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COMBINED TAURINE AND CHOLECALCIFEROL WITH METFORMIN PROTECTS AGAINST CARDIAC COMPLICATIONS IN DIABETIC RATS

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The management of type 2 diabetes involves navigating various risk factors and medications to prevent cardiovascular complications and premature death, with hyperglycemia and oxidative stress playing pivotal roles in diabetic cardiac damage. This study aimed to evaluate the impact of a combination therapy comprising cholecalciferol and taurine on Streptozotocin-induced diabetic cardiac damage in male Sprague Dawley rats treated with metformin. Rats were categorized into six groups, and after inducing diabetes with a high-fat diet and streptozotocin, treatments were administered orally for six weeks. Results indicated that the combination of cholecalciferol, taurine, and metformin exhibited superior myocardial protection in diabetic rats compared to those receiving metformin alone. This conclusion was drawn based on various assessments, including histopathology, CK-MB levels, and complete blood count. The study suggests incorporating cholecalciferol and taurine into diabetes treatment regimens, alongside metformin, may effectively mitigate cellular cardiac damage associated with hyperglycemia

Keywords: *Diabetes; Complications; Streptozotocin; Cardiovascular; Metformin*

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex condition that necessitates the management of various risk factors and medication therapy to mitigate cardiovascular complications and premature mortality[1]. The primary causes of morbidity and mortality in individuals with T2DM are cardiovascular diseases[2]. Patients with diabetes mellitus face a significantly higher risk of developing cardiovascular disorders, including ischemic heart disease, stroke, and heart failure, compared to healthy individuals[3]. In 2015, Mozaffarian et al. explained that patients with diabetes mellitus have a 2- to 4-fold higher likelihood of developing heart disease[4]. Additionally, Pappachan et al. stated in 2013 that cardiovascular diseases (CVDs) account for 50% to 80% of fatalities among individuals with diabetes mellitus[5]. Consequently, diabetes mellitus is considered a risk comparable to coronary heart disease.

T2DM manifests three distinct effects on the heart: diabetic cardiomyopathy (DCM), coronary artery disease (CAD), and cardiac autonomic neuropathy (CAN)[5]. CAD, characterized by the hardening and narrowing of coronary arteries due to plaque accumulation, is the most prevalent cardiovascular disease and poses a significant global health and welfare concern[6]. This condition impedes the heart muscles' ability to receive necessary blood and oxygen, resulting in adverse health effects[7]. Additionally, diabetes-associated damage to the autonomic nerve fibers of the heart and blood vessels can lead to irregularities in heart rate and arterial dynamics, impacting various organ systems and contributing significantly to morbidity and

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mortality in diabetic patients[8]. T2DM alters the ionic currents traversing the heart chambers, modifies the origin and spread of action potentials, promotes arrhythmias in both the atrium and ventricle as well as increases automaticity and recovery mechanisms[9]. Mechanical anomalies in the cardiac muscle, including severe pump failure, congestive heart failure, and an elevated risk of hospital admissions due to heart failure development, may result from advanced heart fibrosis and increased inflammation[9].

Cardiac troponin is one of the cardiac biomarkers utilized to identify myocardial damage in both symptomatic and asymptomatic individuals[10]. The cardiovascular troponin-I test, which can identify myocardial damage, is more sensitive and tissue-specific than other cardiac markers. Following myocardial ischemia-induced damage, the integrity of the myocardial cell membrane weakens, leading to the swift release of free cardiac troponin-I from the cytoplasm into the bloodstream[11].

The CK-MB test is a biological parameter in myocardial infarction (MI). As the myocardial injury progresses, CK-MB levels rise[12]. The elevated serum level of CK-MB in untreated diabetic rats indicates DCM, corroborating previous reports on increased serum CK-MB levels in myocardial[13].

Taurine (TAU), or tauric acid, constitutes 50% of the heart's total free amino acids in human and animal models. Numerous studies on humans and animals have demonstrated the role that taurine plays in preventing cardiovascular disease through a variety of beneficial actions, including cardioprotection, regulation of blood pressure, modulation of hemostasis, delay of atherogenesis, prevention of obesity, increase vascular health by improving endothelial function and defense against the complications of diabetes mellitus because of its antioxidant qualities[14,15].

