Effect of quercetin on postprandial glucose excursion after mono- and disaccharides challenge in normal and diabetic rats

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ABSTRACT

Postprandial hyperglycemia is a major risk factor for diabetic complications leading to disabilities and mortality in diabetics. Quercetin, a flavonoid, has been tried in traditional medicine for treating diabetes. The present study was designed to evaluate the potential of quercetin to control postprandial blood glucose level after maltose and glucose loading in normal and STZ-induced diabetic rats. Normal male Albino wistar rats and STZ-induced diabetic rats were treated with 300 and 600 mg/kg quercetin orally to evaluate the effect on postprandial hyperglycemia after carbohydrate loading, using acarbose as comparator. The results clearly showed ameliorated postprandial hyperglycemia due to the use of quercetin (300 and 600 mg/kg), it significantly dampened the postprandial hyperglycemia by 32.0% and 64.0% respectively, in maltose loaded diabetic rats, and 30.3% after 300 mg/kg dose in normal rats, compared to control; while acarbose produced 51% and 54% decrease in this respect in the two models respectively. Quercetin in 600 mg/kg dose produces significantly more reduction in postprandial hyperglycemia compared to acarbose, while in rats that received glucose and quercetin, postprandial hyperglycemia was not significantly affected. In conclusion, quercetin effectively suppresses postprandial hyperglycemia in STZ-induced diabetic rats loaded with maltose, which may be attributed to α-glucosidase inhibition. Quercetin could be used as a potential supplement for treating postprandial hyperglycemia.

Keywords: Quercetin; Postprandial Hyperglycemia; Diabetes; α-Glucosidase; Rats

1. INTRODUCTION

In individuals with type II diabetes, nutrient intake related first-phase insulin response is severely diminished or absent, resulting in persistently elevated postprandial glucose (PPG) throughout most of the day [1]. This is due to the delayed peak insulin levels which are insufficient to control PPG excursions adequately [2]. Postprandial hyperglycemia is a major risk factor for micro- and macro-vascular complications associated with diabetes [3], and controlling postprandial plasma glucose level is critical during early treatment of diabetes mellitus and in reducing chronic vascular complications [4]. The acute glucose fluctuations during the postprandial period exhibits a more specific triggering effect on oxidative stress than chronic sustained hyperglycemia which suggests that therapy in type II diabetes should target not only hemoglobin A1c and mean glucose concentrations but also acute glucose excursions [5]. α-glucosidase inhibitors delay breakdown of carbohydrate in small intestine and diminish postprandial blood glucose excursion in diabetic subjects [6], and thus have a lowering effect on postprandial blood glucose and insulin levels. Commercially available α-glucosidase inhibitors such as acarbose, miglitol and voglibose are widely used to treat patients with type 2 diabetes [7]. Several α-glucosidase inhibitors have been isolated from medicinal plants to develop as an alternative drug with increased potency and lesser adverse effects than the existing drugs [8]. Quercetin, a flavonoid antioxidant, is a leading potential candidate for treating DM [9]. The long-term consumption of quercetin appears to control blood glucose levels...
in streptozotocin (STZ)-induced diabetic animals [10,11]. It has been suggested that quercetin protects the pancreas against oxidative stress in STZ-treated animals, improving hyperglycemia [12]. Quercetin has been reported to lower plasma glucose, normalize glucose tolerance tests, preserve pancreatic β-cell integrity and function, and help protect against diabetes-induced declines in cognition, mood, and renal function in rat models of diabetes [13,14]. Quercetin also appears to be beneficial in diabetic neuropathy and neuropathic pain in streptozotocin (STZ)-induced diabetic rats [15]. It has also been reported that QE inhibits α-glucosidase activity in vitro [16,17]; however, no direct in vivo evidence available for its effect on postprandial hyperglycemia after disaccharides load. The present project was designed to evaluate the effect of quercetin on postprandial glucose excursion associated with disaccharide and monosaccharide challenge in normal and diabetic rats.

