Review

The effect of curcumin supplementation on circulating adiponectin: A systematic review and meta-analysis of randomized controlled trials

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A B S T R A C T

Objective: Our objective was to perform a systematic review and meta-analysis on randomized controlled trials (RCTs) assessing the effect of curcumin on serum adiponectin concentration.
Methods: We searched PubMed/Medline, Scopus, ISI Web of Science, Cochrane Library, and Google scholar databases up to April 2019. RCTs conducted among human adults studied the effects of curcumin on serum adiponectin concentrations as an outcome variable was included. The weighted mean differences (WMD) and standard deviations (SD) of change in serum adiponectin levels were calculated. The random effects model was used for deriving a summary of mean estimates with their corresponding SDs.
Results: Out of 313 records, 6 trials that enrolled 652 subjects were included. The pooled results showed that curcumin supplementation significantly increased adiponectin concentrations in comparison with placebo (WMD: 0.82 Hedges' g; 95% confidence interval (CI): 0.33 to 1.30, P<0.001). Greater effects on adiponectin were observed in trials lasting ≤10 weeks (WMD: 1.05 Hedges' g; 95% CI: 0.64 to 1.45, P<0.001).
Conclusion: Curcumin significantly improves adiponectin concentrations. However, due to some limitations in this study, further studies are needed to reach a definitive conclusion about the effect of curcumin on the levels of adiponectin.

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1. Introduction

Metabolic abnormalities and metabolic syndrome are a well-known cause of cardiovascular diseases (CVDs), whilst insulin resistance is a prominent factor in the aetiology of metabolic syndrome [1]. Adiponectin is a protein hormone with 244 amino acids that mediates numerous of metabolic processes, including glucose regulation and oxidation of fatty acids [2], and is an important adipokine produced by adipose tissues and is circulated in high concentrations. Moreover, adiponectin is regarded as a key regulator of insulin sensitivity, ameliorating inflammation of the tissue,

recues systemic insulin resistance, and may be used as a predictor of CVDs [3—5]. Furthermore, low levels of adiponectin have been found to be correlated with increased risk of diseases, including; diabetes, dyslipidaemia, hypertension and metabolic syndrome [3,6,7].

Nutraceuticals, or foods with known health-promoting benefits, have been identified as potential interventions for CVDs, attributable to their lipid-lowering effects [8], amelioration of metabolic syndrome components, and improvements in vascular function and arterial blood pressure [9]. Furthermore, attributable to the high costs and side effects associated with traditional pharmacotherapy, attention has been paid to the treatment through herbal medicine [10]. Curcumin has a pivotal role in reducing complications of diabetes and related metabolic disorders, attributed to antidiabetic, anti-inflammatory, and antioxidant properties and its purported ability to increase circulating adiponectin [11—13].

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Experimental and clinical studies have reported the effectiveness of curcumin supplementation on hyperlipidaemia and inhibiting atherosclerosis [14–18]. Curcumin is also asserted to regulate the secretion of inflammatory cytokines through proteins and enzymes signalling, resulting in reduced secretion of inflammatory cytokines, including interleukin-6 (IL-6), interleukin-8 (IL-6), tumour necrosis factor-α (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) [19,20]. In a population of prediabetic participants, curcumin supplementation resulted in enhanced prevention of type II diabetes, improved β-cell function, reduced insulin resistance, and higher levels of circulating adiponectin [21]. Moreover, in a study of participants affected by obesity, with type II diabetes, reported that curcumin supplementation resulted in significant a reduction of high sensitivity C-reactive protein (hs-CRP), TNF-α, and IL-6 [22]. Further, studies on rodent models suggest that curcumin may conceivably protect against vascular complications of diabetes, and other metabolic disorders, via its effects on Thioredoxin-interacting protein, intercellular adhesion molecule-1, and nitric oxide synthase 2 enzyme expression [23].

Given the positive role adiponectin has on moderating a number of metabolic processes, the recently reported, positive, biological effects of curcumin supplementation, and the distinct lack of unifying consensus on the topic; our objective was to perform a systematic review and meta-analysis on randomized controlled trials (RCTs) assessing the effect of curcumin supplementation on serum adiponectin concentration.

2. Methods

We conducted this meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, which was adhered to during all stages of design, implementation, analysis, and reporting [24].

2.1. Data sources and search strategy

We searched multiple electronic databases from the earliest available online indexing year through to April 2019, without language restrictions, including PubMed/Medline, Scopus, ISI Web of Science, Cochrane Library, and Google scholar. The keywords used in our search strategy were ("Curcumin" OR "Curcuma" OR "Curcuminoid" OR "Tumeric" OR "Turmeric") AND ("adipokines" OR "adiponectin" OR "adipocytokines"). Reference lists from all related reviews and original primary studies were also screened to avoid missing any relevant articles.

2.2. Study selection

To accelerate the process of screening citations, the search results were imported into a bibliographic database and duplicates were removed automatically (EndNote X6; Thomson Reuters, New York). Subsequently, titles and abstracts screened by two independent authors (A.H and E.Gh) for relevance to the topic. Following this, full-texts of selected articles were retrieved and assessed for eligibility. Studies were included if they were randomized controlled trials of curcumin supplementation that evaluated adiponectin as an outcome. Studies were excluded if participants were children (<18 years) or if they had a concomitant intervention for which effects could not be separated; were of less than 2 weeks' duration; did not report the baseline and final values of outcome variables (or changes) in both curcumin and control groups; were letters, commentaries, reviews, ecological and animal studies, duplicate publication from the same study, or were published in non-English languages. Unpublished documents and grey literature, such as conference papers, dissertations, and patents

were also excluded. Discrepancies were resolved by consensus and discussion with a third, independent, reviewer.