Additionally, cholecalciferol (vitamin D3) significantly impacts the cardiovascular system[16]. Its absence is strongly linked to cardiovascular disease and eventual death. Based on some research, vitamin D may reduce the incidence of CVDs by reducing systemic inflammation and facilitating the production of cytokines that reduce inflammation[17]. Cholecalciferol's cardioprotective impact may be attributed to its antioxidant, anti-inflammatory, and antiapoptotic capabilities. Furthermore, its supplementation has a hypoglycemic effect in patients with diabetes[18]. Both taurine and cholecalciferol control calcium balance by affecting Ca2+ and K+ channels, impacting cardiac electrical activity, myocardial contractility, relaxation, and vascular tone[16,17].

Diabetes care is increasingly focused on preventing diabetes-related complications. Managing diabetes without side effects is a significant challenge. Anti-diabetes treatment aims to lower blood glucose levels to near normal, but free radicals present an additional obstacle[19]. Anti-diabetic drugs like metformin may successfully manage high blood sugar levels but are unable to prevent diabetic complications. This study suggests incorporating cholecalciferol and taurine into diabetes treatment regimens, alongside metformin, may effectively mitigate cellular cardiac damage associated with hyperglycemia.

MATERIALS AND METHODS

Chemicals

Reagent kits and streptozotocin (STZ) were obtained from Sigma Chemicals in St. Louis, MO, USA. Vitamin D (cholecalciferol) in the form of Vidrop® was acquired from a local pharmacy. Cidophage (1gm) pills containing metformin were purchased from SEDICO Pharmaceutical Co., 6th of October City, Egypt. Taurine, marketed by the Middle East Company, was in powder form and needed to be dissolved in distilled water.

Animals

Laboratory animals were utilized per ethical research guidelines, and their use was reviewed and approved by the ZU-IACUC committee (Ethical sanction number: ZU-IACUC/2/F/47/2022). Seventy-five healthy male albino rats (Sprague Dawley), weighing approximately 200-250 grams, were sourced from the animal house at the Faculty of Veterinary Medicine, Zagazig University, and employed in this study. The rats were housed in cages under standard laboratory conditions, ensuring proper ventilation during the light-dark cycle and maintaining a temperature between 20 and 25°C. Before the

commencement of the experiments, the rats were acclimatized to laboratory conditions for four weeks, during which they were provided with a high-fat diet and unrestricted access to water.

Induction of T2DM

Before the induction of T2DM, the rats were fed a high-fat diet, with approximately 58% of the total caloric intake from fat (580 g of vegetable ghee per kilogram of standard pellet diet), to promote the development of insulin resistance. Then, diabetes was induced in overnight-fasted rats through a single intraperitoneal administration of STZ dissolved in citrate buffer (pH 4.5) at a 45 mg/kg body weight[15]**. To prevent hypoglycemia, fructose solution 20% was given directly after receiving STZ.** The onset of diabetes was noted 48 hours after the STZ injection, and rats with blood glucose levels surpassing 250 mg/dL were classified as diabetic. Control rats were fed a normal pellet (25% protein) throughout the experimental period.

Experimental design

Sixty Sprague Dawley rats were divided into six equal groups, each comprising ten rats:

1. Control Group: Rats in this group received a single intraperitoneal injection of a citrate buffer solution (0.1mMol).
2. STZ Group: This group served as the diabetic non-treated group, receiving an intraperitoneal injection of streptozotocin (STZ) (45 mg/kg body weight) after experimental diabetes induction.
3. MET-treated group: Diabetic rats in this group were orally administered a daily dose of metformin (250 mg/kg b.wt) for six weeks using a metallic stomach tube[16]**.**
4. CHO+MET- treated group: Diabetic rats in this group received a daily oral dose of cholecalciferol (7500 IU/kg) along with a daily oral dose of metformin (250 mg/kg b.wt) for six weeks using a metallic stomach tube[19].
5. TAU+MET- treated group: Diabetic rats in this group were orally administered a daily dosage of taurine (100 mg/kg) in combination with a daily oral dose of metformin (250 mg/kg b.wt) for six weeks using a metallic stomach tube[20].
6. TAU+CHO+MET-treated group: In this group, ten diabetic rats received a daily oral dose of taurine (100 mg/kg), (7500 IU/kg) of cholecalciferol, and (250 mg/kg b.wt) of metformin for six weeks.