2. MATERIALS AND METHODS

2.1. Experimental Animals

Sixty six adult male albino Wistar rats were maintained during the experiments in the animal house, College of Pharmacy, University of Sulaimani; 12 - 13 weeks old rats, weighing 160 - 210 g were kept in a room with a 12-hr light/12-hr dark cycle at 25°C ± 2°C, fed with standard rodent diet (National Center for Drug Research and Quality Control, Baghdad) and water ad libitum. All animal procedures were approved by the ethical committee in accordance with the institutional Animal Ethics Committee.

2.2. Induction of Diabetes

Thirty six rats previously fasted for 16 hr were given single intraperitoneal injection of 45 mg/kg body wt. streptozotocin (Sigma, USA) dissolved in freshly prepared citrate buffer (0.1 M, pH 4.5). Animals with fasting blood glucose over 250 mg/dl, three days after streptozotocin (STZ) administration were considered diabetic [15]. It has also been reported that QE inhibits α-glucosidase activity in vitro [16,17]; however, no direct in vivo evidence available for its effect on postprandial hyperglycemia after disaccharides load. The present project was designed to evaluate the effect of quercetin on postprandial glucose excursion associated with disaccharide and monosaccharide challenge in normal and diabetic rats.

2.3. Maltose Loading in Normal Rats

Total of eighteen normal rats were allocated into three groups of six animals each. After 16 hours fasting, group 1 had received maltose (2 g/kg; p.o.) as the normal control; group 2 was coadministered with maltose (2 g/kg; p.o.) and quercetin dihydrate (Xia’n Co, China) (300 mg/kg body wt; p.o.); group 3 was coadministered with maltose (2 g/kg; p.o.) and acarbose (Bayer, Germany) (5 mg/kg; p.o.). The selected doses of quercetin and acarbose were determined to be safe based on previous studies [18,19]. Blood glucose level was measured before and 30, 60, 90 and 120 minutes after the maltose loading using a glucometer (Beurer Medical™ GmbH, Germany). The change in blood glucose from the basal level after the maltose load was analyzed and represented as delta blood glucose.

2.4. Maltose Loading in Diabetic Rats

Total of 24 diabetic rats were allocated into 3 groups of six animals each. Group 1 had received maltose (2 g/kg; p.o.) as the diabetic control; groups 2 and 3 were coadministered with maltose (2 g/kg; p.o.) and quercetin dihydrate (300 and 600 mg/kg; p.o., respectively); group 4 was coadministered with maltose (2 g/kg; p.o.) and acarbose (5 mg/kg; p.o.). Blood glucose level was measured as previously indicated.

2.5. Glucose Loading in Normal Rats

Total of twelve normal rats were allocated into two groups of six animals each. After 16 hours fasting, group 1 had received glucose (2 g/kg; p.o.) as the control, while group 2 was coadministered with glucose (2 g/kg; p.o.) and quercetin dihydrate (300 mg/kg; p.o.). Blood glucose level was measured as mentioned previously.

2.6. Glucose Loading in Diabetic Rats

Total of twelve diabetic rats were allocated into two groups of six animals each. After 16 hours fasting, group 1 had received glucose (2 g/kg; p.o.) as diabetic control; group 2 was coadministered with glucose (2 g/kg; p.o.) and quercetin dihydrate (300 mg/kg; p.o.). Blood glucose level was measured as indicated before.

2.7. Statistical Analysis

The delta blood glucose levels were expressed as mean ± SE for six animals in each group. Statistical analysis was performed using t-test or one-way analysis of variance (ANOVA) followed by Dunnett’s Multiple Comparison Test using GraphPad Prism 5 for Windows software (GraphPad Software, Inc., USA). P-values less than 0.05 were considered to be statistically significant.

