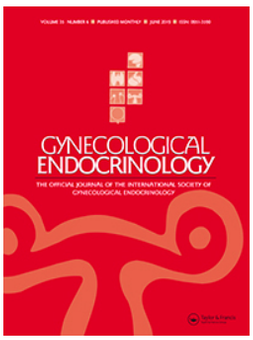

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Potential roles of carnitine in patients with polycystic ovary syndrome: a systematic review

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ABSTRACT

Polycystic ovary syndrome (PCOS) is recognized as the most prevalent endocrinopathy in reproductive-aged women. This systematic review was performed with focus on the current knowledge on carnitine concerning metabolic variables in PCOS. PubMed, Scopus, Embase, ClinicalTrials.gov and Google Scholar databases were searched from inception until May 2018. All clinical trials and observational studies published in English-language journals were eligible. Studies that provided insufficient outcomes, animal and *in vitro* studies were excluded. Out of 451 articles identified in our search, only six articles were eligible for analysis. Two observational studies evaluated the association of serum carnitine levels with metabolic variables, and four clinical trials examined the effect of carnitine supplementation in patients with PCOS. Serum carnitine levels had inverse relationship with glycemic status, body mass index (BMI) and waist circumference. Also, carnitine supplementation resulted in improved weight loss, glycemic status, oxidative stress, follicles and size of ovarian cells; no significant effects were reported on sex hormones and lipid profile. According to the current evidence, carnitine might improve weight loss, glycemic status and oxidative stress. However, to explore the exact mechanisms of carnitine role in patients with PCOS, further studies are recommended.

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Carnitine; polycystic ovary syndrome; glycemic status; oxidative stress

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinological abnormality in reproductive-aged women, with a prevalence of approximately 2–20% worldwide [1]. It is marked by hyperandrogenic anovulation and oligo-amenorrhea, leading to symptoms of hirsutism, acne, alopecia, increased androgens, irregular menstruation and infertility [2]. Although various factors including genetic, behavioral and environmental factors have been emerged in the pathophysiology of PCOS, the exact pathogenesis of the disease remains unexplored [3]. Hyperandrogenism caused by excess androgen production from ovaries is the key feature in PCOS [4]. Hyperandrogenism and insulin resistance have potential roles in evoking metabolic abnormalities, inflammation and oxidative stress. These lead to the development of obesity, type 2 diabetes (T2DM) and cardiovascular diseases in these patients [4,5]. Carnitine or 'b-hydroxy-g-N-trimethylamino-butyric acid' as an essential nutrient in β-oxidation of fatty acids, is the carrier of fatty acids across the inner mitochondrial membrane [6]. Animal foods including meat, fish, milk and dairy products are rich sources of carnitine; carnitine can also be synthesized from lysine and methionine in the liver and kidney [6,7]. Previously published studies have reported that carnitine supplementation may improve insulin sensitivity by increasing the rate of fatty acids oxidation, glucose metabolism and improvement of oxidative stress in patients with T2DM [8,9]. Carnitine as a shuttle, transfers acetyl groups from outside to inside of the mitochondrial membrane and decreases acyl-CoA to acetyl-CoA ratio, leading to improved lipid-induced insulin resistance through altering cell metabolism of glucose and lipids (Figure 1) [8,10]. Furthermore, recent studies have addressed carnitine insufficiency as a cause of developing insulin resistance during states of chronic metabolic stresses, such as T2DM and obesity [11,12]. In addition, sex steroids and their precursors are known to play a modulating role in carnitine turnover [13]. Also, there is an inverse correlation between estrogen and free carnitine levels in women [14]. Although several studies have investigated the role of carnitine in patients with PCOS, no comprehensive study has summarized the findings to increase our knowledge in this regard, thus far. The purpose of this systematic review was to highlight the available information on the correlation between carnitine and metabolic as well as hormonal status, and the effect of its supplementation in PCOS. Furthermore, exploring knowledge gaps and providing suggestions for future studies were addressed.