2.3. Data extraction

OF the included studies, two authors (A.H and E.Gh) independently extracted the following information into a data spread sheet: first author's last name, publication year, study design, country, participants' gender and mean age of subjects, type of study population, follow-up duration and dose of curcumin supplement. When the values for outcome variable were reported in different time points, data for the end of the trial were extracted. We emailed corresponding authors in cases of any unclear data. Any disagreements between the two reviewers were resolved in consultation with a third investigator (A.A).

2.4. Quality assessment

Two authors (A.H and E.Gh) independently evaluated the methodological quality of the included trials using the instrument developed by Jadad et al. [25]. Briefly, this scale comprises 3 domains: 1) allocation concealment explanation (maximum of 2 points); 2) double-blinding explanation (maximum of 2 points); and 3) withdrawal explanation and follow-up completeness (maximum of 1 point). In total, a maximum score of 5 points can be achieved and studies with a Jadad score of <3 and ≥ 3 were considered as low and high-quality publications, respectively. Any discrepancies were discussed and resolved by a third investigator (M.P).

2.5. Statistical analysis

The difference in the mean values of adiponectin was calculated for all eligible studies and considered as the effect size. The net changes in adiponectin concentrations were estimated as the difference (curcumin minus control) between its changes (end values minus baseline) in the control group and the intervention group. Standard deviation (SD) of the mean difference was calculated using the following formula: SD = square root [(SD pre-treatment)^2 + (SD post-treatment)^2 − (2 × R × SD pretreatment × SD post-treatment)] [26]. To ensure the meta-analysis was not sensitive to the selected correlation coefficient (R = 0.5), all analyses were repeated using correlation coefficients of 0.2 and 0.8. Where a standard error (SE) was only reported, SD was estimated using the following formula: SD = SE × $\sqrt{n}$ (n is the number of subjects in each group). The weighted mean difference (WMD) and its corresponding 95% confidence intervals (CIs), was calculated by conducting random effect model, taking the between study heterogeneity into account. The inconsistency index (I^2) was used to quantify statistical heterogeneity in meta-analyses, and values greater than 50% were considered indicative of high heterogeneity. To find the sources of heterogeneity, subgroup analyses were performed based on the following categories: intervention dosage, duration of follow up, baseline BMI, and mean age of participants. Sensitivity analysis was used to explore the extent to which inferences might depend on a particular study or group of studies. In addition, plausible publication bias was specified visually by funnel plot and confirmed by the statistical evidence of Egger's test. All statistical analyses were conducted using STATA, version 11.2 (Stata Corp, College Station, TX). P-values less than 0.05 were considered as statistically significant.

3. Results

3.1. Study selection process

From 313 potentially relevant citations identified in our

structured searches, 229 records were screened (after removing duplicates) and 13 full-text articles were assessed for eligibility. Next, 7 articles were excluded due to the following reasons: studied children (n = 1) [27], administered curcumin in combination with other components (n = 2) [28,29], duplicate dataset (n = 1) [30], published in non-English language (n = 1) [31], and studies that did not provide sufficient data for outcomes (n = 2) [32,33]. Finally, 6 trials [34–39] were included in this meta-analysis. The flow chart for selecting studies is presented in Fig. 1.

3.2. Characteristics of the included studies

Selected studies comprised a total of 652 participants in an intervention (322 participants receiving curcumin treatment) or control groups (330 participants receiving placebo treatment). These articles were published between 2012 and 2019, which among them, three studies were performed in Iran [37–39], two in the Thailand [34,36], and other study conducted in USA [35]. The design of all the nominated trials was parallel. All records examined the effect of curcumin in both genders except for one study [35] that was restricted to men. Participants in these studies were patients with type 2 diabetes [34,38], pre-diabetic subjects [36], obese men [35], and those with metabolic syndrome [37,39]. The mean age of the participants ranged from 27.1 to 59.37 years old and mean baseline BMI varied from 24.13 to 32.4 kg/m^2. The range of dosage of curcumin supplementation varied from 200 to 1500 mg/day. The duration of intervention was between 6 and 39 weeks in different studies. The general characteristics of the included studies are outlined in Table 1.

According to Jadad scale, all studies had high quality (score ≥ 3). All studies were randomized trials, of them 4 records [34,37–39] had properly explained the randomization procedure. In addition, all included studies had mentioned blindness whereas only four studies [35,36,38,39] clearly described the blinding procedure. Details concerning a number of participants that dropped out and the reasons for this were reported in all studies. The general characteristics of the included studies are outlined in Table 1.

