

# Research Progress of Coenzyme Q in Diabetes Mellitus and Its Common Complications

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**Abstract:** Coenzyme Q has garnered significant attention due to its potential role in enhancing cellular energy production and its antioxidant properties. We delve into the therapeutic potential of coenzyme Q in managing diabetes mellitus and its complications, highlighting its capacity to improve mitochondrial function, reduce inflammation and oxidative stress, and correct lipid profiles. Coenzyme Q has shown promise in ameliorating insulin resistance and alleviating complications such as diabetic peripheral neuropathy, kidney disease, retinopathy, and cardiomyopathy. However, its clinical application is limited by poor bio-availability. This review also provides a comprehensive overview of current therapeutic strategies for diabetes complications involving coenzyme Q, including stimulating endogenous synthesis and utilizing carrier transport systems, offering insights into mechanisms for enhancing coenzyme Q bio-availability. These findings suggest that, with improved delivery methods, coenzyme Q could become a valuable adjunct therapy in the management of diabetes mellitus.

**Keywords:** coenzyme Q, diabetes mellitus, diabetic complications

## Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by chronic hyperglycemia and defects in insulin production, secretion and signaling. The two primary types of DM are type 1 diabetes mellitus (T1DM), an autoimmune condition that results in the destruction of insulin-producing beta cells in the pancreas, and type 2 diabetes mellitus (T2DM), which is characterized by insulin resistance (IR) and relative insulin deficiency. T2DM is more prevalent, accounting for the majority of DM cases. As the incidence of DM continues to rise, it has escalated to become the ninth leading cause of death worldwide.<sup>1</sup> According to the International Diabetes Federation, the global prevalence of DM among individuals aged 20–79 years was estimated to be 536.6 million in 2021, with projections reaching 783.2 million by 2045.<sup>2</sup> DM can give rise to life-threatening complications that jeopardize various organs and tissues, including the cardiovascular, hepatic, renal, retinal, peripheral, and central nervous systems, significantly shortening patients' lifespan.

Effective glycemic control is paramount in the management of DM, yet many oral hypoglycemic agents frequently elicit a range of adverse effects, and reversing diabetic complications remains challenging. Furthermore, the lack of tailored drug treatments necessitates the search for medications that offer enhanced benefits with minimal side effects for the treatment of DM and its associated complications. Fazakerley et al observed that concentrations of coenzyme Q (CoQ), a crucial component of mitochondria, were lower from insulin resistant (IR) adipose and muscle tissue. Notably, CoQ supplementation has been shown to enhance insulin sensitivity in both in vitro and in vivo models of IR,<sup>3</sup> suggesting its potential as a therapeutic target for DM. Additionally, CoQ offers subtle yet significant benefits in the management of diabetic complications. Despite its therapeutic potential, its poor bio-availability and safety profile warrants careful consideration during application. Study indicates that CoQ is generally well-tolerated, with a safe dosage up to 1200 mg/day, although gastrointestinal discomfort has been reported at higher doses, particularly above 2400 mg/day.<sup>4</sup> This highlights the importance of adhering to recommended dosages and monitoring patient responses carefully to ensure safety while maximizing therapeutic efficacy. In the following sections, we will delve into the mechanism of action, therapeutic targets, and the latest therapeutic strategies employing CoQ for the treatment of DM and its common complications. Table 1 summarizes the in vivo and in vitro studies included in this review.

**Table 1** Effects of CoQ on Diabetes Mellitus and Its Associated Complications.

Author	Disease	Model	Dosage and Duration	Mode of Administration	Described Effects	Potential Mechanism
Luo K, <sup>10</sup> 2019	Diabetes mellitus	Male SD rats, Tac (1.5 mg/(kg•day))	CoQ10, 20 mg/kg/day, 4 weeks	Orally	Blood glucose↓ AUCg↓ HbA1c↓ insulin↑ mitochondrial ultrastructural changes (reversed) TUNEL positive cell percentage↓	8-OHdG↓ 4-HHE↓ ROS↓
		INS-1 cells, Tac (50 µg/ml)	CoQ10, 1 pg/ml–10 µg/ml, 12 h	Incubated	Annexin V positive cells percentage↓ mitochondrial morphology and respiration (improved)	ROS↓
Amin MM, <sup>18</sup> 2014	Diabetes mellitus	Male Wistar albino rats, HFFD, STZ	CoQ10, 20 mg/kg/day, 2 weeks	Orally	Blood glucose↓ FFA↓ TG↓ TC↓ HOMA-IR↓ fructosamine↓ insulin levels↓ ALT↓ <b>AST</b> ↓	GLUT4↓ GLUT2↓ TK↑ PI3K/Akt signaling↑ oxidized LDL↓ MPO↓ NF-κB↓ AGE/RAGE axis(inhibited) sRAGE↑ adiponectin and receptors↑ visfatin↓ ROS↓ NF-κB↓ MDA↑ GSH↑ IL-1β↓ TNF-α↓ IL-6↓
Alshogran OY, <sup>28</sup> 2021	Diabetic kidney disease	Male Wistar rats, STZ	CoQ10, 10 mg/kg/day, 6 days	Injected intraperitoneally	Serum Cr↓ inulin clearance↑ RBF↑ RVR↓ soluble non-protein thiols↑	Prostaglandin-1↑ prostacyclin↑ NO↑ ROS ↓ soluble non-protein thiols↑
Yue T, <sup>27</sup> 2017	Diabetic kidney disease	Male SD rats, STZ	CoQ10, 5 mg/ml/day(plus UTMD), 8 weeks	Orally	Kidney volume↓ blood glucose↓ 24h urinary protein↓ body weight↑ CVF↓ TUNEL positive apoptotic cell↓	MDA↓(in the serum) SOD↑(in the serum) Nphs2 level↑ caspase-3↓(in the kidney tissue) Bcl-2/Bax↑
Alshogran OY, <sup>28</sup> 2021	Diabetic kidney disease	Male SD rats, STZ	CoQ10, 20 mg/kg/day, plus NAC, 100 mg/kg/day or atorvastatin, 10 mg/kg/day, 5 days	Orally	Serum Cr (no alter) serum urea (no alter)	CAT activity ↑(in the kidney tissue) GPx↑(in the kidney tissue) TBARS(no alter)
Maheshwari R, <sup>26</sup> 2017	Diabetic kidney disease	Adult Wistar rats, STZ, nicotinamide	CoQ10, 10 mg/kg/day, plus sitagliptin 10 mg/kg/day, 6 weeks	CoQ10, Injected intraperitoneally, sitagliptin, Orally	Body weight (no alter) kidney weight ↓ urine volume (no alter) urinary protein↓ HbA1c↓ serum creatinine↓ urea ↓ uric acid↓ TG↓ TC↓ HDL-C↑ glomerulosclerosis (improved) glomerular fibrosis (improved)	MDA↓ GSH↑ SOD↑ CAT↑ TNF-α↓ MPO↓ TGF-β↓ nitrite content↓(All of the above in renal tissue)
Shi TJ, <sup>44</sup> 2013	Diabetic peripheral neuropathy	C57BL/KsJm/Leptdb (db -/db-) mice	CoQ10 was added to the food pellets(1 g/kg), 6 months	Orally	Body weight (no alter) blood glucose (no alter) Hypoalgesia (improved) CV↑ DRG neuronal cell loss (counteracted)	Bax↓ p-Akt↑ p-Erk1/2(no alter) Bcl-2(no alter) PLCβ3↑ UCP-2↓
Zhang YP, <sup>45</sup> 2016	Diabetic peripheral neuropathy	CBA/Caj mice, spontaneously develop mild hyperglycemia	CoQ10, 100 µL/30 g, twice before 20 h and 4 h of the induction of hypoglycemia	Injected intraperitoneally	Blood glucose (no alter) mechanical hypersensitivity (prevented)	c-Fos expression↓(in the spinal cord)
Sadeghiyan Galeshkalami N, <sup>47</sup> 2019	Diabetic peripheral neuropathy	Male Wistar rats , STZ	CoQ10, 10 mg/kg/day, plus alpha lipoic acid, 100mg/kg, 5 weeks	Orally	DRG neurons (improved) the number of large cells↑ Diameter of large and small cells↑ motor function (improved)	ROS↓ MDA↓ TAC↑ GSH↑ ADP/ATP ratio↓ caspase 3 protein↓ UCP-2 protein(no alter)
Huynh K, <sup>52</sup> 2012	Diabetic Cardiomyopathy	Female C57BL/6 db/+ and db/db mice	receive water with CoQ10, 10 mg/kg/day	Orally	HbA1c levels↓ body weight (no noticeably alter) left ventricular diastolic function (improved) Cardiac fibrosis (ameliorated) cardiomyocyte hypertrophy (improved) CardioTACS positive apoptotic cell↓ SBP↓ DBP (no alter)	Serca2a expression↑ Myh7 expression↓ MDA↓ ROS↓

