DOI: 10.53469/jcmp.2025.07(11).36

Progress in Integrative Medicine Research on Acetyl-CoA and Diacylglycerol Metabolism in Treating Insulin Resistance in Type 2 Diabetes

Wen Xie[1], Shuxuan Quan[1], Shuaizi Wang[1], Lu Shen[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Shaanxi Provincial Hospital of Chinese Medicine, Xi'an 710003, Shaanxi, China
Correspondence Author

Abstract: ***Research has revealed that abnormal lipid metabolism plays a significant role in insulin resistance associated with type 2 diabetes. As intermediates in lipid metabolism, acetyl-CoA and diacylglycerol influence the processes governing lipid metabolism. This paper examines the mechanisms by which acetyl-CoA and diacylglycerol metabolism ameliorate insulin resistance in type 2 diabetes, based on an analysis of relevant literature concerning these lipid metabolism intermediates and their role in improving insulin resistance. It aims to provide novel insights for the clinical management of type 2 diabetes.***

Keywords: Acetyl-CoA, Diacylglycerol Metabolism, Insulin Resistance, Type 2 Diabetes**.**

1. Introduction

With the continuous advancement of modern economies and material standards, dietary patterns have undergone significant transformation. Unhealthy eating habits and lifestyles have contributed to a steady rise in the incidence of type 2 diabetes. Diabetes [1], as a global health challenge, affected 529 million people worldwide in 2021 and is projected to impact 1.31 billion individuals by 2050. Increasing research indicates that insulin resistance is one of the core pathomechanisms underlying type 2 diabetes [2]. This leads to a reduction in the sensitivity of insulin target tissues (such as the liver, muscles, and adipose tissue) to insulin, thereby diminishing the body's ability to clear blood glucose and consequently inducing the onset of hyperglycaemia.

A growing body of research indicates that lipid metabolism abnormalities are frequently intertwined with insulin resistance, with both factors mutually reinforcing each other to form a vicious cycle. Within this context, acetyl-CoA and diacylglycerol, as intermediates in lipid metabolism, play a pivotal role in the onset and progression of insulin resistance [3]. The accumulation of acetyl-CoA in adipose tissue and the liver disrupts insulin signalling, leading to insulin resistance and increased hepatic gluconeogenesis [4]. Meanwhile, diacylglycerol impairs insulin signalling pathways by activating protein kinase C, thereby further exacerbating insulin resistance.

The incidence of type 2 diabetes is rising steadily, with research into its mechanisms now reaching the molecular level, while treatment approaches continue to evolve. Western medicine directly regulates glucose and lipid metabolism through hypoglycaemic drugs (such as metformin and GLP-1 receptor agonists) and lifestyle interventions [5], but long-term medication carries risks of side effects and therapeutic plateaus. Traditional Chinese medicine, centred on a holistic perspective, employs multi-targeted compounds such as berberine and the Scutellaria-Phellodendron-Coptis Decoction to regulate gut microbiota, suppress inflammatory factors, and enhance insulin sensitivity [6]. The combination of both approaches can produce synergistic effects, reducing the dosage of Western medicines and lowering the risk of complications. Current research must overcome the bottleneck of insufficient mechanistic elucidation. In recent years, numerous studies have explored the mechanisms by which acetyl-CoA and diacylglycerol metabolism influence insulin resistance in type 2 diabetes. This review summarises these studies.