3.3. Effect of curcumin supplementation on circulating adiponectin

The individual trial results and the pooled estimate for the effect of curcumin supplementation on adiponectin are shown in Fig. 2. Combining 6 effect sizes from 6 studies based on the random-effects model, we found that curcumin supplementation significantly increased adiponectin (WMD: 0.82 Hedges' g; 95% CI: 0.33 to 1.30, P‹0.001) compared to the control group. However, the heterogeneity among the studies was high ($I^2 = 87.2\%$, P < 0.001). To identify the sources of the between-study heterogeneity, subgroup analyses were conducted (Table 2). Mean age of study participants, baseline BMI, and curcumin dosage did not explain this heterogeneity. However, duration of intervention could explain the heterogeneity ($I^2 = 49.5\%$, P = 0.13). In this analysis, we found that the effect of curcumin supplementation on circulating adiponectin was only significant in trials lasting ≤10 weeks (WMD: 1.05 Hedges' g; 95% CI: 0.64 to 1.45, P‹0.001). Sensitivity analysis showed that the removal of each trial did not significantly influence the pooled effect of curcumin on adiponectin concentrations. The funnel plot was visually symmetrical (Fig. 3) and the result of Egger's test did
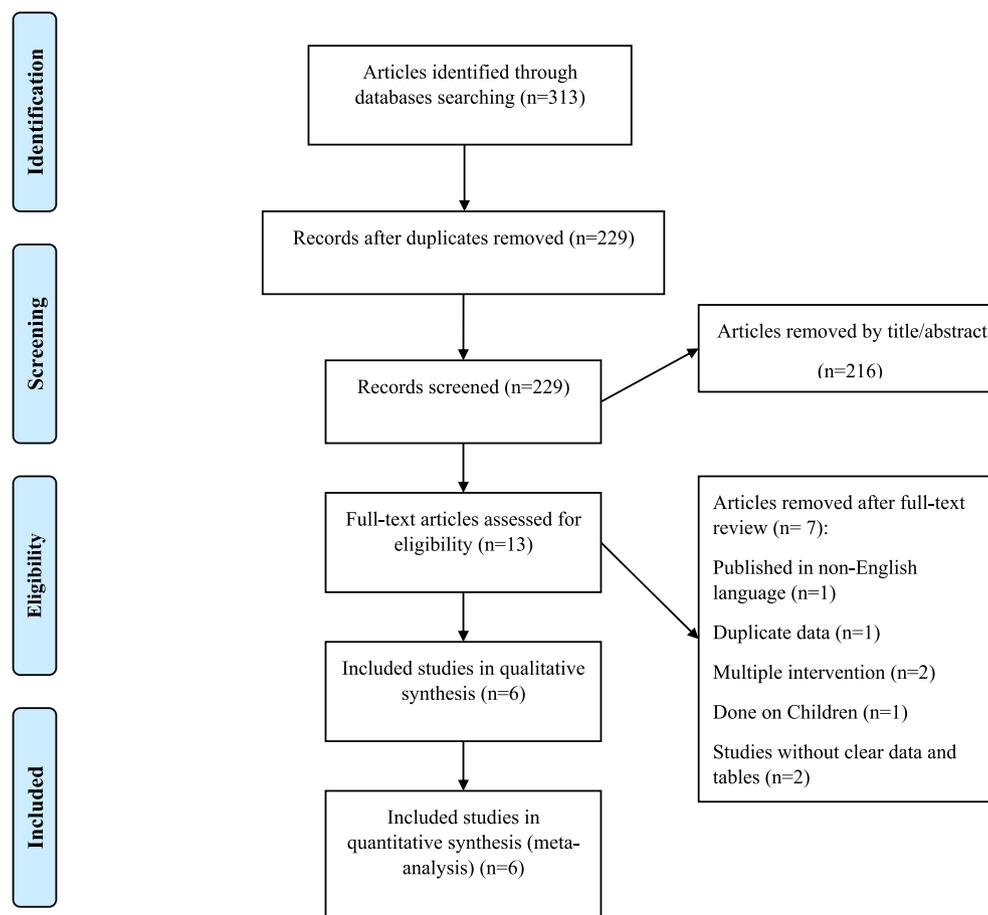

Fig. 1. PRISMA flow diagram of study selection process.

Table 1
Characteristics of included trials.

| First author (publication year)	Country	Sample size	RCT design (Blinding)	Gender	Mean age (years)	Basline BMI (kg/m²)	Patient Features	Duration (weeks)	Intervention	Comparison	Jadad score
Chuengsamarn et al. (2012)	Thailand	201	Parallel (Double)	Both	56.95	26.6	Pre-diabetic	39	1500 mg/d curcuminods	Placebo	4
Chuengsamarn et al. (2014)	Thailand	213	Parallel (Double)	Both	59.37	26.96	Type 2 diabetes	26	1500 mg/d curcuminods	Placebo	4
Panahi et al. (2016)	Iran	100	Parallel (Double)	Both	44.13	24.13	Metabolic syndrome	8	1000 mg/d curcumin	Placebo	4
Salahshooh et al. (2017)	Iran	72	Parallel (Double)	Both	38.2	31.1	Metabolic syndrome	6	1000 mg/d curcumin	Placebo	5
Campbell et al. (2019)	USA	22	Parallel (Double)	Men	27.1	32.4	Obese	12	200 mg/d curcuminoids + fenugreek fiber	Fenugreek fiber	4
Adibian et al. (2019)	Iran	44	Parallel (Double)	Both	59.3	28.6	Type 2 diabetes	10	1500 mg/d curcumin	Placebo	5