De Blasio MJ, <sup>53</sup> 2015	Diabetic Cardiomyopathy	Male dnPI3K transgenic mice (FVB/N background), STZ	CoQ10, 10 mg/kg/day, three times per week, 8 weeks	Injected intraperitoneally	Blood glucose (no alter) Body weight↓ HW/TL↓ left ventricular diastolic function (improved) Heart rate (no alter) SBP (no alter) cardiomyocyte hypertrophy (attenuated) cardiac fibrosis (attenuated)	Nox2 protein levels↓ LV 3-NT content↓ MDA levels↓ LV β-myosin heavy chain expression↓ CTGF expression↓ ANP↓
Jbrael YJ, <sup>57</sup> 2024	Diabetic Cardiomyopathy	24 Wister rats, STZ	5 g of CoQ10 per kilogram of diet, 3 weeks	Orally	blood glucose↓ <b>GRA%</b> ↓ <b>MID%</b> ↓ <b>LYM%</b> ↑ cTnl↓ CK-MB↓	TNF-α(in the serum)↓ NF-κB↓ serum resistin levels↓ serum LPPLA2 level↓ Serum omentin level↓
Tsai, <sup>63</sup> 2016	Diabetic macrovascular disease	Unilateral hindlimb surgery to induce ischemia	High glucose combined with CoQ10 (10 μM) cultured EPCs were injected into the ischemia limbs	injected	Hindlimb perfusion (improved)	P-AMPK↑ p-Akt↑ p-eNOS↑ HO-1↑
		EPCs, high glucose-induced	CoQ10 (10 μM) for 1 day	Incubated	EPCs viability and migration(improve) ΔΨm↑ cellular apoptosis↓	Activated-caspase 3↓ Bcl-2↑ ROS↓ p-Akt↑ p-eNOS↑ HO-1↑ p-AMPK↑
Yoo JY, <sup>14</sup> 2018	Diabetes mellitus	80 adults with impaired glucose tolerance	CoQ10, 200 mg/day, 8 weeks	Orally	TC (no alter) TG (no alter) LDL (no alter) HDL (no alter) HOMA-IR↓ FBG (no alter) HbA1c (no alter)	Free oxygen radical levels↓
Gholami M, <sup>15</sup> 2019	Diabetes mellitus	80 women with T2DM	CoQ10, 100 mg/day, 12 weeks	Orally	FBG↓ HOMA-IR↓ TC↓ LDL-C↓ ferritin↓ HDL-C↑	FAS↓ ACCI↓ PEPCK↓ PPARα↑
Sangouni AA, <sup>20</sup> 2022	Diabetes mellitus	88 volunteers with MetS	CoQ10, 60 mg/day, plus curcumin, 200 mg/day, 12 weeks	Orally	TG↓ TC↓ LDL-c↓ BMI((no alter) weight((no alter) HDL-C((no alter) SBP ((no alter) DBP((no alter) FBG((no alter)	AMPK↑ PPAR-α↑
Gholnari T, <sup>24</sup> 2018	Diabetic kidney disease	50 subjects with DKD	CoQ10, 100 mg/day, 12 weeks	Orally	Serum insulin levels↓ HOMO-IR↓ HOMO-β cell function (improved) HbA1c↓ FBG (no alter) lipid profiles (no alter)	MDA↓ AGEs↓ MMP-2(no alter)
Rodríguez-Carrizalez AD, <sup>36</sup> 2016	Diabetic retinopathy	60 with NPDR	CoQ10, 400 mg/day, combined antioxidant therapy, 6 months	Orally	HbA1c(no alter) Lipid profiles(no alter) nitrites/nitrates↓	MDA levels↓ 4-HDE↓ TAC↓ CAT activity↑ GPx activity↑
Amini P, <sup>48</sup> 2022	Diabetic peripheral neuropathy	176 patients with PDN	CoQ10, 300 mg/day, 8 weeks	Orally	average pain NRS scores(improved) average SIS scores(improved) HbA1c↓ FBG↓	-
Serag H, <sup>61</sup> 2021	Diabetic macrovascular disease	49 T1DM pediatric patients	CoQ10, 100 mg/day, 3 months	Orally	FBG(no alter) HbA1c(no alter) lipid profile(no alter) sICAM-1 (no alter) TG↑	-

