Antioxidant effects of curcuminoids in patients with type 2 diabetes mellitus: a randomized controlled trial

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Received: 21 October 2016 / Accepted: 26 November 2016 © Springer International Publishing 2016

Abstract
Background Oxidative stress has a key role in the pathogenesis of type II diabetes mellitus (T2DM) and its vascular complications. Antioxidant therapy has been suggested as a potential approach to blunt T2DM development and progression. The aim of this study was to assess the effects of supplementation with curcuminoids, which are natural polyphenolics from turmeric, on oxidative indices in diabetic individuals.

Methods In this randomized double-blind placebo-controlled trial, 118 subjects with T2DM were randomized to curcuminoids (1000 mg/day co-administered with piperine 10 mg/day) or matching placebo for a period of 8 weeks. Serum total antioxidant capacity, superoxide dismutase (SOD) activities and malondialdehyde (MDA) concentrations were measured at baseline and after the supplementation period.

Results Curcuminoids supplementation caused a significant elevation in serum total antioxidant capacity (TAC) (p < 0.001) and SOD activities (p < 0.001), while serum MDA levels were significantly reduced compared with the placebo group (p < 0.001). These results remained statistically significant after adjustment for potential confounders (baseline differences in body mass index and fasting serum insulin).

Conclusion The present results support an antioxidant effect of curcuminoids supplementation in patients with T2DM, and call for future studies to assess the impact of these antioxidant effects on the occurrence of diabetic complications and cardiovascular endpoints.

Keywords Curcumin · Diabetes mellitus · Oxidative stress · Malondialdehyde · Total antioxidant capacity · Superoxide dismutase

Introduction
The World Health Organization (WHO) has reported that the prevalence of type II diabetes mellitus (T2DM) is about 311 million worldwide, increasing particularly in developing and low-income countries (Hogan et al. 2003). T2DM is a coronary heart disease (CHD) risk equivalent and prediabetes increases the risk of CHD (Huang et al. 2014). The overall risk of cardiovascular disease (CVD) has been reported to be at least twofold higher in diabetic versus non-diabetic subjects. It has been reported that around 50–70% of all subjects with type I and II diabetes mellitus die due to CVD (Standl et al. 2009).

Oxidative stress has a key role in the development of T2DM. Increased production of oxidative species and reduced antioxidant capacity have been repeatedly shown...
in subjects with T2DM (Palanisamy et al. 2011; Uchegbu and Ishiwu 2016). Hyperglycemia can contribute to oxidative stress through enhancement of the polyol pathway flux, activation of protein kinase C, alteration of eicosanoid metabolism and induction of glucose autoxidation that collectively results in increased reactive oxygen species (ROS) generation (Giacco and Brownlee 2010; Johansen et al. 2005). ROS can exert numerous detrimental effects that induce and aggravate diabetes including reduction of glucose transport channels, reduction of insulin secretion from pancreatic β cells, protein fragmentation and oxidation, DNA damage, free fatty acid generation and increased vascular permeability (Giacco and Brownlee 2010). Moreover, oxidative stress-induced formation of advanced glycation end products contributes to endothelial dysfunction and development of microvascular and macrovascular complications of T2DM (Giacco and Brownlee 2010; Johansen et al. 2005).

Owing to the aforementioned detrimental effects of oxidative stress on the development of T2DM and progression of its vascular complications, antioxidant therapy has been considered a potentially effective approach in reversing T2DM pathogenesis (Ceriello and Testa 2009; Johansen et al. 2005). Although epidemiological and observational studies support an inverse association between antioxidant intake and T2DM (Montonen et al. 2004), large-scale clinical trials with classical antioxidants, such as vitamin C and vitamin E, have provided mixed and ambiguous results (Boaz et al. 2000; Lonn et al. 2001; Sacco et al. 2003). Therefore, new antioxidant compounds that could reduce oxidative stress via different mechanisms including quenching free radicals and the enhancement of biological enzymatic antioxidant activity, warrant testing for possible beneficial effects in diabetic subjects.

