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REVIEW

Acupuncture and Drug Combination Therapy for Abnormal Glucose Metabolism: Exploring Synergistic Enhancement and Reduced Toxicity Mechanisms

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Abstract: This review examines the impact of combining acupuncture with drug therapy on abnormal glucose metabolism and investigates their underlying mechanisms. Conditions like diabetes pose significant health risks due to irregular glucose metabolism. Traditional drug treatments often encounter challenges related to side effects and drug resistance. Acupuncture, as a non-pharmacological intervention, is thought to enhance glucose metabolism and mitigate medication side effects. We selected the relevant studies of acupuncture or electroacupuncture combined with drugs in the treatment of abnormal glucose metabolism in the past five years, and the results indicate that the combination of acupuncture or electroacupuncture and drug therapy markedly enhances glucose metabolism and mitigates medication-related side effects such as gastrointestinal discomfort and hypoglycemia. Overall, this review underscores the synergistic benefits of acupuncture and drug therapy in improving treatment efficacy and reducing adverse effects, offering promising new approaches for managing abnormal glucose metabolism. Our review provides evidence for the potential benefits of combining acupuncture with drug therapy for abnormal glucose metabolism, which could lead to improved treatment outcomes and reduced side effects for patients with type 2 diabetes mellitus.

Keywords: acupuncture, drug, medicine, combination therapy, abnormal glucose metabolism, synergistic enhancement, reduced toxicity

Introduction

Abnormal glucose metabolism is becoming more prevalent as a type of metabolic disorder with significant global health implications. These abnormalities not only affect patients' quality of life directly but also elevate the risk of serious conditions like cardiovascular disease and diabetes.[1] Abnormal glucose metabolism encompasses a range of conditions such as diabetes, insulin resistance, and metabolic syndrome.[2] Type 2 diabetes mellitus (T2DM) is particularly noteworthy due to its widespread prevalence and significant impact on global health.[3] According to data from the World Health Organization, the global adult diabetes prevalence has quadrupled since 1980. This increase is most pronounced in low- and middle-income countries, particularly in urbanized and rapidly developing economic regions.[4] Risk factors for T2DM include genetic predisposition, unhealthy dietary habits (such as high-sugar and high-fat diets), physical inactivity, obesity, age, and ethnicity. The global surge in obesity, particularly among children and adolescents, has contributed to the rising incidence of T2DM. This condition not only heightens the risk of severe complications such as cardiovascular diseases, stroke, blindness, and kidney disease but also diminishes patients' quality of life, imposing

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substantial burdens on families and societal economies.[5] Hence, effective prevention and management strategies are crucial. These include health education initiatives, promoting healthy diets and lifestyle improvements, encouraging physical activity, and timely medical interventions.[6] Comprehensive health policies and global cooperation can effectively mitigate the adverse impacts of abnormal glucose metabolism and its complications worldwide. This approach promises to enhance global population health and improve overall quality of life.[7]

Chemical drug intervention remains the primary approach for managing glucose metabolism disorders; however, it also has limitations such as drug side effects, tolerance issues, individual variability, and suboptimal long-term efficacy. Adverse effects, including gastrointestinal discomfort and the risk of hypoglycemia, often impact patient adherence and may exacerbate metabolic burdens with prolonged use.[8] Consequently, an increasing number of studies are focusing on alternative methods to improve treatment outcomes, aiming to control blood glucose levels while reducing adverse drug reactions and enhancing patients' quality of life.