Abbreviations: RCT, randomized controlled trial.
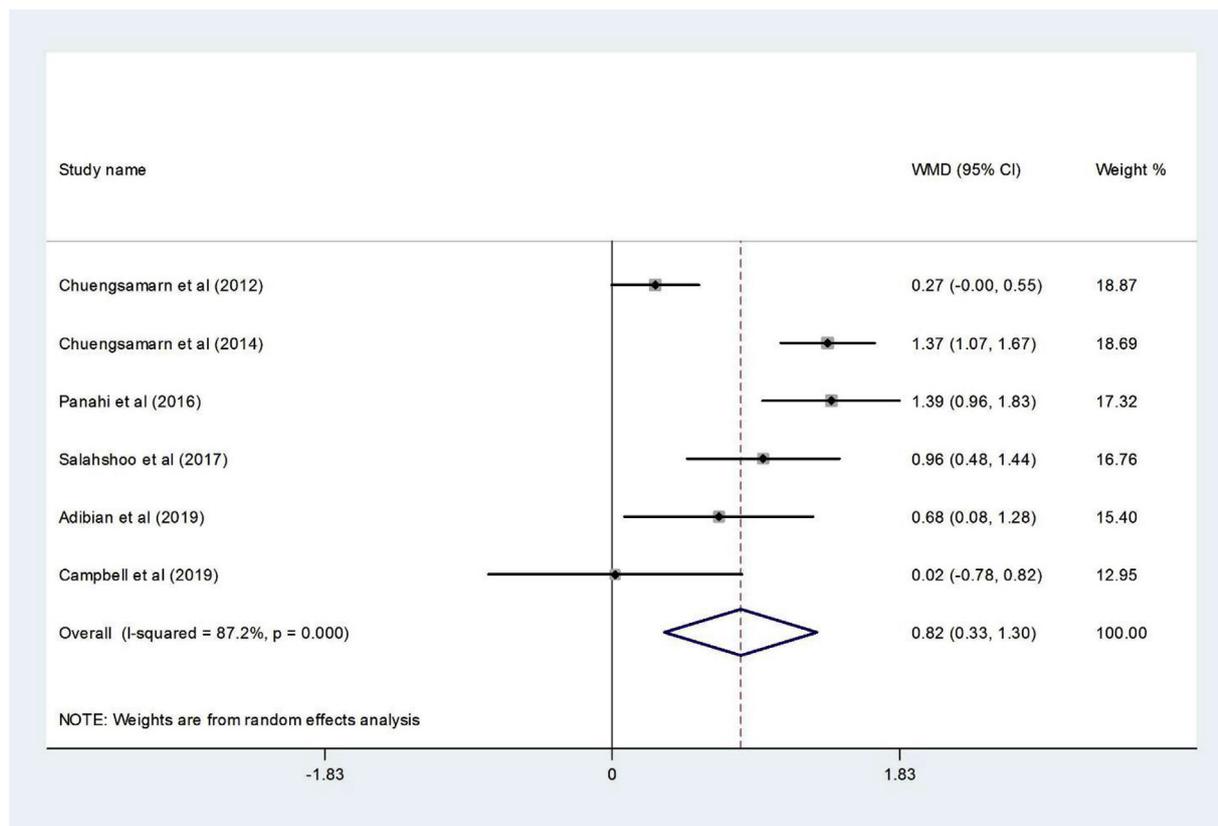
Fig. 2. Forest plot of the effect of curcumin supplementation on circulating adiponectin.

not show any evidence of publication bias (P = 0.91).

4. Discussion

Curcumin is a bioactive yellow-orange pigment of turmeric and extracted from the rhizomes of Curcuma longa Linn. (Zingiberaceae) [40]. The therapeutic effects of curcumin and its analogues have been shown efficacious in a number of pathological conditions such as cancer [41,42], osteoarthritis [43], non-alcoholic fatty liver disease [44], anxiety and depression [45], pulmonary diseases [46], and ischemia/reperfusion injury [47]. Given the purported capability of curcumin to elicit positive, biological effects, and the known ability of adiponectin to protect against metabolic diseases, our objective was to perform a systematic

review and meta-analysis on RCTs assessing the effect of curcumin on serum adiponectin concentration. In accord with this objective, the pooled results showed that curcumin supplementation significantly increased adiponectin concentrations in comparison with placebo; whilst greater effects on adiponectin were observed in trials lasting ≤10 weeks.

Adiponectin is an anti-inflammatory cytokine produced and secreted by adipose tissue. Adiponectin serum level reportedly has an inverse relationship with insulin resistance, dyslipidaemia, CVDs, and obesity [21,48,49]; whilst decreases in adiponectin may resultantly increase the risk of atherosclerotic disease [50]. Adiponectin has a positive effect in reducing the risk of cardiometabolic disease, which is associated with lipid and glucose metabolism, anti-inflammatory, and anti-atherosclerotic

Table 2
Subgroup analysis to assess the effect of curcumin supplementation on adiponectin level.

