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Original Article

Exploring the Combined Effects of Vitamin D and Pioglitazone on Lipid Dysregulation, Hepatic Function, and Adipocytokine Alterations in Type 2 Diabetic Rats

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ABSTRACT

Background: This study assessed the effects of Vitamin D (Vit D) and Pioglitazone (PIO) on metabolic and histopathological parameters in STZ-NA-induced diabetic rats, focusing on lipid metabolism, liver enzymes, adipocytokines, and liver tissue structure. **Materials and Methods:** Diabetes was induced using streptozotocin and nicotinamide, and rats were separated into five groups: normal control, diabetic control, and three treatment groups receiving Vit D, PIO, or a combination. Treatments were administered daily for eight weeks, and biochemical analyses included glucose, lipid profiles, liver enzymes, and adipocytokines (adiponectin and resistin). Liver tissue was examined histologically. **Results:** Diabetic rats showed dyslipidaemia with elevated cholesterol, triglycerides, and LDL, and decreased HDL. Vit D, PIO, or their combination treated rats reduced cholesterol and LDL, with the combination also increasing HDL, suggesting a synergistic effect. Both Vit D and PIO treatments lowered liver enzymes, with combination therapy providing the greatest improvement. Adipocytokine analysis revealed a reduction in resistin levels, particularly with the combination therapy, while adiponectin levels remained unchanged. Histopathological analysis showed liver damage in diabetic rats, but the combination therapy preserved liver architecture with minimal degenerative changes. **Conclusion:** The combination of Vit D and PIO shows promising potential for improving lipid metabolism, liver function, and adipocytokine regulation in diabetes, offering a therapeutic strategy for handling metabolic complications. More study is required to explore the essential mechanisms and optimize treatment protocols.

Keywords: Diabetes, Vitamin D, Pioglitazone, Dyslipidaemia, Adipocytokines, Lipid profiles.

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a long-term metabolic condition marked by the body's inability to effectively use insulin, resulting in insulin resistance and dysregulated lipid metabolism, often leading to associated complications such as hepatic dysfunction and adipocytokine imbalance. Dyslipidaemia, notably defined by elevated Low-Density Lipoprotein (LDL), Triglycerides (TG), and Total Cholesterol (TC) levels, and reduced High-Density Lipoprotein (HDL), is a hallmark feature of T2DM and a major contributor to cardiovascular risk in diabetic patients (Shams *et al.*, 2011; Calanna *et al.*, 2014). Additionally, alterations in adipocytokine profiles, such as increased resistin and decreased adiponectin levels, further exacerbate insulin resistance and promote systemic inflammation (Lu *et al.*, 2006; Kusminski *et al.*, 2005; Fasshauer and Paschke, 2003). Vitamin D (Vit D), a fat-soluble vitamin with well-established roles in calcium metabolism, has recently been recognized for its potential in modulating metabolic pathways, including insulin sensitivity and lipid regulation (Mostafa *et al.*, 2016). Emerging evidence suggests that Vit D deficiency is linked to worsening metabolic dysfunction in T2DM (Wimalawansa, 2018), though its therapeutic application remains under investigation. Pioglitazone (PIO), a thiazolidinedione, is a widely used insulin sensitizer in T2DM treatment. Beyond its effects on glucose metabolism, PIO has been shown to improve lipid profiles, reduce hepatic fat accumulation, and modulate inflammatory cytokines (Chilcott *et al.*, 2001; Collino *et al.*, 2010).

Given the multifactorial nature of T2DM, combination therapies that address multiple aspects of the disease could offer enhanced therapeutic effects. Recent studies have proposed the possible synergistic impacts of combining Vit D and PIO diminishes type-2 diabetes-persuaded hepatic damage (Hamouda *et al.*, 2022). However, the combined impact of these interventions on lipid dysregulation and adipocytokine alterations remains unclear. The purpose of this research is to explore the effects

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of Vit D supplementation in conjunction with PIO on lipid metabolism, liver function, and adipocytokine profiles in a rat model of T2DM. We hypothesize that the combined treatment will synergistically improve metabolic outcomes compared to monotherapy, offering a promising strategy for managing lipid dysregulation and associated complications in T2DM.