**Notes:** ↓ indicates inhibition/reduction while ↑ indicates increase/promotion

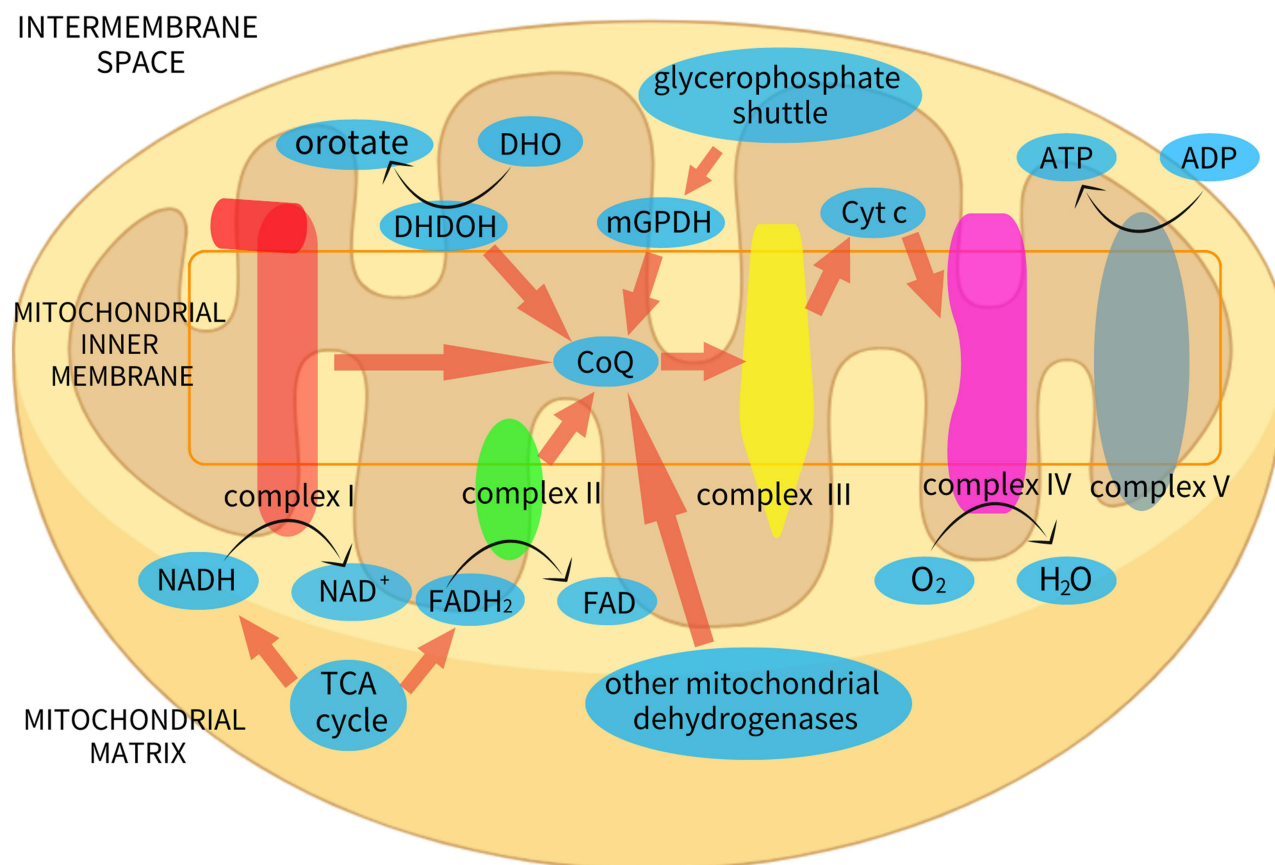
**Abbreviations:** AUCg, area under the curve of glucose; HbA1c, glycated hemoglobin; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; HOMA-IR, homeostasis model assessment of insulin resistance; FBG, fasting blood glucose; FFA, free fatty acid; ALT, glutamic pyruvic transaminase; AST, glutamic oxaloacetic transaminase; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; 4-HHE, 4-hydroxy hexenal; ROS, reactive oxygen species; GLUT4, glucose transporter protein 4; GLUT2, glucose transporter protein 2; TK, tyrosine kinase; PI3K, phosphatidylinositol 3 kinase; Akt, serine/threonine protein kinase; MPO, myeloperoxidase; NF-κB, nuclear factor kappa-B; AGEs, advanced glycation end-products; sRAGE, soluble receptor for AGE; FAS, fatty acid synthase; ACCI, acetyl-CoA carboxylase I; PEPCK, phosphoenolpyruvate carboxykinase; PPARα, peroxisome proliferator-activated receptor α; MDA, malondialdehyde; GSH, glutathione; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; p-AMPK, phosphorylated-adenosine monophosphate-activated protein kinase; MMP-2, matrix metalloproteinase-2; GLUT1, glucose transporter protein 1; TGF-β, transforming growth factor-β; IL-8, interleukin-8; NO, nitrogen monoxide; RBF, renal blood flow; RVF, renal vascular resistance; UTMD, ultrasound-targeted microbubble destruction; CVF, collagen volume fraction; NAC, N-acetyl cysteine; Cr, creatinine; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; STZ, streptozotocin; DKD, diabetic kidney disease; NPDR, nonproliferative diabetic retinopathy; TAC, total antioxidant capacity; CV, conduction velocity; DRG, dorsal root ganglion; PLCβ3, phospholipase Cβ3; p-Erk1/2, phosphorylated-extracellular regulated protein kinase 1/2; p-Akt, phosphorylated-Akt; DR, diabetic retinopathy; DPN, diabetic peripheral neuropathy; ATP, adenosine triphosphate; NRS, numeric rating scale; SIS, sleep-interference scores; T1DM, type 1 diabetes mellitus; ADP, adenosine diphosphate; UCP-2, uncoupling protein 2; sICAM-1, s-I; DCM, diabetic cardiomyopathy; HW/TL, heart weight to tibia length ratio; LV, left ventricular; 3-NT, 3-nitrotyrosine; Nox2, non-phagocytic cell oxidase 2; CTGF, connective tissue growth factor; ANP, atrial natriuretic peptide; Myh7, β-myosin heavy chain 7; Serca2a, sarco/endoplasmic reticulum Ca<sup>2+</sup>-ATPase; GRA%, granulocytes percentage; MID%, medium size cells percentage of monocytes, eosinophils and basophils; LYM%, lymphocyte percentage; cTnl, cardiac troponin I; CK-MB, creatinine kinase MB; LPPLA2, Lipoprotein-associated phospholipase A2; EPCs, endothelial progenitor cells; HO-1, heme oxygenase-1; p-eNOS, phosphorylated-endothelial nitric oxide synthase.