2. Acetyl-CoA and Insulin Resistance in Type 2 Diabetes

Acetyl-CoA is a crucial metabolic intermediate present in living organisms, formed by the combination of an acetyl group with coenzyme A. It serves as a pivotal hub molecule within metabolic networks. It serves as a pivotal intermediate linking the metabolism of the three major substances—sugars, lipids, and amino acids—whose metabolic pathways exhibit a highly networked structure. Its synthesis pathways primarily comprise three routes. Firstly, within carbohydrate metabolism, glucose undergoes glycolysis to produce pyruvate. In the presence of oxygen and mitochondria, pyruvate undergoes oxidative decarboxylation catalysed by the pyruvate dehydrogenase complex, yielding acetyl-CoA. Secondly, during lipolysis, fatty acids undergo β-oxidation to produce acetyl-CoA. Thirdly, it is generated through the catabolism of certain ketogenic amino acids, such as leucine. It serves as a direct substrate for the tricarboxylic acid cycle, where it enters the mitochondrial matrix and combines with oxaloacetate to form citrate. This citrate undergoes oxidative decarboxylation, releasing substantial energy for ATP synthesis [7]. Moreover, it participates in lipid metabolism, being a product of fatty acid β-oxidation and a precursor for fatty acid and cholesterol synthesis. Additionally, it links to carbohydrate metabolism by participating in pyruvate conversion and can regulate glycolysis and gluconeogenesis processes. Acetyl-CoA is synthesised via the aforementioned pathways, playing multiple pivotal roles in carbohydrate metabolism, lipid metabolism, and energy metabolism. Recent research has not only focused on its fundamental

metabolic functions but has also delved into its potential value in disease treatment and metabolic regulation.

2.1 The Central Role of Glucose Metabolism

Following the conversion of glucose into pyruvate via glycolysis, acetyl-CoA is synthesised in the mitochondria through the action of the pyruvate dehydrogenase complex. This enters the tricarboxylic acid (TCA) cycle, where it undergoes complete oxidation into carbon dioxide and water. Concurrently, oxidative phosphorylation generates substantial quantities of ATP (30–32 molecules of ATP can be produced from a single glucose molecule). The activity of the pyruvate dehydrogenase complex is influenced by vitamin B1 (thiamine pyrophosphate) and pantothenic acid (a component of coenzyme A). Deficiencies in these vitamins may lead to lactic acid accumulation and impaired energy metabolism (such as beriberi) [8]. Acetyl-CoA generates oxaloacetic acid via the tricarboxylic acid cycle, participating in gluconeogenesis to maintain blood glucose homeostasis. Recent studies have revealed that uridine diphosphate glucose (UDPG), an intermediate in glycogen synthesis, promotes glycogen storage rather than lipogenesis by inhibiting the lipogenic enzyme S1P. This mechanism offers a novel therapeutic target for non-alcoholic fatty liver disease (NAFLD) [9].

2.2 Bidirectional Regulation of Fat Metabolism

Acetyl-CoA carboxylase (ACC) is a key enzyme in fatty acid synthesis, catalysing the conversion of acetyl-CoA into malonyl-CoA. This reaction represents the rate-limiting step in fatty acid biosynthesis. Its activity is regulated by hormones (such as insulin), nutritional status, and gene expression. Recent research highlights indicate that the cloning and expression regulation of the ACC gene exhibit functional variations across different tissues. For instance, overexpression of ACC in skeletal muscle may lead to lipid accumulation, while ACC inhibition in the liver can reduce lipogenesis. These alterations may all result in metabolic dysfunction. Moreover, it also represents a potential therapeutic target for certain metabolic disorders. ACC activation may improve pancreatic β-cell function by promoting insulin secretion, thereby alleviating hyperglycaemia; however, tissue-specific agonists must be developed to prevent skeletal muscle lipid deposition. In non-alcoholic fatty liver disease, studies indicate that inhibiting adenosine synthase (ACC) or blocking the sphingosine-1-phosphate (S1P) pathway via uridine diphosphate glucose (UDPG) reduces hepatic lipogenesis. The efficacy of these approaches has been validated in mouse models and human organoids [10]. Acetyl-CoA also participates in lipolysis and energy supply. Acetyl-CoA generated through fatty acid β-oxidation enters the tricarboxylic acid (TCA) cycle. During periods of insufficient glucose metabolism, such as in a state of starvation, it is converted by the liver into ketone bodies, providing metabolic energy for the brain and muscles.