Methods

Search strategy

PubMed, Scopus, Embase, ClinicalTrials.gov and Google Scholar were searched using keywords including 'carnitine' or

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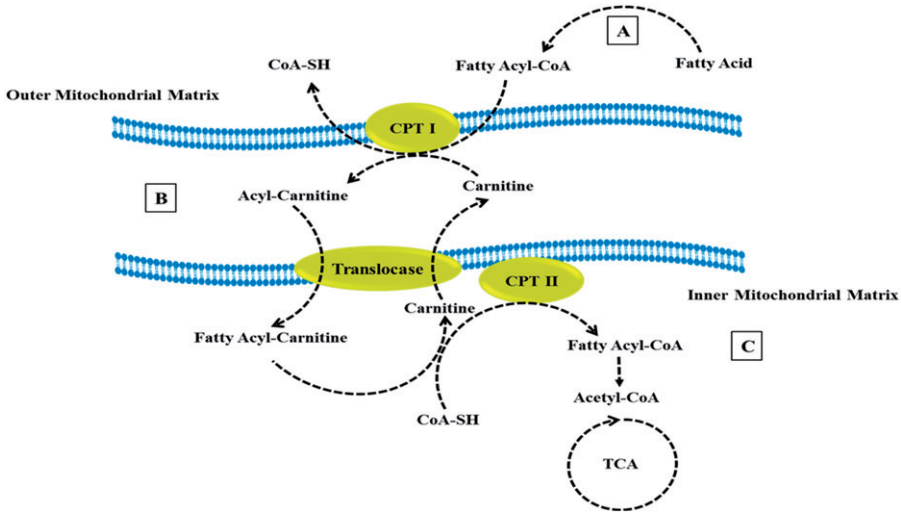

Figure 1. (A) Activation of fatty acid to acyl-coA and (B) carnitine transferase and (C) fatty acid oxidation. CPT I: Carnitine palmitoyltransferase I; CPT II: Carnitine palmitoyltransferase II;CoA-SH: Coenzyme A.

'L-carnitine' or 'Acetyl-L-carnitine' or 'propionyl-L-carnitine' or 'Levocarnitine' and 'polycystic ovary syndrome' or 'PCOS' or 'sclerocystic ovary syndrome' or 'dysmetabolic Syndrome'. The search was limited to studies published in the English language, and up to March 2018. Guideline of the Preferred Reporting for Systematic Reviews (PRISMA) was used for designing this systematic review, and the review protocol was registered at PROSPERO database of Systematic Reviews (registration number: CRD42018090881).

Inclusion and exclusion criteria

Two researchers independently performed the screening of titles or abstracts. Studies were eligible only if it complied withthe following criteria: (1) clinical trials (2) observational studies (3) published in English-language journals and (4) reporting the dosage as well as duration of carnitine administration; studies that (1) provided insufficient information and (2) involved animals and in vitro models were excluded.

Data extraction and assessment of study quality

Two researchers reviewed independently the full text of the studies screened for data extraction and analyzed them according to a checklist of aims. Studies with insufficient information were excluded from the review. Then, a third reviewer assessed the accuracy and quality of the included data.

Results

Figure 2 presents a summarized flowchart of the process of selecting studies for the systematic review. In total, 451 potentially eligible articles were identified by the search strategy, which decreased to 443 after removal of duplicate records; titles and abstracts were then screened. Of these, 437 were excluded based on their title or abstract, because they did not meet the inclusion criteria, and seven full-text documents were retrieved and reviewed. After reading the full texts of articles, one study was removed for it met the exclusion criteria. Only six articles had the inclusion criteria for qualitative synthesis (Table 1).

Carnitine and weight changes in PCOS

About 50% of patients with PCOS suffer from obesity, which can exacerbate symptoms of the disease [15]. Serum carnitine levels in patients with PCOS and the effects of carnitine supplementation on their weight loss have been examined in some studies. In a cross-sectional study [16], plasma concentration of L-carnitine had a negative and significant correlation with BMI in patients with PCOS. But, in a study by Fenkci et al., no such association was observed [17]. In the study by Jamilian et al. carnitine supplementation (250 mg/day) for 12 weeks in PCOS patients resulted in a significant reduction of BMI and weight compared to placebo group [18]. In another study, the same amount of carnitine for the same intervention period did not reveal any significant decrease in weight, BMI and WC in comparison with the control group [19]. Also, in a study by Ismail et al. among clomiphene resistant PCOS women, receiving clomiphene citrate combined with 3000 mg per day of L-carnitine for 12 weeks, significantly decreased BMI in the L-carnitine group [20].