Collection of blood and tissue samples

After a designated period of six weeks, the animals were anesthetized using ketamine-xylazine, and blood was collected in heparinized tubes through the retro-orbital puncture. The rats were subsequently sacrificed and immediately dissected, with their hearts fixed in 10% formalin for histopathological study. Concurrently, blood plasma was separated by centrifugation at 3000rpm for 6-8 minutes at 8°C. The whole blood sample obtained was utilized to estimate the total leukocyte count (WBCs), hemoglobin concentration (Hb), and platelet count (PLT). Another sample was allowed to clot and then centrifuged to obtain a separate serum, which was used for determining troponin I and creatine kinase MB (CK-MB) levels.

Measurements of biochemical markers

WBC, PLT counts, and Hb concentration were measured using an automated blood cell counter (XN-1000, Sysmex, Germany). Creatine Kinase levels were determined using a Spectrum kit **(*Catalog No. 239 000*)**, following the method outlined by Friedman and Young (1989)[19]**. A Finecare kit (*Catalog No. W203*) was used to determine the troponin-I level.**

Statistical Analysis

The data are presented as mean ± standard error of the mean (SEM). Statistical analysis was conducted using one-way analysis of variance (One-way ANOVA) followed by Tukey's post hoc test, utilizing the Statistical Package for the Social Sciences for Windows (SPSS), version 26 software. The level of statistical significance was set at $p < 0.05$ for all analyses. Graphs were created using GraphPad Prism 9

RESULTS AND DISCUSSION

Results

Hematological study

The results showed no significant difference in platelet count between the

diabetic and control groups, consistent across all four treated groups, as presented in **Table 1** and **Fig. 1A**. In contrast, the STZ diabetic group demonstrated a noteworthy increase in WBC count compared to the control group. Furthermore, the MET, TAU+MET, and TAU+CHO+MET treated groups exhibited a significant elevation in WBC count compared to the STZ diabetic group. Notably, no marked alteration in hemoglobin concentration was observed in the diabetic group compared to the control group. Correspondingly, all treated groups (MET, CHO+MET, TAU+MET, and TAU+CHO+MET) did not manifest a significant difference in hemoglobin concentration compared to the diabetic group.

Table 1: Platelets and WBC counts and hemoglobin concentration in control and different experimental groups.

Groups	Platelets (count)	WBC (count)	Hemoglobin (g/dl)
Control	**630.17 ± 24.45**	**13.91 ± 0.66**	**14.70 ± 0.16**
STZ	**562.5 ± 117.74**	**23.28 ± 2.20***	**15.91 ± 0.27**
MET	**448.33 ± 107.18**	**13.9 ± 0.93#**	**15.66±0.37**
CHO+MET	**537.67 ± 30.17**	**18.51 ± 2.34**	**15.28 ± 0.59**
TAU+MET	**537.67 ± 36.56**	**15.60 ± 0.97#**	**15.28 ± 0.31**
TAU+CHO+MET	**652.17 ± 9.31**	**13.45 ± 0.33#**	**16.36 ± 0.14**

The data, presented as means ± SEM (n=6), indicate significant differences at $p < 0.05$. The asterisk (*) indicated significance compared to the control group, and the hash (#) denoted significance compared to the STZ diabetic group.