Curcuminoids (including curcumin, demethoxycurcumin and bisdemethoxycurcumin) are turmeric-extracted polyphenolic pigments that possess numerous health benefits. Molecular targets of curcuminoids are diverse and include transcription factors, enzymes, cytokines, micro-RNAs, hormones and receptors (Kasi et al. 2016; Montazi et al. 2016a, b; Zhou et al. 2011). This wide spectrum of biological targets confers multiple pharmacological activities on curcuminoids including anti-tumor (Mirzaei et al. 2016; Montazi and Sahebkar 2016), anti-inflammatory (Panahi et al. 2012b, 2015b, 2016c; Sahebkar 2014a), analgesic (Sahebkar and Henrotin 2016), lipid-modifying (Mohammadi et al. 2013; Panahi et al. 2016d; Sahebkar 2013, 2014b), anti-arthritis (Panahi et al. 2014b), anti-ischemic (Sahebkar 2010), hepatoprotective (Rahmani et al. 2016; Zabihi et al. 2016) and immunomodulatory (Derosa et al. 2016; Ghandadi and Sahebkar 2016; Karimian et al. 2016; Sahebkar et al. 2016) properties. Moreover, curcuminoids have strong antioxidant properties and can suppress lipid peroxidation and scavenge hydroxyl and superoxide radicals (Ruby et al. 1995; Sahebkar et al. 2015). It has been shown that curcuminoids can improve activities of enzymatic antioxidants such as catalase, glutathione peroxidase and superoxide dismutase (SOD) (DiSilvestro et al. 2012a; Panahi et al. 2012a), and detoxifying enzymes, such as glutathione-S-transferase (Piper et al. 1998). However, previous studies investigating the antioxidant properties of curcuminoids in diabetic patients have been very limited with no evidence on the effect of bioavailability-improved preparations of curcuminoids. This study aimed to undertake this task in the context of a randomized double-blind placebo-controlled trial.

Materials and methods

Subjects

Adult subjects aged 18-65 years were recruited from those referring to the Diabetes Clinic of the Baqiyatallah Hospital (Tehran, Iran). The inclusion criteria included the presence of T2DM based on fasting plasma glucose (FPG) ≥126 mg/dL, glycated hemoglobin (HbA1C) ≥6.5%, or the use of standard anti-diabetic treatments. Exclusion criteria were pregnancy or breastfeeding, impossibility to give informed consent, participation in a concomitant trial, presence of malignancies, chronic liver disease (alanine aminotransferase levels three times upper limit of normal value range, renal failure (serum creatinine ≥2.0 mg/dL or being on dialysis), chronic inflammatory diseases, such as rheumatoid arthritis and acute infections, endocrine diseases other than T2DM (e.g. hypothyroidism or hyperthyroidism), obsessive compulsive disorder, hyperglycemia due to secondary causes, receiving hormone therapy or other herbal medicines, hypersensitivity to the study medication, and lack of compliance with the study medication.

Study design

This study was designed as a randomized double-blind placebo-controlled trial with a parallel-group design. Subjects who met the aforementioned inclusion criteria (n = 118) were randomly allocated to either curcuminoids (Curcin C3 Complex®, Sami Labs LTD, Bangalore, India) or placebo for a period of 3 months. Curcuminoid and placebo capsules were matched in shape, size and color, and the color of placebo (microcrystalline cellulose) was matched to that of curcuminoid powder. To enhance the oral bioavailability of curcuminoids, 5 mg piperine (Bioperine®; Sami Labs LTD, Bangalore, India) was added to each 500 mg curcuminoid capsule. C3 Complex®
preparation that was used in this study contains the three major curcuminoids including curcumin, demethoxycurcumin and bisdemethoxycurcumin in patented ratio.

The study protocol was approved by the Ethics Committee at the Baqiyatallah University of Medical Sciences, registered in the Iranian Registry of Clinical Trials (Code: IRCT201505301165N4), and written informed consent was obtained from all individuals. The study was performed between June 22, 2015 and April 20, 2016.

Blood sampling

Overnight fasting blood samples were collected at baseline and at the end of the study. The samples were allowed to clot for about 30 min and then centrifuged at 750 g for 10 min to obtain serum. Sera were aliquoted and frozen at –80 °C until measurements.

Measurements

Serum concentrations of insulin and hemoglobin A1C (HbA1C) were measured using immunoassay and ion exchange chromatography techniques, respectively. Homeostasis model of assessment-insulin resistance (HOMA-IR) was calculated as: fasting insulin (µIU/mL) × fasting glucose (mmol/L)/22.5.

Serum activities of SOD and concentrations of malondialdehyde (MDA) were determined spectrophotometrically using routine methods. Serum total antioxidant capacity (TAC) was measured colorimetrically using a previously described procedure (Miller et al. 1993).

Weight, height, and systolic and diastolic blood pressures were measured according to standard procedures. To calculate BMI, weight (in kilograms) was divided by height (in squared meters [m²]).

Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows Version 20.0 (IBM Corp., Armonk, NY, USA). Data were expressed as mean ± SD or number (%). Within-group comparisons were performed using paired samples t test or Wilcoxon signed-ranks test for normally and non-normally distributed data, respectively. Between-group comparisons were performed using independent samples t test or Mann–Whitney U test for normally and non-normally distributed data, respectively. Comparison of categorical variables between the groups was performed using Chi-square test. Bivariate correlations between changes in serum levels of SOD, MDA and TAC were performed using Pearson’s and Spearman’s correlation coefficients for normally and non-normally distributed data, respectively. Univariate analysis of covariance (ANCOVA) using general linear model was used to adjust for the effect of potential confounders on the association between curcuminoids supplementation and changes in serum levels of SOD, MDA and TAC.