Sub-grouped by	No. of trials	Effect size[1]	95% CI	I^2 (%)	P for heterogeneity	P for between subgroup heterogeneity
Mean age (year)						**0.14**
‘50	3	0.87	0.20, 1.54	77.3	0.01	
≥50	3	0.78	0.00, 1.55	92.9	‘0.001	
Mean baseline BMI (kg/m^2)						**0.47**
‘30	4	0.93	0.30, 1.56	91.3	‘0.001	
≥30	2	0.55	−0.37,1.46	74.1	0.04	
Dose (mg/d)						**0.14**
≤1000	3	0.87	0.20, 1.54	77.3	0.01	
’1000	3	0.78	0.00, 1.55	92.9	‘0.001	
Duration (week)						**0.05**
≤10	3	1.05	0.64, 1.45	49.5	0.13	
’10	3	0.59	−0.28, 1.47	93.6	‘0.001	

[1]Calculated by Random-effects model.
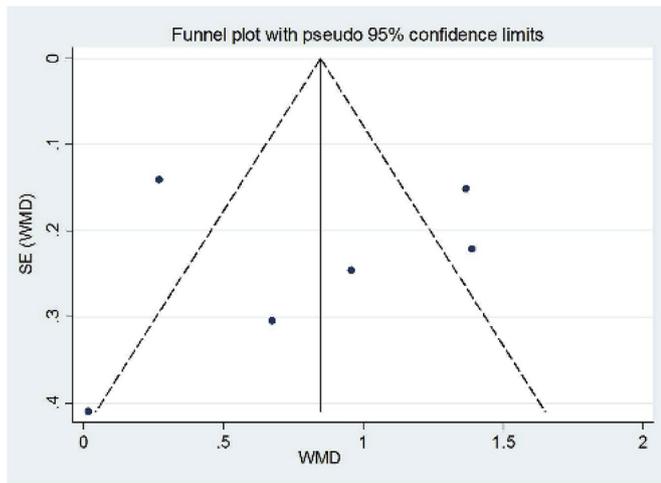BMI: body mass index.

Fig. 3. Funnel plot with pseudo 95% confidence limits.

properties [51]. The results of some empirical studies have shown that supplementation of curcumin leads to a significant increase in serum adiponectin [40,52]; whist in patients with metabolic syndrome, Panahi et al. [37] showed that supplementing with 1000 mg of curcumin daily for 8 months increased adiponectin and decreased leptin. In another example, consumption of 1500 mg curcumin daily, for 9-months, in patients affected by pre-diabetes resulted in higher level of adiponectin [52]. In the present study, we were able to confirm the veracity of a number of independent studies, highlighting that curcumin supplementation, particularly when consumed for less than 10 weeks, ay significantly increase adiponectin levels, even when controlling for numerous biological and sociological variables.

Insulin resistance is frequently defined as an impairment of insulin action on glucose, lipid and protein metabolism, and is closely associated with adipose tissue. Excessive visceral and subcutaneous adipose tissue causes adipocyte dysfunction which can result in inflammation through activation of JNK and NFκB. Such inflammation results in impaired adipokine secretion, manifest as decreased adiponectin and increased leptin levels [53,54]. Adiponectin and leptin mediate insulin sensitivity through the AMPK (5′AMP-activated protein kinase) pathway. AMPK is considered a 'master switch' capable of controlling the energy status in a cell, and its activation resultantly enhances β-oxidation and reduced fatty acid esterification to triglycerides [55]. Moreover, several empirical investigations have asserted that leptin-to-adiponectin ratio my conceivably serve as an effective index of insulin

resistance and atherogenic risk in both diabetic and non-diabetic populations [56,57]. Moreover, there are also reports demonstrating the association between leptin-to-adiponectin ratio and low-grade inflammation, carotid *intima media* thickness, arterial stiffness, time of first cardiovascular event and number of metabolic syndrome components [58]. It has been shown that curcumin can influence numerous components of metabolic syndrome, including insulin resistance, low HDL-C, hypertension and obesity. This is due to the reaction of phytochemical materials with various molecular targets, such as transcription factors, receptors, enzymes, growth factors, hormones, cell adhesion molecules, lipoproteins and anti-oxidants, which are involved in the pathophysiology of metabolic syndrome [59–61]. Qu et al. [59]reported that culturing curcumin at a concentration of 100 μg/ml increased adiponectin secretion and lessened IL-6 secretion in cultured human adipose tissues, whilst the effect of curcumin on the expression of adiponectin in rodent models has also been documented. In Bai et al. [62], 64 mice were trichotomized (control group, a group receiving 50 mg of curcumin and a group receiving 250 mg of curcumin for 11 weeks), and in the group receiving 250 mg of curcumin, a significant increase in adiponectin levels was observed compared to the control group. In another study in rodent models, Weisberg et al. [63] found that the consumption of 30% dietary curcumin for 10 weeks increased the adiponectin level.

As reported previously [64,65], and importantly, curcumin supplementation is safe. Moreover, curcumin has been approved by the United States FDA and considered a 'generally recognized as safe' supplement, whilst its tolerability has been confirmed in several clinical studies. Therefore, owing to its safety and beneficial effects on several features of metabolic syndrome, and results of the present meta-analysis, curcumin may be suggested as a routine supplement for patients with metabolic syndrome, and other metabolic disorders.

