

Effects of epigallocatechin gallate on total antioxidant capacity, biomarkers of systemic low-grade inflammation and metabolic risk factors in patients with type 2 diabetes mellitus: the role of *FTO*-rs9939609 polymorphism

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Abstract

Introduction: Type 2 diabetes mellitus (T2DM) is known as one of the most common metabolic diseases and *FTO* polymorphism has been implicated in the susceptibility to this disease. Epigallocatechin-3-gallate (EGCG) has shown favorable effects on risk factors related to T2DM. The present study aimed to investigate the effects of EGCG on total antioxidant capacity, biomarkers of systemic low-grade inflammation and metabolic risk factors in patients with T2DM considering the role of *FTO* polymorphism.

Material and methods: In this double-blind randomized clinical trial, 60 patients with T2DM (20–60 years) were randomly allocated to three groups. Group 1 received 300 mg of EGCG (TT genotype). Group 2 received 300 mg of EGCG (AA + AT genotypes) and Group 3 received placebo. We genotyped *FTO* (rs9939609) and measured body mass index (BMI), blood pressure, profile lipid, interleukin-6, high sensitivity C-reactive protein and total antioxidant capacity, before and after the intervention, at 2 months.

Results: In carriers of A allele, EGCG intervention caused a significant decrease in BMI, diastolic blood pressure (DBP), mean arterial pressure and serum cholesterol level compared with placebo ($p < 0.05$). Also, we found a significant gene-treatment interaction effect between *FTO*-rs9939609 and EGCG on BMI and DBP ($P > 0.05$).

Conclusions: These findings suggest that carriers of the risk alleles (A) of *FTO*-rs9939609 have a better response to EGCG in improving BMI and DBP in patients with T2DM.

Key words: body mass index, diabetes mellitus, epigallocatechin-3-gallate, *FTO*.

Introduction

Type 2 diabetes mellitus (T2DM) is known as one of the most common metabolic diseases. According to the International Federation of Diabetes (IDF) statistics, the prevalence of diabetes mellitus was about 415 million people worldwide in 2015 and this will rise to 642 million in 2040 [1]. Type 2 diabetes mellitus mainly results from the interaction among genetic, environmental and other risk factors [2–4]. Furthermore, the increase in the prevalence of T2DM is closely linked to obesity (especially abdominal obesity). Obesity causes elevation of free fatty acids (FFAs) in the bloodstream, which inhibit glucose transport activity, diminution of glucose uptake by muscle, glycogen synthesis in skeletal muscle and induce insulin resistance (IR) [5]. Increasing evidence suggests that obesity (especially visceral adipose tissue) induces low-grade inflammation affects the pathogenesis of T2DM in obese patients [6]. During low-grade systemic inflammation, the insulin-dependent tissues are exposed to infiltration of inflammatory macrophages which interferes with the ability of these tissues to respond to insulin [7]. Type 2 diabetes mellitus is a multifactorial disease and needs multi-therapy for more effective treatment [8]. Although pharmacotherapy and lifestyle modifications can improve T2DM [9–11], studies have shown that therapeutic approaches can be affected by genetic factors such as the polymorphism of diabetes-related genes [12].

FTO (fat mass and obesity-associated) is a candidate gene for predisposing to T2DM, identified through genome-wide association studies (GWASs) [13]. The studies reported a strong correlation between the sequence variation of the *FTO* gene, obesity, T2DM and metabolic risk factors [14]. Although some diabetes-associated variants of the *FTO* gene are dependent on body mass index (BMI) and obesity, recently a meta-analysis indicated obesity-independent associations between the SNP rs9939609 of the *FTO* gene and T2DM risk [15].

Epigallocatechin-3-gallate (EGCG) is a polyphenolic compound, belonging to the catechin family. Epigallocatechin-3-gallate is the most abundant (approximately 65%) and has the highest biological activity among catechins of green tea [16]. Epigallocatechin-3-gallate is classified as an antioxidant (based on its chemical structure) and a potential mechanism for beneficial health effects may be attributable to its anti-oxidative function. Recently, studies reported direct effects of EGCG that are independent of anti-oxidative mechanisms [17]. Epigallocatechin-3-gallate has beneficial effects on obesity through increased cellular production

of reactive oxygen species, leading to the activation of adenosine monophosphate-activated protein kinase (AMPK), which suppresses gene and protein expression of transcription factors and enzymes involved in adipogenesis and lipogenesis, and stimulates lipolysis [18]. Previous studies suggested that EGCG causes reduced fasting blood sugar (FBS) levels by a change in the expression of the *GLUT4* gene, increase in insulin sensitivity and facilitates entry of glucose into cells [19]. Epigallocatechin-3-gallate reduces the rate of cholesterol absorption by affecting the micellar solubilization of cholesterol in the digestive tract [20].

