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Review

Review on the mechanisms of the effects of coenzyme Q10 supplementation on serum levels of leptin and adiponectin

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Abstract

Coenzyme Q10 (CoQ10) is a fat-soluble benzoquinone structurally similar to vitamin K, which acts as an antioxidant in scavenging free radicals and inhibiting lipid and protein oxidation. It has been reported that CoQ10 deficiency is linked to multiple chronic diseases. The current study aimed to review the effects of coenzyme Q10 on serum levels of leptin and adiponectin, their ratio and their role in future treatment strategies. We extended the literature search for all relevant articles published in English from the database, including PubMed, Scopus and Google Scholar, until September 2022. CoQ10 plays a protective role against the release of proinflammatory markers and provides an attractive anti-inflammatory therapeutic for treating some human diseases. It has been shown that there is a positive and negative correlation between CoQ10 and adiponectin and between levels of leptin and CoQ10, respectively. Studies showed that CoQ10 supplementation causes an increase in the value of the adiponectin/leptin ratio. In summary, taking medications such as CoQ10 supplements is recommended as a potential therapeutic target to increase adiponectin levels and modulate the effects of oxidative stress.

Keywords: coenzyme Q10, antioxidant, oxidative stress, adiponectin, leptin.

Introduction

Coenzyme Q10 (CoQ10) is a fat-soluble benzoquinone that acts as an antioxidant in scavenging free radicals and inhibiting lipid and protein oxidation [1]. Normal blood ranges of CoQ10 are 0.7 to 1.0 μg/mL [2]. CoQ10 is essential for the energy production process in mitochondria, and this coenzyme is produced by most human cells [3]. Studies have shown that CoQ10 deficiency is linked to the incidence of diseases such as cancer, diabetes mellitus, heart disease, hypertension, liver disease, decreased immune function and periodontal disease [2, 3]. Recent studies have shown the beneficial effects of CoQ10 supplementation in type 2 diabetes mellitus (T2DM), cardiovascular diseases, huntington disease, metabolic syndrome, kidney disease, inflammation, neurodegenerative diseases and human infertility [3, 4]. CoQ10 reduces oxidative stress [1], and its reduced form acts as an antioxidant that inhibits the function of free radicals [2], inhibits lipid peroxidation, and protects biological membranes from oxidation [5]. It also has potential beneficial effects in increasing neuroprotection and reducing inflammation [5]. The clinical application of CoQ10 in inhibiting and treating metabolic syndrome and T2DM has been investigated [6, 7]. CoQ10 supplementation may be beneficial for the prevention of some metabolic complications [7]. In addition, CoQ10 administration may improve markers of insulin resistance through the modulation of insulin and adiponectin receptors [1].

Adipose tissue affects body metabolism through the secretion of several hormones with specific physiological roles in the body, including adipokines leptin and adiponectin [8]. Adiponectin, a well-known adipokine, is exclusively secreted by white adipose tissue with the greatest plasma concentration among

adipokines [8, 9] and plays a key role in the modulation of lipid metabolism, fatty acid oxidation, carbohydrate metabolism and insulin sensitivity [8]. Adiponectin is also an anti-inflammatory cytokine with anti-atherogenic and cardioprotective effects [1].

Leptin is secreted originally from the adipocytes and is thought to be an anti-obesity hormone [5, 10]. Recent studies have shown that leptin abundance or deficiency is directly related to nutritional status. Serum levels of leptin are also associated with diseases caused by obesity [10]. Because leptin modulates food intake and energy homeostasis, many studies have confirmed a strong association between reduced leptin production and obesity [5].

In metabolic syndrome disorders, adipocytokine adiponectin has anti-inflammatory, lipid-lowering and insulin-sensitizer properties, while adipocytokine leptin induces insulin resistance and inflammation [8, 9]. Because these adipocytokines have opposite metabolic effects, the adiponectin/leptin ratio and the leptin/adiponectin ratio have been proposed as negative and positive risk factors for metabolic diseases, respectively [11].