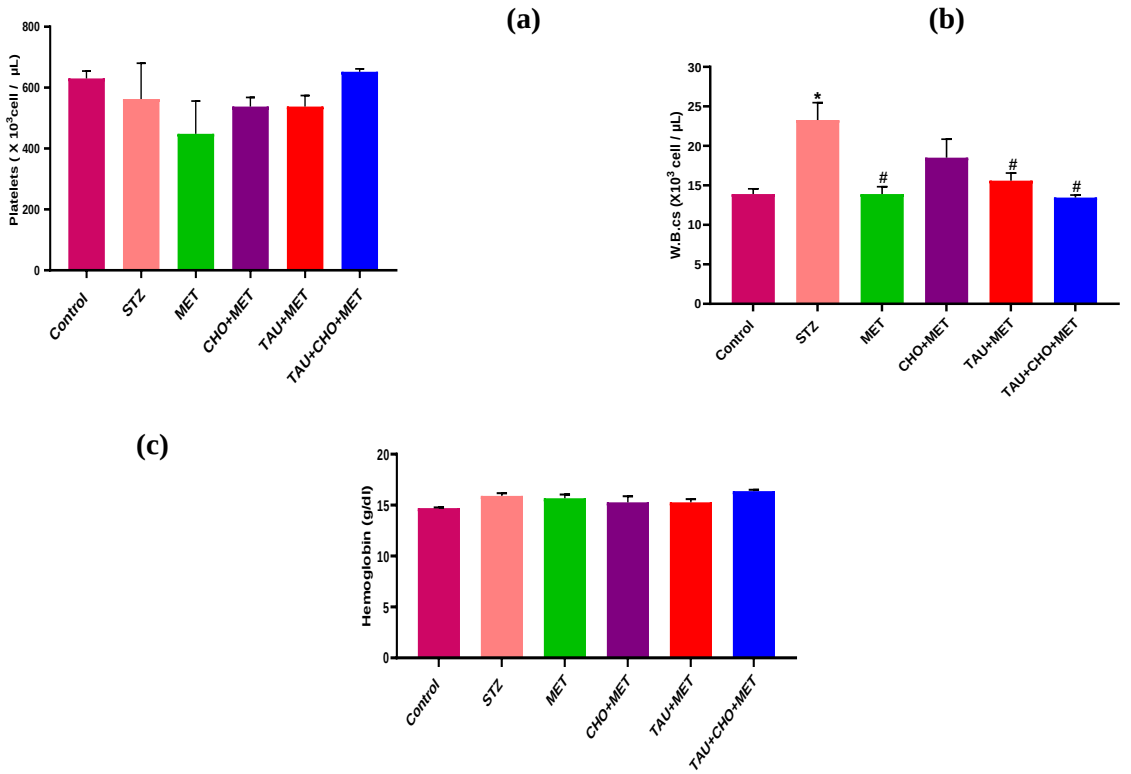

Fig. 1: Hematological Study Results in Control and Experimental Groups. Platelet counts (a), WBC counts (b), and hemoglobin concentration (c) were measured in the control and the other experimental groups. The data, presented as means ± SE (n=6), indicate significant differences at $p < 0.05$. The asterisk (*) indicated significance compared to the control group, and the hash (#) denoted significance compared to the STZ diabetic group.

Cardiac markers

The data presented in **Table 2** and **Fig. 2 (A and B)** revealed no statistically significant change in troponin-I levels in the STZ diabetic group compared to the control group. However, all other treated groups (MET, CHO+MET, TAU+MET, and TAU+CHO+MET) exhibited a significant decrease in troponin-I levels compared to the STZ diabetic group. Notably, the TAU+CHO+MET-treated group demonstrated a more substantial improvement in troponin-I levels than the MET-treated group. The CHO+MET and TAU+MET treated groups did not significantly differ in troponin-I levels compared to the MET-treated group.

Conversely, the STZ diabetic group showed a significant increase in CK-MB levels compared to the control group. All treated groups, except the MET-treated group, exhibited a significant decline in CK-MB levels compared to the STZ diabetic group. However, the MET-treated group indicated a non-significant change in CK-MB levels compared to the STZ diabetic group. On the other hand, the three treated groups (CHO+MET, TAU+MET, and TAU+CHO+MET).

Table 2: The levels of Cardiac Creatine Kinase MB concentration (CK-MB) and Troponin I in control and different experimental groups.