2.3 Integration and Dynamic Equilibrium of Energy Metabolism

Acetyl-CoA participates in the tricarboxylic acid cycle and oxidative phosphorylation. It generates substantial quantities of NADH and $FADH_2$ via the TCA cycle, ultimately producing ATP through oxidative phosphorylation to supply the cell with its primary energy source. Cells dynamically regulate the metabolic pathways of acetyl-CoA according to their energy status. When energy is abundant, they prioritise the synthesis of glycogen or fat; when energy is scarce, they release energy through fatty acid β-oxidation or ketone body production. Fatty acid oxidation may increase reactive oxygen species (ROS) via reverse electron transport, whilst glycogenolysis generates NADPH through the pentose phosphate pathway to scavenge ROS. This difference accounts for the physiological strategy whereby the liver prioritises glycogen storage to prevent fatty degeneration. The UDPG-mediated mechanism counteracting glycogen synthesis and lipogenesis reveals the molecular basis by which the liver dynamically balances energy storage forms through metabolic intermediates [11]. Recent research has further revealed that liver cancer cells activate the ketone body degradation pathway through metabolic reprogramming, utilising the SUCLA2 enzyme to promote acetyl-CoA production and thereby support tumour proliferation. This discovery sheds light on the regulatory mechanisms governing energy metabolism under pathological conditions [12].

As a key molecule in metabolism, the interaction between acetyl-CoA and insulin signalling pathways constitutes one of the core mechanisms governing metabolic regulation. Acetyl-CoA serves as a pivotal node in insulin-regulated energy metabolism. The metabolic fate of acetyl-CoA —whether oxidised for energy or converted into lipids—is directly governed by insulin signalling [13]. Through this mechanism, insulin coordinates the equilibrium between short-term energy demands and long-term energy reserves. On the other hand, both possess feedback regulatory mechanisms, with the energy sensor AMPK serving as a bridge in this process: Under low-energy conditions, AMPK inhibits ACC through phosphorylation, thereby reducing acetyl-CoA production, promoting fatty acid oxidation, and enhancing insulin sensitivity [14]. However, during periods of energy surplus, elevated levels of acetyl-CoA may inhibit AMPK activity, thereby diminishing its metabolic protective effects and perpetuating a vicious cycle of metabolic disorder. Acetyl-CoA serves not only as a metabolic intermediate but also as a key cofactor in histone acetylation modification. Histone acetyltransferases (HATs) rely on acetyl-CoA to transfer acetyl groups to histones, thereby loosening chromatin structure and activating gene transcription. Insulin signalling may amplify its role in promoting glucose uptake and lipid synthesis by regulating the expression of metabolism-related genes (such as GLUT4 and PPARγ) through modulating acetyl-CoA levels. For instance, during adipocyte differentiation, insulin-induced elevations in acetyl-CoA may activate PPARγ via epigenetic mechanisms, thereby promoting lipodendron formation. Conversely, the efficiency of acetyl-CoA production within mitochondria is directly linked to TCA cycle activity. Insulin maintains mitochondrial function by promoting glucose oxidation, whereas mitochondrial dysfunction—such as impaired acetyl-CoA metabolism—leads to pyruvate accumulation and increased lactate production. This concurrently reduces ATP synthesis, ultimately inducing insulin resistance in muscle and

liver tissues [15]. This integration of metabolism with organelle function reveals the pivotal role of acetyl-CoA in linking nutritional status to gene expression, and energy metabolism to signalling pathways. This imbalance in interactions is particularly pronounced in metabolic disorders such as type 2 diabetes and obesity. Chronic nutritional excess induced by high-fat diets or obesity leads to excessive intracellular accumulation of acetyl-CoA [16]. This process simultaneously exacerbates hyperglycaemia by inhibiting pyruvate dehydrogenase (PDH) and thereby reducing glucose oxidation, whilst simultaneously promoting lipid synthesis via the ACC pathway, resulting in fatty liver and elevated circulating free fatty acids. Moreover, metabolites derived from acetyl-CoA (such as ceramides) may directly interfere with insulin signalling pathways, whilst abnormal epigenetic modifications (such as dysregulated histone acetylation) may lead to the silencing of insulin target gene expression [17]. These mechanisms collectively constitute a multi-layered pathological network of insulin resistance. Therapeutic strategies targeting this network are beginning to emerge. For instance, AMPK activators such as metformin reduce acyl-CoA carboxylase (ACC) activity to decrease acetyl-CoA production, thereby promoting fatty acid oxidation. Conversely, ACC inhibitors directly block lipid synthesis, thereby improving metabolic disorders.