Potential strategies for treating disorders associated with decreased adiponectin levels and improving blood circulation are suggested, including lifestyle changes, dietary adjustments and some supplements [11].

In addition, the adiponectin/homeostatic model assessment insulin resistance (HOMA-IR) (A/H) ratio and the adiponectin/leptin (A/L) ratio have been introduced as reliable biomarkers of insulin resistance [11].

This study aimed to review the effects of coenzyme Q10 on serum levels of leptin and adiponectin, their ratio and their role in future treatment strategies.

Search strategy

This study was approved by the Ethics Committee of Arak University of Medical Sciences, Arak, Iran (Approval ID: IR.ARAKMU.REC.1400.264). The last time of the search was performed on September 2022. We extended the literature search for all relevant articles from the database, including PubMed, Scopus and Google Scholar. Our search was restricted to studies published just in the English language. In our search strategy, the keywords used to search in the above databases in titles and abstracts included coenzyme q10, CoQ10, ubiquinone, ubiquinol-10, ubidecarenone, leptin, adiponectin, adiponectin to leptin ratio, diabetes, type 2 diabetes, T2DM, diabetes mellitus.

Eligibility criteria

Clinical trial studies were included in our search with the following inclusion criteria:

1. Clinical trial studies investigating the effects of CoQ10 on serum levels of adiponectin and leptin;
2. Placebo-controlled, randomized with a crossover design or parallel;
3. Intervention in the target and control groups with supplementation of CoQ10 and placebo, respectively.

Studies were excluded if they were: 1) without a placebo group; 2) without intervention or nonclinical trials and 3) duplicate studies [8].

Data extraction and quality assessment

The authors independently evaluated articles for eligibility, titles, and abstracts for the present study. The authors subsequently independently reviewed the full text of the articles. The information and mechanisms related to the purpose of the study were extracted from eligible articles.

As a whole, the information regarding the most important human studies is presented in Table 1.

Table 1: Data from clinical trial studies evaluating the effects of CoQ10 supplementation on inflammation and oxidative stress.

First author (reference no)	Participants	N (participants)	CoQ10	Duration	Results
Gholami et al. [20]	Women with T2DM	68 (34/34)	100 mg/day	12 weeks	Serum values of adiponectin and the A/L ratio were increased, while values of leptin were decreased significantly in the CoQ10 group after the intervention.

Table 1: Continued.

First author (reference no)	Participants	N (participants)	CoQ10	Duration	Results
Bagheri et al. [31]	Patients with mildly hypertensive	60 (30/30)	100 mg/day	12 weeks	Significant increase in circulating adiponectin and Significant declines in the median of IL6, hs-CRP in the intervention group compared with the placebo group and no significant statistical changes in TNF-α and IL2.
Farsi et al. [32]	Patient with NAFLD	42 (21/21)	100 mg/day	12 weeks	Significant decrease in hs-CRP and TNF-α. In addition, intervention group had higher serum levels of adiponectin compared with the placebo group.
Moazen et al. [33]	People with T2DM	52 (26/26)	100 mg twice a day	8 weeks	That adiponectin levels showed no significant differences in both groups.
Gökbel et al. [34]	Sedentary men	14 (7/7)	100 mg/day	8 weeks	Coenzyme Q10 supplementation did not affect plasma adiponectin, IL-6, and TNF-α levels in sedentary men.

Association between adiponectin and oxidative stress

Studies have shown that conditions such as metabolic syndrome can cause changes in adipose tissue. With the development of obesity and insulin resistance, the levels of malondialdehyde (MDA) in plasma and adipose tissue are increased, indicating an increase in oxidative stress in the body [12].