Acupuncture, as one of the traditional Chinese medical therapies, is gradually recognized as a complementary and alternative treatment for glucose metabolism disorders. Numerous studies have demonstrated that acupuncture can positively influence T2DM and other glucose metabolism disorders through multiple pathways, such as modulating the neuroendocrine-immune system.[9,10] Specifically, acupuncture may promote glucose metabolism by activating metabolic signaling pathways, such as AMPK, or by regulating the nervous system to affect insulin secretion and utilization efficiency, thereby assisting in blood glucose control. Furthermore, the mechanisms of acupuncture also include the regulation of serotonin levels, bile acid metabolism, and gut microbiota, which can alleviate gastrointestinal discomfort caused by certain medications.[11,12]

The mechanism of the combined effects of acupuncture and pharmacotherapy is a complex and synergistic process that integrates the strengths of both treatments, enhancing therapeutic efficacy and reducing side effects through interaction and complementarity. Many clinical and basic studies have confirmed that the combined use of acupuncture and medication demonstrates superior effectiveness in lowering blood glucose and alleviating medication-related side effects.[13] Specifically, acupuncture can enhance the therapeutic pathways of drugs to strengthen their efficacy while also modulating metabolic pathways or blocking certain routes to mitigate potential side effects. By interacting with medications, acupuncture not only improves the safety of treatments but also significantly enhances patient efficacy and tolerance over the long term.[14]

In summary, the combination of acupuncture and pharmacotherapy for treating glucose metabolism disorders shows promising prospects, potentially becoming an effective and viable integrative approach in managing diabetes and other metabolic diseases. Future research exploring the mechanisms of action and applicability across different patient populations will facilitate the standardization and promotion of this approach in clinical practice.

Conventional Therapies for Intervening in Abnormal Glucose Metabolism

Pharmacological Interventions for Abnormal Glucose Metabolism

Chemical drug intervention remains the primary approach for treating abnormal glucose metabolism. Commonly prescribed drug classes include Biguanides, sulfonylureas, meglitinides, thiazolidinediones (TZDs), alpha-glucosidase inhibitors, dipeptidyl peptidase inhibitors (DDP-4 inhibitors), sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors), GLP-1 receptor agonists, and insulin. Biguanides like metformin exert robust hypoglycemic effects by reducing hepatic glucose output, enhancing peripheral tissue insulin sensitivity, and improving glucose uptake and utilization. They are typically recommended as first-line therapy for type 2 diabetes due to their favorable safety profile and relatively low cost.[15] Sulfonylureas such as gliclazide and glimepiride stimulate insulin release from pancreatic β-cells, improve insulin sensitivity, reduce insulin resistance, and thereby lower hepatic glucose production. They are prescribed when metformin alone proves insufficient in controlling blood glucose levels and are also considered a first-line therapy for treating type 2 diabetes mellitus.[16] In addition, GLP-1 receptor agonists like liraglutide and exenatide replicate the effects of GLP-1. They enhance insulin release by binding to GLP-1 receptors, suppress glucagon secretion, reduce blood glucose levels, and contribute to weight loss.[17] SGLT-2 inhibitors such as empagliflozin and dapagliflozin are newer additions to antidiabetic medications. They lower blood glucose levels by blocking renal glucose reabsorption, which facilitates the excretion of excess glucose through urine.[18] Alongside traditional first-line drug therapies, α-glucosidase inhibitors such as acarbose delay carbohydrate absorption by inhibiting α-glucosidase in the small intestine's brush border. This mechanism helps to decrease postprandial hyperglycemia and is suitable for individuals resistant to metformin or experiencing significant side effects.[19] Insulin is appropriate for all patients with type 1 diabetes and for those with type 2 diabetes who do not respond adequately to oral hypoglycemic drugs and dietary management. It is typically administered through regular subcutaneous injections.[20] Meglitinides lower blood glucose levels by stimulating the release of insulin from the beta cells in the pancreas, with their effects primarily focused on controlling postprandial glucose levels. Thiazolidinediones (TZDs) primarily reduce blood glucose by increasing the sensitivity of target cells to insulin. Dipeptidyl Peptidase-4 (DPP-4) inhibitors lower blood glucose by inhibiting the activity of the DPP-4 enzyme, thereby prolonging the half-life of incretin hormones such as glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP).[21] The specific drug classification and side effects are shown in Table 1.