## CoQ's Metabolism and Function

CoQ, also known as ubiquinone, is an endogenous lipophilic quinone composed of a fully substituted quinone ring and variable-length polyisoprene tails. The length of the isoprene chain varies from organism to organism (CoQ<sub>n</sub>, where *n* represents the number of isoprene units), and in humans, it is referred to as CoQ10.<sup>24–26</sup> CoQ10 can be obtained through diet, but it is primarily synthesized endogenously in mitochondria by a group of nuclear-encoded proteins known as COQ proteins.<sup>24</sup> CoQ typically exists in biofilms, and its most vital function is to facilitate the transfer of electrons and protons within the respiratory chain, thereby maintaining biological energy production. Essentially, CoQ serves as a mitochondrial cofactor that generates the proton motive force necessary for ATP synthesis by transferring electrons from mitochondrial respiratory chain complexes I and II to complex III.<sup>26</sup> Furthermore, the discovery of additional functions of CoQ is ongoing. It acts as an electron receptor for numerous mitochondrial dehydrogenases, offering diverse routes for electrons to reach complex III,<sup>27</sup> as shown in Figure 1. Previous studies have indicated that a deficiency of CoQ, particularly the reduced form, in the body increases the risk of developing DM in patients.<sup>28</sup> Fortunately, exogenous CoQ supplementation can alleviate oxidative stress, protect mitochondrial function, and thereby improve blood glucose levels.<sup>7,20,28–31</sup>

## The Role of CoQ in the Pathogenesis of DM

The occurrence and development of DM are intimately linked to mitochondrial dysfunction, IR and pancreatic  $\beta$ -cell dysfunction.<sup>32</sup> A primary function of CoQ is to ameliorate mitochondrial dysfunction. For instance, in a rat model of tacrolimus-induced DM, CoQ safeguarded the mitochondria of pancreatic  $\beta$ -cells, significantly alleviating tacrolimus-induced mitochondrial damage and enhancing ATP production,<sup>8</sup> thereby highlighting the potential therapeutic effects of



**Figure 1** The central role of CoQ in the mitochondrial respiratory chain, and its relationships with extramitochondrial electron transfer systems. Red arrows indicate electron flow.

**Abbreviations:** TCA cycle, tricarboxylic acid cycle; Cyt c, cytochrome c; mGPDH, mitochondrial glycerol-3-phosphate dehydrogenase; DHODH, dihydroorotate dehydrogenase.

CoQ in managing DM. IR is one of the earliest pathological hallmarks of T2DM. Evidence suggests that the accumulation of mitochondrial reactive oxygen species (ROS) plays a pivotal role in the pathogenesis of IR in adipose and skeletal muscle tissues.<sup>33</sup> Given its essential antioxidant properties *in vivo*, CoQ deficiency may be implicated in the development of IR.<sup>3</sup> For example, Diaz-Vegas et al reported that excessive expression of sphingomyelin phosphodiesterase 5 (SMPD5), a mitochondrial enzyme in mice, specifically increases ceramide levels in mitochondria, depleting components of the oxidative phosphorylation system, such as CoQ, resulting in mitochondrial dysfunction and ultimately leading to increased ROS production and IR.<sup>34</sup> Similarly, another study corroborates that phosphatidylethanolamine N-methyltransferase (PEMT), a positive regulatory factor for CoQ synthesis, can increase mitochondrial CoQ levels in mice adipocytes, thereby improving the glucose utilization rate and mitigating IR induced by a high-fat diet.<sup>35</sup> These findings suggest that stimulating CoQ synthesis or using drugs to induce CoQ production *in vivo* may offer promising strategies for improving IR.

Furthermore, earlier animal research has demonstrated that CoQ enhances insulin sensitivity and mitigates metabolic disorders associated with hyperglycemia or hyperinsulinemia, as well as soluble receptors for advanced glycation end-products (AGEs) by modulating insulin and lipocalin receptors, tyrosine kinase, phosphatidylinositol 3-kinase, glucose transporter protein 4 and glucose transporter protein 2,<sup>7</sup> as shown in Figure 2. While animal models provide foundational insights into the biological mechanisms, translating these findings to human physiology is essential for clinical applications. CoQ deficiency has been associated with impaired insulin action and hyperinsulinemia in humans, similar to what has been observed in animal studies.<sup>7,29</sup> In this context, several clinical trials have demonstrated the benefits of CoQ supplementation in improving insulin sensitivity and reducing markers of insulin resistance in prediabetic patients. For instance, in a randomized controlled trial involving 80 patients with impaired glucose tolerance, administration of 200 mg of CoQ for eight weeks significantly reduced homeostasis model assessment of insulin resistance (HOMA-IR) in prediabetic patients.<sup>21</sup> Other studies corroborate these findings, indicating that even low-dose CoQ supplementation (<200mg/d) can effectively reduce the HOMA-IR.<sup>20,29</sup> Additionally, multiple clinical studies suggest that supplementing CoQ can effectively reduce the fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) levels in serum, and even improve insulin sensitivity and insulin secretion.<sup>29–31</sup> Collectively, these suggest that CoQ may represent an innovative strategy to prevent the development of DM from its early stages.

However, some clinical studies have reported conflicting results, where CoQ failed to significantly improve FBG, HbA1c and insulin levels.<sup>19,21</sup> These disparities in the results regarding the metabolic effects of CoQ on DM may be attributed to variations in the dosage and duration of CoQ intake, as well as differences in the patients' underlying conditions. Given these inconsistencies, further reliable clinical controlled studies are necessary to understand better the specific conditions under which CoQ supplementation might be most effective.

Additionally, the benefits of CoQ for diabetic complications cannot be ignored, as shown in Figure 3.