Groups	CK-MB (ng/ml)	Troponin-I (ng/ml)
Control	**2.23 ± 0.15**	**0.09 ± 0.035**
STZ	**11.52 ± 0.83***	**0.15 ± 0.019**
MET	**10.9 ± 0.72***	**0.07 ± 0.005**$^{\#}$
CHO+MET	**7.20 ± 0.46**$^{*\#\$}$	**0.04 ± 0.016#**
TAU+MET	**7.88 ± 0.59**$^{*\#\$}$	**0.03 ± 0.014**$^{\#}$
TAU+CHO+MET	**4.03±0.28**$^{\#\$}$	**0.05 ± 0.015**$^{\#}$

The data, presented as means ± SE (n=6), indicate significant differences at $p < 0.05$. The asterisk (*) indicated significance compared to the control group, and the hash (#) denoted the significance compared to the STZ diabetic group.

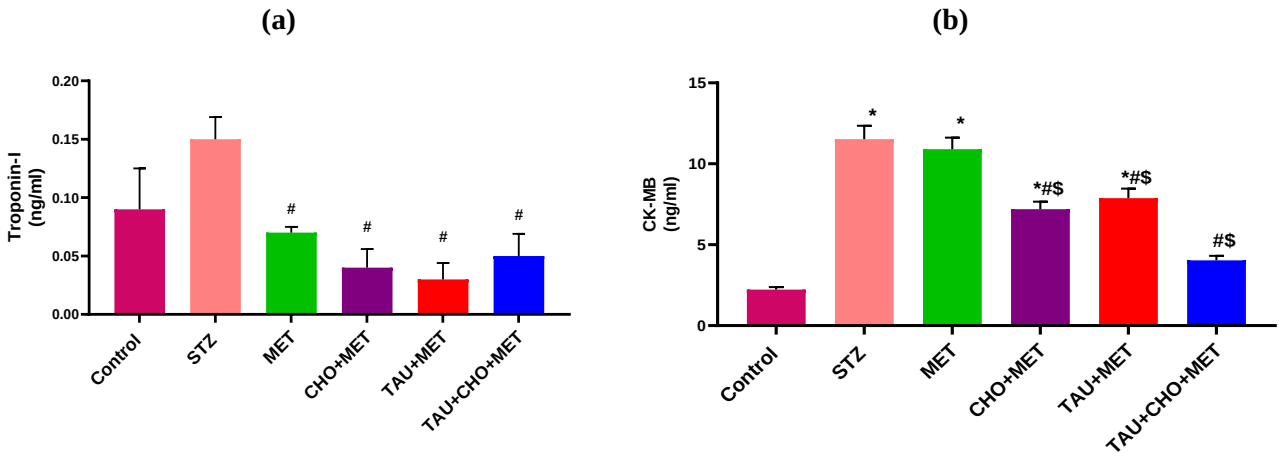

Fig. 2: Measurement of cardiac biomarkers. Cardiac troponin-I (a) and creatine kinase MB (CK-MB) (b) levels in control and various experimental groups. The data, presented as means ± SE (n=6), indicate significant differences at $p < 0.05$. The asterisk (*) indicated significance compared to the control group, and the hash (#) denoted significance compared to the STZ diabetic group.

Histological observations

Histological examination using H&E staining is presented in **Fig. 3**. The myocardium of the control group exhibited a typical arrangement of cardiac muscle fibers, as depicted in **Fig. 3(a) and 3(b)**. In contrast, the myocardium of diabetic rats displayed areas of cardiac muscle injury, characterized by the separation of myocytes, fibers disarray, and the multiple regions of hemorrhage, as shown in **Fig. 3(c) and 3(d)**. The metformin-treated group exhibited areas of hemorrhage between cardiac muscle fibers and some areas of hyalinization in **Fig. 3(e)**, while **Fig. 3(f)** showed increased vascularity between cardiac muscle fibers. Conversely, the myocardium of the cholecalciferol and metformin-treated group displayed a regular arrangement of cardiac muscle fibers in **Fig. 3(g)** and **Fig. 3(h)**. However, rats treated with the combination of taurine and metformin showed mild cardiac muscle injury, characterized by focal separation of myocytes with fibers disarray, as seen in **Fig. 3(i) and 3(j)**. Ultimately, the co-administration of cholecalciferol, taurine, and metformin resulted in the restoration of a usual arrangement of cardiac muscle fibers in the myocardium, as evidenced in **Fig. 3(k & l)**.