Furthermore, these drugs exert their effects through various mechanisms, including improvements in intermittent inflammation,[22] activation of the AMPK signaling pathway,[23] modulation of intestinal microbiota,[24] regulation of cellular autophagy,[25,26] binding with cytokines to enhance cellular function,[27,28] and other pathways to improve abnormal glucose metabolism.

Table 1 Classification of T2DM Medications and Their Mechanisms of Action and Side Effects

Drug Class	Representative Drugs	Mechanism of Action	Related Side Effects
Biguanides	Metformin	Reduces blood glucose by decreasing hepatic glucose production, increasing muscle insulin sensitivity, and improving lipid metabolism.	Gastrointestinal discomfort (eg, diarrhea, nausea), lactic acidosis (rare).
Sulfonylureas	Glimepiride, Glyburide	Stimulates insulin release from pancreatic β-cells, thereby lowering blood glucose levels.	Hypoglycemia, weight gain, rash.
Meglitinides	Repaglinide, Nateglinide	Stimulates insulin release from pancreatic β-cells, mainly used for postprandial glucose control.	Hypoglycemia, weight gain.
Thiazolidinediones (TZDs)	Rosiglitazone, Pioglitazone	Activates PPAR-γ to increase insulin sensitivity in target cells.	Edema, weight gain, increased risk of heart disease (to be used with caution).
α-Glucosidase Inhibitors	Acarbose, Miglitol	Inhibits the activity of α-glucosidase in the small intestine, slowing carbohydrate absorption and reducing postprandial blood glucose.	Bloating, diarrhea, gastrointestinal discomfort.
Dipeptidyl Peptidase-4 Inhibitors (DPP-4 Inhibitors)	Sitagliptin, Vildagliptin	Inhibits the activity of DPP-4 enzyme, prolonging the half-lives of GLP-1 and GIP, promoting insulin secretion and inhibiting glucagon.	Gastrointestinal discomfort, hypoglycemia (rare), rash.
Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2 Inhibitors)	Dapagliflozin, Empagliflozin	Inhibits SGLT-2 in the renal tubules, reducing glucose reabsorption and promoting glucose excretion.	Urinary tract infections, ketoacidosis, dehydration.
GLP-1 Receptor Agonists	Liraglutide, Exenatide	Mimics the action of GLP-1, promoting insulin secretion, inhibiting glucagon, and slowing gastric emptying.	Gastrointestinal discomfort (eg, nausea, vomiting), hypoglycemia (rare).
Insulin	Regular insulin, long-acting insulin (eg, glargine insulin)	Directly replaces the insulin deficiency in the body, promoting cellular uptake and utilization of glucose.	Hypoglycemia, weight gain, allergic reactions.

Limitations of Pharmacological Therapy

Traditional pharmacological therapies for treating abnormal glucose metabolism have limitations, including drug side effects, tolerance issues, individual variability in response, and questions about long-term efficacy.

Drug Side Effects

Traditional pharmacological therapies for treating abnormal glucose metabolism face limitations, such as drug side effects, tolerance issues, individual variability in response, and concerns regarding long-term efficacy.[29] GLP-1 receptor agonists like exenatide, liraglutide, and semaglutide have been noted to induce gastrointestinal discomfort as a side effect.[30–32] While metformin is widely acknowledged for its efficacy and safety, approximately 30% of patients using this medication may experience severe adverse effects such as nausea, vomiting, and diarrhea.[33–35]

According to a clinical trial, nearly half of the patients experienced hypoglycemia after taking sulfonylurea drugs such as glimepiride.[36] Case reports also suggest that using non-sulfonylurea insulin secretagogues like repaglinide alone or in combination with clopidogrel increases the risk of hypoglycemia.[37,38] Since the discovery of insulin, hypoglycemia has been a well-documented complication associated with its use.[39]

Drug Tolerance, Individual Differences, and Long-Term Efficacy

Long-term use of the same drug may lead to drug resistance, where patients gradually become less responsive to the medication. This often requires dose adjustments or switching to alternative treatments to maintain therapeutic effectiveness. Individual differences in drug absorption, distribution, metabolism, and excretion directly impact the long-term efficacy and tolerance of medications. Thus, understanding these factors is crucial in managing abnormal glucose metabolism effectively.[40] Other studies have shown taxonomic and functional differences in the intestinal microbiota between patients who are intolerant to metformin and those who tolerate the medication well.[41] Differences in patients' intestinal microbiota directly or indirectly influence drug tolerance, thereby affecting the long-term efficacy of medications.