## The Role of CoQ in the Prevention and Control of DM-Related Complications

### CoQ and Diabetic Kidney Disease

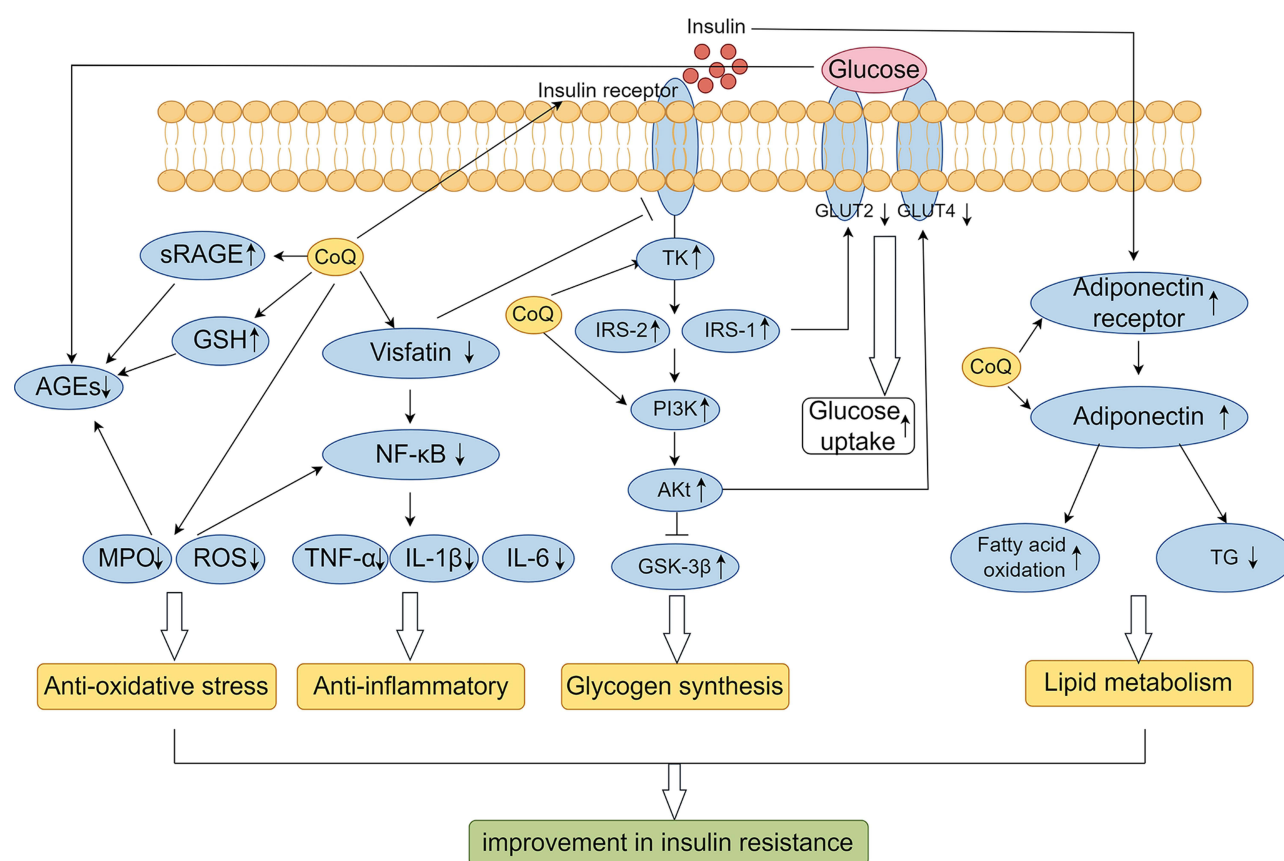
Diabetic kidney disease (DKD) is a form of kidney damage resulting from DM, serving as the primary cause of chronic kidney disease.<sup>36</sup> Typically, elevated blood glucose concentrations may directly trigger mitochondria damage in renal tubular cells, podocytes, mesangial cells, and glomerular endothelial cells. Additionally, mitochondrial dysfunction and excessive production of free oxygen radicals exacerbate the progression of DKD.<sup>37</sup> Consequently, managing blood glucose levels is paramount in improving the prognosis of DKD.

Research indicates that a decreased concentration of CoQ and oxidative stress could give rise to the progression of renal dysfunction in chronic renal disease patients.<sup>38</sup> However, the study failed to establish a direct correlation between the decrease in CoQ and the development of DKD. Consequently, a more standardized and rigorous clinically controlled study will be warranted. In diabetic rats submitted to the contrast-induced acute kidney injury model, CoQ treatment improved renal hemodynamics by stimulating the production of prostaglandin E-1 and prostacyclin, promoting nitric oxide (NO) synthesis to vasodilate blood vessels and reduce peripheral resistance.<sup>18</sup> While these animal studies provide a foundation for understanding CoQ's potential, the application in human patients requires further investigation. A clinical trial demonstrated



that twelve-week CoQ supplementation in patients with DKD exerted beneficial effects on glucose metabolism, malondialdehyde, and AGEs levels.<sup>39</sup> Nevertheless, the small sample size in these studies is insufficient to draw definitive conclusions, prompting the need to enroll a larger cohort to validate the efficacy of CoQ in DKD.

Currently, researchers are increasingly exploring the use of CoQ in combination with other therapeutic modalities for the treatment of DKD. For instance, in the DKD rats model, co-administration of CoQ and sitagliptin effectively ameliorated DKD, evident by the reduction in oxidative stress, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), transforming growth factor beta, and myeloperoxidase activities, nitrite levels, along with histopathological improvements compared to the administration of CoQ or sitagliptin alone.<sup>11</sup> Additionally, Yue et al identified early-stage DKD using real-time contrast-enhanced ultrasound quantitative analysis technique and employed an approach by combining CoQ with ultrasound-targeted microbubble destruction for the treatment of DKD rats, resulting in significantly improvements in renal hemodynamics and renal function.<sup>5</sup> This technology altered the distribution of CoQ in the body and impelled more CoQ to the target kidney noninvasively. However, the application of this method to treat other complications of DM remains informative and merits further exploration. In a rat model of contrast-induced nephropathy and DM, Alshogran et al utilized a combination of CoQ



**Figure 2** CoQ improves insulin resistance through various pathways. CoQ is an endogenous lipophilic quinone that exerts its effects on diabetes through multiple mechanisms. On the one hand, CoQ can enhance the activities of TK and PI3K, and the activation of TK stimulates tyrosine phosphorylation of IRS-1. This, in turn, regulates hepatic GLUT2 levels and activates the downstream Akt, thereby inhibiting gluconeogenesis and mediating glycogen synthesis. Additionally, the activation of Akt also modulates GLUT4 content in skeletal muscle, ultimately leading to a reduction in glucose levels. Furthermore, CoQ possesses the ability to elevate the levels of adiponectin and its receptor, thereby enhancing fatty acid oxidation, decreasing muscle TG content, and improving muscle fat metabolism. On the other hand, visfatin binds to and activates insulin receptors. However, it also induces the expression and production of inflammatory mediators such as IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 through NF- $\kappa$ B activation. In contrast, CoQ suppresses the level of visfatin, exerting anti-inflammatory effect. Additionally, CoQ reduces the production of AGEs and counteracts oxidative stress by increasing sRAGE levels, decreasing ROS and MPO production, and lowering GSH levels. Collectively, CoQ may ameliorate insulin resistance by mediating glycogen synthesis, correcting lipid profiles, suppressing inflammation, and resisting oxidative stress. An upward arrow ( $\uparrow$ ) within the circle indicates the stimulatory effect of coenzyme Q, while a downward arrow ( $\downarrow$ ) within the circle indicates the inhibitory effect of coenzyme Q. The T-shaped bar signifies the binding of a substance to a receptor.

