The Effect of Quercetin Supplementation on Oxidative Stress, Glycemic Control, Lipid Profile and Insulin Resistance in Type 2 Diabetes: A Randomized Clinical Trial

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Abstract

Background: Diabetes Mellitus (DM) is closely associated with reduction of antioxidant defense system. In the present study, we investigated the antioxidant effect of quercetin supplementation on the glycemic control, lipid profile and oxidative stress indices in patients with type 2diabetes.

Methods: Forty seven patients with type 2 diabetes, aged 30-60 years old, were randomly assigned to supplement their daily diet with either an oral quercetin (250 mg/d) or identical placebo (cellulose) capsules for 8 weeks. The supplements were provided to the patients biweekly. Anthropometric data as well as glycemic indices, lipid profile and oxidative stress parameters of blood samples were determined at the baseline and endpoint of the study.

Results: Dietary quercetin supplementation significantly improved the total antioxidant capacity (TAC) in the intervention group, when compared to the placebo group (P=0.043). It also resulted in a statistically significant reduction in serum concentration of atherogenic oxidized LDL (ox-LDL) (P<0.001). However, the 8-week supplementation of this natural flavonol neither altered glycemic parameters (FBS, serum insulin and glycosylated Hb (HbA1c) level) nor lipid profile and insulin function measurement in diabetic patients (P>0.05).

Conclusions: Oral quercetin supplementation was beneficial in improving the antioxidant status of patients with type 2 diabetes while having no other significant effect on glycemic control and lipid profile; however, conducting further studies, using different doses, on the glycemiccontrol and/or hyperlipidemia of thepopulation seems to be valuable.

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Keywords: Quercetin; Diabetes Mellitus; Insulin Resistance; Oxidative Stress; Dyslipidemia

Introduction

Diabetes Mellitus (DM) is considered to be the world's fastest growing heterogeneous metabolic disease,[1-4] the mortality of which is raised tremendously in both developed and underdeveloped societies; it is estimated to reach 300 million patients by almost a decade.[5] Type 2 diabetes is characterized by insulin resistance, insulin insufficiency or both[3] and is usually associated with oxidative stress and increased risk of cardiovascular disease.[6,7] A growing body of evidence suggests that oxidative stress, which is due to overproduction of

reactive oxygen species (ROS) as well as a significant reduction in antioxidant defense system, plays a major role in development of type 2 diabetes and the consequent complications, including vascular disease and endothelial dysfunction.[8-11] The potential sources of free radical production in patients with diabetes are lipid peroxidation, protein glycation, autoxidation of plasma glucose, and leukocyteactivation.[2,7,12]

Studies show that free radical scavenging ability of patients with diabetes is lower than that of healthy people. This may be due to lower concentration of natural antioxidants.[13] Thus, it seems that natural-antioxidant supplementation might be useful in ameliorating the side effects of chronic hyperglycemia.[10] Recent studies showed that a number of plant products including flavonoids and various plant or herb extracts might be a potent natural antioxidant.[10]

Quercetin(3, 3', 5, 7-pentahydroxyflavone) is one of the most abundant bioflavanoid in human diet.[14] It is widely distributed in plant-food including onions (*Allium cepa*), unpeeled apples, berries, citrus fruits, tea (*Camellia sinensis*) and red wine.[15] This strong bioflavonoid has been found to have beneficial effects on lowering blood pressure,[16] inflammation,[17] and endothelial function.[18] Beneficial effects of quercetin have also been observed in LDL-C and protein oxidation reduction.[19,20]

The health promoting properties of quercetin is not limited to lowering blood pressure and inflammation; it has also been reported that it exerts antioxidant properties on oxidative DNA damage.[21] Quercetin can inhibit various cytokines, including tumor necrosis factor-α (TNF-α)[22] and reduce LDL glycation.[23] Quercetin administration to STZ-treated rats showed a significant reduction in fasting, and post-prandial blood glucose level as well.[24]

Few clinical trials have investigated the impacts of quercet in supplementation on human subjects with type 2 diabetes. Thus, the aim of the present study was to examine the effect of quercetin supplementation on oxidative stress, glycemic control and lipid profile of type 2 diabetic patients.

Materials and Methods

Study Population

The present randomized, placebo-controlled, single-blind clinical trial consisted of an 8-week treatment period with quercetin. Forty seven patients (31womenand 16 men), diagnosed with type 2 diabetes by an endocrinologist were voluntarily recruited from the outpatients of Motahari and Nader-Kazemi clinics at Shiraz University of Medical Sciences from April to September of 2012. The exclusion criteria included smoking and alcohol use. Patients receiving either insulin or multivitamin and mineral supplements in the previous three months, those with liver/kidney and/or lung diseases or any other type of chronic and/or acute inflammatory disorder were also excluded.