Relevant studies have confirmed that abnormal acetyl-CoA metabolism is closely associated with insulin resistance, specifically manifested in the liver, skeletal muscle, and adipose tissue [18]. Elevated levels of acetyl-CoA in the liver are closely associated with insulin resistance. Under conditions of high-fat diets or obesity, excessive free fatty acids enter hepatic cell mitochondria for β-oxidation, leading to the accumulation of acetyl-CoA [19]. This subsequently promotes insulin resistance through multiple pathways. Firstly, it inhibits the insulin pathway by allowing excess acetyl-CoA to activate protein kinase Cε (PKCε) and the JNK pathway, thereby interfering with tyrosine phosphorylation of insulin receptor substrates (IRS) and blocking Akt activation. Secondly, driving gluconeogenesis, acetyl-CoA activates pyruvate carboxylase (PC), promoting oxaloacetate production. Concurrently, it upregulates phosphoenolpyruvate carboxylase kinase (PEPCK) and glucose-6-phosphatase (G6Pase) expression via histone acetylation modifications, exacerbating fasting hyperglycaemia. Thirdly, it promotes lipogenesis, whereby acetyl-CoA is converted into acyl-CoA via ACC, inhibiting mitochondrial fatty acid uptake. This leads to the accumulation of lipid intermediates (such as DAG and ceramide), further impairing insulin signalling. Within muscle tissue, acetyl-CoA primarily originates from fatty acid β-oxidation, entering the mitochondrial tricarboxylic acid cycle to supply energy. Two theories exist regarding the metabolic abnormalities promoting insulin resistance. The first is the loss of metabolic flexibility theory, In obese individuals, an elevated acetyl-CoA/CoA ratio inhibits pyruvate dehydrogenase (PDH), reducing glucose oxidation while simultaneously enhancing fatty acid-dependent acetyl-CoA production. This creates a 'lipid-glucose metabolic cycle competition,' diminishing muscle cells' glucose uptake capacity and consequently leading to insulin resistance. The second hypothesis concerns mitochondrial inactivation. Chronic acetyl-CoA overload triggers excessive mitochondrial reactive oxygen species (ROS) production, activating inflammatory pathways (such as NF-κB) and promoting serine phosphorylation of IRS-1. This inhibits insulin signalling, thereby inducing insulin resistance. Moreover, within lipid metabolism, acetyl-CoA-dependent histone acetylation modifications (such as H3K27ac) drive the expression of pro-inflammatory genes (e. g., TNF-α, IL-6), inducing chronic low-grade inflammation in adipose tissue. Furthermore, by inhibiting AMPK activity, acetyl-CoA reduces adiponectin secretion and diminishes its role in enhancing insulin sensitivity [20]. Collectively, these mechanisms contribute to the development of insulin resistance.

3. Diacylglycerol and Insulin Resistance in Type 2 Diabetes

Diacetylglycerol (DAG) is an ester formed by the condensation of two fatty acids with two of the three hydroxyl groups of a glycerol molecule, resulting in the loss of two molecules of water. It is a neutral lipid substance. DAG is widely present within the phospholipid bilayer structure of biological membranes in the tissue cells of animals. It serves as a crucial precursor for the formation of numerous phospholipids and functions as an important intermediate product in the complex metabolism of lipid substances. Furthermore, acting as a precursor or intermediate for various hormones, it plays a particularly vital role in the regulation of hormone levels within the organism. Its synthesis primarily occurs via three pathways: (1) The degradation of phosphatidylinositol (PI): In cellular signal transduction, upon activation, phospholipase C (PLC) hydrolyses phosphatidylinositol-4, 5-bisphosphate (PIP_2) into inositol trisphosphate (IP_3) and DAG. This process constitutes a pivotal step in the signalling pathways of G protein-coupled receptors (GPCRs) or receptor tyrosine kinases (RTKs). (2) Degradation of triglycerides (TG): Triglycerides within adipose tissue undergo progressive hydrolysis under the action of lipases (such as hormone-sensitive lipase, HSL), yielding diacylglycerol (DAG) and free fatty acids (FFA), ultimately forming monoglycerides (MAG). (3) Conversion of Phosphatidic Acid: Phosphatidic acid (PA) undergoes dephosphorylation catalysed by phosphatidic acid phosphatase (PAP) to yield diacylglycerol (DAG), an intermediate step in phospholipid and triglyceride synthesis. It is utilised by the body through phosphorylation to form phosphatidic acid and hydrolysis to monoglycerides.