Application and Research of Acupuncture and Medicine Combination in Intervening Abnormal Glucose Metabolism

Clinical and Basic Research on Acupuncture and Moxibustion Intervention of Abnormal Glucose Metabolism

Acupuncture, valued for its simplicity, affordability, safety, and effectiveness,[42,43] is recognized as a complementary and alternative therapy for abnormal glucose metabolism.[44–47] Acupuncture can positively influence type 2 diabetes mellitus (T2DM) and other metabolic disorders by regulating the neuroendocrine immune system, enhancing insulin sensitivity, and adjusting metabolic functions.

In clinical research, a recent 2024 study indicates that electroacupuncture can reduce plasma glucose levels by enhancing insulin production and improving insulin sensitivity. Additionally, it lowers sympathetic nervous activity by promoting the secretion of endogenous β-endorphin and serotonin.[48] A three-arm randomized controlled trial demonstrated that acupuncture improves glucose metabolism more effectively than metformin and has a lower incidence of gastrointestinal reactions compared to metformin. Acupuncture may therefore serve as a low-risk non-pharmacological treatment option for patients with polycystic ovary syndrome.[49] Additionally, several meta-analyses have demonstrated that acupuncture, as an adjunctive therapy to antidiabetic medications, has a statistically significant effect on lowering fasting blood glucose and improving insulin resistance. Although its effects on HbA1c, 2-hour blood glucose, and fasting insulin are less certain, acupuncture is generally considered safe for patients with mild diabetes. As a multifaceted intervention, acupuncture is recommended as a complementary or alternative therapy for T2DM, particularly for patients with obesity or metabolic disorders. In summary, acupuncture and electroacupuncture, as supplementary therapies, offer effective intervention for abnormal glucose metabolism with a favorable safety profile.[43,44]

In basic research, a study indicated that abdominal acupuncture regulates the FGF21 signaling pathway and related adipokines in obese rats with type 2 diabetes mellitus (T2DM). This intervention resulted in reduced fasting blood glucose levels, decreased body weight, and improved insulin sensitivity.[50] Multiple studies have demonstrated that acupuncture or electroacupuncture achieves glycemic control by modulating the intestinal microbiota,[51,52] regulating the Akt/FoxO1 signaling pathway,[53] activating the AMPK signaling pathway,[54,55] regulating the macrophage-islet adipocyte-islet β-cell network,[56] and inhibiting the PKCβ/P66shc signaling pathway and oxidative stress.[57]

Clinical and Basic Research on Intervention of Abnormal Glucose Metabolism by Combination of Acupuncture and Medicine

The mechanism of combining acupuncture with medicine is a complex and synergistic process that integrates the benefits of both therapies. Through interaction and complementation, this approach aims to enhance therapeutic efficacy and minimize side effects.[58,59] Acupuncture can enhance the efficacy of drugs by facilitating their pathways of action, while also potentially reducing drug-related side effects by blocking specific pathways.