MATERIALS AND METHODS

Drugs and Chemicals

PIO was acquired from Bharat Parenteral Limited in Vadodara, India, and Vit D was purchased from local markets. Streptozotocin (STZ) and Nicotinamide (NA) were acquired from Himedia, Mumbai, India. The diagnostic kits utilized in the research were sourced from a reliable supplier, and all other reagents and chemicals used were of analytical grade quality.

Experimental animals

The study protocol (SVU/DP/IAEC/2019/09/43) was permitted by the Institutional Animal Ethics Committee and followed the standards outlined by the Committee for Control and Supervision of Experiments on Animals (CCSEA). It involved healthy adult Wistar rats, ranging in weight from 200 to 250 g and of both genders. They were kept in polypropylene cages under a controlled setting (12-hr light/dark cycle, 24°C temperature, and 35-60% humidity) and were served a normal diet, with access to purified drinking water.

Experimental Design

Diabetes was persuaded in the rats by administering a mixture of STZ and NA (Maheshwari *et al.*, 2017). The rats were randomly allocated to five groups, each containing six animals. Group I acted as the normal control (NC), while Group II, the diabetic control (DC), received no treatment. Group III was treated with Vit D (400 IU/kg/day) (Alsolami, 2019), Group IV with PIO (20 mg/kg) (Ding *et al.*, 2005), and Group V received both Vit D and PIO. All treatments were given orally once a day for eight weeks. Upon completion of the study, Blood samples were drawn from the retro-orbital plexus using glass capillaries under light ether anaesthesia. The samples were stored either with or without disodium ethylenediaminetetraacetate for subsequent biochemical analysis. The blood was permitted to clot for 15 min, sample was centrifuged at 5000 rpm for 20 min to separate the serum, which was then stored at -20°C for future analysis. Biochemical markers such as lipid profiles, and liver enzymes were assessed using standard kits. Additionally, serum levels of adiponectin and resistin were measured using ELISA.

Histopathology

After euthanasia, liver tissues from each group were promptly dissected, washed with saline, and fixed in 10% phosphate-buffered formalin. The samples were subsequently embedded in paraffin and sectioned into 5 µm thick slices, which were stained with hematoxylin and eosin. These sections were then examined under a light microscope, and images were captured with an Olympus DP12 camera (Japan) to assess histopathological changes. The pathologist performing the analysis was blinded to the group assignments.

Statistical analysis

All data are presented as mean±SEM. Statistical differences between groups were assessed using one-way ANOVA, followed by the Bonferroni post hoc test when applicable and using Prism software (GraphPad). A p-value of less than 0.05 was regarded as statistically significant for all analyses.

RESULTS

Effect of Vit D and PIO on lipid profiles in STZ-NA-induced diabetes

In the diabetic control rats, significantly elevated levels of TC, TG, and LDL were observed, while HDL levels were notably decreased compared to the normal control rats. This lipid imbalance reflects the harmful effects of diabetes on cardiovascular health, as such dyslipidaemia is often linked to an increased risk of cardiovascular diseases. Treatment with Vit D, PIO, and their combination led to substantial reductions in both TC and LDL levels in comparison to the untreated diabetic group, suggesting that these treatments can mitigate the lipid disturbances associated with diabetes. Notably, the combination therapy not only improved cholesterol and LDL levels but also resulted in a notable rise in HDL levels-an effect not seen with the monotherapies. This finding points to a potential synergistic effect of combining Vit D and PIO to enhance lipid profile improvements. Additionally, the combination therapy revealed a greater fall in both TC and LDL levels than either Vit D or PIO alone, underscoring its superior efficacy in correcting lipid imbalances and possibly reducing cardiovascular risk in diabetic conditions (Figure 1).

Effect of Vit D and PIO on liver enzymes levels in STZ-NA-induced diabetes

In the diabetic control rats, the levels of ALT and AST were expressively elevated compared to the normal control group, indicating liver stress and possible hepatocellular damage resulting from diabetes. These elevated enzyme levels point to increased liver strain, a common issue in metabolic disorders like diabetes. However, treatment with Vit D, PIO, and their combination ensued in major reductions in both ALT and AST levels, in comparison to the untreated diabetic group, demonstrating their protective effects on liver function. Among the treatments, the combination of Vit D and PIO showed the most substantial improvements, with ALT and AST levels approaching normal levels more effectively than either monotherapy. This suggests that the combination therapy has a synergistic effect,

providing enhanced protection against liver damage compared to each treatment used alone. Overall, these results emphasize the potential of Vit D and PIO, both separately and together, to mitigate liver enzyme elevations associated with diabetes induced liver injury (Figure 2).