**Abbreviations:** MPO, myeloperoxidase; GSH, glutathione; ROS, reactive oxygen species; GSK-3 $\beta$ , Glycogen synthase kinase-3 $\beta$ ; TG, triglyceride; TK, tyrosine kinase; PI3K, phosphatidylinositol 3 kinase; IRS-1, insulin receptor substrate-1; GLUT2, glucose transporter protein 2; Akt, serine/threonine protein kinase; GLUT4, glucose transporter protein 4; IL-1 $\beta$ , interleukin-1 $\beta$ ; TNF- $\alpha$ , tumor necrosis factor; IL-6, interleukin-6; NF- $\kappa$ B, nuclear factor kappa-B; AGEs, advanced glycation end-products; sRAGE, soluble receptor of advanced glycated end product.

and atorvastatin to regenerate distal tubules and delay renal tissue changes.<sup>6</sup> Overall, CoQ-based combinations are basically used in animal experiments but not in human trials, so their reliability needs to be further investigated.

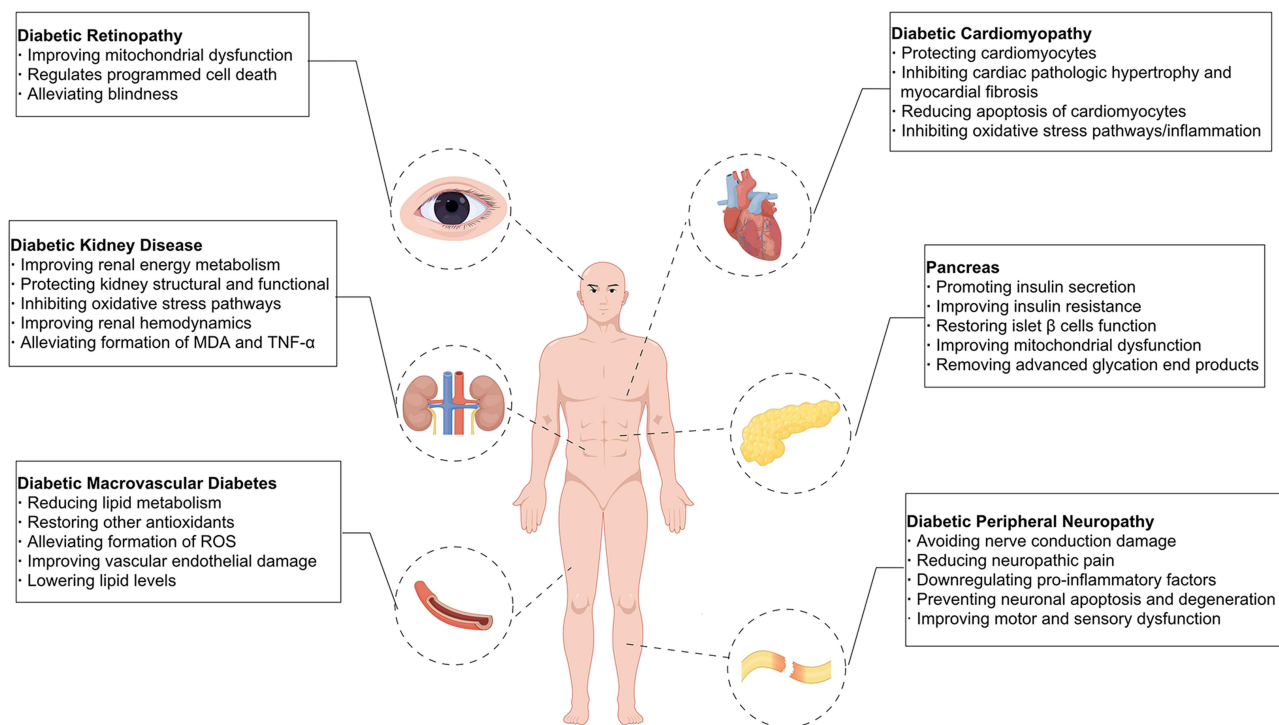
Beyond these combinations, stimulating CoQ synthesis *in vivo* may present a relatively novel therapeutic approach. A recent study suggests that tocotrienols can scavenge excess free radicals in T2DM mice by inducing CoQ biosynthesis, thus exerting an antioxidant role and ultimately mitigating renal structural and functional damage.<sup>40</sup> Similarly, another study has demonstrated that L-Carnosine can significantly reduce proteinuria by stimulating the expression of the CoQ gene and enhancing renal vascular permeability, thereby improving renal function in DKD mice.<sup>41</sup>

Given the relatively poor bioavailability and intestinal absorption of CoQ, the induction of CoQ synthesis *in vivo* for the treatment of DKD may yield promising results. However, further studies are necessary to fully elucidate the mechanisms involved and to optimize the therapeutic regimens. These advancements in the field of DKD treatment hold the potential to significantly improve the quality of life for patients suffering from this chronic condition.

## CoQ and Diabetic Retinopathy

Diabetic retinopathy (DR) is a microvascular complication of DM and a significant cause of acquired blindness in diabetic patients.<sup>42</sup> The principal pathological changes associated with DR involve altered blood flow, enhanced vascular permeability, and retinal cell death. As DR progresses, neovascularization becomes unstable, predisposing individuals to vitreous hemorrhage and retinal detachment, ultimately leading to severe visual impairments.<sup>43</sup> Consequently, controlling the progression of DR is an effective strategy to mitigate blindness symptoms.

The retina is particularly sensitive to variations in CoQ concentrations due to lipid antioxidantation and its high metabolic demands.<sup>44</sup> Consequently, the progression of DR may be linked to CoQ deficiency. Pericyte apoptosis is a prominent feature of early DR, which has been linked to increased ROS production. Co-culture study with activated microglia have shown that this process significantly increases pericyte ROS production, whereas pretreatment with the antioxidant CoQ reduces ROS production and inhibits the decrease in mitochondrial membrane potential.<sup>45</sup> These findings suggest that CoQ supplementation may serve as an adjunct therapy to alleviate DR symptoms by reducing oxidative stress.



**Figure 3** Extensive effects of CoQ on diabetes and its associated complications.

**Abbreviations:** TNF- $\alpha$ , tumor necrosis factor; ROS, reactive oxygen species; MDA, malondialdehyde.

Clinical study has shown that administering 400 mg of CoQ alone can benefit patients by correcting oxidative and nitrosative stress, with even more significant improvements observed when combined with other antioxidant therapies.<sup>17</sup> However, CoQ alone does not appear to improve vision or intraocular pressure. These findings have been consistently supported by other researches.<sup>46</sup> On the other hand, a mixture of lutein and zeaxanthin has been observed to improve visual acuity and foveal thickness.<sup>46</sup> Combining this mixture with CoQ may yield unexpected and potentially synergistic benefits. These findings suggest a favorable impact of the oral antioxidants as adjuncts in enhancing antioxidant systems in hyperglycemic conditions. Thus, the combined use of CoQ with other antioxidants may represent a potential therapeutic strategy for DR in the future.