5. Strength and limitations

The primary strength of this study was that this is the first meta-analysis to assess the impact of curcumin supplementation on adiponectin; and given the potential influence on clinical practice, this is a major finding. The evidence base, prior to this meta-analysis, was somewhat equivocal, and required a meta-analytical assessment, which we have provided. We demonstrated that there is sufficient evidence for curcumin supplementation to elicit significant, positive effects on adiponectin levels. A further strength of the current meta-analysis is the accrual of the heterogeneous sample of participants, with a range of demographic status, ethnicities and ages. We were also able to stratify analyses based on

both duration of supplementation and dosage, affording clinicians foresight into expected outcomes based on such information.

Notwithstanding, the current study has some limitations worth considering. The analyses were not restricted to solitarily include patients of one type; although this permitted a larger number of studies and participants to be included for analyses, there may be disease specific modulators to the efficacy of curcumin, which requires further investigation. Some included trials were relatively small in sample size, and it has been asserted by Sterne et al. that it is conceivable for studies with small sample sizes to report bigger effect sizes in intervention arms than studies with larger participant pools [66], nevertheless, this was out of the operational control of the meta-analysis. A further limitation of the present study was the paucity of eligible studies, highlighting the need for a greater number of high-quality RCTs.

6. Conclusion

In conclusion, this systematic review and meta-analysis of randomized controlled clinical trials suggests that curcumin supplementation moderately increases circulating adiponectin. These findings support potential beneficial effects of curcumin supplementation on pathways related to adipocyte health and adiponectin metabolism.

Conflicts of interest

The authors declare no conflict of interest.

Author contribution

A.H and E.Gh carried out the concept, design, and drafting of this study. A.H AND E.Gh searched databases, screened articles and extracted data. A.H performed the acquisition, analysis, and interpretation of data. C.C critically revised the manuscript. All authors approved the final version of the manuscript. C.C and A.H are the guarantors of this study.

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References

[1] Qin Z, Zhi-Qing W, Ping F, Jian-Hua P, Yuan T, Jie X, et al. Association between adiponectin and metabolic syndrome in older adults from major cities of China. Biomed Environ Sci 2010;23:53–61.

[2] Whitehead J, Richards A, Hickman I, Macdonald G, Prins J. Adiponectin—a key adipokine in the metabolic syndrome. Diabetes Obes Metab 2006;8:264–80.

[3] Rodina A, Severin S. The role of adiponectin in the pathogenesis of the metabolic syndrome and approach to therapy. Patologicheskaia Fiziol Eksperimentalnaia Terapiia 2013;15–26.

[4] Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. Endocr Rev 2005;26:439–51.

[5] Straub LG, Scherer PE. Metabolic messengers: adiponectin. Nat Metab 2019;1: 334–9.

[6] Oh DK, Ciaraldi T, Henry RR. Adiponectin in health and disease. Diabetes Obes Metab 2007;9:282–9.

[7] Shetty S, Kusminski CM, Scherer PE. Adiponectin in health and disease:

[8] evaluation of adiponectin-targeted drug development strategies. Trends Pharmacol Sci 2009;30:234–9.

[8] Cicero AFG, Colletti A, Bajraktari G, Descamps O, Djuric DM, Ezhov M, et al. Lipid-lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel. Nutr Rev 2017;75:731–67.

[9] Patti AM, Al-Rasadi K, Giglio RV, Nikolic D, Mannina C, Castellino G, et al. Natural approaches in metabolic syndrome management. Arch Med Sci : AMS 2018;14:422–41.

[10] Chuengsamarn S, Rattanamongkolgul S, Luechapudiporn R, Phisalaphong C, Jirawatnotai S. Curcumin extract for prevention of type 2 diabetes. Diabetes Care 2012;35:2121–7.

[11] Hussain HEMA. Hypoglycemic, hypolipidemic and antioxidant properties of combination ofCurcumin fromCurcuma longa, Linn, and partially purified product fromAbroma augusta, Linn. in streptozotocin induced diabetes. Indian J Clin Biochem 2002;17:33–43.

[12] Zhang D-w, Fu M, Gao S-H, Liu J-L. Curcumin and diabetes: a systematic review. Evid Based Complement Altern Med 2013;vol. 2013.

[13] Pagano E, Romano B, Izzo AA, Borrelli F. The clinical efficacy of curcumin-containing nutraceuticals: an overview of systematic reviews. Pharmacol Res 2018;134:79–91.

[14] Calabrese V, Bates TE, Mancuso C, Cornelius C, Ventimiglia B, Cambria MT, et al. Curcumin and the cellular stress response in free radical-related diseases. Mol Nutr Food Res 2008;52:1062–73.

[15] Zheng B, Yang L, Wen C, Huang X, Xu C, Lee K-H, et al. Curcumin analog L3 alleviates diabetic atherosclerosis by multiple effects. Eur J Pharmacol 2016;775:22–34.

[16] Panahi Y, Ahmadi Y, Teymouri M, Johnston TP, Sahebkar A. Curcumin as a potential candidate for treating hyperlipidemia: a review of cellular and metabolic mechanisms. J Cell Physiol 2018;233:141–52.

[17] Maithilikarpagaselvi N, Sridhar MG, Swaminathan RP, Sripradha R, Badhe B. Curcumin inhibits hyperlipidemia and hepatic fat accumulation in high-fructose-fed male Wistar rats. Pharm Biol 2016;54:2857–63.

[18] Li ZY, Ding LL, Li JM, Xu BL, Yang L, Bi KS, et al. (1)H-NMR and MS based metabolomics study of the intervention effect of curcumin on hyperlipidemia mice induced by high-fat diet. PLoS One 2015;10. e0120950.