Although the effect of EGCG on T2DM was evaluated in *in vivo* and *in vitro* studies, the results of clinical trials are inconsistent. In addition, the role of genetic differences in response to EGCG have never been evaluated. Therefore, the present study aimed to evaluate the effects of EGCG supplementation on biomarkers of systemic low-grade inflammation and metabolic risk factors in patients with T2DM and to study the effects of the *FTO* (rs9939609) gene polymorphism on response to EGCG supplementation.

Material and methods

Participants

Sixty-six patients with T2DM, screened from an endocrine clinic, were recruited. Inclusion criteria were as follows: 20–60 years old, BMI of 18.5 to 35 kg/m², fasting blood glucose \geq 126 mg/dl, T2DM patients with disease duration more than 2 years since diagnosis. Exclusion criteria were as follows: suffering from diabetes mellitus complications such as foot ulcer and kidney failure, pregnant or lactating women, inflammatory disease, biliary tract obstruction and gallstones, liver dysfunction, Cushing's syndrome, adrenal or thyroid dysfunction, cancer, cardiovascular diseases and recent surgery.

Moreover, taking antioxidant supplements (for example lycopene, β -carotene, selenium, vitamin A, vitamin C, vitamin E and fish oil) during the past 6 months, using insulin and corticosteroids and following a weight-loss diet over the past 3 months were also considered as exclusion criteria.

Ethical approval

The study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (ID: IRAJUMS.REC.1395.548), and all patients completed an informed consent form. The study was registered in the Iranian Registry of Clinical Trials (IRCT), available at <http://www.irct.ir> (ID: IRCT2017021612949N3).

Study design and randomization

This study was a randomized double-blind placebo-controlled trial conducted in Ahvaz, Iran, from August 2017 to March 2018. Prescreening was applied by interview for patients; eligible participants were included in the study after *FTO*-rs9939609 polymorphism assays. The group design was based on *FTO* variant alleles (homozygous = AA and heterozygous = AT) and 2 wild-type alleles (TT). The participants were randomly allocated to the three groups: EGCG supplement (TT genotype, $n = 22$), EGCG supplement (AT + AA genotype, $n = 22$) and placebo (A + T genotype, $n = 22$). The flowchart of the study is presented in Figure 1. The participants were grouped randomly by a third person and the researchers were blinded to the supplement type given to patients. The participants were matched for age and BMI. The intervention groups received two tablets of EGCG supplement containing 300 mg/day EGCG of *Camellia sinensis* leaves for 2 months. The placebo group received the same number of placebo tablets (corn starch) for 2 months. All subjects were contacted and monitored weekly by telephone to ensure that they were using prescribed capsules. Also, they were asked to return the remaining tablets for evaluation of compliance. During the study, all subjects were asked to maintain their dietary

intake and physical activity and report about any possible adverse effects.

Anthropometric and blood pressure measurement

Weight (accuracy of 0.1 kg) and height (accuracy of 0.1 cm) of participants were determined in an overnight fasting status using a standard scale (Seca) at the onset of the study and after 2 months' intervention. Body mass index was calculated using the formula: (weight (kg))/(height² (M)). The participants were asked to sit on a chair and have no physical activity for 1 h before sampling. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate were measured. The mean arterial pressure (MAP) was calculated using the formula: (2DBP + SBP)/3.

Biochemical measurements

The blood samples (5 ml) were collected during the study (2 months) in the 12-hour fasting condition. The blood samples were centrifuged (3,000 rpm for 10 min). The lipid profile levels were determined immediately after sampling and the remnants of sera were stored at -80°C for later assessment. The concentrations of serum triglyceride (TG), total cholesterol (TC), very low-density lipoprotein (VLDL), low-density lipoprotein

