroni (A) and Games-Howell (B) post-hoc test results used in the multiple comparison of group means after one-way ANOVA analysis are indicated with "*". *p <0.05 was considered significant,
G: ghrelin, M: metformin, S100A4: S100 calcium-binding protein A4, SD: standard deviation, T2DM: Type 2 diabetes mellitus).

this difference was not statistically significant. In contrast, serum S100A4 levels were significantly higher in the metformin-treated group than in the control, T2DM, and T2DM+G groups (p≤0.001, Fig. 2A).

Liver S100A4 levels were also significantly increased in the T2DM group compared with controls ($p \leq 0.001$, Figure 2B). Both metformin

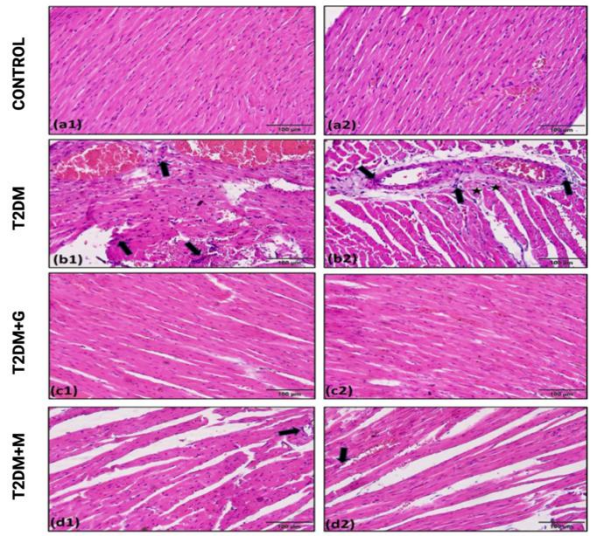

Fig. 3. Histological images of Hematoxylin-Eosin (H&E)-stained sections of cardiac tissue. Control group (a1–a2), Untreated T2DM group (b1–b2), Diabetes + Ghrelin (T2DM+G) group (c1–c2), and Diabetes + Metformin (T2DM+M) group (d1–d2). Black arrow: Lymphatic infiltration, Black star: Vacuole. (H&E staining, Scale bar: 100 µm). (G: ghrelin, M: metformin, T2DM: Type 2 diabetes mellitus)

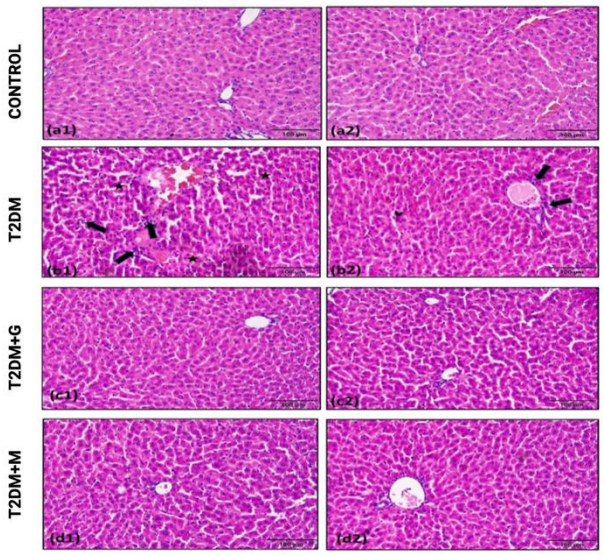

Fig. 4. Histological images of H&E-stained liver tissue sections. Control group (a1–a2), Untreated diabetic (T2DM) group (b1–b2), Diabetes + Ghrelin (T2DM+G) group (c1–c2), Diabetes + Metformin (T2DM+M) group (d1–d2). Black arrow: Lymphatic infiltration; Black star: Vacuole; Black arrowhead: Apoptotic bodies (H&E staining, Scale bar: 100 µm). (G: ghrelin, M: metformin, T2DM: Type 2 diabetes mellitus)

(T2DM+M) and ghrelin (T2DM+G) significantly decreased liver S100A4 levels relative to the untreated diabetic group ($p \leq 0.001$). There was no significant difference observed among the T2DM+M, T2DM+G, and control groups (Fig. 2B).

