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Effects of Vitamin C Supplementation on the Metabolic Abnormalities Associated with Diabetes Mellitus

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ABSTRACT

It is known that exogenous antioxidant supplementation may be beneficial against micro and macrovascular complications of diabetes. This study aimed to investigate the effect of vitamin C supplementation on insulin secretion, hyperlipidemia, oxidative stress and paraoxonase-1 enzyme (PON1) activity which are impaired due to chronic hyperglycemia in diabetic rats. For this purpose, twenty-four Wistar albino rats were divided into 3 groups as group C, DC and DCC. The rats in DC and DCC groups were induced diabetes by single dose streptozotocin injection (45 mg/kg). C and DC groups fed with standard rat diet (vitamin C free), DCC group fed with experimental diet supplemented with vitamin C at a dose of 200 mg/kg. According to the findings, rats in group C consumed less feed and water compared to diabetic rats during 8-weeks experimental period ($p<0.001$). In addition, total cholesterol and triglyceride levels of group C were lower than diabetic groups while PON1 activity and insulin values were higher ($p<0.05$). On the other hand, there were no significant differences between DC and DCC groups in terms of insulin, triglyceride, HDL, LDL and total cholesterol levels but TAS and PON1 activity levels of group DCC were significantly higher than group DC ($p<0.05$). As a conclusion, vitamin C supplementation may be helpful in increasing PON1 activity and antioxidant capacity in the presence of diabetes.

Keywords: Diabetes mellitus; oxidative stress; hyperlipidemia; paraoxonase 1; ascorbic acid

C Vitamini Desteğinin Diabetes Mellitus ile İlişkili Metabolik Anormallikler Üzerindeki Etkileri

ÖZET

Eksojen antioksidan takviyesinin, diyabetin mikro ve makrovasküler komplikasyonlarına karşı faydalı olabileceği bilinmektedir. Bu çalışmada C vitamini desteğinin, diyabetik ratlarda, kronik hiperglisemiye bağlı olarak bozulan insülin sekresyonu, hiperlipidemi, oksidatif stres ve paraoksonaz-1 enzim (PON1) aktivitesi üzerine etkilerinin araştırılması amaçlanmıştır. Bu amaçla, yirmi dört adet Wistar albino cinsi rat C, DC ve DCC grupları olarak 3 gruba ayrıldı. DC ve DCC grubundaki ratlarda, tek doz streptozotosin enjeksiyonu ile diyabet oluşturuldu (45 mg/kg). C ve DC grubundaki ratlar standart rat yemi (C vitamini içermeyen) ile beslenirken, DCC grubundaki ratlar 200 mg/kg dozunda C vitamini ile desteklenmiş deneysel yemle beslendi. Elde edilen bulgulara göre, C grubundaki ratların sekiz haftalık deney süresinin sonunda diyabetik ratlara göre daha az yem ve su tükettiği görüldü ($p <0,001$). Bunun yanı sıra C grubundaki ratların toplam kolesterol ve trigliserid düzeylerinin diyabetik gruplara göre daha düşük, PON1 aktivite ve insülin değerlerinin ise daha yüksek olduğu saptandı ($p <0,05$). Bir diğer yandan, DC ve DCC grupları arasında toplam kolesterol, trigliserid, HDL kolesterol, LDL kolesterol ve insülin düzeyleri açısından anlamlı farklılık gözlenmese de, DCC grubunun TAS ve PON1 aktivite düzeylerinin DC grubuna göre anlamlı olarak daha yüksek olduğu belirlendi ($p <0,05$). Sonuç olarak, diyabet varlığında, C vitamini takviyesi PON1 aktivite düzeyini ve antioksidan kapasiteyi artırmada etkili olabilir.

Anahtar Kelimeler: Diyabet; oksidatif stres; hiperlipidemi; paraoksonaz 1; askorbik asit

Diabetes Mellitus (DM) is a group of metabolic diseases that are characterized by hyperglycemia. The generation of reactive oxygen species (ROS) increases in DM due to chronic hyperglycemia and increased ROS levels have a crucial role in the pathogenesis of diabetes related complications. The ROS production can be controlled by nonenzymatic and enzymatic antioxidants in healthy people. However, endogenous antioxidants can not downregulate the production of ROS in diabetic people (1). Therefore, routine antioxidant support in diabetic people is a matter of debate. Antioxidant supplementation to diabetic people is more discussed in these days due to the COVID-19 pandemic process. High fasting blood glucose level (>7.00 mmol/L) is a strong and independent predictor of COVID-19-related poor outcomes (2) and 28-day mortality (3). On the other hand, it is currently being discussed that intravenous high-dose vitamin C supplementation may be beneficial in the early stages of COVID-19. Vitamin C supplementation may improve alveolar fluid clearance, regeneration of antioxidant molecules such as α-tocopherol, urea, glutathione and β-carotene and epithelial cell functions in diabetic patients (4), and may be beneficial in protecting against a variety of diseases including COVID-19.