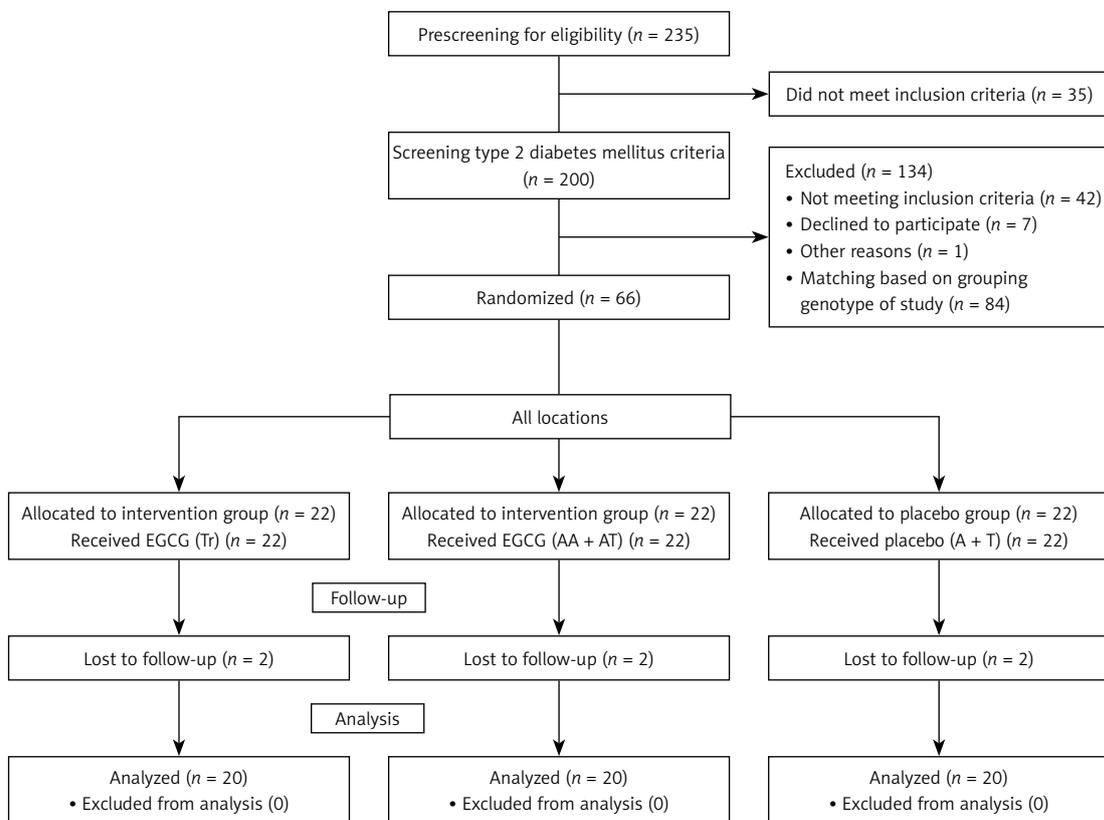


Figure 1. Flowchart of the study

(LDL-C) and high-density lipoprotein (HDL-C) were measured by auto-analyzer. The atherogenic index of plasma (AIP) was calculated as the logarithm of the molar ratio of TG/HDL-C. The serum interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP) and total antioxidant capacity (TAC) concentrations were assessed by ELISA kits.

Genotyping

A 5 ml blood sample was collected in EDTA containing tubes and stored (at -80°C) for extraction of DNA. Genomic DNA was extracted from whole blood samples using DNA purification kit (Sinacolon, Iran). Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used for genotyping the single-nucleotide polymorphisms (SNPs) of the *FTO*-rs9939609. A DNA fragment (containing rs9939609 polymorphism) was amplified using primers. The polymerase chain reaction product of the *FTO* gene was digested by *ScaI* restriction enzyme to analyze for polymorphism by RFLP assay.

Statistical analysis

All analyses were performed with SPSS 20.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to assess normality of data. In order to assay differences before and after the intervention within groups, the paired sample *t* test was used. Baseline characteristics were compared by χ^2 and ANOVA. Comparison between groups was done by ANOVA. A *p*-value < 0.05 was considered significant.

Results

Of the 235 volunteers, 200 were eligible and underwent genotyping, anthropometric and bio-

chemical assessments. Among them, 66 patients with T2DM were recruited to the study. After 2 months, there were two dropouts in each group. Consequently, the data were analyzed for 60 patients (Figure 1).

Baseline characteristics for placebo and EGCG groups according to the *FTO*-rs9939609 genotypes are shown in Table I. No significant differences between any of the three group means were detected in age, gender, BMI, education, disease duration and marital status (Table I).