In rats with metabolic syndrome, apocynin, an inhibitor of NADPH oxidase (NOX), decreases MDA levels in white adipose tissue. On the other hand, with increasing NOX activity, the amount of reactive oxygen species (ROS) increases. Studies have also shown that not only NOX but also adipocyte mitochondria can be a source of ROS production. Studies have also shown that increased lipid peroxidation not only increases ROS production but also decreases antioxidant protection. Mechanisms related to oxidative stress have been shown to reduce the activity of superoxide dismutase and glutathione peroxidase enzymes and also increase ROS [12].

There is a direct relationship between chronic stress, oxidative stress and changes in adipose tissue and, ultimately, the development of Metabolic Syndrome [12]. Following lipid peroxidation in susceptible individuals with metabolic syndrome, the level of MDA increases up to 32% and the leptin level is doubled compared to healthy individuals. At the same time, the concentration of adiponectin is decreased [12]. Both hormones, leptin and adiponectin, are synthesized by adipocytes. In experiments performed on pre-fat mice, it has been shown that oxidative stress leads to reduce adiponectin secretion. Experiments have shown that ROS reduces the expression of adiponectin and increases the expression of tumor necrosis factor α (TNFα) and interleukin 6 (IL-6) [12]. On the other hand, it has been found that exposure of adipose tissue cells to oxidative stress causes an increase in the mRNA levels of leptin, IL-6 and monocyte chemoattractant protein 1(MCP-1) and an increase in the secretion of these proteins by adipocytes [13–15]. Therefore, oxidative stress promotes increased synthesis and secretion of leptin, MCP-1, TNF-α and IL-6 and reduces adiponectin production by adipocytes [12].

To exert its biological effects, adiponectin must bind to its specific receptors. The AdipoR1 receptor, AdipoR2 and T cadherin receptors are members of the AdipoQ and progestin receptor superfamily [16]. AdipoR1 receptor is mainly expressed in skeletal muscles and AdipoR2 in the liver and pancreatic beta cells. Subsequently, expression of the R2 receptor has been identified in other tissues such as the adipose tissue, macrophages, brain tissue, endothelial cells,

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myocardium and lymphocytes [17–19]. The expression levels of these receptors are inversely correlated with obesity and body fat [19].

Obesity-induced oxidative stress and inflammation inhibit adiponectin secretion [16]. In cultured kidney podocytes, administration of adiponectin was associated with increased AMP-activated protein kinase (AMPK) activity. It has been shown that adiponectin has beneficial effects on the kidneys due to its antioxidant activities. Studies have shown that adiponectin in diabetic nephropathy reduces oxidative stress through the AMPK pathway [16]. Adiponectin does this by suppressing the activity of NOX4, an abundant oxidase in the kidneys [16, 17].

Adiponectin and its mechanisms for a therapeutic role

Adiponectin is considered a therapeutic target for T2DM and metabolic syndrome. Decreased serum adiponectin levels are predominant in prediabetes. Low levels of adiponectin predict insulin resistance and T2DM. As a result, a normal concentration of adiponectin or even an increase in it will be beneficial [18, 20]. Researchers claim that higher adiponectin concentrations play an important role in protecting against the risk factors for T2DM [18]. Studies have shown that circulating adiponectin levels are lower in individuals with diabetes, insulin resistance, hypertension and obesity. In addition, many studies indicate that adiponectin level strongly predicts metabolic syndrome and diabetes in both men and women [19, 21].

Adiponectin is known to be a key regulator through the activation of peroxisome proliferator-activated receptors (PPARs) and AMPK in skeletal muscle and liver [18]. The effects of adiponectin are through the following mechanisms:

1. In skeletal muscles, adiponectin reduces fat content and improves insulin sensitivity via increasing fatty acid oxidation. It also enhances triglyceride catabolism, mitochondrial biogenesis and fatty acid uptake [18];
2. Adiponectin enhances the expression of PPARα regulated genes such as acyl-CoA oxidase, cluster of differentiation 36 (CD36) and uncoupling protein 2 [18];
3. Adiponectin increases fatty acid combustion reactions, PPAR- α activity and energy consumption. It also lowers triglyceride levels in muscle and liver [22];
4. Adiponectin also regulates the expression of hepatic genes critical for fat metabolism by modulating the acetyl CoA carboxylase (ACC) activity and the AMPK pathway [23];
5. Adiponectin increases glucose uptake and fat oxidation by activating AMPK and inhibiting the ACC [24];
6. In adipose tissue, AMPK activation reduces PPARγ expression and thereby reduces lipolysis, which results in TNF-α and IL-6 secretion reduction while adiponectin secretion increases [25];
7. AMPK activation has been shown that leads to decreasing cholesterol and triglyceride synthesis and increasing fatty acid oxidation in animals and humans [26, 27];
8. Adiponectin has been shown to suppress nuclear factor-κB (NF-κB) via inhibiting monocyte adhesion to endothelial cells and subsequently inhibits TNF-α expression (Figure 1) [28, 29].

CoQ10 supplementation mechanism in the modulating of oxidative stress and inflammatory biomarkers

Oxidative stress and chronic inflammation are typical components of age-related diseases such as T2DM, cancer, cardiovascular, and neurodegenerative diseases, including Parkinson's and Alzheimer's disease [30].

Coenzyme Q10 is an important component of the electron transport chain in the mitochondria, which is involved in the synthesis of ATP. It also acts as a powerful antioxidant that quenches free radicals in cell membranes and mitochondria [31–34].

Adiponectin is a collagen-like protein released by adipose tissue. Several anti-inflammatory mechanisms have been proposed for adiponectin, including a direct effect on inflammatory cells, interaction with TNF-α and actions on NF-κB [29]. Adiponectin can inhibite TNF-α- induced monocyte adhesion and the production of ROS in neutrophils [29]. It also stimulates the release of the anti-inflammatory cytokine IL-10 from macrophages and the activation of NF-κB in macrophages and adipocytes [29].

Studies have shown that serum adiponectin levels had an inverse relationship with body weight, insulin resistance and body mass index (BMI) [8].

A study has shown a positive correlation between CoQ10 and adiponectin in T2DM [20]. Oxidative stress situation can suppress adiponectin gene expression [35]. On the other hand, it has been stated that CoQ10