All the enrolled participants were informed of the purpose and procedure of the trial and completed a written informed consent. Patients were free to discontinue the trial at any time during the study. The subjects were randomly, through blocked randomization, assigned to receive either 250 mg quercetin (Life Extension, USA) or placebo (acetate cellulose) for 8 weeks. Patients received daily doses of supplement or placebo every 2 weeks and were asked to return the non-used capsules to help measure their intake. Compliance was also monitored biweekly through phone call. Quercetin and placebo capsules were identical in shape. The subjects started the supplemention after the baseline blood sample collection and continued it for 8 weeks.

All the participants were asked to maintain their regular lifestyles throughout the study and inform the author if any changes occurred. A 24-hour diet recall was completed both at the baseline (starting day) and endpoint of the trial.

Height and weight were measured using a portable stadiometer and Seca scales to the nearest 0.5 cm and 0.1 kg, respectively. Body mass index (BMI) was also calculated as weight in kg divided by height in meters squared. Quicki index and homeostatic model assessment insulin resistance (HOMA-IR) were calculated as follows:

(1) Quicki index=1/log (glucose mg/dl)+log (insulin μu/ml)

(2) HOMA-IR=(fasting insulin [μu/ml] * fasting glucose [mmol/l])/22.5[25]

The inclusion criteria were having controlled diabetes with maximum duration of less than 10 years and no secondary complication of the disease.

Protocol

At the beginning of the study in order to measure the baseline fasting blood glucose, serum insulin, HbA1c level and lipid profile, 10 milliliter of their venous blood was collected from the forearm after an overnight fasting. Ox-LDL and Total Antioxidant Capacity (TAC) were also measured. At this point, the treatment group received 250 mg/day quercetin and the control group received cellulose acetate, as placebo, for 8 weeks. Following this period, fasting blood was drowned and all biochemical parameters measured.

Blood glucose and lipid profile were measured

using Biosystem A-25 auto-analyzer, colorimetric method and commercial kits (Pars Azmoon, Tehran, Iran). The HbA1c was analyzed by high-performance liquid chromatography (HPLC); Insulin, ox-LDLand TAC were also measured using commercial ELISA kits (Pars Azmoon, Tehran, Iran; Glory Science Co. Ltd., China and Cayman, Michigan, USA, respectively).

This study was approved by the Ethics Committee of Human Experimentation of Shiraz University of Medical Sciences.

Statistical Analysis

The collected data were analyzed using SPSS, version 16 and presented as mean±standard deviation (SD) or percent. Baseline characteristics between quercetin and control groups were compared using independent t-test and Chi-square test. Differences of the measured glycemic indices, oxidative stress parameters and lipid profile were analyzed using Independent Sample *t*-test and paired *t*-test following testing the normality of the parameters. It was considered statistically significant, if p values were less than 0.05.

Results

All 47 participants, including 31 women and 16 men, with the mean age of 51.5±8.6 and 52.9±7.0 for quercetin-supplemented (n=26) and placebo subjects (n=21), respectively, completed the study. There was no reported side effect of either quercetin or placebo during the course of the trial in all participants.

The demographic characteristics, anthropometric data and the daily doses of drug intake for the intervention and control groups are shown in Table 1. Age, sex, duration of diagnosis, daily dosage of hypoglycemic drugs, body weight, and BMI and also biochemical parameters (including glycemic and oxidative stress indices and lipid parameters) did not differ between the quercetin and control groups at the beginning of the trial (Table 1). No statically significant differences were seen in macronutrient components of 24-h dietary recalls between the two groups of the study, both at the beginning and end point of the trial (data not shown).

A statistically significant increase in serum concentration of TAC was seen in the quercetin supplemented group compared to the controls (P<0.043) (Table 2). The level of atherogenic ox-LDL also significantly decreased by the end of 8-weeks of quercetin supplementation in the treatment group (P<0.001). However, parameters like fasting blood glucose, serum insulin and HbA1c did not differ significantly throughout the study in either group (Table 2). The observed mean±SD of Quicki index, as an indirect measurement of insulin function, remained unchanged in the intervention group as compared to that of the controls following the study period (0.33±0.03 vs. 0.35±0.04, respectively, P=0.15). The mean±SD value of HOMA-IR in the quercetin-supplemented group was also not statistically different from that of the control group after the intervention period (4.72±2.47 vs. 2.97±1.42, respectively, P=0.284). No significant differences were also observed in lipid profile (Total cholesterol, HDL-C, and LDL-C/HDL-C) of the patients after taking quercetin supplementation (Table 3).