Moreover, recent research has implicated programmed cell death mechanisms, such as ferroptosis, are implicated in the pathogenesis of DR.<sup>47</sup> Yang et al further investigated the ferroptosis pathway in retinal pigment epithelial cell degeneration. They discovered that over-expression of ferroptosis suppressor protein 1 (FSP1) effectively protected cells from sodium iodate-induced injury, which was accompanied by significant down-regulation of CoQ10/NADH and lipid peroxidation, ultimately alleviating retinal dysfunction.<sup>48</sup> However, whether CoQ can also attenuate DR by regulating other cell death pathways remains to be further explored and confirmed, potentially opening new avenues for identifying treatment targets for DR.

## CoQ and Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy (DPN) is one of the microvascular complications of DM. It is estimated that more than half of DM patients develop DPN, which is more prevalent than nephropathy and retinopathy.<sup>49</sup> DPN is a crucial risk factor for lower limb amputation and disability in later stages,<sup>50</sup> significantly affecting patients' prognosis and quality of life. Inflammation, oxidative stress, and mitochondrial dysfunction, all induced by hyperglycemia, are pivotal pathogenic mechanisms underlying DPN.<sup>51,52</sup> Consequently, therapies targeting these mechanisms may offer a potential avenue for treating DPN.

Existing evidence suggests that CoQ is effective in alleviating DPN-related symptoms and delaying disease progression.<sup>53</sup> In animal study, pretreatment with CoQ has been shown to attenuate mechanical hypersensitivity, decrease the expression of the stress factor, and down-regulate pro-inflammatory factors, ultimately mitigating inflammation and neuropathic pain symptoms.<sup>10</sup> Furthermore, long-term (six months) oral CoQ intervention in T2DM mice has been demonstrated to prevent late-onset hyperalgesia by counteracting the loss of dorsal root ganglion (DRG) neurons through anti-apoptotic mechanisms. This intervention also prevents the decline of phospholipase C $\beta$ 3 expression in DRG neurons, thereby minimizing nerve conduction damage.<sup>9</sup> However, it is noteworthy that the profound preventive effect observed in this study may stem from the administration of CoQ during elevated blood glucose levels, suggesting that early clinical administration of CoQ may have unintended implications for neuropathic pain prognosis, which warrants further investigation.

Based on the current evidence, CoQ may be particularly beneficial for DPN treatment when combined with other drugs or administered as monotherapy at higher-than-usual doses.<sup>53,54</sup> A recent study has revealed that five weeks of oral treatment with a combination of CoQ (10 mg/kg) and  $\alpha$ -lipoic acid (100 mg/kg) reduced oxidative stress and lipid peroxidation, increased glutathione (GSH) levels and total antioxidant capacity (TAC), and modulated the expression of caspase 3 and uncoupling protein 2. This treatment effectively contained the apoptosis and degeneration of DRG neurons, ultimately leading to significant improvements in motor dysfunction in diabetic rats.<sup>15</sup> Building on these findings, clinical study has explored that CoQ as an adjunct therapy to pregabalin, may aid in improving pain intensity and sleep interference associated with painful diabetic neuropathy.<sup>23</sup> Hence, diabetic patients suffering from DPN may benefit from using antioxidant and anti-inflammatory supplements like CoQ, but further studies are required before supplementation with CoQ can be recommended as a treatment for DPN.

Despite these promising findings, a large number of controlled clinical studies are required to firmly establish the beneficial effects of CoQ in DPN patients. Such studies would provide invaluable insights and guidance for the treatment of DPN.

## CoQ and Diabetic Cardiomyopathy

Diabetic Cardiomyopathy (DCM) is one of the common complications of DM. It is typically defined as damage to the structure and function of the heart that occurs in DM patients in the absence of other cardiovascular diseases, such as



coronary artery disease, uncontrolled hypertension, severe valvular heart disease and congenital heart disease.<sup>55</sup> The pathophysiological mechanisms underlying DCM include myocardial hypertrophy, myocardial fibrosis, and impaired coronary microvascular perfusion.<sup>56</sup> However, its pathogenesis has not been thoroughly investigated.

Myocardial tissue contains the highest concentration of CoQ. Nevertheless, hyperglycemia leads to lipid overload, which severely depletes CoQ, resulting in mitochondrial dysfunction and decreased resistance to oxidative stress, eventually inducing myocardial injury.<sup>57</sup> This suggests that CoQ deficiency may be closely associated with the development of DCM.

CoQ can improve structural and functional changes in the DCM heart. Previous study has demonstrated that ten weeks of continuous CoQ supplementation (10 mg/kg) reduced hyperglycemia-induced oxidative stress and superoxide production, ameliorated left ventricular diastolic dysfunction, and reduced cardiomyocyte hypertrophy, fibrosis, and apoptosis in T2DM mouse model.<sup>14</sup> Also in another animal experiment, after eight weeks of CoQ supplementation at a dosage of 10 mg/kg, there was a notable reduction in the expression of atrial natriuretic peptide, connective tissue growth factor, and  $\beta$ -myosin heavy chain, in addition to the aforementioned effects.<sup>13</sup> Additionally, CoQ may protect against fibrosis and cardiac remodeling by lowering cardiac markers. A recent study showed that CoQ administration improved biomarkers in hyperglycemic rats, including serum adipokines (omentin, resistin, and TNF- $\alpha$ ) and cardiomyopathy markers (cardiac troponin I and creatine kinase isoenzymes).<sup>12</sup>

Given these findings, chronic CoQ supplementation may serve as an attractive adjunctive therapy for diabetic heart failure. However, the evidence from clinical studies is relatively limited, which may be attributed to the challenges in screening for this condition or the relatively small sample sizes of these studies. Therefore, its efficacy and safety remain to be thoroughly investigated.

Recently, new molecular targets and genes related to DCM have been continuously discovered. Gomes et al observed down-regulation of the atypical kinase COQ8A, an essential fat-soluble electron transport protein involved in the biosynthesis and electron transport process of CoQ, in the left ventricle of T2DM mice using proteomic analysis.<sup>58</sup> Therefore, promoting endogenous CoQ synthesis by upregulating COQ8A expression may be an effective therapeutic strategy for treating DCM. Furthermore, endothelin-1 (ET-1) is a crucial gene for DCM and has the potential to serve as a biomarker for DCM.<sup>59</sup> An early study demonstrated that CoQ prevented nucleoside reverse transcriptase inhibitor-induced elevation of ET-1 levels.<sup>60</sup> Therefore, the question of whether CoQ can treat DCM by regulating ET-1 expression needs to be further explored and investigated. Collectively, these findings have the potential to provide novel insights into the molecular mechanisms underlying DCM and may lead to the development of new therapeutic targets.