Histological Evaluation of Cardiac Tissue: Given the well-established link between cardiovascular diseases and diabetes, histopathological analyses were conducted to identify diabetes-induced structural alterations in cardiac tissue. The histological architecture of the myocardial layer in cardiac tissue sections from all groups was morphologically evaluated under a light microscope. In the sections belonging to the control group, the overall histological architecture of the heart tissue was found to be regular. The cardiomyocytes exhibited a normal histological structure and size, the myocardial nuclei appeared uniform, the myocardial space was normal, myocardial fibers were well-organized in regular arrays, and the vascularized areas displayed a normal appearance (Fig. 3a1 and a2).

In the cardiac tissue sections from untreated diabetic (T2DM) rats, marked alterations were observed. These included disorganization of myocardial fibers, reduced cardiomyocyte size, focal vacuolization, fragmentation, and areas of myofibrillar lysis. Furthermore, lymphatic infiltration areas were identified in both vascular and perivascular regions in certain areas of the myocardium layer (Fig. 3b1 and b2).

In the cardiac tissue of rats treated with ghrelin (T2DM+G) or metformin (T2DM+M), diabetes-induced myocardial damage and degenerative changes were markedly improved compared to the diabetic group (Fig. 3c1, c2, d1, and d2). In particular, in diabetic animals treated with ghrelin, myocardial damage, vacuolization, and myocardial fibers appeared more organized. A reduction in vacuolization and disorganization of myocardial fibers was observed. The myocardial cells in the treated groups exhibited a histological architecture close to normal (Fig. 3c1 and c2). Furthermore, compared with the T2DM group, a notable reduction in lymphatic infiltration areas in both vascular and perivascular regions was detected. Compared with the T2DM group, both treatment groups demonstrated improvement in cell populations. Mild inflammatory foci were observed in the T2DM+M group (Fig. 3d1 and d2). However, in the T2DM+G group, the reduction in inflammatory areas was particularly prominent. These findings suggest that exogenous ghrelin ameliorates diabetes-induced cardiac injury.

Histological Evaluation of Liver Tissue: Histopathological examination of liver sections from the control group displayed normal

histological architecture, characterized by portal triads located between regularly arranged lobules and central veins. Hepatocytes exhibited prominent, round, and euchromatic nuclei and the hepatic cords were regularly organized (Fig. 4a1 and a2).

In contrast, liver tissues from untreated diabetic rats exhibited marked structural alterations, including areas of necrosis and degeneration. Dilated and hyperemic sinusoids, thickened vascular walls, extensive and widespread vacuolar degeneration, pyknotic nuclei indicative of nuclear condensation were observed. Additionally, intense mononuclear cell infiltration was evident in the stromal regions surrounding the portal triads, along with significant lobular disorganization and severe hepatocyte damage (Fig. 4b1–b2).

Treatment with ghrelin (T2DM+G) or metformin (T2DM+M) partially restored hepatic architecture compared to the untreated diabetic group. These treatments resulted in reduced lymphocytic infiltration and restoration of hepatic tissue organization. Hepatocytes exhibited normal architecture with clearly visible portal triads, central veins, and regularly arranged sinusoidal cords. These findings indicate that both ghrelin and metformin ameliorated liver damage in diabetic rats (Fig. 4c1, c2, d1, and d2).

Discussion

In this study, exogenous ghrelin treatment was shown to exert protective effects on the liver, heart, and positive effects on some serum parameters in a fat-fed streptozotocin rat model of T2DM.

Ghrelin administration significantly reduced HbA1c, cholesterol, and triglyceride levels and mitigated histopathological damage in both hepatic and cardiac tissues. Moreover, ghrelin treatment significantly decreased liver S100A4 levels, with a non-significant downward trend observed in serum S100A4 levels.