3. RESULTS

3.1. Maltose Loading in Normal Rats

Postprandial blood glucose variation was measured after loading maltose to the normal rats with and without coadministration of quercetin. In the control group, blood glucose level increased by an average of 55 mg/dl at 30 minutes after the maltose load, while the standard comparator, acarbose produces 22.5 mg/dl decrease at the same time. In the group that received 300 mg/kg quercetin along with maltose, the 30 minutes post-load glu-
cose level increased only by 37 mg/dl on an average (Figure 1). This indicates the potency of quercetin to significantly suppress high maltose diet associated post-prandial glucose elevation. Compared to control, the whole glycemic response is reduced by 32.7% on quercetin, while acarbose showed 59% decrease in glucose elevation which is significantly higher compared to both other groups (Figure 2).

3.2. Maltose Loading in Diabetic Rats

As quercetin exhibited appreciable postprandial blood glucose lowering effect in normal rats, we evaluated its inhibitory effect on STZ-induced diabetic rats. In the control group, blood glucose level increased to an average of 370 mg/dl above the basal level 30 min after maltose loading and decreased thereafter (Figure 3). However, the rise of the post-load blood glucose has been significantly impeded in a dose dependent pattern on coadministering quercetin with maltose at different doses (300 and 600 mg/kg). Similar kind of suppression effect was observed in the group that received acarbose (5 mg/kg) as the positive control along with maltose. Compared to control, the whole glycemic response is reduced by 29.2%, 59% and 51.3% when treated with 300, 600 mg/kg of quercetin and 5 mg/kg of acarbose, respectively (Figure 4).

3.3. Glucose Loading in Normal Rats

To confirm that the observed suppression of post-prandial glucose, reported during maltose loading is due to the inhibition of α-glucosidase, postprandial blood glucose variation was measured after loading glucose to the normal rats with and without the coadministration of quercetin. In control group, blood glucose level increased by an average of 26 mg/dl at 30 min after the glucose load. In the group that received 300 mg/kg quercetin along with glucose, the 30 minutes post-load glucose level increased by 22 mg/dl on an average (Figure 5), which shows that the glucose absorption is not significantly affected due to the use of quercetin (Figure 6).

3.4. Glucose Loading in Diabetic Rats

To evaluate the effect of quercetin on glucose toler-
Figure 5. Effect of single oral dose of 300 mg/kg quercetin on blood glucose after glucose loading in normal rats. The glycemic response curve in normal rats after glucose challenge. ns = non-significantly different compared to control ($P > 0.05$).

Figure 6. Effect of quercetin on the incremental blood glucose AUC$_{0-120}$ min in normal rats after glucose load; ns = non-significantly different compared to control ($P > 0.05$).

Figure 7. Effect of single oral dose of 300mg/kg quercetin on blood glucose after glucose loading in diabetic rats. The glycemic response curve in diabetic rats after glucose challenge. ns = non-significantly different compared to control ($P > 0.05$).

Figure 8. Effect of quercetin on the incremental blood glucose AUC$_{0-120}$ min in diabetic rats after glucose load; ns = non-significantly different compared to control ($P > 0.05$).

ance in diabetic condition and to elucidate whether the observed postprandial glucose suppression is mostly due to $\alpha$-glucosidase inhibition, postprandial blood glucose variation was measured after glucose loading to the diabetic rats with and without coadministration of 300 mg/kg quercetin. In the control group, blood glucose level increased by an average of 305 mg/dl at 30 min after the glucose load. In the group that received quercetin along with glucose, the 30 min post-load glucose level increased by 312 mg/dl (Figure 7), which shows that glucose absorption is not significantly affected due to administration of quercetin, as shown by the non-significant differences in AUC of postprandial glucose spike compared to control (Figure 8).