The metabolism of diacylglycerol is regulated by multiple enzymes and signalling pathways, wherein it plays a double-edged role in insulin signalling pathway regulation [21]. Its effects encompass both enhancing insulin sensitivity and potentially inducing insulin resistance under conditions of metabolic dysfunction. The regulatory effects of DAGs are highly dependent on their source of generation, site of action, and metabolic state. This complexity renders them key targets in the study of metabolic disorders. On the one hand, under physiological conditions, DAG supports insulin function by activating specific PKC subtypes [22]. DAG activates atypical PKC to form a specific signalling axis, enhancing the activity of the PI3K-Akt pathway. This subsequently regulates downstream targets, accelerating the translocation of the glucose transporter GLUT4 to the cell membrane and

thereby increasing glucose uptake in muscle and adipose tissue. Moreover, DAG can synergise with the mTORC2 complex to maintain Akt in a fully activated state, thereby further consolidating insulin sensitivity. On the other hand, DAG promotes insulin secretion. Within pancreatic β-cells, DAG facilitates insulin vesicle exocytosis by activating protein kinase C (PKC), such as PKCα, thereby indirectly enhancing insulin release and establishing a positive feedback regulatory mechanism. When DAG accumulates abnormally in specific tissues such as muscle, liver, and adipose tissue, it triggers insulin resistance by activating typical PKC subtypes. In an obese state, excess DAG in muscle and adipose tissue activates PKCθ, which catalyses serine phosphorylation of insulin receptor substrate (IRS-1) (e.g., at the Ser307 site). This modification inhibits tyrosine phosphorylation of IRS-1, impeding its binding to PI3K. This results in disruption of the PI3K-Akt pathway, reduced GLUT4 membrane translocation, and diminished glucose uptake capacity. In the liver, the DAG-PKCε signalling pathway inhibits tyrosine kinase activity at the insulin receptor (IR), thereby blocking IRS-2 activation. This prevents downstream FoxO1 transcription factors from being phosphorylated by Akt, leading to sustained activation of hepatic gluconeogenesis (as evidenced by increased PEPCK and G6Pase expression) and exacerbating fasting hyperglycaemia. The DAG-PKC signalling pathway can activate inflammatory pathways such as NF-κB, promoting the secretion of inflammatory mediators including TNF-α and IL-6. These factors further induce serine phosphorylation of IRS through the JNK or IKKβ pathways, forming a vicious cycle that amplifies insulin resistance effects [23]. This mechanism reveals the complexity of interactions between lipid signalling and insulin pathways in metabolic disorders, providing a theoretical basis for developing tissue-specific therapies. Future research should further elucidate the dynamic metabolic network of DAGs and its synergistic interactions with other lipid messengers, such as ceramides, to comprehensively understand the molecular basis of metabolic dysregulation.

4. Advances in Modern Medical Treatment of Type 2 Diabetes Insulin Resistance via Acetyl-CoA and Diacylglycerol Metabolism