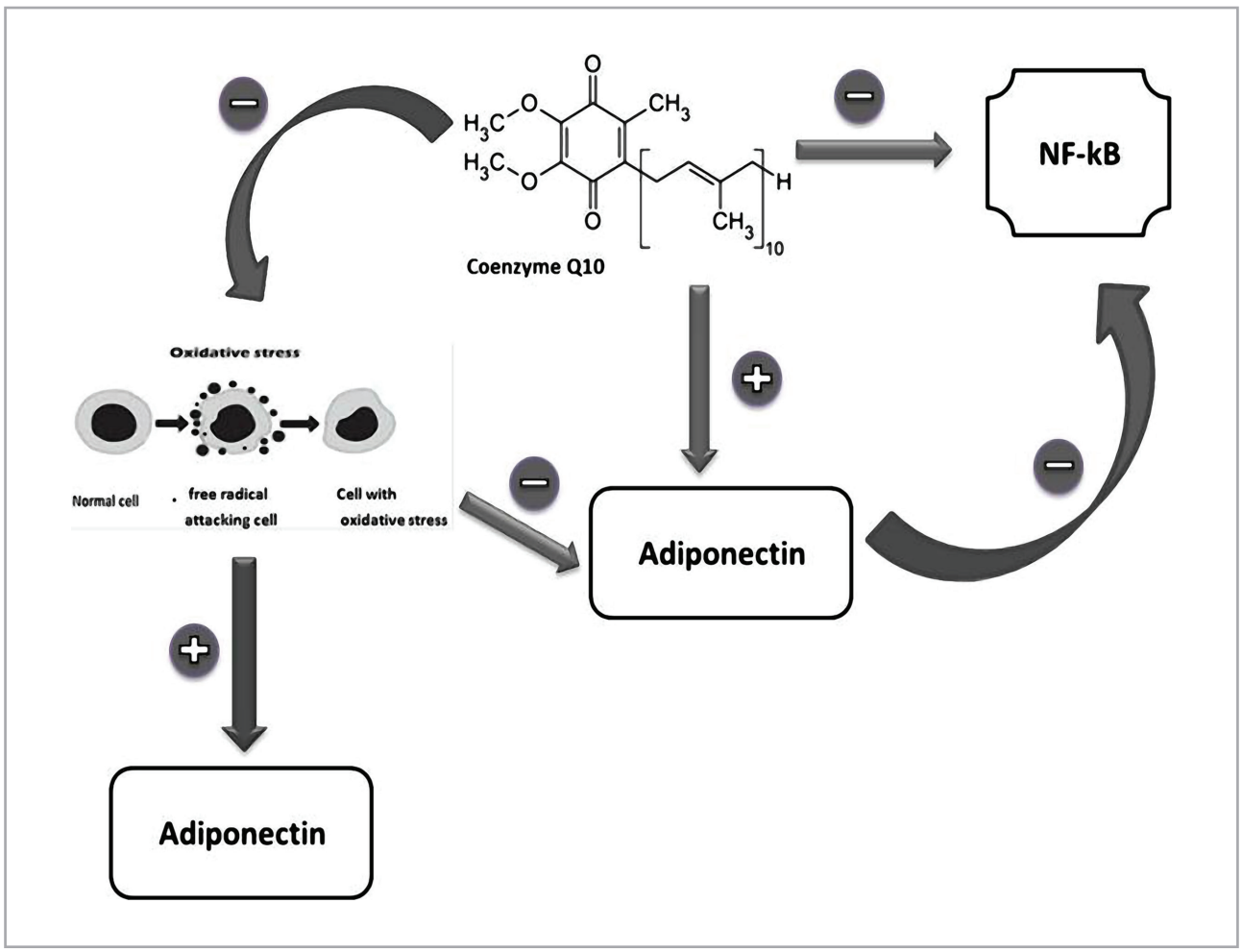

Figure 1: CoQ10 supplementation increases circulating levels of adiponectin and reduces oxidative stress and inflammation by suppressing nuclear factor-κB (NF-κB).

can suppress oxidative stress via suppression of ROS production and it is the proposed mechanism of CoQ10 action for adiponectin mRNA expression induction [32]. In order to confirm this mechanism, positive effects of vitamin E [9] and sesamin [35] have been observed in the production of adiponectin which is related to their antioxidant properties.

The elevation in circulating levels of adiponectin by nutritional supplementation and/or lifestyle change can prevent the progression of diabetes by promoting the survival and function of beta cells and also can have therapeutic effects, especially in insulin resistance situations [9, 20].

The role of leptin is to body weight controlling by regulating food intake and energy consumption [29]. Leptin has pro-inflammatory properties and increases NOX activity through monocyte proliferation, leading to increased oxidative stress [36, 37]. Oxidative stress can activate nuclear factor NF- kB, which leads to increased gene expression of proinflammatory cytokines. It has been observed that CoQ10 has an anti-inflammatory function via the reduction of NF-kB gene expression. CoQ10, as an antioxidant, can trap free radicals and inhibit the activation of NF-kB [38, 39]. It has been shown that leptin levels are decreased in the CoQ10 group after intervention in T2DM (Figure 2) [20].