## CoQ and Diabetic Macrovascular Disease

The pathophysiology of diabetic macrovascular disease primarily involves cardiac, cerebral, and peripheral macrovascular complications, encompassing atherosclerosis, thrombosis, IR, and inflammation.<sup>61</sup> This condition stands as the leading cause of mortality and disability among patients with DM.<sup>62</sup> Its significant impact on patients' quality of life underscores the critical need for rigorous glycemic control.

The pathogenesis of macrovascular diseases in diabetes exhibits similarities to that of diabetic microvascular diseases, such as retinopathy, nephropathy, and microvascular lesions. Notably, macrovascular diseases, including cardiovascular disease and peripheral artery disease, have been shown to increase the flux of free fatty acids released from the adipose tissue into the endothelial cells. This, in turn, elevates ROS production, ultimately inducing endothelial dysfunction,<sup>63</sup> which is a pivotal factor in the development of diabetic macrovascular disease. Fortunately, CoQ supplementation has been shown to counteract this endothelial damage.<sup>22,64</sup> Tsai et al further discovered that CoQ reduced high glucose-induced endothelial progenitor cell (EPC) apoptosis and dysfunction by up-regulating of endothelial nitric oxide synthase (eNOS) and heme oxygenase-1 through the adenosine monophosphate-activated protein kinase (AMPK) pathway.<sup>16</sup> This finding presents potential therapeutic strategy aimed at targeting dysfunctional EPCs in diabetic patients. Additionally, CoQ restores other antioxidants, such as  $\alpha$ -tocopherol, further bolstering its ability to counteract lipid peroxidation and oxidative stress,<sup>65</sup> providing a new perspective for the treatment of the diabetic macrovascular disease.

Building on these findings, recent human studies have further investigated the therapeutic potential of CoQ. A meta-analysis incorporating 12 randomized controlled trials revealed that dietary supplementation with CoQ increases TAC,

improves vascular tone and endothelial function, and lowers total cholesterol and low-density lipoprotein (LDL) levels, collectively reducing the risk of cardiovascular disease in diabetic patients.<sup>66</sup> It is noteworthy that most of the randomized controlled trials in this study had a duration of three months or less. Nevertheless, as a dietary supplement, the long-term intervention of CoQ on diabetic patients with cardiovascular diseases is also worthy of exploration, which is crucial for prolonging the lifespan of diabetic patients. And the beneficial effect of CoQ in improving lipid levels or cardiometabolic risk factors in diabetic patients may be related to its increased intracellular antioxidant response. A systematic review demonstrated that short-term intake of various dietary supplements, including CoQ, could potentially enhance cardiometabolic function by elevating plasma GSH levels, as well as reducing blood pressure and LDL-cholesterol levels.<sup>67</sup>

Studies have demonstrated that a decrease in serum CoQ levels is directly correlated with a reduction in LDL cholesterol.<sup>66,67</sup> Conversely, an increase in high-density lipoprotein cholesterol (HDL-C) may serve as a potential strategy to maintain or elevate serum CoQ levels.<sup>68</sup> Further research is required to clarify the relationship between CoQ and HDL subfractions to identify the primary carrier of CoQ during fluctuations in cholesterol levels. This lipid-modulating effect reinforces the potential of CoQ in the management of diabetic macrovascular disease, as dyslipidemia is a significant risk factor for cardiovascular events in diabetes. While CoQ shows promise as an adjunctive therapy for diabetic macrovascular disease, further well-designed and controlled clinical trials are essential to definitively establish its therapeutic role.

## Summary and Future Prospects

The review concludes the potential of CoQ as a therapeutic agent in managing DM and its complications. Traditional treatments for DM, including glycemic control through oral hypoglycemic agents, often result in adverse effects and fail to adequately reverse complications, prompting the need for more effective therapies.

Although a large amount of literature has proven CoQ supplementation can improve insulin sensitivity, reduce insulin resistance, and ameliorate the progress of DKD, DPN and DCM, much of the evidence supporting the efficacy of CoQ in DM management comes from animal studies, with limited clinical data available. The clinical studies that do exist often vary in terms of dosage, duration, and patient populations, leading to inconsistent results. Thus, while CoQ presents a promising therapeutic option for DM and its complications, further research, particularly well-designed clinical trials, is necessary to confirm its efficacy and establish optimal treatment protocols.

Given the promising results from preclinical studies, future research should focus on large-scale, randomized controlled trials to validate the effectiveness of CoQ in humans. These studies should aim to standardize CoQ dosages and treatment durations to determine the most effective therapeutic regimen. Additionally, exploring the potential of CoQ in combination with other therapeutic agents could provide more comprehensive management strategies for DM and its complications. Another area worth exploring is the stimulation of endogenous CoQ synthesis. Genetic or pharmacological interventions that enhance CoQ production within the body could offer a novel approach to managing DM, particularly in patients with CoQ deficiencies. For instance, targeting specific genes like COQ8A or using compounds that induce CoQ biosynthesis could lead to more effective treatments. Furthermore, improving the bio-availability and intestinal absorption of CoQ remains a critical challenge. Future research should investigate advanced delivery systems or synthetic vehicles, such as micelles, nanoparticles and liposomal formulations, to enhance CoQ's therapeutic potential. Additionally, combining CoQ with other antioxidants or anti-inflammatory agents may enhance its effectiveness in treating DM-related complications.

Overall, while CoQ shows significant potential as a therapeutic agent for DM, further research is essential to fully understand its mechanisms of action and optimize its use in clinical practice. This could ultimately lead to more effective and tailored treatments for DM, improving patient outcomes and quality of life.

## Abbreviations

DM, diabetes mellitus; CoQ, coenzyme Q; IR, insulin resistant; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; SMPD5, sphingomyelin phosphodiesterase 5; PEMT, phosphatidylethanolamine N-methyltransferase; ROS, reactive oxygen species; HOMA-IR, homeostasis model assessment of insulin resistance; AGEs, advanced glycation end-

products; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; DKD, diabetic kidney disease; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; DR, diabetic retinopathy; FSP1, ferroptosis suppressor protein 1; DPN, diabetic peripheral neuropathy; DRG, dorsal root ganglion; GSH, glutathione; TAC, total antioxidant capacity; DCM, diabetic cardiomyopathy; ET-1, endothelin-1; EPC, endothelial progenitor cell; AMPK, adenosine monophosphate-activated protein kinase; LDL, low density lipoprotein; HDL-C, high density lipoprotein-cholesterol; eNOS, endothelial nitric oxide synthase.

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