In recent years, targeted intervention studies on the metabolic pathways of acetyl-CoA and diacylglycerol (DAG) have garnered increasing attention. More familiar examples include ACC inhibitors, which act by inhibiting ACC—the enzyme catalysing the conversion of acetyl-CoA to acetyl-CoA — thereby reducing de novo lipogenesis and suppressing hepatic/adipose tissue lipid synthesis. This mechanism works by lowering acetyl-CoA levels, thereby releasing its inhibition of carnitine palmitoyltransferase 1 (CPT1) and powerfully promoting fatty acid adipose tissue lipid synthesis. By lowering acetyl-CoA levels, they release its inhibition on carnitine palmitoyltransferase 1 (CPT1), thereby powerfully promoting fatty acid oxidation. These inhibitors also reduce the flux of acetyl-CoA towards lipid synthesis. Consequently, they improve fat accumulation and alleviate clinical symptoms [24]. The drug Firsocostat, which is currently well-studied, demonstrated in Phase II clinical trials that it significantly reduces hepatic fat content (by approximately 28%) in patients with non-alcoholic steatohepatitis (NASH), while also improving hepatic insulin sensitivity and relevant biomarkers [25]. However, this medication also carries side effects, potentially inducing compensatory hypertriglyceridaemia, necessitating concomitant use of DGAT2 inhibitors to mitigate these adverse effects. The classic first-line drug metformin also improves fat accumulation by inhibiting ACC through phosphorylation, thereby enhancing glucose uptake and utilisation. Intervention strategies targeting the DAG-PKC signalling axis have garnered significant attention in recent years. While highly promising, directly inhibiting PKC subtypes (particularly PKCε and PKCθ) that play a pivotal role in insulin resistance and blocking their suppression of serine phosphorylation of IRS presents considerable challenges.

Reducing DAG accumulation is also an intervention strategy, but the safest approach remains dietary control and physical exercise, with the latter proven to be the most effective method [26]. Moderate exercise reduces DAG levels in muscle and liver while improving insulin sensitivity. Dietary control and rational dietary adjustments decrease total calorie and fat intake, directly reducing substrate sources for acetyl-CoA and DAG production, thereby effectively improving insulin resistance.

In recent years, traditional Chinese medicine has conducted extensive mechanistic research centred on the acetyl-CoA and diacylglycerol metabolic axis. Findings indicate that ‘spleen deficiency with phlegm-dampness and stagnant heat intertwined’ constitutes the core pathogenesis of insulin resistance in type 2 diabetes. The accumulation of acetyl-CoA and diacylglycerol mediating PKCε-IRS1 signalling inhibition represents one of the modern biological foundations for this traditional Chinese medical syndrome. Recent studies indicate that individual Chinese herbal compounds can precisely modulate acetyl-CoA/diacidglyceride (DAG) metabolism. For instance, extracts from the root of Platycodon grandiflorum (Jiegeng) downregulate phosphorylation of hepatic acetyl-CoA carboxylase (ACC), thereby reducing malonyl-CoA monolaurin production and inhibiting de novo DAG synthesis. This approach decreased hepatic DAG levels by 34% in mice fed a high-fat diet. restore the PKCε-IRS1 pathway, and increase glucose infusion rates by 28% [27]. Traditional Chinese medicinal formulae may also exert multi-target regulation over acetyl-CoA/diacid glyceride metabolism. Following eight weeks of gastric administration of Alisma and Atractylodes Decoction, lipidomics revealed significant reductions in hepatic DAG, TAG, and phosphatidylserine, alongside increased mitochondrial oxidative shunting of acetyl-CoA. Transcriptomics indicated upregulation of adipose tissue AMPK and PGC-1α, alongside downregulation of DGAT2, thereby remodelling the gut-adipose axis and ameliorating high-fat diet-induced insulin resistance. Relevant literature indicates that Linggui Zhugan Decoction reduces acetyl-CoA carboxylation by inhibiting SREBP-1c activation mediated via hepatic X receptors, thereby diminishing DAG-PKCε-IRS1 inhibitory signalling. Beyond oral administration of traditional Chinese medicine, external therapeutic methods in Chinese medicine may also regulate acetylation and DAG metabolism. Electroacupuncture at points such as Zhongwan (CV12) and Fenglong (ST40) downregulates ACC1 and FAS expression, enhances AMPK phosphorylation, and reduces hepatic acetyl-CoA

accumulation. Concurrently, it inhibits DAG-PKCε membrane translocation and restores IRS1 tyrosine phosphorylation, thereby increasing glucose infusion rates by 25% in high-fat diet-fed rats [28]. In summary, traditional Chinese medicine modulates the acetyl-CoA/diacid glyceride (DAG) metabolic axis through multiple mechanisms. Its efficacy in improving insulin resistance in type 2 diabetes mellitus has been validated at cellular, animal, and early clinical levels, thereby laying the groundwork for subsequent multicentre randomised controlled trials and formula optimisation studies.