Effect of Vit D and PIO on adipocytokines levels in STZ-NA-induced diabetes

In diabetic rats, a significant drop in adiponectin levels and an increase in resistin levels were observed relative to the normal control group, suggesting a disruption in adipokine balance that could contribute to the metabolic disturbances seen in diabetes. Treatment with Vit D, PIO, or their combination did not result in any significant changes in adiponectin levels when relative to the untreated diabetic group. However, these treatments did lead to a notable decrease in resistin levels relative to the diabetic control. Across the treatment groups, the combination of Vit D and PIO exhibited the most substantial reduction in resistin levels, outperforming each monotherapy. This finding underscores the potential enhanced therapeutic effect of combining Vit D and PIO in modulating adipokine levels and improving metabolic dysfunction associated with diabetes. The combination therapy, therefore, appears to offer a more effective approach to regulating adipokines like resistin, which plays a role in insulin resistance and inflammation (Figure 3).

Histopathology study

In the normal control group, liver tissue exhibited healthy histological features, with hepatocytes (black arrow) showing intact nuclei, well-defined cell boundaries, and a normal central vein (red arrow). In the diabetic control group, hepatocytes near the central vein (blue arrow) showed signs of degeneration, along with congestion in the liver tissue (yellow arrow). The Vitamin D treatment group largely maintained a normal liver structure, with moderate hepatocyte degeneration (yellow arrow), although the cells retained intact nuclei and cell borders. Some focal degenerative changes, such as granular cytoplasm and cellular swelling, were also observed. The PIO treatment group showed similar results, where hepatocytes preserved their normal structure but displayed mild degenerative features (yellow arrow), including granular cytoplasm and localized swelling, along with congestion (black arrow). In the Vitamin D+PIO treatment group, liver tissue generally kept its normal histological characteristics, with hepatocytes having intact nuclei, defined cell borders, and uniform arrangement. However, minimal degenerative changes (black arrow) were noted, including granular cytoplasm, cellular swelling, and sinusoidal congestion (yellow arrow) (Figure 4).

DISCUSSION

This study investigated the effects of Vit D and PIO on several metabolic and histopathological parameters in rats with diabetes induced by STZ-NA. The focus was on lipid profiles, liver enzyme activity, changes in adipocytokines, and histological alterations. In the diabetic control group, rats showed significant