In terms of enhancing efficacy, several basic studies have demonstrated that electroacupuncture at the "Tianshu" acupoint (ST 25) promotes the activation of AMPK in the liver tissue of rats with type 2 diabetes mellitus (T2DM) treated with metformin. This intervention helps mitigate the negative effects of metformin on pancreatic tissue AMPK and enhances its glucose-lowering effects. The mechanism may involve upregulation of AMPK expression and inhibition of the pancreatic intrinsic nervous system,[55,60] and activation of GLUT4 activation.[61] Furthermore, electroacupuncture can enhance the glucose-lowering ability of acarbose in T2DM rats and alleviate insulin resistance, with superior effects compared to acarbose alone.[62] Clinical studies have shown that knife-edge acupuncture combined with metformin hydrochloride tablets can improve blood glucose, clinical symptoms, and quality of life in patients with T2DM, possibly through modulation of inflammatory responses.[63] Furthermore, electroacupuncture has been shown to enhance the glucose-lowering efficacy of acarbose in rats with type 2 diabetes mellitus (T2DM) and alleviate insulin resistance. This combined approach demonstrates superior effects compared to acarbose treatment alone,[64] this effect may be achieved through improvements in weight reduction and reduction of inflammation, thereby alleviating insulin resistance.[65,66] Additionally, it may improve lipid metabolism and regulate adipokines.[67]

In terms of reducing toxicity, a systematic review indicated that acupuncture effectively alleviates nausea and vomiting caused by glucagon-like peptide-1 receptor agonists,[68] possibly through mechanisms involving 5-HT,[69] intestinal microbiota,[70] and other factors.[71] Moreover, acupuncture has been shown to alleviate drug-induced liver damage. A basic study indicated that acupuncture at Zusanli and Taichong points may have a therapeutic effect on carbon tetrachloride-induced liver damage in rats, effectively reducing biochemical and pathological indicators of liver damage,[72] possibly through mechanisms involving apoptosis and ferroptosis.[73] Additionally, acupuncture combined with herbal medicine is commonly used to treat various complications of diabetes, such as diabetic nephropathy,[74] diabetic peripheral neuropathy,[75] diabetic stroke,[76] and diabetic cardiovascular diseases[77] and so on.

Exploring the Mechanisms of Acupuncture and Medicine Combination Therapy for Abnormal Glucose Metabolism

Potential Mechanisms of Synergistic Enhancement

AMP-activated protein kinase (AMPK) has garnered significant attention as a potential therapeutic target for metabolic disorders. Mammalian AMPK is activated in response to decreased cellular energy levels, indicated by an increase in AMP/ATP and ADP/ATP ratios. Activation of AMPK can transcriptionally regulate metabolic pathways, enhancing glucose uptake and utilization, and inhibiting hepatic glycogen synthesis, thereby lowering blood glucose levels.[78] Earlier high-quality studies have demonstrated that metformin, when combined with PEN2, initiates signaling pathways where AMPK activation intersects with ATP6AP1, specifically involving the lysosomal glucose sensing pathway,[23] Metformin induces energy stress by inhibiting mitochondrial respiratory complex I, thereby altering ATP/AMP ratios and activating the AMPK pathway. This process inhibits hepatic gluconeogenesis, enhances insulin sensitivity in the liver, and increases glucose uptake in muscles, thereby achieving glycemic control.[79,80]

Furthermore, numerous studies have indicated that electroacupuncture or acupuncture can improve insulin resistance and regulate energy metabolism by activating AMPK and related pathways. For example, electroacupuncture intervention improves lipid metabolism in middle-aged and elderly obese rats, promotes browning of white adipose tissue, possibly through activation of the AMPK/Sirt1 signaling pathway, and upregulation of Nrg4 levels.[81] Electroacupuncture effectively improves insulin resistance in Zucker diabetic fatty (ZDF) rats and regulates energy metabolism. Potential mechanisms underlying these effects include modulation of AMPK/mTORC1/p70S6K signaling and related molecules.[82] Moxibustion at ST36 improves lipid levels in Sprague-Dawley (SD) rats with hyperlipidemia by activating the AMPK/mTOR signaling pathway. This activation initiates the transcription of autophagy genes like LC3 and promotes lysosomal synthesis, thereby enhancing autophagy levels in liver cells and improving hepatic fat accumulation.[83] Electroacupuncture effectively promotes browning of white adipose tissue, which may involve several mechanisms. These include activation of GLP-1 neurons in the solitary nucleus, promotion of AMPK phosphorylation in the hypothalamic arcuate nucleus, and upregulation of UCP1.[84] Electroacupuncture can enhance brain glucose metabolism by promoting AMPKα phosphorylation in the caudate putamen (CPu), motor cortex (MCTX), and somatosensory cortex (SCTX) regions.[85] Electroacupuncture can increase insulin sensitivity in insulin-resistant rats, with one of the mechanisms potentially involving the positive regulation of the skeletal muscle AMPK/ACC pathway.[86] Electroacupuncture can improve lipid metabolism disorders in insulin-resistant rats, potentially by reducing the activity of enzymes involved in fatty acid synthesis and regulating the AMPK/p38MAPK/PPARγ signaling pathway to enhance insulin sensitivity.[87] Electroacupuncture can improve diet-induced insulin resistance, likely through the activation of the AMPK signaling pathway in skeletal muscle.[88]