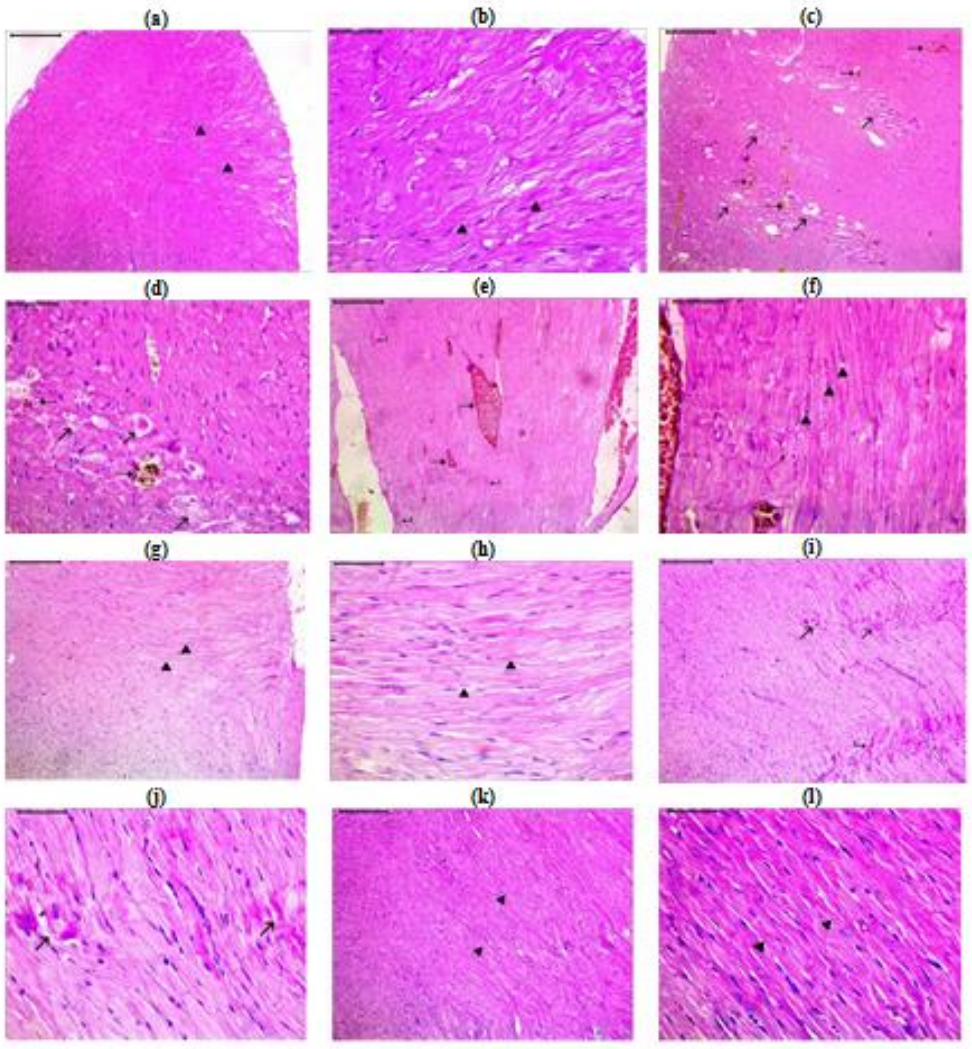

Fig. 3: Histopathological alterations in myocardial sections of rats from the six study groups. Photomicrographs depict myocardial sections of (a & b) control group, (c & d) STZ diabetic group, (e & f) MET-treated group, (g & h) CHO + MET-treated group, (i & j) TAU + MET-treated group, and (k & l) TAU + CHO + MET-treated group. Scale bars for photomicrographs at 100X (a, c, e, g, i, and k) are 100 µm, and scale bars for photomicrographs at 400X (b, d, f, h, j, and l) are 40 µm.