Results

One hundred subjects completed the trial, including 50 in each group. Drop-outs were due to being lost to follow-up and occurred at equal rates in both groups. Curcuminoids were safe and no severe adverse events were reported during the course of study.

Clinical and biochemical features of the study groups at baseline are summarized in Table 1. The groups were comparable in their baseline serum levels of SOD, MDA and TAC. BMI (p = 0.047), serum insulin (p = 0.029) and HOMA-IR (p = 0.005) were significantly higher in the curcuminoids group. Serum glucose and HbA1c were not significantly different between the study groups at baseline.

Comparison of parameters before vs. after intervention revealed significant reductions in weight (p < 0.001) and BMI (p < 0.001) in the curcuminoids group. In contrast, there were increases in the placebo group (p = 0.020 for weight and p < 0.023 for BMI). With respect to oxidative indices, significant elevations in serum SOD (p = 0.001)

<table>
<thead>
<tr>
<th></th>
<th>Curcuminoids</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>25/25</td>
<td>26/24</td>
<td>1.00</td>
</tr>
<tr>
<td>Age (year)</td>
<td>43 ± 8</td>
<td>41 ± 7</td>
<td>0.190</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.14 ± 6.65</td>
<td>168.78 ± 7.31</td>
<td>0.095</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.66 ± 7.37</td>
<td>77.9 ± 6.77</td>
<td>0.866</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.53 ± 2.32</td>
<td>27.33 ± 1.58</td>
<td>0.047</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.25 (6.80–8.10)</td>
<td>7.45 (6.90–8.10)</td>
<td>0.671</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>171.0 (142.5–187.0)</td>
<td>179.0 (156.0–195.0)</td>
<td>0.074</td>
</tr>
<tr>
<td>Insulin (mIU/L)</td>
<td>20.24 ± 3.54</td>
<td>21.72 ± 3.11</td>
<td>0.029</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>8.10 ± 2.11</td>
<td>9.38 ± 2.30</td>
<td>0.005</td>
</tr>
<tr>
<td>SOD (U/mL)</td>
<td>3.46 ± 0.49</td>
<td>3.39 ± 1.01</td>
<td>0.715</td>
</tr>
<tr>
<td>MDA (nmol/mL)</td>
<td>3.90 ± 1.06</td>
<td>3.74 ± 1.32</td>
<td>0.490</td>
</tr>
<tr>
<td>TAC (nmol/mg)</td>
<td>3.17 (2.65–3.89)</td>
<td>3.17 (2.42–3.80)</td>
<td>0.591</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD for normally distributed data, and median and interquartile range for non-normally distributed data. Between groups comparisons were assessed by parametric statistical analysis for normal distributed data and non-parametric test for non-normally distributed data.

BMI body mass index, HOMA-IR the homeostasis model assessment-estimated insulin resistance, SOD superoxide dismutase, MDA malondialdehyde, TAC total antioxidant capacity.
Disturbed metabolism of lipids and carbohydrates in T2DM leads to oxidative stress which is itself a contributing factor to the detrimental vascular complications of T2DM (Chait and Bornfeldt 2009; Palanisamy et al. 2011). Hyperglycemia increases the production of ROS and induces DNA single-strand breaks (Giacco and Brownlee 2010; Johansen et al. 2005). Oxidative stress can deteriorate β-cell function and contribute to the pathogenesis of T2DM, while promoting gluotoxicity and lipotoxicity in diabetic individuals (Giacco and Brownlee 2010; Johansen et al. 2005; Rother 2007). It has been shown that reduced expression of antioxidant enzymes in pancreatic β cells makes these cells susceptible to ROS-induced damage (Poitout and Robertson 2008). Brownlee reported that accumulation of diacylglycerols followed by protein kinase C activation in vascular cells and production of advanced glycation end products (AGEs) have key roles in increasing oxidative and nitrosative burden and release of ROS and reactive nitrogen species in hyperglycemic states (Brownlee 2001). Vikramadithyan et al. showed that augmented glucose efflux through the aldose reductase pathway has an important role in this process (Vikramadithyan et al. 2005). Increased intracellular glucose levels cause higher glucose oxidation and higher NADH and FADH2 entry to the mitochondrial electron transport chain. Subsequently,
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Table 4  Comparison of the changes in oxidative indices at baseline and at the study end in each gender