By recognizing that both metformin and electroacupuncture activate the AMPK signaling pathway through common mechanisms, we can hypothesize that acupuncture enhances the glucose-lowering effects of metformin by aiding in the activation of the AMPK pathway.

It is well-known that glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as semaglutide, liraglutide, and dulaglutide, target GLP-1 receptors to stimulate insulin secretion from pancreatic β-cells while inhibiting glucagon secretion, thereby achieving glycemic control and effectively reducing body weight.[89]

Multiple high-quality clinical and preclinical studies suggest that acupuncture may improve obesity and insulin resistance through GLP-1 receptor activation. Preclinical studies have shown that electroacupuncture activates GLP-1 receptors via the GLP-1–VTADA reward pathway, alleviating obesity and insulin resistance.[90] Clinical trials further demonstrate that acupuncture-activated acupoints contain somatic afferent nerves that send sensory signals to neurons in the spinal cord, brainstem, and hypothalamus, activating GLP-1 receptors to produce glucose-lowering effects.[91] Additionally, electroacupuncture has been observed to help restore islet morphology, reduce fasting blood glucose levels, and decrease insulin resistance markers.[92]

Given the shared GLP-1 receptor activation mechanism between GLP-1 receptor agonists and acupuncture, we hypothesize that acupuncture may enhance the glucose-lowering effects of GLP-1RAs by supporting GLP-1 receptor activation.

Possible Mechanisms of Reducing Toxicity

Common side effects of metformin include gastrointestinal reactions such as nausea, vomiting, and diarrhea. These symptoms may be related to metformin's impact on the energy metabolism of intestinal cells. Activation of AMPK can influence the metabolic function of intestinal cells, potentially contributing to these side effects.

Studies have demonstrated that electroacupuncture at Zhongwan, Tianshu, and Shangjuxu can effectively alleviate symptoms such as diarrhea in rats with ulcerative colitis. This effect may be attributed to the promotion of autophagy in the colon, increased levels of AMPK phosphorylation, and reduced levels of mTOR phosphorylation.[93] Another study suggests that regulating the AMPK/TSC2/Rheb-mediated mTOR inhibition pathway to alter ghrelin levels is a significant mechanism for electroacupuncture in the treatment of functional dyspepsia.[94] Electroacupuncture at ST36 can promote gastrointestinal motility in rats with functional dyspepsia, potentially by downregulating the AMPK/ULK1 signaling pathway, which inhibits excessive autophagy of interstitial cells of Cajal.[88]

We have reason to believe that electroacupuncture alleviates the gastrointestinal reactions caused by metformin through regulation of the AMPK pathway.