Discussion

Our results disagree with Fagbohun et al., 2020, who examined an association between insulin resistance and hemoglobin levels in diabetic patients. Thus, diabetic patients with complications are characterized by a decrease in hemoglobin concentration[21]. However, the administration of cholecalciferol, taurine, and metformin caused a slight increase in the hemoglobin level of treated rats compared to control ones. This is due to the antidiabetic effect of cholecalciferol, taurine, and metformin together.

Diabetic patients often experience alterations in hematological markers[22]. Regarding hematological indices, platelet count and mean platelet volume serve as risk factors for microvascular issues in diabetics and markers of thrombotic potential[23]. The results of this study demonstrated no significant difference in platelet (PLT) count in both diabetic and treated rats. This aligns with the findings of Sánchez-González et al. (2021), attributed to the short duration of the experiment[24]. However, research comparing rats with and without diabetes over a more extended period revealed considerably lower platelet counts, significantly greater mean platelet volume (MPV), and higher platelet distribution width (PDW), indicating stronger platelet reactivity and turnover in rats with long-term diabetes[25].

Moreover, WBCs are a helpful biomarker for diabetes risk[23]. In a large-scale population-based Tabari cohort study, Kheradmand et al. (2021) found a significant relationship between WBC count and T2DM[26]. Our results indicated a significant increase in WBC levels in the streptozotocin (STZ) diabetic group compared to the control group, consistent with the findings of Kheradmand et al. (2021). However, this contrasts with Rehman et al. (2023), who reported a significant decline in WBC levels in diabetic animals compared to controls[27].

The elevated WBC level in diabetic rats may be attributed to factors such as oxidative stress in diabetes[28], reduced insulin effectiveness, the onset of T2DM[29], or the damaging effects of streptozotocin (STZ)[21]. Conversely, the MET, TAU+MET, and TAU+CHO+MET treated groups showed a significant decrease in WBC levels compared to the diabetic group. Moreover, the combination of CHO, TAU, and MET brought the WBC levels in treated rats closer to the normal range observed in the control group. This suggests the antioxidant effects of cholecalciferol, taurine, and metformin. Both Ibrahim et al. (2023) and Wu (2020) have reported that taurine and metformin possess marked anti-inflammatory, anti-oxidative, anti-apoptotic, and anti-cancer activities[30,31]. Additionally, Bella et al. (2017) confirmed that cholecalciferol supplementation might improve hematological parameters and reduce cell counts of BAL and PeL fluids during diabetes[22].

Meanwhile, 90% of the erythrocyte weight consists of the essential protein, hemoglobin, a hematological marker for assessing substance toxicity[32]. Our findings showed no significant change in the hemoglobin level of the diabetic group, likely attributed to the short duration of the study. These results align with Rehman et al. (2023), who found that hemoglobin levels in diabetic rats remained within the normal range, likely due to the short duration of diabetes in the study, which minimized the impact on hemoglobin levels[27]. Adequate nutrition throughout the experiment may have contributed to stable hemoglobin levels, consistent with Eniwati et al. (2019), who emphasized the crucial role of protein in the body's hemoglobin production[33]. On the contrary, our results differ from those of Fagbohun et al. (2020), who reported an association between insulin resistance and decreased hemoglobin levels in diabetic rats with complications[21]. In the meantime, the administration of Cholecalciferol, taurine, and metformin caused a slight increase in the hemoglobin levels of treated rats compared to control ones, which can be attributed to the synergistic antidiabetic effects.

In terms of cardiac markers, our findings demonstrated an increased level of creatine kinase MB (CK-MB) in diabetic rats compared to the control group. This is consistent with Salau et al. (2023) [34], who reported that a high concentration of CK-MB in diabetic rats is a potent predictor of the probability of cardiovascular problems. This increase is attributed to cardiac muscle degeneration and ventricular dysfunction, leading to elevated

lactate dehydrogenase (LDH) and CK-MB movement in diabetic individuals[35].