Within-group analysis after EGCG intervention on profile lipid, BMI, BP, inflammatory markers and TAC levels, regarding *FTO*-rs9939609 are presented in Table II.

In both EGCG groups we observed a significant reduction of BMI after intervention compared with baseline ($p < 0.05$). However, a significant reduction was observed in DBP, MAP and TC in group EGCG (AA + AT).

Between-group analysis of EGCG effects, regarding *FTO*-rs9939609, showed that the at-risk (AA/AT) carriers of *FTO*-rs9939609 had a better response to EGCG in improving BMI and DBP compared with participants with the nonrisk (TT) genotype (Table III). There were no significant differences in other variables after 2 months between risk and nonrisk carriers.

Discussion

In the current study, we investigated the modulation of metabolic and inflammatory responses to EGCG supplementation by polymorphism of *FTO*-rs9939609 in patients with T2DM. After 2 months of intervention, the levels of DBP and BMI were significantly decreased in carriers of the A allele of *FTO*-rs9939609 in the EGCG group compared with nonrisk carriers (TT).

Table I. Baseline characteristics of study patients

Variables	EGCG group (TT)	EGCG group (AA + AT)	Placebo group (A + T)	<i>P</i> -value ^a
Age [years]	52.25 \pm 6.78	53.60 \pm 8.03	55.25 \pm 11.04	0.56
Female, <i>n</i> (%)	12 (60)	11 (55)	13 (72.2)	0.81
BMI [kg/m ²]	29.48 \pm 4.48	29.59 \pm 4.06	28.35 \pm 3.57	0.57
Education, <i>n</i> (%):				
Diploma or less	17 (85)	17 (85)	18 (90)	0.86
University	3 (15)	3 (15)	2 (10)	
Marital status, <i>n</i> (%):				
Had partner	19 (95)	19 (95)	18 (90)	0.77
Without partner	1 (5)	1 (5)	2 (10)	
Disease duration [months]	97.20 \pm 61.66	92.40 \pm 60.07	95.40 \pm 58.97	0.96

BMI – body mass index. All values are means \pm SD, numbers and percentage. ^aPost-baseline changes within groups.

Table II. Effects of epigallocatechin-3-gallate (EGCG) on anthropometric indexes and blood pressure, regarding FTO-rs9939609

Variables	EGCG group (TT)			EGCG group (AA + AT)			Placebo (A + T)		
	Baseline	End	P ^a	Baseline	End	P ^a	Baseline	End	P ^a
BMI	29.48 ±4.48	29.10 ±4.22	0.03	29.59 ±4.06	29.20 ±4.03	0.01	28.35 ±3.57	28.52 ±3.75	0.37
SBP	14.28 ±2.39	14.03 ±2.02	0.65	14.69 ±2.63	13.99 ±2.20	0.25	13.18 ±2.24	12.68 ±2.09	0.13
DBP	8.96 ±1.05	8.92 ±1.13	0.88	9.16 ±1.24	8.55 ±0.95	0.03	8.08 ±1.32	7.88 ±1.23	0.32
Heart rate	82.17 ±9.85	81.29 ±10.54	0.64	80.15 ±9.82	80.26 ±10.85	0.95	87.17 ±12.05	89.58 ±15.01	0.41
MAP	10.74 ±1.26	10.62 ±1.25	0.71	11.01 ±1.46	10.37 ±1.20	0.03	9.78 ±1.56	9.48 ±1.42	0.18
TG	169.10 ±80.32	161.75 ±74.21	0.47	188.70 ±133.52	159.40 ±79.74	0.10	210.95 ±106.114	221.35 ±97.22	0.62
TC	171.65 ±34.62	163.15 ±42.12	0.13	170.55 ±32.85	157.90 ±37.87	0.01	154.70 ±39.22	157.00 ±43.95	0.69
LDL-C	84.55 ±28.11	82.83 ±36.08	0.70	79.70 ±27.99	78.14 ±33.56	0.71	68.68 ±26.67	69.00 ±30.66	0.94
HDL-C	50.35 ±8.65	49.70 ±8.26	0.28	52.15 ±7.87	50.95 ±6.95	0.25	47.35 ±9.33	48.60 ±10.49	0.32
VLDL	33.89 ±16.27	32.44 ±15.04	0.49	39.42 ±29.69	31.97 ±16.20	0.09	41.90 ±20.82	44.29 ±19.37	0.57
AIP	0.46 ±0.22	0.49 ±0.23	0.48	0.49 ±0.27	0.45 ±0.22	0.15	0.45 ±0.21	0.49 ±0.30	0.45
IL-6	2.04 ±1.23	1.96 ±1.31	0.85	2.60 ±2.17	2.15 ±1.36	0.45	1.88 ±1.76	1.83 ±1.22	0.89
hs-CRP	3.55 ±0.65	3.74 ±0.29	0.25	3.68 ±0.27	3.63 ±0.39	0.47	4.68 ±0.42	4.65 ±0.36	0.77
TAC	0.38 ±0.16	0.39 ±0.08	0.69	0.38 ±0.18	0.40 ±0.09	0.76	0.36 ±0.14	0.29 ±0.30	0.32

BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, MAP – mean arterial pressure, TG – triglyceride, TC – total cholesterol, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, VLDL – very low-density lipoprotein, AIP – atherogenic index of plasma, IL-6 – interleukin-6, hs-CRP – high-sensitivity C-reactive protein, TAC – total antioxidant capacity. All values are means ± SD. ^aPost-baseline changes within group.

Table III. Between-group analysis of epigallocatechin-3-gallate (EGCG) effects, regarding *FTO*-rs9939609

Variables	EGCG group (TT)	EGCG group (AA + AT) Δ	Placebo (A + T)	P-value ^a
BMI [kg/m ²]	0.37 ±0.72 ^c	-0.39 ±0.66 ^{b,d}	0.16 ±0.81	0.03
SBP [mm Hg]	-0.24 ±2.38	-0.70 ±2.57	-0.49 ±1.34	0.99
DBP [mm Hg]	-0.04 ±1.35	-0.61 ±1.17 ^{b,d}	-0.20 ±0.84	0.03
Heart rate	0.88 ±7.72	0.10 ±7.87	2.41 ±9.80	0.43
MAP	-0.11 ±1.32	-0.64 ±1.22	-0.29 ±0.91	0.21
TG [mg/dl]	-7.35 ±45.18	-29.30 ±76.80	10.40 ±92.89	0.24
TC [mg/dl]	-8.50 ±24.11	-12.65 ±20.39	2.30 ±25.42	0.12
LDL-C [mg/dl]	-1.72 ±20.17	-1.56 ±18.53	0.31 ±20.53	0.93
HDL-C [mg/dl]	0.65 ±2.64	1.20 ±4.54	-0.65 ±2.64	0.18
VLDL [mg/dl]	-1.44 ±9.27	-7.44 ±18.72	-2.39 ±18.52	0.16
AIP	-0.03 ±0.17	-0.03 ±0.11	0.04 ±0.22	0.33
IL-6	-0.08 ±0.41	-0.45 ±2.67	-0.04 ±1.27	0.78
hs-CRP	0.19 ±0.75	0.05 ±0.32	0.02 ±0.33	0.25
TAC	0.01 ±0.19	0.01 ±0.23	0.07 ±0.32	0.44

BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, MAP – mean arterial pressure, TG – triglyceride, TC – total cholesterol, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, VLDL – very low-density lipoprotein, AIP – atherogenic index of plasma, IL-6 – interleukin-6, hs-CRP – high-sensitivity C-reactive protein, TAC- total antioxidant capacity. All values are means ± SD. ^aChanges between the three groups. ^bSignificant changes in EGCG group (AA + AT) compared to placebo. ^cSignificant changes in EGCG group (TT) compared to placebo. ^dSignificant changes in EGCG group (AA + AT) compared to EGCG group (TT).

Evidence demonstrated that the minor A allele of the *FTO* variant rs9939609 has a significant association with the risk of T2DM [21]. However, there are few clinical trials about the effect of this polymorphism on clinical outcomes resulting from interventions.