The adiponectin/leptin ratio and the leptin/adiponectin ratio have been proposed as negative and positive risk factors for metabolic diseases because these adipocytokines have opposite metabolic effects [11]. The adiponectin/leptin ratio has been reported as a reliable biomarker of insulin resistance [20]. It has also been reported that the adiponectin/leptin ratio is more closely related to insulin resistance than adiponectin, leptin alone or even the HOMA-IR index. This ratio indicates the function of adipose tissue and a decrease in this ratio is associated with an increase in the number of metabolic risk factors [39]. If the ratio decreases, it will increase insulin resistance, oxidative stress and inflammation, which are hallmarks of metabolic syndrome [40]. A Study found that CoQ10 supplementation can cause an increase in the adiponectin/leptin ratio [20].

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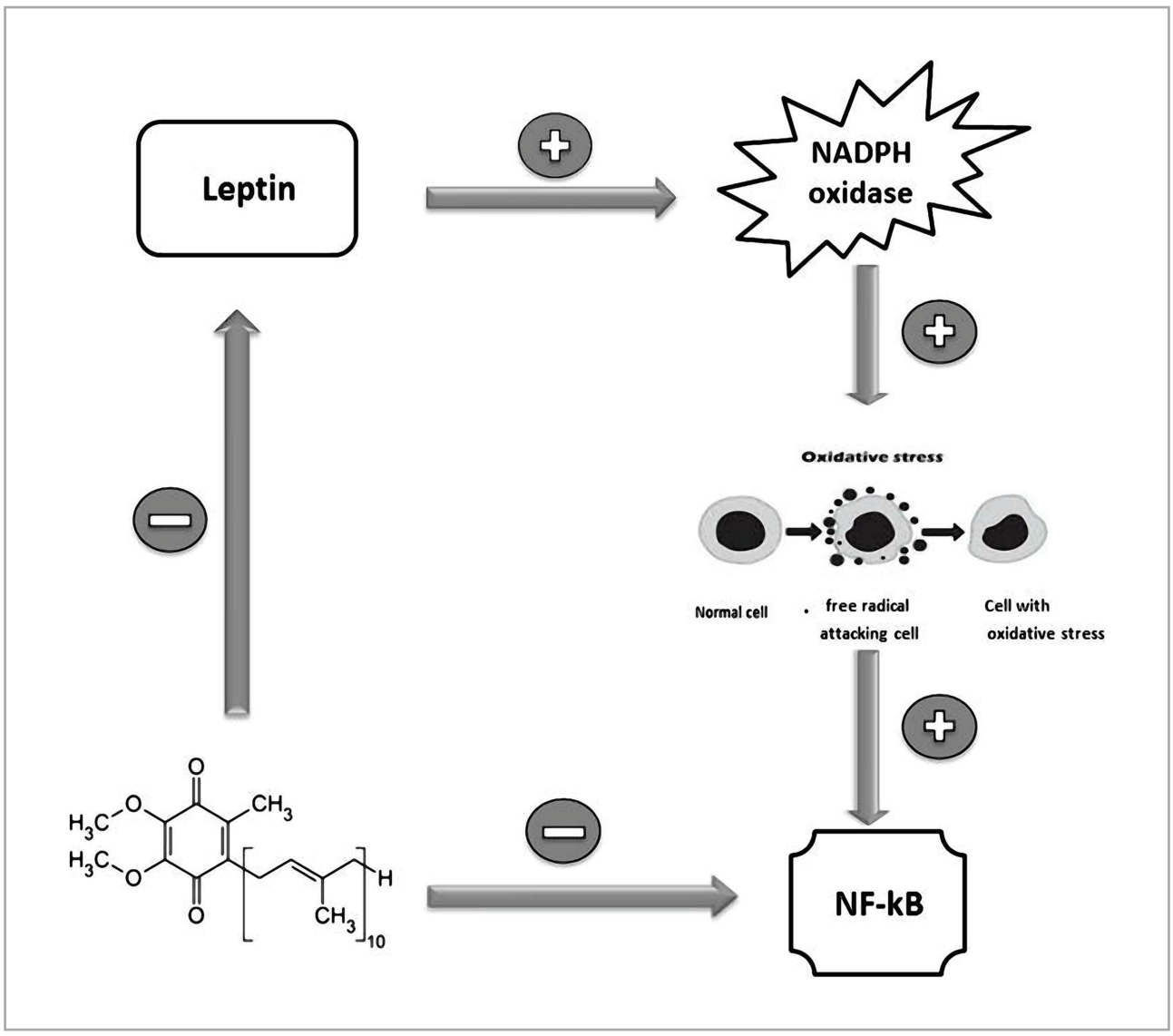

