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EDITORIAL

Enhancing metformin efficacy with cholecalciferol and taurine in diabetes therapy: Potential and limitations

Gehan El-Akabawy, Nabil Eid

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Abstract

Diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), poses a significant global health challenge. Traditional management strategies primarily focus on glycemic control; however, there is a growing need for comprehensive approaches addressing the complex pathophysiology of diabetes complications. The recent study by Attia *et al* explores the potential of a novel therapy combining metformin with cholecalciferol (vitamin D3) and taurine to mitigate T2DM-related complications in a rat model. The findings indicate that this treatment combination improves glycemic control and reduces oxidative stress, inflammation, and lipid abnormalities. However, the study is limited by a lack of safety profile data and in-depth molecular mechanism insights. This editorial critically highlights the study's strengths and weaknesses, compares it against other combination therapy research in T2DM, and underscores the need to explore further the mechanisms underpinning the observed therapeutic effects and investigate the safety profile of this novel approach.

Key Words: Diabetes; Metformin; Cholecalciferol; Taurine; Hyperglycemia; Oxidative stress; Triglycerides

Core Tip: Diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), poses a significant global health problem. Metformin is commonly used to control hyperglycemia linked to T2DM. Supplementing metformin with cholecalciferol (vitamin D3) and taurine can mitigate diabetes-related complications in a rat model of T2DM by reducing oxidative stress, inflammation, and lipid abnormalities. These findings suggest a synergistic effect between metformin, cholecalciferol, and taurine in managing T2DM complications, potentially offering a more holistic approach to diabetes care.

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INTRODUCTION

Diabetes mellitus (DM) is a global health crisis, with type 2 diabetes mellitus (T2DM) being the most prevalent form. Effective management of T2DM and its associated complications remains a significant challenge. Traditional treatments primarily focus on glycemic control, but recent research emphasizes the need for comprehensive strategies that address the complex pathophysiological mechanisms of diabetes complications[1].

METFORMIN, CHOLECALCIFEROL AND TAURINE: A NEW TRIPLE THERAPY FOR T2DM

The recent study by Attia *et al*[2] provides evidence that metformin supplemented with cholecalciferol (vitamin D3) and taurine can mitigate diabetes-related complications in a rat model of streptozotocin (STZ)- induced T2DM. The study demonstrates that this combination not only improves glycemic control but also reduces oxidative stress, inflammation, and lipid abnormalities. These findings suggest that together, these agents exert a synergistic effect in managing T2DM complications, potentially offering a more holistic approach to diabetes care. The authors used immunohistochemical and biochemical methods to demonstrate enhanced β-cell mass and reduction of inflammatory, oxidative stress, and lipid overload markers in the triple therapy-treated T2DM group. However, the experimental methods lacked sufficient detail and the necessary ethical approval statement, thereby compromising the reproducibility and credibility of the study.

MECHANISMS OF IMPROVED T2DM BY THE TRIPLE THERAPY

While this novel triple therapy approach[2] appears to enhance the therapeutic efficacy of metformin, the study notably lacks in-depth mechanistic insights. An understanding of the molecular pathways through which cholecalciferol and taurine augment metformin's effects could significantly advance the development of targeted therapies and improve treatment outcomes. Moreover, the results of the oxidative stress and antioxidant profile failed to explain the superior therapeutic outcomes of metformin with cholecalciferol and taurine combination therapy compared to metformin with either cholecalciferol or taurine alone. The results did not report significant differences between the malondialdehyde, superoxide dismutase and catalase levels in the three treated experimental groups, which raises questions about the proposed synergistic effect of the metformin with cholecalciferol and taurine combination therapy. In addition, the possible mechanisms related to the increased size of pancreatic islets with the triple combination therapy are not discussed or proposed.

Investigation of combination therapies with metformin, the established first-line treatment for T2DM has emerged as a promising research direction, with several advances being recently reported. Combinations such as metformin with berberine have been explored extensively, demonstrating significant improvements in metabolic outcomes and providing detailed mechanistic insights. One such study by Zhang *et al*[3], investigated the synergistic effects of a combination of metformin and berberine on diabetic nephropathy, identifying a mechanistic pathway involving enhanced expression of *Trib1*, which subsequently downregulated the CCAAT/enhancer binding protein a, and eventually inhibiting fatty acid synthesis proteins and nuclear factor kappa-B signalling. This study is exemplary in its thorough exploration of the molecular pathways involved, providing a robust framework for understanding how combination therapies can enhance the efficacy of diabetes treatments. In another study on STZ-treated rats, a combination of metformin, berberine, and mangiferin mitigated apoptotic TUNEL-positive pancreatic β-cells and enhanced their mass[4]. There is a possibility of a similar mechanism explaining the enhanced β-cells mass observed with combination therapy in the study by Attia *et al*[2]. Other studies have provided detailed mechanistic insights into the modulation of the gut microbiota and the enhancement of insulin sensitivity through combination treatment with metformin and berberine[5]. Taken together, these studies provide details on the molecular mechanisms involved in the enhancement of T2DM outcomes using combination therapy.