Previous studies reported a genotype-intervention interaction for the *FTO* (rs9939609) gene polymorphism [22–24]. Luis *et al.* investigated the role of the rs9939609 polymorphism of the *FTO* gene in insulin resistance, metabolic changes and weight loss following a high monounsaturated fat diet vs. a high polyunsaturated fat hypocaloric diet. Their results showed that reductions in BMI, weight and fat mass were better in A allele carriers than TT genotype subjects with a high polyunsaturated fat hypocaloric diet in obese subjects over 3 months [22]. In another study, Zou *et al.* examined the effects of exercise combined with dietary intervention on obese children and adolescents associated with the *FTO*-rs9939609 polymorphism. After 4 weeks of intervention, the levels of TC and LDL were significantly reduced in genotype AA (or AT) compared with genotype TT [23]. In addition, a clinical trial in obese subjects with the *FTO*-rs9939609 gene variant demonstrated that decreases in hs-CRP, TC and LDL levels were larger in A carriers during 3 months of low fat hypocaloric diet [24]. In contrast, some studies did not report the role of *FTO*-rs9939609 polymorphism in response to interventions. Schum *et al.*

studied the effects of *FTO* (rs9939609) gene polymorphism on body composition and metabolism following a 6-month lifestyle intervention in overweight children. *FTO* variant rs9939609 had no impact on BMI, body composition and metabolic profile (insulin, HOMA, lipids, liver function tests) before and after lifestyle intervention [25]. Different interventions, type and characteristics of study persons are potential reasons for discrepant findings.

This study showed that taking EGCG supplements for 2 months in patients T2DM was associated with a significant decrease in serum cholesterol level, but did not influence other lipid profiles (TG, HDL and LDL). Similar to our findings, a systematic review suggested that administration of EGCG (107–856 mg/day) for 4 to 14 weeks reduced the level of serum LDL-C (by -9.29 mg/dl) in healthy individuals [26]. In addition, Zheng *et al.* in a meta-analysis observed that the consumption of beverages and extracts of green tea caused a decrease in serum concentrations of TC (by 7.20 mg/dl) and LDL cholesterol (by 2.19 mg/dl), but did not significantly improve HDL cholesterol level [27]. Possible mechanisms by which EGCG decreases plasma cholesterol include: interfering with the micellar solubilization of cholesterol in the digestive tract and decreased absorption [20], enhanced biliary cholesterol secretion and attenuated liver cholesterol accumulation [28], induced up-regulation of LDL receptor in HepG2 cells [29].

In contrast to our results, a double-blind clinical trial studied the effect of decaffeinated green tea extract (856 mg of EGCG) on obese individuals with type 2 diabetes [30]. No significant differences were reported between the EGCG and placebo groups in FBS and lipid profile (TG, Chol, HDL and LDL). However, a significant reduction in WC, HbA_{1c}, insulin and HOMA-IR levels was reported after EGCG intervention compared to baseline [30]. Also, Mielgo-Ayuso *et al.* examined the effects of EGCG (300 mg/day for 12 weeks) in obese women. No significant difference was reported in the weight, fat mass, energy and fat metabolism, TG, cholesterol and LDL, or insulin resistance after EGCG intervention [31]. These discrepancies in results might be due to the different dosages, duration of the intervention, sample size, and clinical characteristics of the patients at baseline.

In our study, intervention of EGCG caused a significant reduction in DBP level. In the context, most previous studies were consistent with our results. A meta-analysis suggested that green tea consumption significantly decreased SBP (−1.98 mm Hg) and DBP (−1.92 mm Hg) levels compared with the placebo group [32]. Furthermore, a meta-analysis (thirteen studies) reported that green tea and its catechins can improve blood pressure (SBP, by −2.08 mm Hg, and DBP, by −1.71 mm Hg), and the effects may be greater in people with hypertension (SBP ≥ 130 mm Hg) [33]. In another study, Han *et al.* reported that EGCG inhibited caffeine-induced cardiovascular activity such as arterial pressure and heart rate [34]. Epigallocatechin-3-gallate reduces blood pressure through several mechanisms such as: maintaining vascular tone through balancing vasoconstricting and vasodilating substances [35], improving ventricular function and increasing nitric oxide production from endothelium [36] and reducing oxidative stress and managing the generation of ROS through inducing antioxidant enzymes and inhibiting pro-oxidant enzymes [37].

The present study is among the first clinical trials to investigate the effects of genotype-intervention interaction for the *FTO*-rs9939609 polymorphism on response to EGCG supplementation on metabolic and inflammatory changes in T2DM.

In conclusion, the results of this study show that intervention with EGCG supplements for 2 months in patients with T2DM had a significant improvement on BMI and DBP in A allele carriers of *FTO*-rs9939609 polymorphism, a high-risk group for T2DM; however, it did not affect inflammation and other lipid profiles. This study suggests that administration of EGCG supplement may provide an advantageous therapy for patients with T2DM by using genome-customized approaches.

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Conflict of interest

The authors declare no conflict of interest.

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