Carnitine and glycemic control in PCOS

Insulin resistance and metabolic disorders are key features in PCOS. The effects of carnitine on these parameters have been studied in several studies [21]. In a cross-sectional study, plasma concentrations of L-carnitine had a negative and significant correlation with HOMA-IR-index in PCOS patients [16]. Moreover, 250 mg of oral carnitine supplement for 12 weeks resulted in a significant decrease in HOMA-IR, levels of fasting blood glucose and insulin levels compared to the control group [19]. In a similar study, a significant reduction was observed in glucose by carnitine supplementation [20].

Carnitine and ovarian hormones, androgens and anovulation in PCOS

Insulin resistance and hyperinsulinemia are caused by increased androgens in patient with PCOS [22]. Also, insulin resistance and hyperinsulinemia may increment LH/FSH ratio and production of androgens [2]. The effect of carnitine on ovarian hormones has been shown in the previous studies [23,24].

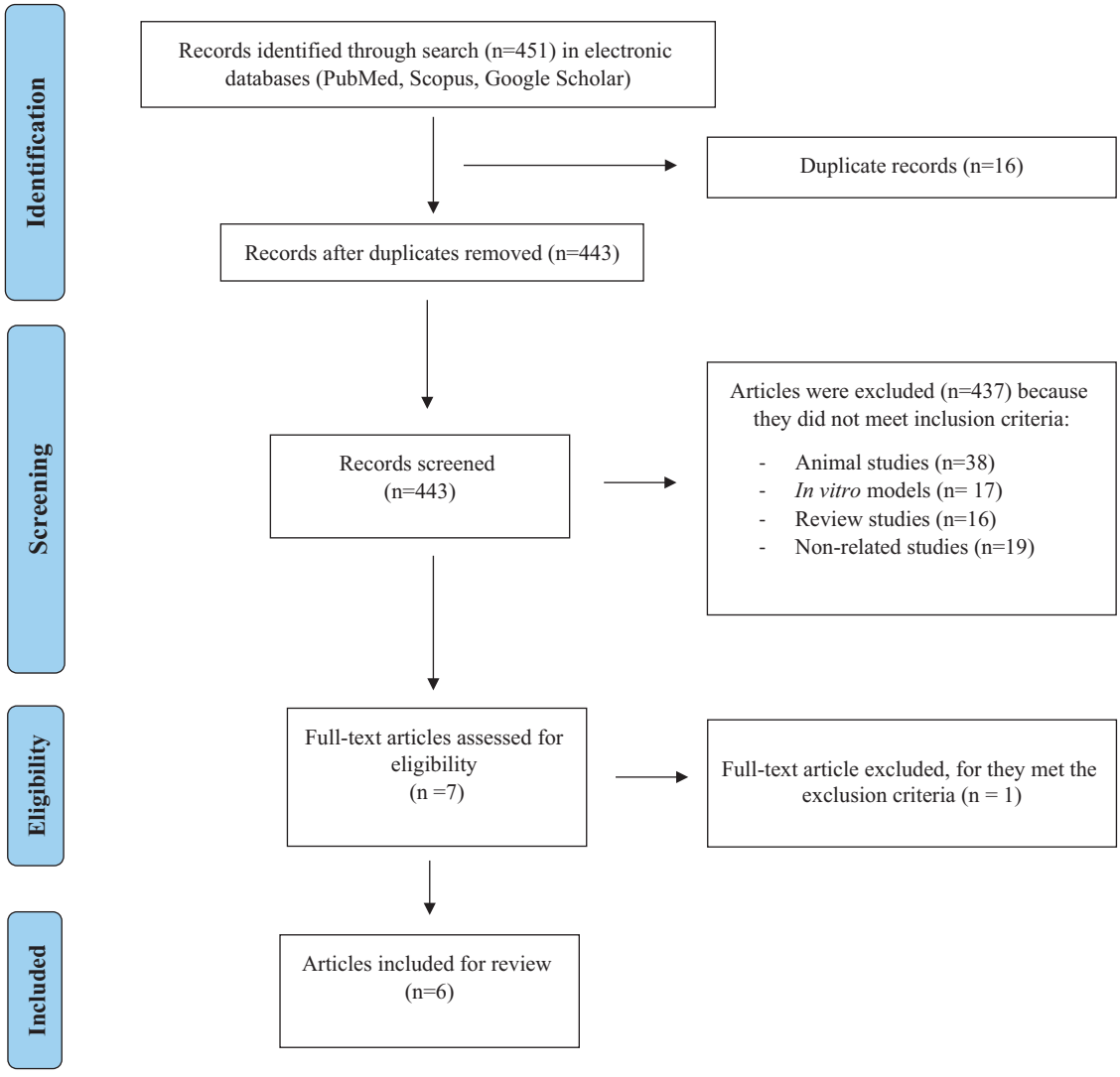

Figure 2. Flowchart of the studies search and selection process.