Macroautophagy (hereafter referred to as autophagy) is a prosurvival mechanism for the clearance of damaged cellular components in response to various stressors such as oxidative stress, inflammation, and lipid overload[6,7]. Therefore, the

possible induction of autophagy in pancreatic islets as an anti-apoptotic mechanism in diabetic animals, inducing their regeneration and enlargement as reported by Attia *et al*[2] warrants investigation. This hypothesis is supported by emerging evidence highlighting the pro-autophagic effects of metformin on pancreatic β-cells, thus preventing their apoptosis and reducing inflammation under conditions of lipotoxicity in animal models of T2DM[6-9].

Importantly, taurine has been reported to reduce endoplasmic reticulum stress-mediated apoptosis of pancreatic β-cells in high-fat, high-glucose diet-induced rat models of T2DM[10], supporting the anti-apoptotic potential of metformin. Moreover, taurine was found to enhance spinal cord axon repair in a model of spinal cord axon injury in STZ-induced diabetic rats, *via* nerve growth factor-dependent activation of the Akt/mTOR pathway[11]. There is additional clinical evidence of taurine improving the glycaemic, lipid and inflammatory profile in T2DM patients, as reported in a randomised trial study[12]. The pathogenesis of diabetes is linked to reduced taurine bioavailability, which is critical to normal β-cell function and its anti-oxidative and anti-inflammatory properties[13]. A recent randomized clinical trial found that taurine supplementation significantly mitigated homeostatic model assessment for insulin resistance, as well as oxidative stress, inflammation, and endothelial markers in individuals with T2DM[14].

A growing body of evidence indicates the inverse relationship between vitamin D concentrations and multiple metabolic disorders, including insulin resistance, glucose intolerance, metabolic syndrome, obesity, cardiovascular disease, and elevated pro-inflammatory marker levels. Several long-term studies have also revealed an inverse correlation between vitamin D levels and the incidence of DM[15]. A previous study found that vitamin D enhanced insulin secretion and suppressed pancreatic inflammation in STZ-treated mice. Furthermore, vitamin D increased the mRNA expression levels of autophagy genes *LC3* and *Beclin 1*, as well as increased the expression of anti-apoptotic Bcl-2 protein levels in STZ-treated MIN cells[16]. Additionally, vitamin D3 improved lipophagy (selective autophagy of lipid droplets) in the kidneys of diabetic mice, resulting in suppression of oxidative stress and inflammation, and apoptosis[17,18]. A recent pilot study revealed that combination therapy with lansoprazole and cholecalciferol is associated with a slower decline in residual β-cell function and lower insulin requirements in children with recent onset type 1 diabetes[19]. In addition, high dose cholecalciferol supplementation was found to reduce morning blood pressure in patients with type 1 DM and improve associated cardiovascular autonomic neuropathy. Mechanistically, this protective effect of cholecalciferol is mediated by modulation of the inflammatory pathway and regulation of neurotrophins[20].

Collectively, the addition of taurine and cholecalciferol improved the anti-diabetic effects of metformin *via* mechanisms linked to the reduction of inflammatory mediators and apoptosis, in addition to the possible activation of pro-survival autophagy in various organs, including the endocrine pancreas and kidneys, in addition to the cardiovascular and nervous systems.

SAFETY AND GENERAL CONDITION IMPACTS OF THE TRIPLE THERAPY

The study by Attia *et al*[2] is limited by the absence of comprehensive safety and impact profiling of the combination therapy on the physiological state of diabetic animals. It is crucial to evaluate both the therapeutic efficacy and potential adverse effects on overall health. Parameters such as general appearance, food and water intake, and urine output should be monitored[21-23]. The absence of long-term side effects data and general well-being assessments limits complete evaluation of the risk-benefit profile of this therapeutic approach. More comprehensive research is needed to address these aspects and provide a complete assessment of the therapy's benefits and risks.

Additional limitations in the study by Attia *et al*[2] include insufficient address of the gaps in current cholecalciferol and taurine research; dosage variations and larger-scale, long-term clinical trials could provide significant details regarding the efficacy and safety profile of these supplements when used alongside metformin. Future investigations into these areas would provide more significant perspectives and better guide future investigations.

Further research is needed in human and animal models of DM to identify the specific molecular mechanisms underlying the beneficial outcomes of triple therapy, such as activation of pro-survival autophagy and reduction of apoptosis in pancreatic β-cell, as well as potential effects on the cardiovascular and nervous system function. *In vitro* studies using cultured β-cells could provide mechanistic insights into this triple therapy in DM.

CONCLUSION

The study by Attia *et al*[2] provides promising evidence for the combined use of cholecalciferol and taurine with metformin in managing T2DM complications. Despite the lack of mechanistic and safety profile data, the study opens new avenues for research into combination therapies that could offer more holistic management strategies for T2DM. Longer-term animal studies are essential to fully understand the benefits and risks associated with these combinations. By addressing these limitations, future research can better inform clinical practices and improve outcomes for patients with T2DM.

FOOTNOTES

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