Discussion

In the present study, oral administration of 250 mg quercetin supplementation resulted in a significant increase in TAC status of diabetic patients. These finding are in agreement with those of Boots et al. (2008) who revealed a significant increase in plasma antioxidant status of healthy subjects following a 97 mg/day quercetin supplementation.[26] Ajay *et al.*(2007) suggested that quercetin is a potent antioxidant; it has been shown to have free radical scavenging properties.[27] Serafiniand DelRio (2004) also discussed the feasibility of the 'TAC' as an innovative tool for investigating the association between diet and oxidative stress.[28] The antioxidant properties of quercetin and other flavonoids compounds are thought to be particularly due to their scavenging ability. Flavonoids can protect the cells through direct scavenging of ROS by forming flavonoid phenoxyl radical. It has also been reported that antioxidant property of quercetin is closely associated to iron- chelating activity which in turn prevents ROS formation in Harber-Weiss/Fenton reaction. Inhibition of superoxide ($O_2^{\bullet-}$) production through enzymatic

Table 1: Baseline characteristicsof the patients [a]

	Quercetin (n=26)	Placebo (n=21)	P value
Female (%)	57.7	76.2	0.183
Age (years)	51.5±8.6	52.9±7.0	0.535
Duration of diabetes (years)	6.25±4.35	7.12±3.88	0.479
Daily dose of Metformin (g/d)	1.35±0.76	1.34±0.76	0.986
Daily dose of Glibenclamide (mg/d)	10.05±9.85	7.63±7.70	0.379
Weight (kg)	69.80±11.00	72±12.52	0.524
BMI (kg/m^2)	26.86±3.78	28.36±3.92	0.189

[a]Values are means±SD or %

Table 2: Glycemic and oxidative stress indices of serum in patients with type 2 diabetes after an 8-week period of quercetin or placebo supplementation[a]

	Quercetin (n=26)	Placebo (n=21)	P value	ES[b] (95% CI) at 8 weeks
oxLDL (U/L)				
Baseline	127.15±30.19	111.62±30.65	0.088	0.510 (-0.08,1.09)
Endpoint	113.35±25.51	103.28±20.12	0.148	0.438 (-0.16,1.01)
P value	<0.001*	0.077		
TAC (mM)				
Baseline	1.20±0.47	0.99±0.43	0.124	0.466 (-0.13,1.04)
Endpoint	1.33±0.40	1.07±0.44	0.043†	0.618 (0.02, 1.20)
P value	0.032*	0.076		
FBS (mg/dl)				
Baseline	149.47±22.44	151.12±42.20	0.888	-0.048 (-0.62,0.53)
Endpoint	160.65±37.29	149.41±36.73	0.549	0.303 (-0.28,0.88)
P value	0.120	0.848		
Hb A1C (%)				
Baseline	7.63±1.97	7.39±1.81	0.675	0.126 (-0.45,0.70)
Endpoint	7.68±1.52	7.52±2.03	0.762	0.089 (-0.49,0.66)
P value	0.814	0.445		
Insulin (μU/ml)				
Baseline	9.76±5.93	6.97±3.92	0.115	0.555 (-0.05,1.12)
Endpoint	12.42±4.67	7.17±3.76	0.413	1.238 (0.58,1.83)
P value	0.831	0.501		

[a]Values are means±SD; [b]Effect size; *Paired *t* test, P<0.05; †Independent *t* test, P<0.05

reaction may also occur via quercetin supplementation in patients with diabetes.[29]

A significant decrease in serum ox-LDL level was observed in the quercetin treated group compared to the placebo group. The findings of this study are in agreement with the results of the study conducted by Egert *et al.* (2009) on quercetin supplementation of overweight but healthy subjects; it was revealed that serum concentration of ox-LDL markedly reduced after oral supplementation of quercetin.[19] However, Pfeuffer *et al.* (2011) suggested no significant change due to 150 mg/d quercetin supplementation of healthy men with different apolipoprotein E (APOE) genotypes.[30] The precise mechanism of the protective effect of the polyphenol quercetin has not been recognized yet. However, it has been suggested that polyphenolic compounds cause ionic interaction at the interface between both hydrophilic and lipophilic phases which allow the close association of the polyphenol to lipoproteins.[31]