Among the numerous neurotransmitters involved in the digestive process, serotonin (5-HT) and 5-hydroxytryptophan (5-HTP) are known to play crucial roles. Studies indicate that metformin shares structural similarities with known selective 5-hydroxytryptamine 3 (5-HT3) receptor agonists.[95] Metformin induces the non-dependent release of 5-HT3 receptors in the duodenal mucosa through both neuronal and non-neuronal mechanisms. This can lead to gastrointestinal reactions such as nausea, vomiting, and diarrhea.[96]

A basic experiment has demonstrated that electroacupuncture can downregulate the expression of 5-HT1A receptors (5-HT1AR) and c-fos protein in the hypothalamus and colon tissues of rats with functional dyspepsia.[97] Another head-to-head trial has demonstrated that both electroacupuncture and moxibustion treatment significantly reduce the expression of serotonin (5-HT), 5-HT3 receptors (5-HT3R), and 5-HT4 receptors (5-HT4R) in the mucosal tissues of the sigmoid colon in patients with diarrhea-predominant irritable bowel syndrome. These treatments were associated with significant improvements in abdominal pain and bloating.[98]

We have reason to believe that electroacupuncture alleviates gastrointestinal reactions caused by metformin by potentially reducing elevated levels of intestinal serotonin (5-HT) following metformin intake.

Additionally, metformin may inhibit bile acid reabsorption by altering the function of sodium-dependent bile acid transporters, thereby increasing the pool of bile acids in the intestine.[99] This alteration in bile acid reabsorption may affect stool consistency, secretion of GLP-1, cholesterol levels, and the composition of the microbiota,[35] which could be a direct cause of metformin-induced diarrhea.

Nuclear receptors (NRs) play crucial roles in bile acid signaling. Studies suggest that acupuncture can modulate changes in relevant NRs and influence the circulation of bile acids.[100] Mild moxibustion combined with separated moxibustion has been shown to improve colonic symptoms in rats with segmental enteritis, suppress inflammation, and repair colonic mucosal damage. Additionally, moxibustion can improve abnormal expression of bile acids (BAs) in the colon, liver, and serum.[101]

We have reason to believe that acupuncture alleviates gastrointestinal reactions caused by metformin by potentially regulating abnormal expression of nuclear receptors (NRs) induced by metformin and modulating bile acid circulation.

Other studies suggest that gastrointestinal adverse effects caused by metformin may be associated with changes in the intestinal microbiota induced by the medication.[102] Metformin may affect the intestinal microbiota by potentially regulating inflammation, intestinal permeability, glucose homeostasis, and the abundance of bacteria producing short-chain fatty acids.[103] An analysis focusing solely on the therapeutic impact of metformin reveals a notable rise in Enterobacteriaceae levels and a decrease in Enterococcaceae. These shifts in microbiota are closely linked to gastro-intestinal side effects associated with metformin treatment. These effects include diminished absorption of intestinal lipids, localized inflammation triggered by lipopolysaccharides, and increased butyrate production. Notably, elevated butyrate levels have been observed to enhance the expression of genes involved in intestinal gluconeogenesis, potentially directly contributing to the gastrointestinal reactions induced by metformin.[104]

Several studies have demonstrated acupuncture's efficacy in alleviating gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Additionally, a retrospective study suggests that acupuncture may ameliorate abdominal discomfort associated with irritable bowel syndrome by influencing the composition of intestinal microbiota.[105] Furthermore, several basic and clinical studies indicate that acupuncture can alleviate various gastrointestinal discomfort symptoms by regulating the intestinal microbiota.[106–109]

There is reason to believe that acupuncture alleviates gastrointestinal reactions caused by metformin by modulating metformin-induced changes in gut microbiota.

GLP-1 receptor agonists, such as semaglutide, may lead to gastrointestinal adverse effects like nausea and vomiting due to their direct effects on the gastrointestinal tract and the delay in gastric emptying. Studies suggest that the delayed gastric emptying induced by semaglutide may be associated with the inhibition of gastrin, motilin, and cholecystokinin secretion. Gastrin promotes gastric acid secretion, stimulates gastrointestinal smooth muscle, and enhances gastrointestinal motility;[110] motilin initiates the "migrating motor complex" (MMC), which helps clear residuals from the stomach and small intestine, thereby promoting gastric emptying;[111] cholecystokinin promotes bile secretion, facilitates gastric emptying, and regulates appetite.[112]