Cardiovascular diseases represent the primary cause of mortality among individuals with T2DM, which constitutes approximately 90% of all diabetes cases (9). Individuals with T2DM typically exhibit multiple cardiovascular risk factors such as elevated blood glucose levels, dysregulated lipid profiles, and changes in inflammatory mediators (23). In the current study, HbA1c and serum lipid parameters were evaluated to assess the metabolic effects of Ghrelin in a fat-fed STZ rat model of T2DM. As expected, T2DM group showed significantly elevated HbA1c levels, indicating poor glycemic control. Both metformin and ghrelin treatments significantly reduced HbA1c levels. These findings are in agreement with our previous observations on blood glucose levels (19) and support the long-term antihyperglycemic potential of ghrelin. In the present study, the T2DM group exhibited significantly elevated triglyceride, cholesterol, and LDL levels, along with a significant reduction in HDL levels. Metformin significantly reduced LDL, cholesterol, and triglyceride levels, and significantly increased HDL levels compared to the T2DM group. Ghrelin led to a marked decrease in cholesterol and triglyceride levels compared to the T2DM group. However, it also caused a significant increase in LDL and a further decrease in HDL levels. A previous study reported that ghrelin improved fasting glucose and insulin, HOMA index, triglycerides, LDL-C, and total cholesterol levels, except for HDL-C, in a T2DM model (24). The present findings indicate that ghrelin administration significantly reduced cholesterol and triglyceride levels but did not improve LDL or HDL levels. This discrepancy may be attributed to the difference in fat content between the HFD used in the previous study (22.5%) (24) and that used in our study (60%).

Diabetes can influence the function and structure of the heart, even in the absence of alterations in blood pressure or the presence of coronary artery disease (25). In this study, untreated diabetic rats (T2DM) showed marked structural and morphological alterations in cardiac tissue, including lymphatic infiltration, myocardial vacuolization, fragmentation, lysis, and myocardial fiber atrophy and separation, consistent with diabetes-induced cardiac injury. Our results are supported by previous reports indicating that STZ induces structural damage in cardiac tissue (26). In this study, metformin and ghrelin treatments markedly attenuated diabetes-induced cardiac tissue injury, with both treatments preserving myocardial organization and reducing inflammatory responses.

T2DM affects the function and structure of the liver (27) and heart (25). It is emphasized that oxidative stress and inflammation play an important role in diabetes-related liver damage (27). In the present study, alterations in serum ALT, AST, and LDH levels, as well as liver S100A4 expression and histological findings, in the untreated T2DM group compared with controls, indicate structural and functional alterations in the liver caused by T2DM. Similar to

our study, a previous study reported increased levels of ALT and AST and structural damage-related changes in liver tissue in the diabetic group (28). Consistent with our results, a previous study found severe damage in the liver tissue of rats induced with T2DM using STZ and HFD (29). The present findings indicate that ghrelin or metformin treatments attenuated diabetes-induced liver damage through reduction of lymphocytic infiltration and restoration of hepatic tissue organization. Despite histopathological improvement, AST and ALT levels were found to be higher in both treatment groups compared to the untreated T2DM group. This may be due to the fact that tissue healing has not yet been reflected in serum AST and ALT levels.

S100A4 is a calcium-binding protein found within normal rodent and human cells (30). It has been reported as promoting inflammatory responses by inducing the release of cytokines under various pathological conditions (20). S100A4 has additionally been linked to insulin resistance and T2DM (31). Systemic low-grade inflammation has been observed in individuals with T2DM (32). In the present study, S100A4 levels of both serum and liver tissues significantly increased in the T2DM group. Consistent with our findings, a previous study comparing non-obese male individuals with and without T2DM found significantly higher serum S100A4 levels in the diabetic group (33). These observations suggest that S100A4 may contribute to low-grade chronic inflammation underlying the pathogenesis of T2DM. In the present study, both metformin and ghrelin significantly decreased hepatic S100A4 levels compared with the T2DM group. However, serum S100A4 levels were significantly elevated following metformin treatment, whereas a non-significant reduction was observed with ghrelin treatment compared with untreated T2DM group. This finding is consistent with our previous observations of proinflammatory cytokine levels of pancreatic, renal and brain tissues (19) and supports the anti-inflammatory potential of ghrelin in a fat-fed induced rat model of T2DM. Taken together, the present data suggest that ghrelin may represent a potential therapeutic candidate for attenuating cardiac and hepatic damage associated with T2DM; however, further experimental and clinical studies are required to confirm these effects.