Accordingly, it appears that carnitine improves insulin sensitivity which in turn affects androgens and ovarian hormones levels [25]. Association between serum levels of carnitine and hormonal status such as estrogen and testosterone has been investigated in some studies. In one study, there was an inverse relationship between SHBG and total as wells as free carnitine in obese PCOS women; but, there was no relationship between carnitine and androgens levels [26]. According to the results of a study by Ismail et al. [20], combination of L-carnitine and clomiphene citrate for 12 weeks in patient with clomiphene-resistant PCOS significantly improved ovulation, pregnancy rates, and significantly increased ovulation rate, number of pre-ovulatory follicles, estradiol and progesterone. Latifian et al. [27] examined the effects of carnitine in PCOS infertile women who were both gonadotropin and clomiphene resistant; the results showed that carnitine lead to the growth of dominant follicles, rise the mean thickness of endometrium and inculcate positive variations in the size of left ovarian follicles. Fenkci et al. [17] showed that there was a significant and negative correlation between carnitine levels and free androgen index (FAI), and a positive and significant relationship with SHBG; they concluded that attenuated levels of carnitine may be due to hyperandrogenism and/or insulin resistance in nonobese women with PCOS. In another study, 250 mg oral carnitine supplementation for 12 weeks did not significantly alter free testosterone levels compared to control group [19].

Carnitine and dyslipidemia in PCOS

Dyslipidemia is one of the co-existing features in patients with PCOS [28]. The relationship between serum carnitine and lipid profile has been assessed in some studies [29,30]. Fenkci et al. showed an inverse association between carnitine levels and high serum LDL-C levels; an insignificant relationship was observed between carnitine levels and other components of lipid profile as well [16]. The result of 3000 mg/day of oral carnitine supplementation for 12 weeks was a significant reduction in total cholesterol, triglyceride and LDL-C, and an increase in HDL-C [20]. But Samimi et al. indicated that 250 mg daily oral carnitine supplementation for 12 weeks had no effect on lipid profile [19].

Discussion

Hyperandrogenism and insulin resistance are the most important features of PCOS, which is associated with decreased total serum carnitine levels [16,17]. Generally, the increase in LH/FSH ratio

Table 1. Summary of included publications.

Author, year and place	Type of study	Sample size and age	Daily dose	Duration	Main outcomes
a. Clinical trials					
Jamilian et al. Iran [18]	Randomized controlled study	$N = 60$ 18–40 years	250 mg carnitine supplement	12 weeks	Significant: reduction in weight and BMI, improvement of TAC, MDA and MDA/TAC ratio. Insignificant: GSH levels
Samimi et al. Iran [19]	Randomized controlled study	$N = 60$ 18–40 years	250 mg carnitine supplement	12 weeks	Significant: reduction in weight, BMI, WC, FPG, insulin, HOMA-IR and DHEAS Insignificant: lipid profile and free testosterone.
Latifian et al. Iran [27]	Randomized controlled study	$N = 50$ 20–30 years	2 g carnitine orally every 12 h	third day	Significant: mean of left ovary follicles size, mean endometrial thickness
Ismail et al. Egypt [20]	Randomized controlled study	$N = 170$ <35 years	Carnitine 3 g daily and 250 mg clomiphene citrate	12 weeks	Significant: improvement of the ovulation, cholesterol, TG, LDL-C, HbA1c, glucose, BMI, increase of HDL-C, insulin, improvement of ovulation rate, endometrial thickness, mean number of pre-ovulatory follicles, estradiol and progesterone levels. Insignificant: FBS
b. Observational studies					
Fenkci et al. Turkey [17]	Case-control study	27 non-obese women with PCOS and 30 healthy 16–37 years			Significant: total carnitine and SHBG levels were lower; carnitine level was negatively correlated with FAI and positively with SHBG, LDL-C, LH/FSH ratio, FAI and HOMA-IR in PCOS group. Insignificant: waist measurements, WHR, serum FSH, TC, TG, HDL-C
Celik et al. Turkey [16]	Cross-sectional study	60 PCOS and 28 healthy 17–50 years			Significant: lower carnitine level negatively correlated with BMI and HOMA-IR index in PCOS group.