[19] Jain SK, Rains J, Croad J, Larson B, Jones K. Curcumin supplementation lowers TNF-α, IL-6, IL-8, and MCP-1 secretion in high glucose-treated cultured monocytes and blood levels of TNF-α, IL-6, MCP-1, glucose, and glycosylated hemoglobin in diabetic rats. Antioxidants Redox Signal 2009;11:241–9.

[20] Babu PS, Srinivasan K. Hypolipidemic action of curcumin, the active principle of turmeric (Curcuma longa) in streptozotocin induced diabetic rats. Mol Cell Biochem 1997;166:169–75.

[21] Tan K. Dyslipidaemia, inflammation and endothelial dysfunction in diabetes mellitus. In: International congress series. Elsevier; 2004. p. 511–4.

[22] Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. Int J Biochem Cell Biol 2009;41:40–59.

[23] Na LX, Yan BL, Jiang S, Cui HL, Li Y, Sun CH. Curcuminoids target decreasing serum adipocyte-fatty acid binding protein levels in their glucose-lowering effect in patients with type 2 diabetes. Biomed Environ Sci 2014;27:902–6.

[24] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.

[25] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Contr Clin Trials 1996;17:1–12.

[26] Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to meta-analysis. John Wiley & Sons; 2011.

[27] Ismail NA, Abd El Dayem SM, Salama E, Ragab S, Abd El Baky AN, Ezzat WM. Impact of curcumin intake on gluco-insulin homeostasis, leptin and adiponectin in obese subjects. Res J Pharm Biol Chem Sci 2016;7:1891–7.

[28] Navekar R, Rafraf M, Ghaffari A, Asghari-Jafarabadi M, Khoshbaten M. Turmeric supplementation improves serum glucose indices and leptin levels in patients with nonalcoholic fatty liver diseases. J Am Coll Nutr 2017;36: 261–7.

[29] Panahi Y, Khalili N, Sahebi E, Namazi S, Atkin SL, Majeed M, et al. Curcuminoids plus piperine modulate adipokines in type 2 diabetes mellitus. Curr Clin Pharmacol 2017;12:253–8.

[30] Panahi Y, Hosseini MS, Khalili N, Naimi E, Simental-Mendía LE, Majeed M, et al. Effects of curcumin on serum cytokine concentrations in subjects with metabolic syndrome: a post-hoc analysis of a randomized controlled trial. Biomed Pharmacother 2016;82:578–82.

[31] Bingyan G, Yinghui S, Rui H, Derong H, Yongjun L. Influence of curcumin on serum adiponectin and vascular endothelial function in angina pectoris patients. Mod J Integrated Tradit Chin West Med 2010;(2):131–50. 1.

[32] Campos-Cervantes A, Murillo-Ortiz BO, Alvarado-Caudillo Y, Pérez-Vázquez V, Ramirez-Emiliano J. Curcumin decreases the oxidative damage indexes and increases the adiponectin levels in serum of obese subjects: 224. Free Radic Biol Med 2011;51:S95.

[33] Thota RN, Acharya SH, Abbott KA, Garg ML. Curcumin and long-chain Omega-3 polyunsaturated fatty acids for Prevention of type 2 Diabetes (COP-D): study protocol for a randomised controlled trial. Trials 2016;17:565.

[34] Chuengsamarn S, Rattanamongkolgul S, Phonrat B, Tungtrongchitr R, Jirawatnotai S. Reduction of atherogenic risk in patients with type 2 diabetes

by curcuminoid extract: a randomized controlled trial. J Nutr Biochem 2014;25:144–50.

[35] Campbell MS, Ouyang A, Krishnakumar I, Charnigo RJ, Westgate PM, Fleenor BS. Influence of enhanced bioavailable curcumin on obesity-associated cardiovascular disease risk factors and arterial function: a double-blind, randomized-controlled trial. Nutrition 2019.

[36] Chuengsamarn S, Rattanamongkolgul S, Luechapudiporn R, Phisalaphong C, Jirawatnotai S. Curcumin extract for prevention of type 2 diabetes. Diabetes Care 2012;35:2121–7.

[37] Panahi Y, Hosseini MS, Khalili N, Naimi E, Soflaei SS, Majeed M, et al. Effects of supplementation with curcumin on serum adipokine concentrations: a randomized controlled trial. Nutrition 2016;32:1116–22.

[38] Adibian M, Hodaei H, Nikpayam O, Sohrab G, Hekmatdoost A, Hedayati M. The effects of curcumin supplementation on high-sensitivity C-reactive protein, serum adiponectin, and lipid profile in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. Phytotherapy Research; 2019.

[39] Salahshooh MM, Parizadeh SMR, Pasdar A, Karimian MS, Safarian H, Javandoost A, et al. The effect of curcumin (Curcuma longa L.) on circulating levels of adiponectin in patients with metabolic syndrome. Comp Clin Pathol 2017;26:17–23.

[40] Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Mol Pharm 2007;4:807–18.

[41] Mirzaei H, Naseri G, Rezaee R, Mohammadi M, Banikazemi Z, Mirzaei HR, et al. Curcumin: a new candidate for melanoma therapy? Int J Cancer 2016;139:1683–95.