However, in our study, the level of CK-MB in all treated groups improved compared to the diabetic group. The combination treatment of cholecalciferol, taurine, and metformin was more effective in reducing CK-MB levels than each treatment alone. The marked reduction in serum CK-MB concentration in the TAU+CHO+MET treated group reflects their cardioprotective effect, aligning with the observations of Salem et al. (2019)[36].

Compared to other cardiac markers, cardiac troponin-I detects myocardial injury with greater sensitivity and tissue specificity[37]. Our data revealed that the troponin-I level of the diabetic group increased but was not statistically significant compared to the control group. This increase aligns with Soares et al. (2018), indicating a sign of myocardial damage[38]. After treatment, all treated groups showed a significant decline in troponin-I levels. The combination treatment of TAU+MET or CHO+MET showed the best reduction in the troponin-I level, highlighting the cardioprotective role of taurine, cholecalciferol, and metformin.

The microscopic histopathological examination of heart tissues using H&E staining indicated that diabetic rats exhibited cardiac muscle injury, characterized by the separation of myocytes with fibers disarray and multiple areas of hemorrhage. These findings align with the report by Wang et al. (2020), stating that diabetes is a leading cause of abnormal ultrastructural changes in the heart, including myocardial degeneration and interstitial hemorrhage[35]. Such alterations are linked to increased oxide-nitrosative stress, which is associated with elevated reactive oxygen species (ROS) generation. Additionally, the myocardium of the metformin-treated group displayed areas of hemorrhage between cardiac muscle fibers, some regions of hyalinization, and increased vascularity between cardiac muscle fibers. In contrast, the co-administration of cholecalciferol, taurine, and metformin resulted in the typical arrangement of cardiac muscle fibers in the myocardium. This highlights the potential cardioprotective effects of cholecalciferol and taurine supplementation in conjunction with metformin.

Conclusion

In conclusion, while metformin monotherapy falls short in altogether preventing cardiac damage associated with T2DM, the combination treatment of cholecalciferol and taurine proves to be effective in alleviating the damage. This combined approach not only reduces CK-MB and troponin-I levels but also inhibits hemorrhage between cardiac muscle fibers and mitigates cardiac muscle injury. The findings of this study strongly suggest that cholecalciferol and taurine play crucial roles in modulating cardiac damage, complementing the antidiabetic effects of metformin. As a combined therapeutic strategy, cholecalciferol and taurine show promise as potential medicines to prevent diabetic-induced cardiac damage.

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دمج التورين والكوليكالسيفيرول مع الميتفورمين يحمي من المضاعفات القلبية لدى الجرذان المصابة بمرض السكري

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تتضمن إدارة مرض السكري من النوع الثاني التعامل مع عوامل الخطر المختلفة والأدوية لمنع المضاعفات القلبية الوعائية والوفاة المبكرة، حيث يلعب ارتفاع سكر الدم والإجهاد التأكسدي دورًا محوريًا في تلف القلب الناجم عن مرض السكري. هدفت هذه الدراسة إلى تقييم تأثير العلاج المركب الذي يتكون من كوليكالسيفيرول والتورين على تلف القلب السكري الناجم عن ستربتوزوتوسين في ذكور جرذان سبراج داولي المعالجة بالميتفورمين. تم تصنيف الجرذان إلى ست مجموعات، وبعد إحداث مرض السكري باتباع نظام غذائي عالي الدهون وستربتوزوتوسين، تم إعطاء العلاجات عن طريق الفم لمدة ستة أسابيع. أشارت النتائج إلى أن مزيج كوليكالسيفيرول والتورين والميتفورمين أظهر حماية عضلة القلب في الجرذان المصابة بمرض السكري مقارنة بتلك التي تتلقى الميتفورمين وحده. تم التوصل إلى هذا الاستنتاج بناءً على تقييمات مختلفة، بما في ذلك علم الأمراض النسيجي ومستويات CK-MB وصورة الدم الكاملة. لذا تشير الدراسة إلى أن دمج الكوليكالسيفيرول والتورين في أنظمة علاج مرض السكري، إلى جانب الميتفورمين، قد يخفف بشكل فعال من الضرر القلبي المرتبط بارتفاع سكر الدم.