Multiple basic studies have shown that electroacupuncture at the Zusanli (ST36) acupoint can improve gastric motility in stress-induced rats by increasing levels of vasoactive intestinal peptide (VIP) and nitric oxide (NO).[113] Additionally, acupuncture at local and distal points can exert antagonistic or synergistic effects on specific physiological and biochemical indicators related to gastric motility, such as ghrelin, gastrin, and growth factor-1, thus alleviating symptoms of nausea and vomiting.[114] Acupuncture may also relieve nausea and vomiting by promoting cholecystokinin secretion, enhancing bile secretion, and indirectly stimulating gastrointestinal motility.[115,116]

We believe that acupuncture may improve GLP-1RA-induced gastrointestinal reactions by modulating changes in gastrin, motilin, and cholecystokinin levels caused by GLP-1RA use.

Discussion and Prospects

Acupuncture, a traditional Chinese medical therapy, offers substantial benefits when combined with conventional drug treatments. Research indicates that integrating acupuncture with medication effectively enhances blood glucose control in patients with diabetes. This combined approach not only improves medication tolerance but also reduces the occurrence of common drug side effects, such as gastrointestinal discomfort and hypoglycemia.[78] Acupuncture may specifically enhance drug efficacy through various pathways, including activation of the AMPK pathway, a critical energy sensor in cellular metabolism. Additionally, acupuncture has shown potential to mitigate gastrointestinal side effects of medications by regulating serotonin (5-HT) levels, bile acids, and the composition of intestinal microbiota. Understanding these mechanisms is crucial for elucidating the role of acupuncture combined with medication in diabetes treatment. Furthermore, acupuncture has shown potential in managing other conditions associated with glucose metabolism disorders, such as obesity and metabolic syndrome. Studies indicate that acupuncture significantly contributes to weight control in obese patients[117] and improves metabolic syndrome,[118] suggesting its broader applicability in managing metabolic diseases. According to the latest research advancements in 2024, acupuncture may help regulate weight and improve metabolic health by influencing neurocircuits within metabolic pathways,[119] offering new therapeutic approaches for a variety of metabolism-related diseases.

However, as an adjunct therapy, acupuncture also presents certain limitations and challenges. For instance, its therapeutic outcomes may vary significantly among individuals, and the standardization of personalized treatment protocols remains difficult.[120] Future research should therefore weigh its potential efficacy against practical limitations to thoroughly assess its suitability across diverse patient groups. Additionally, acupuncture therapy may increase treatment duration and resource demands, which are important factors to consider in clinical application. In the future, further research should focus on several key areas. First, addressing the standardization and normalization of acupuncture combined with drug therapy in clinical applications requires additional studies on acupuncture protocol standardization, optimal treatment duration, and efficacy evaluation to enable clinicians to implement acupuncture-drug combination therapy more effectively in practice.[121] Second, further investigation into the mechanisms of acupuncture combined with different categories of drugs and the differential effects of these combination therapies across various types of diabetes and patient profiles is essential. Moreover, large-scale, multicenter clinical trials are necessary to validate the long-term efficacy and safety of acupuncture combined with medication in sustained glycemic control, complication prevention, and in the treatment of insulin resistance and insulin resistance-related diseases. Expanding research in these areas will also help explore acupuncture's potential applicability in treating other metabolic disorders.

In conclusion, acupuncture combined with drug therapy represents a comprehensive approach that enhances drug efficacy and reduces the incidence of side effects in patients with type 2 diabetes. This combined treatment shows promising clinical application prospects. With a deeper understanding of its mechanisms and growing clinical evidence, acupuncture-drug combination therapy is poised to gain wider recognition and adoption in the management of diabetes and related metabolic disorders. This approach offers new perspectives and methods for improving patient outcomes in these conditions.

Ethics Statement

This medical review does not require approval from an ethics committee due to its nature and scope. It primarily involves a synthesis and analysis of existing medical literature and research, without conducting any original research studies or clinical trials that would require ethical review. As a result, the ethical considerations that typically apply to research studies do not apply to this medical review.

Author Contributions

Wenjun Wang and Lu Zhang are co-first authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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