SHBG: sex hormone-binding globulin; LH: luteinizing hormone; FAI: free androgen index; DHEA-S: dehydroepiandrosterone sulfate; HOMA-IR: homeostasis model assessment; GSH: glutathione; FPG: fasting plasma glucose; WC: waist circumference; FSH: follicle-stimulating hormone; MDA: malondialdehyde; TAC: total antioxidant capacity; IR: insulin resistance.

leads to stimulation of the ovarian theca cells followed by an increased production of androgens and reduced secretion of estrogen. Androgens with a negative feedback effect due to secretion of GnRH hormone, which result in augmented LH/FSH ratio. Moreover, insulin resistance and hyperinsulinemia can be affected by overproduction of androgens [31,32] which in turn affects the liver cells resulting in decreased production of SHBG and an increase in androgens [31,33]. In addition, both hyperandrogenism and insulin resistance are related to obesity, dyslipidemia and subsequently risk factors for cardiovascular diseases [22]. Studies have shown that serum carnitine levels in obesity and metabolic syndrome decrease following insulin resistance [34]. Also, carnitine supplementation leads to reduction in weight, BMI, WC, waist to hip ratio, body fat mass (FM) and increased lean body mass (LBM), and basal metabolism [8,35–37]. The findings from the observational studies reviewed indicated that relationship between serum level of carnitine and anthropometric status are inconsistent [16,17]. However, clinical trials using 250 mg and 3000 mg carnitine supplements revealed a significant decrease in weight, BMI and WC [18–20]. Due to the limited studies, the exact effect of carnitine on anthropometric indices would require further studies.

Previous studies have shown the useful effects of carnitine supplementation on parameters of glucose homeostasis [38,39]. Disorders of glycemic status are the most frequent complication following insulin resistance in PCOS. In these patients, there is a negative correlation between carnitine levels and FBS, HOMA-IR, insulin and HbA1c [16,20]. Also carnitine supplementation with daily doses 250 and 3000 mg showed a significant decrease in HbA1c [20], glucose, insulin [19,20] and HOMA-IR [19]. Probably, carnitine improves factors of insulin metabolism by moderating the expression of gluconeogenic and glycolytic enzymes [40], improving glucose oxidation in mitochondria, and acting as an acetyl-group donor in high-energy metabolism situation, or a transport molecule for free fatty acids [41] leading to increased insulin sensitivity and improvement in glycemic status. Molecular studies have elucidated some possible mechanisms involved in carnitine action on cellular glucose uptake. It has been reported that carnitine deficiency attenuates insulin sensitivity. Furthermore, carnitine can improve glucose metabolism by enhancement of mitochondrial oxidation of acyl-CoA, which further induces insulin resistance and alters the activity of gluconeogenesis enzymes via modifying expression of genes associated with insulin signaling [42].

Patients with PCOS are susceptible to dyslipidemia [43] leading to increased TC, TG, LDL-C levels and decreased HDL-C, which is mainly attributed to insulin resistance in these patients [44]. It has been revealed that carnitine has a hypo-triglyceridemic effect [45]. Moreover, carnitine supplementation may relieve overload of lipid [46]. Few studies have examined the association between the levels of carnitine and lipid profile, as well as its complementary effect on patients with PCOS. Only one study [17] showed a significant relationship between carnitine levels and lipid profile. A dose of 3000 mg carnitine for 12 weeks significantly improved lipid profile [20]. But at a dose of 250 mg for the same duration, no significant effects were observed [19]. A meta-analysis study showed that carnitine supplementation improves lipid profile in patients with T2D [38]. In a similar meta-analysis study, carnitine supplementation led to improved LDL-C but did not affect triglyceride, total cholesterol and HDL-C in hemodialysis patients [47]. Carnitine in mitochondria transfers acetyl groups to the cytosol [48]. Also,

through the carnitine palmitoyltransferase system, carnitine mediates the transport of activated acyl residues into mitochondria for β-oxidation [49]. Thus, it helps maintain adequate amounts of free CoA for improved function and protection of mitochondria by decreasing the accumulation of space long-chain acyls in mitochondria [50]. Also, carnitine reduction may restrict the availability of fatty acids in the mitochondria to produce ATP [42].