Disclosure Statement: The authors report there are no competing interests to declare.

Data availability Statement: Data available within the article or its supplementary materials.

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References

1. IDF. Diabetes Atlas. 11th edn. ed. Brussels, Belgium2025.
2. WHO. Diabetes 2024 [Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes.
3. Lu X, Xie Q, Pan X, Zhang R, Zhang X, Peng G, et al. Type 2 diabetes mellitus in adults: pathogenesis, prevention and therapy. Signal Transduction and Targeted Therapy. 2024;9(1):262.
4. Wu C, Li A, Zhu Q, Guo J, Li Y, Gu X, et al. Glycemic variability of glycated hemoglobin in patients with type 2 diabetes mellitus and the risk of cardiovascular diseases: a latest systematic review and meta-analysis. Frontiers in Endocrinology. 2025;16:1698360.
5. Lee S, Liu T, Zhou J, Zhang Q, Wong WT, Tse G. Predictions of diabetes complications and mortality using hba1c variability: a 10-year observational cohort study. Acta diabetologica. 2021;58(2):171-80.
6. Zhao L, Yuan J, Yang Q, Ma J, Yang F, Zou Y, et al. Diabetes and its complications: molecular mechanisms, prevention and treatment. Signal Transduction and Targeted Therapy. 2026;11(1):22.
7. 7. Tyagi S, Jain P, Wani CP. Elevation Of Liver Enzymes and Its Correlation with Type 2 Diabetes Mellitus in A Tertiary Care Hospital. European Journal of Cardiovascular Medicine. 2025;15:209-12.
8. Islam S, Rahman S, Haque T, Sumon AH, Ahmed AM, Ali N. Prevalence of elevated liver enzymes and its association with type 2 diabetes: A cross-sectional study in Bangladeshi adults. Endocrinology, diabetes & metabolism. 2020;3(2):e00116.
9. Ma C-X, Ma X-N, Guan C-H, Li Y-D, Mauricio D, Fu S-B. Cardiovascular disease in type 2 diabetes mellitus: progress toward personalized management. Cardiovascular diabetology. 2022;21(1):74.
10. Pappan N, Awosika AO, Rehman A. Dyslipidemia. StatPearls. Treasure Island (FL)2025.