5. Outlook

Future research will increasingly focus on the metabolic regulation of acetyl-CoA and diacylglycerol. Targeting these metabolic pathways represents a highly promising new strategy for fundamentally improving insulin resistance in type 2 diabetes. With the continuous advancement of mechanism research and the ongoing development of novel pharmaceuticals, the future holds promise for delivering more effective and precise treatment options to patients, while simultaneously reinforcing the central role of lifestyle interventions throughout this process. Future research will also employ spatial metabolomics coupled with single-cell epigenomics to decipher the 'syndrome-metabolism-gene' mapping relationships, establishing a dynamic Ac-CoA/DAG biomarker system. Additionally, synergistic strategies combining chemical drug targets with traditional Chinese medicine formulations will be developed, utilising nanocarriers for liver-targeted co-delivery. This approach aims to achieve personalised reversal of insulin resistance and delay the progression of type 2 diabetes mellitus.

Fund Project

Based on the Effects on Acetyl-CoA, Diacylglycerol, and Hepatic/Muscle Glycogen: Exploring the Mechanism by Which Xianghe Xiaopang Wan Improves Insulin Resistance and Alleviates/Reverses Type 2 Diabetes, No.2024SF-YBXM-169.

References

[1] Silbert, Richard et al. "Hypoglycemia Among Patients with Type 2 Diabetes: Epidemiology, Risk Factors, and Prevention Strategies." Current diabetes reports vol. 18, 8 53. 21 Jun. 2018. doi:10. 1007/s11892-018-1018-0

[2] Abel, E Dale et al. "Diabetes mellitus-Progress and opportunities in the evolving epidemic." Cell vol. 187, 15 (2024): 3789-3820.

[3] Elkanawati, Rani Yulifah et al. "Impact of Lipids on Insulin Resistance: Insights from Human and Animal Studies. " Drug design, development and therapy vol. 18 3337-3360. 31 Jul. 2024,

[4] Zabielski, Piotr et al. "The Role of Acyl-CoA Synthetase 1 in Bioactive Lipid Accumulation and the Development of Hepatic Insulin Resistance." Nutrients vol. 16, 7 1003. 29 Mar. 2024.

[5] Zhao Chanjuan, Lin Shouning, Liu Yu, et al. Research Progress on Integrated Traditional Chinese and Western Medicine in the Treatment of Type 2 Diabetes Mellitus [J]. Smart Healthcare, 2025, 11(04): 23-25+29.

[6] Liu Yimin, Ji Yanhua, Chen Mengjie, et al. Research Progress on Gegen Qinlian Decoction and Its Modified Prescriptions in Improving Insulin Resistance of Type 2 Diabetes Mellitus [J]. Chinese Journal of Experimental Traditional Medical Formulae, 2024, 30(15): 256-263.

[7] Zhou Chunyan, Yao Libo. Biochemistry and Molecular Biology (9th Edition). People's Medical Publishing House: Beijing, 2018.

[8] Hernandez-Vazquez, Alain de J et al. "Thiamine Deprivation Produces a Liver ATP Deficit and Metabolic and Genomic Effects in Mice: Findings Are Parallel to Those of Biotin Deficiency and Have Implications for Energy Disorders." Journal of nutrigenetics and nutrigenomics vol. 9, 5-6 (2016): 287-299.

[9] Chen, Jie et al. "Hepatic glycogenesis antagonizes lipogenesis by blocking S1P via UDPG." Science (New York, N. Y.) vol. 383, 6684 (2024): eadi3332.

[10] Zhang S, Kim KH. Glucose activation of acetyl-CoA carboxylase in association with insulin secretion in a pancreatic beta-cell line. J Endocrinol. 1995;147(1):33-41.

[11] Zhou Y, Zhang C, He L, et al. Glucose-1-phosphate promotes compartmentalization of glycogen with the pentose phosphate pathway in CD8+ memory T cells. Mol Cell. 2025;85(13):2535-2549. e10.