Studies have suggested a trend towards a lower risk of type 2 diabetes with intake of higher rich-dietary sources of flavonoid.[32] Although we observed a statistically significant improvement in antioxidant defense system in quercetin supplemented group, monitored by serum TAC and ox-LDL, no alteration was observed in glycemic control of the diabetic patients taking quercetin. Indeed, in spite of studies suggesting the anti-diabetic effect of quercetin, insulin sensitization and inhibition of intestinal carbohydrate hydrolyzing enzymes (α-amylase and α-glycosidase) using 10-100 mg/kg/d in experimental model of type 2 diabetes,[33-35] our study did not support the hypoglycemic effect of quercetin, either on FBS or HbA1c. Indeed, although quercetin-supplemented male smokers with no insulin resistance showed a statistically significant reduction in glucose concentration, by a daily dose of 100 mg,[36] our findings using 250 mg quercetin daily for 8 weeks, does not support this result in insulin-resistant patients with type 2 diabetes. Our result may due in part to low dosage of the quercetin supplementation (250 mg daily), that was not adequate for overcoming the insulin resistance and exerting hypoglycemic effects. Thus applying higher doses of quercetin, i.e. more than 250 mg/d, seems valuable to be discussed.

Moreover, quercetin supplementation (50 mg/kg) of high fructose diet-fed rats was adequate enough to decrease triacylglycerol and free fatty acids[33] and even a lower dose of 10-50 mg/kg reduced both total and LDL-C.[37] At the same time, 10 week supplementation of 100mg/d quercetin in healthy smoker males could significantly improve the components of lipid profile, except TG.[36] However, daily supplementation of 250 mg quercetin in patients with type 2 diabetes in our study exerted no beneficial effect on triacylglycerol, total, LDL and HDL cholesterol. The results of our present study, which was similarly conducted on overweight patients, corroborate with those of Egert *et al.* (2009) who reported that 150mg quercetin supplementation resulted in no significant alterations in lipid profile in overweight healthy subjects with high cardiovascular risk phenotype.[19] However, the study design, duration of the study, doses of quercetin supplementation and more importantly metabolicconditions (e.g. insulin

Table 3: lipid profile of patients with type 2 diabetes before and after an 8-week period of quercetin or placebo supplementation [a]

	Quercetin (n=26)	Placebo (n=21)	P value	ES[b] (95% CI) at 8 weeks
Triglyceride (mg/dl)				
Baseline	171.47±76.35	135.18±52.85	0.117	0.552 (-0.05,1.12)
Endpoint	164.65±75.28	130.94±49.61	0.133	0.528 (-0.08,1.09)
P value	0.461	0.811		
Total cholesterol (mg/dl)				
Baseline	148.24±27.48	151.47±27.40	0.733	-0.117 (-0.69,0.46)
Endpoint	146.71±28.48	155.00±25.24	0.527	-0.308 (-0.88,0.28)
P value	0.832	0.655		
LDL cholesterol (mg/dl)				
Baseline	72.09±21.62	76.97±26.10	0.557	-0.203 (-0.78,0.37)
Endpoint	70.78±20.89	82.06±21.41	0.323	-0.533 (-1.11,-0.06)
P value	0.824	0.453		
HDL cholesterol (mg/dl)				
Baseline	42.06±8.24	44.47±7.27	0.373	-0.310 (-0.88,0.28)
Endpoint	43.00±9.15	45.35±9.15	0.413	-0.256 (-0.83,0.32)
P value	0.426	0.758		
Total cholesterol: HDL cholesterol				
Baseline	3.67±0.86	3.54±1.03	0.692	0.137 (-0.44,0.71)
Endpoint	3.52±0.55	3.57±0.85	0.840	-0.069 (-0.65,0.50)
P value	0.549	0.927		
LDL cholesterol: HDL cholesterol				
Baseline	1.74±0.63	1.76±0.68	0.930	-0.030 (-0.61,0.54)
Endpoint	1.68±0.45	1.85±0.88	0.483	-0.243 (0.82,0.33)
P value	0.751	0.741		

[a]Values are means±SD; [b]Effect size

resistance) of the subjects of this study differ from that of Egert *et al.* It should be noted that animal models may be somehow more sensitive to improvement of lipid profile using quercetin and that the metabolic status of healthy subjects is definitely different from those of patients with diabetes. It is probable that duration of quercetin-treatment period, as a limitation, has also resulted in the alterations. The other limitations of the study were including only the diabetic patients with the study inclusion criteria, which might affect the generalizability of the trial, and also lack of comparing the potential efficiency of several dosages of quercetin supplement.

In summary, we have shown that eight-week quercetin supplementation in type 2 diabetic patients reduces ox-LDL and boosts TAC and antioxidant defense system of the body. Although this level of quercetin supplementation can be used with no side effect, it appeared to be insufficient to exhibit statistically significant hypoglycemic and/or hypolipidemic effects. It seems that the applied dose and duration of the intervention, as the limitations of our study, was not sufficient for overcoming the insulin resistance; thus, the probable potential beneficial effects of higher doses and longer duration of this natural flavonol are worth investigating in future.

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Conflict of Interest: None declared

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