4. DISCUSSION

Diabetic individuals are at an increased risk of developing microvascular complications (retinopathy, nephropathy, and neuropathy) and cardiovascular disease. Abnormalities in insulin and glucagon secretion, hepatic glucose uptake, suppression of hepatic glucose production, and peripheral glucose uptake contribute to higher and more prolonged postprandial glycemic (PPG) excursions than in non diabetic individuals [2]. Elevated PPG even in the absence of fasting hyperglycemia increases the risk of cardiovascular diseases and it is the most common cause of death among the people with diabetes. Acute hyperglycemia induces endothelial dysfunction by generating oxidative stress resulting in impaired vasodilatation [20]. Also, postprandial spikes can result in microvascular damage through oxidation of low density lipoprotein (LDL) and other pro-atherogenic mechanisms [21]. Diet rich in carbohydrate causes sharp rise in the blood glucose level as the complex carbohydrates in the food is rapidly absorbed in the intestine aided by the $\alpha$-glucosidase enzyme which breaks disaccharides into absorbable monosaccharides [22]. $\alpha$-glucosidase inhibitor inhibits the disaccharide digestion and impedes the postprandial glucose excursion to enable overall smooth glucose profile [23]. According to the available evidence about the positive in vitro inhibitory effects of quercetin on $\alpha$-glucosidase activity [16,17], we evaluate its effect on postprandial hyperglycemia associated with carbohydrate challenge using rats as experimental model. The
study design is based on the hypothesis that on adminis-
tering quercetin to the diabetic rats, postprandial glucose
exursion associated maltose challenge gets stymied but
not during glucose challenge. Because, the \( \alpha \)-glucosidase
action is crucial for the digestion of maltose without
which this disaccharide would not be rapidly converted
into absorbable glucose. As expected, quercetin blunted
acute postprandial hyperglycemic spike in normal rats
loaded with maltose but not with glucose. Subsequently,
the postprandial hyperglycemia amelioration of quercetin
was evaluated in the STZ-induced diabetic rats. In general,
the postprandial glucose level of STZ-induced dia-
abetic rat is poorly controlled due to impaired insulin
production [24]. It has been reported that chronic con-
sumption of quercetin (0.1% of diet) decreased blood
sugar in STZ-treated rats [10]. Moreover, quercetin
protected pancreatic \( \beta \) cells from oxidative stress and
damage, resulting in increased insulin secretion in STZ-
treated rats [12]. However, in our study, coadministration
of maltose along with a single dose of quercetin (300
mg/kg and 600 mg/kg) to the diabetic rats attenuated the
increase in postprandial hyperglycemia in a dose de-
pendent manner. On the other hand, control animals
showed an extremely high level of blood glucose that has
been staying high even two hours after the maltose load.
One of the reasons for observing the suppressed post-
prandial glucose level in diabetic rats could be due to the
damping effect of quercetin on the maltose digestion at
small intestine. The standard drug, acarbose similarly
suppressed the postprandial glucose level; this effect
support similar results obtained with different doses of
quercetin in starch loaded rats [25]. As the observed
postprandial glucose suppression could also be possible
because of the secretagogue activity and insulin sensitiz-
ing property of quercetin, we have evaluated the effect of
quercetin on glucose loading in normal and diabetic rats.
Quercetin did not suppress the postprandial hyperglyce-
mia associated with glucose loading significantly but on
maltose loading, which indicates that the major mecha-
nism of action of postprandial glucose suppression may
be exhibited by inhibition of \( \alpha \)-glucosidase. Previous
reports on \( \alpha \)-glucosidase inhibitors isolated from me-
dicinal plants showed that many potential inhibitors be-
long to flavonoid glycoside class, which has the charac-
teristic structural features to inhibit \( \alpha \)-glucosidase en-
zyme [26,27]. Based on these results, we can speculate
that oral administration of flavonoid glycosides might
have contributed to the \( \alpha \)-glucosidase inhibitory effect
and control of postprandial hyperglycemia.

5. CONCLUSION

The results of the present study indicated that orally
administered quercetin suppresses, in a dose dependent
pattern, maltose-induced postprandial blood glucose
spikes in both normal and diabetic rats.

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