11. Radovits T, Korkmaz S, Mátyás C, Oláh A, Németh BT, Páli S, et al. An altered pattern of myocardial histopathological and molecular changes underlies the different characteristics of type-1 and type-2 diabetic cardiac dysfunction. Journal of diabetes research. 2015;2015(1):728741.
12. Zafar M, Naqvi SN-u-H, Ahmed M, Kaimkhani ZA. Altered Liver Morphology and Enzymes in Streptozotocin Induced Diabetic Rats. International journal of morphology. 2009;27(3).
13. Abdalla MMI. Ghrelin–physiological functions and regulation. European endocrinology. 2015;11(2):90.
14. Pulkkinen L, Ukkola O, Kolehmainen M, Uusitupa M. Ghrelin in diabetes and metabolic syndrome. Int J Pept. 2010;2010.
15. Poykko SM, Kellokoski E, Horkko S, Kauma H, Kesaniemi YA, Ukkola O. Low plasma ghrelin is associated with insulin resistance, hypertension, and the prevalence of type 2 diabetes. Diabetes. 2003;52(10):2546-53.
16. Broglio F, Arvat E, Benso A, Gottero C, Muccioli G, Papotti M, et al. Ghrelin, a natural GH secretagogue produced by the stomach, induces hyperglycemia and reduces insulin secretion in humans. The Journal of Clinical Endocrinology & Metabolism. 2001;86(10):5083-.
17. Tong J, Prigeon RL, Davis HW, Bidlingmaier M, Kahn SE, Cummings DE, et al. Ghrelin suppresses glucose-stimulated insulin secretion and deteriorates glucose tolerance in healthy humans. Diabetes. 2010;59(9):2145-51.
18. Goshadrou F, Kazerouni F, Mehranfard N, Sadeghi B. Chronic administration of ghrelin regulates plasma glucose and normalizes insulin levels following fasting hyperglycemia and hyperinsulinemia. General and Comparative Endocrinology. 2015;224:113-20.
19. Ergul Erkec O, Huyut Z, Acikgoz E, Huyut MT. Effects of exogenous ghrelin treatment on oxidative stress, inflammation and histological parameters in a fat-fed streptozotocin rat model. Archives of Physiology and Biochemistry. 2025;131(2):274-84.
20. Ambartsumian N, Klingelhöfer J, Grigorian M. The multifaceted S100A4 protein in cancer and inflammation. Calcium-binding proteins of the EF-hand superfamily: from basics to medical applications. 2019:339-65.
21. Kumari R, Singh Y, Prajapati B, Ahmad S, Srivastava SP. METFORMIN: A Review on it's Biological Activities and functioning. Dialogues in Cardiovascular Medicine. 2025;30:21-8.
22. Furman BL. Streptozotocin-Induced Diabetic Models in Mice and Rats. Curr Protoc Pharmacol. 2015;70:5 47 1-5 20.
23. Kalofoutis C, Piperi C, Kalofoutis A, Harris F, Phoenix D, Singh J. Type II diabetes mellitus and cardiovascular risk factors: current therapeutic approaches. Experimental & Clinical Cardiology. 2007;12(1):17.
24. Hussein A-AM, Abdel-Aziz A, Gabr M, Hemmaid KZ. Myocardial and metabolic dysfunction in type 2 diabetic rats: impact of ghrelin. Canadian journal of physiology and pharmacology. 2012;90(1):99-111.
25. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. Circulation. 2007;115(25):3213-23.
26. He Y, Wang S, Sun H, Li Y, Feng J. Naringenin ameliorates myocardial injury in STZ-induced diabetic mice by reducing oxidative stress, inflammation and apoptosis via regulating the Nrf2 and NF-κB signaling pathways. Frontiers in cardiovascular medicine. 2022;9:946766.
27. Mohamed J, Nafizah AN, Zariyantey A, Budin S. Mechanisms of diabetes-induced liver damage: the role of oxidative stress and inflammation. Sultan qaboos university medical journal. 2016;16(2):e132.
28. Hegazy RA, Abdulbaqi AA, Hassani R, El-kholy SS, Farrag FA, El-Magd MA. Cytoprotective impact of Moringa oleifera leaf extract on liver damage and insulin resistance in diabetic rats. Journal of Radiation Research and Applied Sciences. 2025;18(2):101532.
29. Atta IS, Elnady MR, Alghamdi AG, Alghamdi AH, Aboulata AA, Shatla IM. Assessing the hepatoprotective effects of hesperidin on liver-associated disorders in albino rats with experimentally induced obesity and type II diabetes: a histological and biochemical study. Heliyon. 2023;9(5).
30. Barraclough R. Calcium-binding protein S100A4 in health and disease. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 1998;1448(2):190-9.
31. Hou S, Jiao Y, Yuan Q, Zhai J, Tian T, Sun K, et al. S100A4 protects mice from high-fat diet-induced obesity and inflammation. Laboratory investigation. 2018;98(8):1025-38.
32. Okdahl T, Wegeberg A-M, Pociot F, Brock B, Størling J, Brock C. Low-grade inflammation in type 2 diabetes: a cross-sectional study from a Danish diabetes outpatient clinic. BMJ open. 2022;12(12):e062188.
33. Arner P, Petrus P, Esteve D, Boulomie A, Näslund E, Thorell A, et al. Screening of potential adipokines identifies S100A4 as a marker of pernicious adipose tissue and insulin resistance. International journal of obesity. 2018;42(12):2047-56.