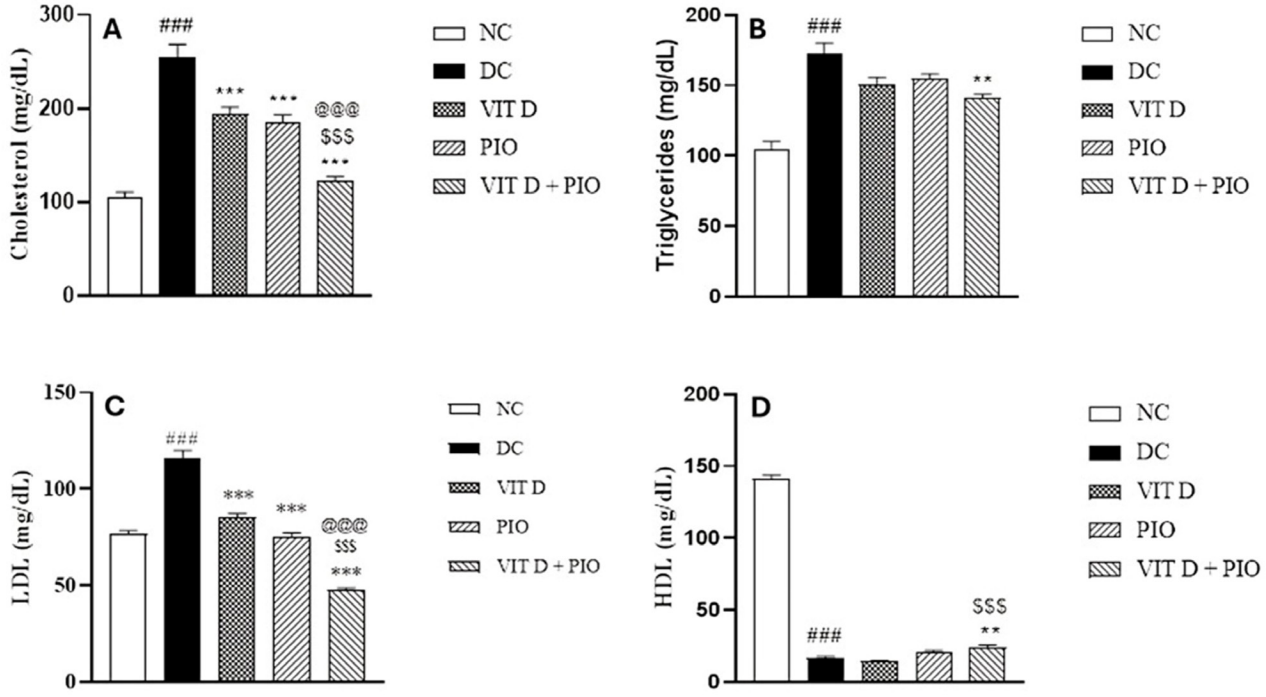

Figure 1: Impact of Vit D and PIO on (A) TC (B) TG (C) LDL and (D) HDL in experimentally induced diabetes. Values are stated as mean±SEM; *n*=6. ###*p*<0.001, relative to NC; **$p<0.01$, ***$p<0.001$, relative to DC; $^{\$\$\$}p<0.001$ relative to Vit D; $^{@@@}p<0.001$ relative to PIO.

dyslipidaemia, characterized by elevated TC, TG, and LDL levels, while HDL levels were reduced. These lipid imbalances are consistent with findings from previous studies, which indicate that diabetes disrupts lipid metabolism and heightens the risk of cardiovascular diseases (Artha *et al.*, 2019; Wu and Parhofer, 2014). The administration of Vit D, PIO, and their combination resulted in significant reductions in TC and LDL levels compared to the untreated diabetic group. This outcome aligns with findings from prior studies, which have shown that both VD and PIO have the potential to positively influence lipid profiles in diabetic individuals. These interventions appear to play a role in modulating lipid metabolism, contributing to improved cardiovascular health and potentially reducing the risk of associated complications in diabetes (Mostafa *et al.*, 2016; Hanefeld, 2009). Importantly, the combination therapy of Vit D and PIO not only resulted in significant reductions in TC and LDL levels but also led to a marked increase in HDL levels. This effect is consistent with previous studies (Hamouda *et al.*, 2022). Elevated HDL levels are beneficial for cardiovascular health, as they help in the removal of excess cholesterol from the bloodstream, thereby reducing the risk of atherosclerosis and other cardiovascular complications often associated with diabetes This suggests a possible synergistic effect between Vit D and PIO, offering enhanced benefits in improving lipid profiles and reducing cardiovascular risks in diabetic conditions.

Regarding liver function, diabetic rats showed marked increases in liver enzymes (ALT and AST), indicative of liver stress and damage, a common consequence of diabetes driven by oxidative stress and inflammation (Mohamed *et al.*, 2016). Treatment with Vit D, PIO, and their combination resulted in notable reductions in ALT and AST levels. While each treatment alone had beneficial effects, the combination therapy resulted in the most pronounced improvements, bringing ALT and AST levels closer to normal. These outcomes are steady with previous research presenting that PIO has hepatoprotective effects (Refaat *et al.*, 2016) and that Vit D supplementation can alleviate liver damage in diabetes (Özerkan *et al.*, 2017).

Concerning adipocytokines, the study observed a decrease in resistin levels and a trend toward the normalization of adiponectin levels, although the latter did not show statistically significant changes. The decrease in resistin levels, especially