[12] Guo D, Yu Q, Tong Y, et al. OXCT1 succinylation and activation by SUCLA2 promotes ketolysis and liver tumor growth. Mol Cell. 2025;85(4):843-856. e6.

[13] Wakil SJ, Abu-Elheiga LA. Fatty acid metabolism: target for metabolic syndrome. J Lipid Res. 2009;50 Suppl (Suppl): S138-S143.

[14] Li Q, Wang Y, Wu S, et al. CircACC1 Regulates Assembly and Activation of AMPK Complex under Metabolic Stress. Cell Metab. 2019;30(1):157-173.

[15] Zhao Z, Chen Q, Xiang X, et al. Tip60-mediated Rheb acetylation links palmitic acid with mTORC1 activation and insulin resistance. J Cell Biol. 2024; 223(12): e202309090.

[16] He A, Chen X, Tan M, et al. Acetyl-CoA Derived from Hepatic Peroxisomal β-Oxidation Inhibits Autophagy and Promotes Steatosis via mTORC1 Activation. Mol Cell. 2020;79(1):30-42. e4.

[17] Naderi J, Johnson AK, Thakkar H, et al. Ceramide-induced FGF13 impairs systemic metabolic health. Cell Metab. 2025;37(5):1206-1222. e8.

[18] Ma QX, Zhu WY, Lu XC, et al. BCAA-BCKA axis regulates WAT browning through acetylation of PRDM16. Nat Metab. 2022;4(1):106-122.

[19] Roszczyc-Owsiejczuk K, Zabielski P. Sphingolipids as a Culprit of Mitochondrial Dysfunction in Insulin Resistance and Type 2 Diabetes. Front Endocrinol (Lausanne). 2021;12:635175. Published 2021 Mar 18.

[20] Perry RJ, Camporez JG, Kursawe R, et al. Hepatic acetyl CoA links adipose tissue inflammation to hepatic insulin resistance and type 2 diabetes. Cell. 2015; 160(4): 745-758.

[21] Li D, Xu T, Takase H, et al. Diacylglycerol-induced improvement of whole-body insulin sensitivity in type 2 diabetes mellitus: a long-term randomized, double-blind controlled study. Clin Nutr. 2008;27(2):203-211.

[22] Kolczynska K, Loza-Valdes A, Hawro I, Sumara G. Diacylglycerol-evoked activation of PKC and PKD

isoforms in regulation of glucose and lipid metabolism: a review. Lipids Health Dis. 2020;19(1):113. Published 2020 May 28.

[23] Zhou X, Yang W, Li J. Ca2+- and protein kinase C-dependent signaling pathway for nuclear factor-kappaB activation, inducible nitric-oxide synthase expression, and tumor necrosis factor-alpha production in lipopolysaccharide-stimulated rat peritoneal macrophages. J Biol Chem. 2006; 281(42): 31337-31347.

[24] Savage DB, Choi CS, Samuel VT, et al. Reversal of diet-induced hepatic steatosis and hepatic insulin resistance by antisense oligonucleotide inhibitors of acetyl-CoA carboxylases 1 and 2. J Clin Invest. 2006; 116(3): 817-824.

[25] Loomba R, Kayali Z, Noureddin M, et al. GS-0976 Reduces Hepatic Steatosis and Fibrosis Markers in Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology. 2018;155(5):1463-1473. e6.

[26] Whytock KL, Goodpaster BH. Unraveling Skeletal Muscle Insulin Resistance: Molecular Mechanisms and the Restorative Role of Exercise. Circ Res. 2025; 137(2): 184-204.

[27] Kim YJ, Choi JY, Ryu R, et al. Platycodon grandiflorus Root Extract Attenuates Body Fat Mass, Hepatic Steatosis and Insulin Resistance through the Interplay between the Liver and Adipose Tissue. Nutrients. 2016;8(9):532. Published 2016 Aug 30.

[28] Jin Shuwen, Liu Jiabao, Li Dan, et al. Effect of Electroacupuncture at “Fenglong” (ST40) Point on Hepatic Lipid Synthesis and Insulin Resistance in Hyperlipidemic Model Rats [J]. Journal of Traditional Chinese Medicine, 2023, 64(22): 2346-2353.