Chronic low-grade inflammation has been observed in patient with PCOS [51]. Serum levels of IL-6, TNF-α and CRP increase in these patients [52]. There is a significant relationship between circulating oxidative stress and inflammatory biomarkers, as well as androgen levels [53]. These findings suggest that in PCOS, hyperandrogenism can induce inflammation and enhance oxidative stress through hyperglycemia and insulin resistance, and/or conversely inflammation stimulated with hyperglycemia may promote excess ovarian androgen production. Furthermore, oxidative stress and inflammatory markers are associated with insulin resistance [54–56]. Therefore, the interaction of oxidative stress and inflammation with insulin resistance and hyperglycemia can lead to exacerbations in hyperandrogenism. The antioxidant effects of carnitine are partly related to free radical scavenging and prevention of free radical formation, maintaining of the integrity of electron-transport chain in mitochondria leading to decreased secretion of ROS under stress conditions, and affecting redox-signaling via inhibition of NF-κB resulting in additional synthesis of antioxidant enzymes and molecules [57]. Carnitine has been reported to maintain cellular energy by improving the mitochondria or by eliminating elements which may cause lipotoxicity [58]. It also promotes cellular proliferation and decreases apoptosis by inhibiting TNF-α and other anti-proliferative agents [59]. Furthermore, carnitine may decrease apoptosis induced by inflammatory cytokines such as TNF-α [59]. Also, previous studies have reported that carnitine may lead to down-regulation of cytokines such as IL-6, IL-1 and TNF-α [60]. In the study of Jamilian et al., supplementation of 250 mg of carnitine for 12 weeks in PCOS patients resulted in a significant improvement in total antioxidant capacity (TAC), malondialdehyde (MAD) and MDA/TAC ratio; no significant changes were found in glutathione (GSH) levels, though [18]. Latifian et al. [27] showed that carnitine supplementation in PCOS infertile women led to growth of dominant follicles, a rise in mean thickness of endometrium and inculcated positive variations in the size of left ovarian follicles. Also, in another study [17], there was a significant and negative correlation between L-carnitine and FAI, and a positive and significant relationship between SHBG and the levels of carnitine, due to hyperandrogenism and/or insulin resistance in PCOS. However, in a clinical trial, supplementation with 250 mg of carnitine did not significantly alter free testosterone levels compared to the control group [19]. More studies with different doses and durations are required to better understand the effect of carnitine on sex hormones in PCOS patients.

Knowledge gaps and future directions

PCOS patients are different in body compositions and distribution of fat mass (FM) and lean body mass (LBM) from their non-PCOS peers. There is a significant relationship between android obesity and the risk of diabetes, arthrosclerosis and other chronic metabolic diseases [61–63]. Also, it seems that body composition influences glycemic status, lipid profile and hormone levels. Therefore, the reported effects of carnitine administration on body composition, FM and LBM in patients with PCOS inspire future studies.

Adipose tissue which secretes adipokines has an important role in regulating hyperandrogenism and insulin resistance in PCOS, and increased secretion of inflammatory adipokines leads to exacerbations of chronic inflammation and oxidative stress [64,65]. Future clinical trials on the effects of carnitine on adipokines in PCOS can increase our knowledge and understanding of its anti-inflammatory and antioxidant effects.

Studies have shown that the development and activation of brown adipose tissue can lead to increased thermogenesis, body metabolism, weight loss, improved insulin sensitivity, fatty acid metabolism and ultimately reduced oxidative stress and inflammation [66–69]. It is postulated that increasing the activity of this tissue may reduce the complications of PCOS [70,71]. On the other hand, studies have shown that carnitine can enhance the function of this tissue [72]. Therefore, studying the effects of carnitine on brown adipose tissue can reveal new pathways and attitudes to control the complications of this disease.

Conclusions

As a whole, the results of this systematic review study showed that carnitine can lead to weight loss and improved glycemic status, and may reduce insulin resistance in patients with PCOS. However, the effects of carnitine on lipid profile were contradictory. Also, in observational studies, low serum levels of carnitine had a reverse association with glycemic status, BMI and WC; no association was reported between carnitine levels and lipid profile. Carnitine improves function of follicles and the size of ovarian cells, but has no significant effect on sex hormones. However, according to the gaps in knowledge and the future direction in this area, more studies are needed to determine the exact mechanisms of the effects of carnitine in patients with PCOS.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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