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Curcuminoids</td>
<td>Placebo</td>
</tr>
<tr>
<td>SOD</td>
<td>0.3636 ± 0.85</td>
<td>−0.5862 ± 1.26</td>
</tr>
<tr>
<td>MDA</td>
<td>−1.0720 ± 0.81</td>
<td>0.2192 ± 1.14</td>
</tr>
<tr>
<td>TAC</td>
<td>0.30 (−0.04 to −0.95)</td>
<td>−0.31 (−1.07 to −0.06)</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD for normally distributed data, and median and interquartile range for non-normally distributed data. Between groups comparisons were assessed by parametric statistical analysis for normal distributed data and nonparametric test for non-normally distributed data

BMI body mass index, SOD superoxide dismutase, MDA malondialdehyde, TAC total antioxidant capacity

electrons accumulate in coenzyme Q leading to the generation of superoxide radicals (Giacco and Brownlee 2010). In addition to increased ROS formation, there is ample evidence suggesting depleted biological antioxidant defenses in diabetic subjects (Bajaj and Khan 2012). Hence, antioxidant pharmacotherapy has been recommended as a viable approach to prevent diabetic complications and comorbidities. In this context, it has been shown that oxidative damage in diabetic individuals can be decreased by the intake of antioxidants. Ascorbic acid, N-acetylcysteine and α-lipoic acid have been demonstrated to be efficacious in preventing diabetic complications (Bajaj and Khan 2012). Curcuminoids are natural antioxidants that can exert protective effects via both free radical scavenging and enhancement of biological antioxidant defense systems (Maheshwari et al. 2006; Sahebkar et al. 2013). The free radical scavenging activities of curcuminoids are mainly exerted by their phenolic hydroxyl functional groups, making curcuminoids chain-breaking antioxidants. Curcuminoids can decrease nitric oxide (NO) bioavailability and protect against NO-driven reactive intermediates (Amin and Bano 2012). Moreover, curcuminoids preferentially chelate the redox-active metals and suppress chain reactions producing metal ion-induced radicals (Baum and Ng 2004). This latter activity of curcuminoids is believed to be due to the action of their α-β-unsaturated β-diketone moiety.

To our knowledge, this study is the first clinical report on the impact of curcuminoid–piperine supplementation on oxidative indices of subjects with T2DM. There has been only one previous study in which 3-month supplementation with curcuminoids (300 mg/day) increased SOD activities but had no effect on glutathione peroxidase and MDA levels in diabetic individuals (Na et al. 2014); the latter effects may be due to the lower administered dose compared with this study.

In spite of the paucity of data from clinical trials, antioxidant effects of curcuminoids have been reported in other conditions closely linked to T2DM. In a cross-over trial, 30-day supplementation with a curcuminoid-piperine combination at the same dose of this study resulted in a significant reduction of pro-oxidant-antioxidant balance (as a surrogate measure of overall oxidative stress status) in obese dyslipidemic individuals (Sahebkar et al. 2013). In another study in subjects with metabolic syndrome, 8-week curcuminoids supplementation with the same dose and formula as that used in this study improved serum SOD activities and reduced MDA concentrations (Panahi et al. 2015c). There are also reports demonstrating amelioriation of oxidative indices in subjects with knee osteoarthritis (Panahi et al. 2016a), chronic obstructive pulmonary disease (Panahi et al. 2016b) and sulfur mustard-induced chronic complications (Panahi et al. 2012a), as well as in healthy (DiSilvestro et al. 2012b) and arsenic-exposed individuals (Biswas et al. 2010).

Clinical use of curcuminoids has been alleged to be limited by low oral bioavailability owing to the rapid intestinal and hepatic metabolism of these compounds which occur mainly in the form of glucuronidation (Anand et al. 2007). To tackle this potential limitation, curcuminoids were co-administered with piperine in this study. Piperine is an alkaloid extracted from Piper species that has absorption-enhancing effects through blocking both intestinal and hepatic glucuronidation (Shoba et al. 1998). The efficacy and safety of such a combination has been shown in several previous trials (Esmaily et al. 2015; Khonche et al. 2016; Panahi et al. 2012a, 2014a, 2015a).

Conclusion

This study produced results on the antioxidant impact of curcuminoids, co-supplemented with piperine, in subjects with T2DM following a 12-week supplementation period. Owing to the detrimental effects of oxidative stress on the pathogenesis of T2DM and its long-term complications, curcuminoids could be regarded as a safe antioxidant supplement in diabetic subjects. Future studies assessing the impact of curcuminoids on the occurrence of diabetic complications and cardiovascular endpoints are warranted.
Acknowledgements This study was financially supported by Clinical Trial Research Center (Tehran, Iran). The authors gratefully acknowledge Sami Labs LTD (Bangalore, India) for providing the drug material used in this trial.

Compliance with ethical standards

Conflict of interest Muhammed Majeed is the CEO of Sabinsa Corporation and Sami Labs Ltd.

References


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