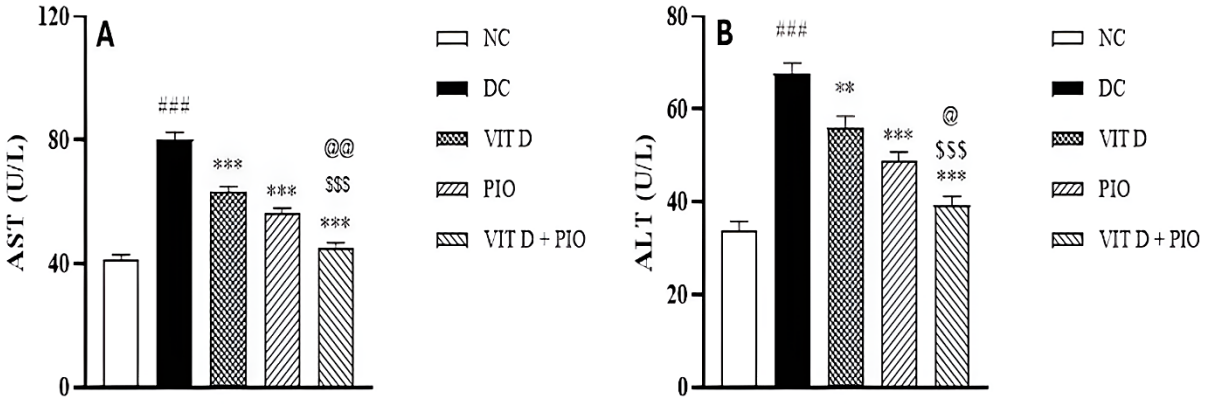

Figure 2: Impact of Vit D and PIO on (A) AST and (B) ALT in experimentally induced diabetes. Values are stated as mean±SEM; *n*=6. ###*p*<0.001, relative to NC; **p<0.01, ***p<0.001 relative to DC; $$$p<0.001 relative to Vit D; @p<0.05, @@p<0.01 relative to PIO.

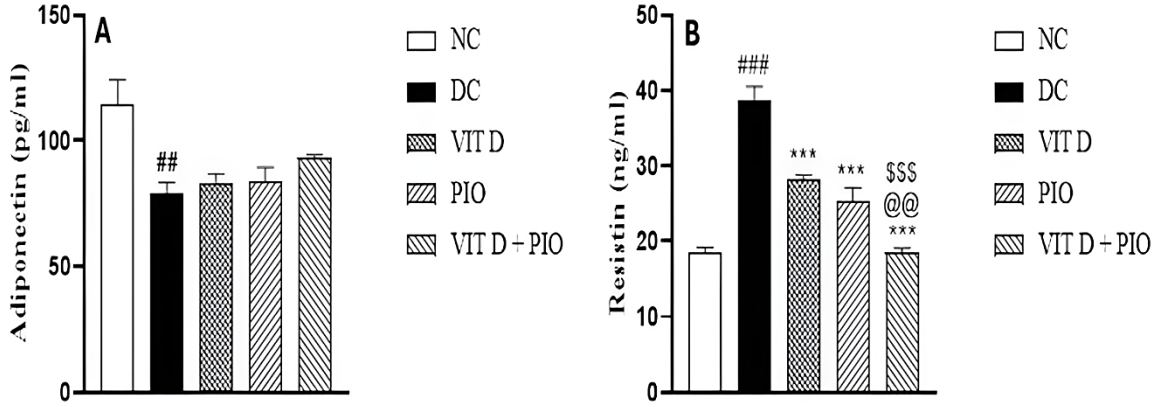

Figure 3: Impact of Vit D and PIO on (A) Adiponectin and (B) Resistin in experimentally induced diabetes. Values are stated as mean±SEM; *n*=6. ##*p*<0.01, ###*p*<0.001 relative to NC; ***p<0.001, relative to DC; $$p<0.01 relative to Vit D; @@p<0.01 relative to PIO.