[42] Momtazi AA, Sahebkar A. Difluorinated curcumin: a promising curcumin analogue with improved anti-tumor activity and pharmacokinetic profile. Curr Pharmaceut Des 2016;22:4386–97.

[43] Panahi Y, Saadat A, Beiraghdar F, Sahebkar A. Adjuvant therapy with bioavailability-boosted curcuminoids suppresses systemic inflammation and improves quality of life in patients with solid tumors: a randomized double-blind placebo-controlled trial. Phytother Res 2014;28:1461–7.

[44] Rahmani S, Asgary S, Askari G, Keshvari M, Hatamipour M, Feizi A, et al. Treatment of non-alcoholic fatty liver disease with curcumin: a randomized placebo-controlled trial. Phytother Res 2016;30:1540–8.

[45] Esmaily H, Sahebkar A, Iranshahi M, Ganjali S, Mohammadi A, Ferns G, et al. An investigation of the effects of curcumin on anxiety and depression in obese individuals: a randomized controlled trial. Chin J Integr Med 2015;21:332–8.

[46] Panahi Y, Ghanei M, Hajhashemi A, Sahebkar A. Effects of curcuminoids-piperine combination on systemic oxidative stress, clinical symptoms and quality of life in subjects with chronic pulmonary complications due to sulfur mustard: a randomized controlled trial. J Diet Suppl 2016;13:93–105.

[47] Sahebkar A. Molecular mechanisms for curcumin benefits against ischemic injury. Fertil Steril 2010;94:e75–6.

[48] Polyzos SA, Toulis KA, Goulis DG, Zavos C, Kountouras J. Serum total adiponectin in nonalcoholic fatty liver disease: a systematic review and meta-analysis. Metabolism 2011;60:313–26.

[49] Antoniades C, Antonopoulos AS, Tousoulis D, Stefanadis C. Adiponectin: from obesity to cardiovascular disease. Obes Rev 2009;10:269–79.

[50] Rothenbacher D, Brenner H, März W, Koenig W. Adiponectin, risk of coronary heart disease and correlations with cardiovascular risk markers. Eur Heart J 2005;26:1640–6.

[51] Esfahani M, Movahedian A, Baranchi M, Goodarzi MT. Adiponectin: an adipokine with protective features against metabolic syndrome. Iran J Basic Med Sci 2015;18:430–42.

[52] Tan K. Dyslipidaemia, inflammation and endothelial dysfunction in diabetes mellitus. Int Congr Ser 2004;1262:511–4.

[53] Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Investig 2006;116:1793–801.

[54] Castro AVB, Kolka CM, Kim SP, Bergman RN. Obesity, insulin resistance and comorbidities? Mechanisms of association. Arquivos Brasileiros Endocrinol Metabol 2014;58:600–9.

[55] Vettor R, Milan G, Rossato M, Federspil G. Adipocytokines and insulin resistance. Aliment Pharmacol Ther 2005;22:3–10.

[56] Zaletel J, Barlovic DP, Prezelj J. Adiponectin-leptin ratio: a useful estimate of insulin resistance in patients with Type 2 diabetes. J Endocrinol Investig 2010;33:514–8.

[57] Finucane F, Luan J, Wareham N, Sharp S, O'Rahilly S, Balkau B, et al. Correlation of the leptin: adiponectin ratio with measures of insulin resistance in non-diabetic individuals. Diabetologia 2009;52:2345–9.

[58] Kappelle PJ, Dullaart RP, van Beek AP, Hillege HL, Wolffenbuttel BH. The plasma leptin/adiponectin ratio predicts first cardiovascular event in men: a prospective nested case–control study. Eur J Intern Med 2012;23:755–9.

[59] Qu XB, Zhao SP, Xu J, Dong LN. Effects of curcumin on secretion of adiponectin and interleukin-6 in human adipose tissues: an in vitro study. J Chin Integr Med 2008;6:711–3.

[60] Sahebkar A. Are curcuminoids effective C-reactive protein-lowering agents in clinical practice? Evidence from a meta-analysis. Phytother Res 2014;28:633–42.

[61] Panahi Y, Rahimnia AR, Sharafi M, Alishiri G, Saburi A, Sahebkar A. Curcuminoid treatment for knee osteoarthritis: a randomized double-blind placebo-controlled trial. Phytother Res 2014;28:1625–31.

[62] Bai YN, Zheng J, Song ZF, Du Y, Wen Y. Effect of curcumin on expression of adiponectin in mice with insulin resistance. J Shanghai Jiaot Univ (Med Sci) 2013;33:136–9.

[63] Weisberg SP, Leibel R, Tortoriello DV. Dietary curcumin significantly improves obesity-associated inflammation and diabetes in mouse models of diabesity. Endocrinology 2008;149:3549–58.

[64] Panahi Y, Khalili N, Hosseini MS, Abbasinazari M, Sahebkar A. Lipid-modifying effects of adjunctive therapy with curcuminoids-piperine combination in patients with metabolic syndrome: results of a randomized controlled trial. Complement Ther Med 2014;22:851–7.

[65] Panahi Y, Hosseini MS, Khalili N, Naimi E, Majeed M, Sahebkar A. Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: a randomized controlled trial and an updated meta-analysis. Clin Nutr (Edinb) 2015;34:1101–8.

[66] Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol 2001;54:1046–55.