Figure 2: Leptin increases oxidative stress and inflammation by activating nuclear factor-κB (NF-κB). CoQ10 supplementation decreases circulating levels of leptin and NF-κB.

It has been reported that women with gestational diabetes have lower adiponectin values and higher leptin and the leptin/adiponectin ratio compared with normal pregnant women. The higher values of the leptin/adiponectin ratio are directly associated with a higher risk of gestational diabetes during pregnancy and a higher risk of cardiovascular diseases after pregnancy [40].

In the development of the metabolic syndrome, decreased adiponectin signaling or adiponectin levels may serve as an upstream pathway of increased oxidative stress and inflammation [6].

A negative correlation has been reported between adiponectin and oxidative stress markers [40]. It has been shown that serum adiponectin levels are correlated negatively with oxidative stress [41]. In addition, oxidative stress in the adipose tissue reduces adiponectin levels [41]. These data suggest that oxidative stress reduces adiponectin levels, which in turn contributes to obesity-associated disease pathogenesis. Oxidative stress is enhanced in AdipoR1- and AdipoR2-deficient rats, which provides evidence that the adiponectin-AdipoR pathway contributes to the suppression of oxidative stress [41].

In a myocardial infarction/reperfusion model, adiponectin plays a protective role against oxidative stress-induced myocardial damage. Adiponectin may decrease oxidative/nitrative stress by inhibiting inducible nitric oxide synthase and suppressing the expression of $gp91^{phox}$, an NADPH oxidase subunit, in an AMPK-independent manner. Similar effects of adiponectin have also been observed in the endothelium. Adiponectin can suppress oxidative/nitrative stress in the arteries of hyperlipidemic rats. In addition, adiponectin exerts cardioprotective effects against the

oxidative stress-induced remodeling processes in cardiomyocytes by activating AMPK and inhibiting extracellular signal-regulated kinases and NF-κB [41].

Recent evidence considers CoQ10 as an agonist of PPARs. For this reason, the anti-inflammatory feature of CoQ10 can be regarding to activate the PPAR-mediated anti-inflammatory response [5].

Conclusions

Interestingly, studies show that CoQ10 supplementation in individuals with metabolic syndrome lowers leptin levels and increases adiponectin levels compared to placebo ones.

Extensive evidence has shown the anti-atherosclerotic, anti-diabetic and anti-inflammatory activities of adiponectin. Adiponectin gene expression is influenced by several factors, including PPAR-γ, mainly expressed in adipose tissue and is considered the main positive regulator of adiponectin gene expression. In contrast, inflammatory factors such as TNF-α inhibit adiponectin gene expression. CoQ10supplementation can increase the PPAR-γ gene expression and greatly reduce the effect of TNF-α on PPAR-γ. Leptin increases oxidative stress and inflammation by activating NF-κB. Consumption of CoQ10 decreases circulating levels of leptin and NF-κB caused by oxidative stress. The adiponectin/leptin ratio has been proposed as a negative risk factor for metabolic diseases and CoQ10 supplementation can cause an increase in the ratio. In addition, elevated adiponectin levels reduce the risk of some diseases, including metabolic syndrome. Therefore, CoQ10 supplementation can be considered a potential therapeutic target. Although more studies are needed to draw definitive conclusions, the current results suggest that adiponectin may be an important pathway and target of CoQ10 for improving lipid and glucose metabolic disorders.

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Conflict of interest

The authors declare no conflict of interest.

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