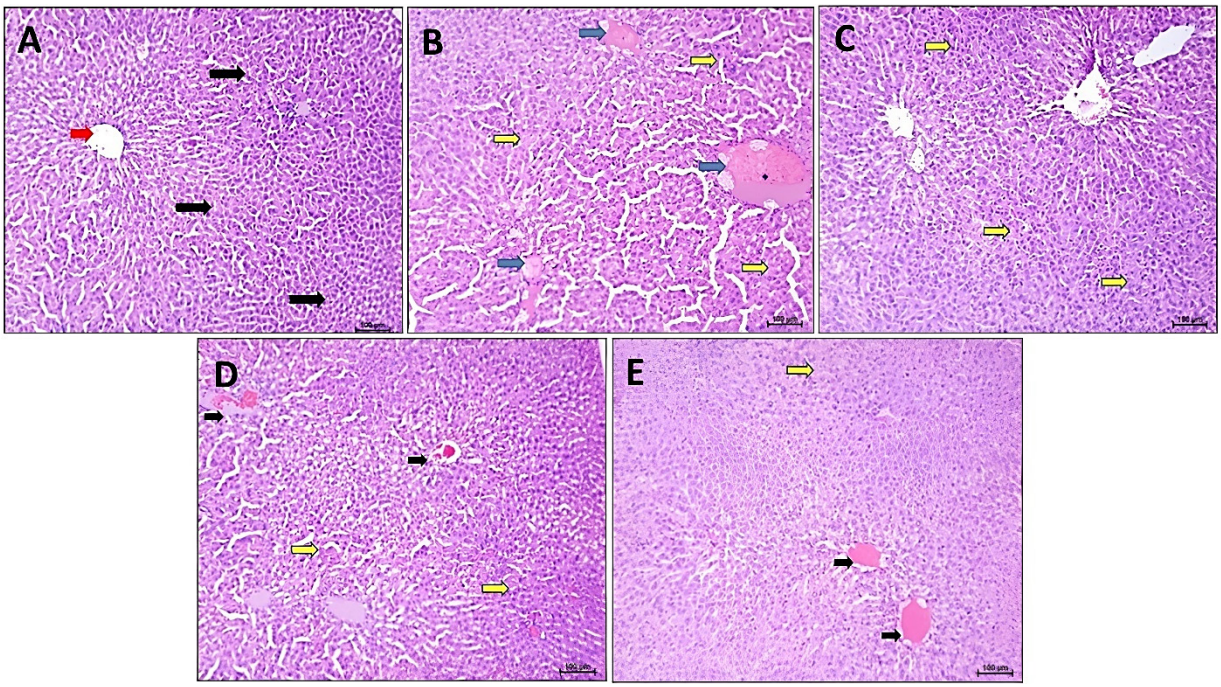

Figure 4: Light microscopy of liver tissue from rats (A) NC (B) DC (C) Vit D (D) PIO and (E) Vit D+PIO.

with either monotherapy or combination therapy, aligns with previous studies indicating that PIO can influence resistin, a key adipocytokine. Additionally, Vit D deficiency has been shown to elevate hepatic resistin gene expression, which is implicated in insulin resistance and inflammation (Al-Muzafar *et al.*, 2021: Roth *et al.*, 2012). However, the lack of significant changes in adiponectin contrasts with other studies, where Vit D supplementation led to improvements in adiponectin in diabetic models (Abbas, 2017). This discrepancy may be related to differences in treatment dosage or duration, pointing to the need for further research to clarify the mechanisms driving these effects.

Histopathological analysis confirmed the biochemical results, showing that while diabetic rats exhibited clear signs of liver damage, such as focal haemorrhages and hepatocyte degeneration, the treatment groups-especially the Vit D and PIO combination—showed mostly preserved liver architecture, with only minimal degenerative changes. This finding is consistent with previous studies showing improvements in liver histology with PIO and Vit D in animals (Özerkan *et al.*, 2017; Radwan and Hasan, 2019). The presence of mild degenerative features in the combination group, such as granular cytoplasm and cellular swelling, suggests partial but not complete liver recovery, indicating the complexity of liver regeneration in diabetic conditions.

CONCLUSION

In conclusion, the findings of this study advocate that combining Vit D and PIO could offer an effective therapeutic strategy for addressing metabolic disturbances in diabetes, including improving lipid profiles, supporting liver health, and regulating adipocytokine levels. This combination therapy appears to provide enhanced benefits beyond what is achieved with each treatment individually, potentially offering a more potent approach to reducing cardiovascular and liver-related risks associated with diabetes. However, more research is necessary to explore the underlying molecular mechanisms and refine treatment protocols for clinical use.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ALT: Alanine Transaminase; **AST:** Aspartate Transaminase; **CCSEA:** Committee for Control and Supervision of Experiments on Animals; **HDL:** High-Density Lipoprotein; **LDL:** Low-Density Lipoprotein; **NA:** Nicotinamide; **PIO:** Pioglitazone; **STZ:** Streptozotocin; **T2DM:** Type 2 Diabetes Mellitus; **TC:** Total Cholesterol; **TG:** Triglycerides; **Vit D:** Vitamin D

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