Although the effects of vitamin C on regulating fasting glucose levels (4), decreasing HbA1c levels (5) and improving insulin sensitivity (6) has been reported, the results differ and the mechanism of action is not fully elucidated. But in the presence of DM, it is stated that ascorbic acid (reduced form of vitamin C) is required to optimize insulin secretion function of islet cells due to impaired insulin secretion and ascorbate cycle (7). It is also noted that vitamin C is an important antioxidant for the protection of pancreatic beta cells against glucose toxicity (8). In addition, Kaneto et al. (1999) determined that β cells of diabetic mice supplemented with antioxidants were larger than those whom were not and it was concluded that antioxidants such as vitamin C prevent apoptosis without affecting the proliferation of beta cells.

It is a well-known fact that the risk of coronary heart disease increases and the lipid profile deteriorates in DM. The protective roles of vitamin C against these problems noted in the literature (9). Additionally vitamin C deficiency can lead to the deterioration of the transport of long-chain fatty acids to the mitochondria and so increased triglyceride synthesis in diabetic patients (10). Considering evidences of lower vitamin C levels in diabetic people than in healthy people (11), and association between low vitamin C levels and increased risk of coronary heart disease (12), meeting the daily requirement of vitamin C may be protective against these complications arising from DM. The aims of this study were to investigate the effects of vitamin C supplementation on lipid profile, insulin secretion, and oxidative stress in diabetic rats.

MATERIALS and METHODS

Animals and Experimental Induction of Diabetes

The study started after the ethical approval (Ankara University Animal Experiments Local Ethics Committee (Meeting No. 2017-3, Decision No. 2017-3-21). Three months old 24 male Wistar albino rats with an average body weight of 304.75 ± 9.35 g (obtained from the Ankara University Animal Research Laboratory, Ankara/Turkey) were used in the study. The rats were housed in the polycarbonate cages in a room with a 12 h day-night cycle, relative humidity at 21 °C and treated according to the "Guide for the Care and Use of Laboratory Animals". Rats were randomly divided into 3 groups (C, DC, DCC) as 8 rats in each group and then diabetes was induced in 2 groups (DC, DCC) by a single intraperitoneal injection of streptozotocin (Sigma-Aldrich, USA / 45 mg/kg in 0.5 mL of 0.01 M sodium citrate buffer, pH: 4.5). Rats with fasting blood glucose levels above 250 mg/dL at 7 days after streptozotocin injection were used as the diabetic animals (group DC and DCC). Then, during the 8 weeks experiment period, C and DC groups were fed with standard rat diet (vitamin C free), the DCC group was fed with experimental diet. Standard rat diet prepared according to National Research Council (NRC) standards. Vitamin C was added to standard rat diet with a dose of 200 mg/kg to prepare experimental diet.

Collection of Blood Samples and Serum Biochemical Assays

The rats were anaesthetized using Ketamine HCl (70 mg/kg) and Xylazine (10 mg/kg) and blood samples were collected via cardiac puncture after overnight fasting at the end of the experimental period. After the centrifugation of blood samples (3500 rpm for 10 min) serum was stored at −80 °C prior to analysis. The serum samples were analyzed for determination of triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), insulin, total oxidant status (TOS), total antioxidant status (TAS), paraoxonase 1 activity (PON1) by using a commercial kit.

Calculation of OSI

The OSI was defined as the ratio of the TOS level to TAS level. The mmol value of TAS level was converted to μmol

value as in the TOS level and calculated according to the following formula.

$$OSI = \frac{\text{TOS, } \mu\text{mol } H_2O_2 \text{ Eq/L}}{\text{TAS, mmol Trolox Eq/L X 10}}$$

Statistical Analysis

All data are expressed as mean ± SEM. The parameters were statistically analyzed by one way analysis of variance (ANOVA) with Tukey post hoc test. Statistical significance was considered at $p<0.05$.

RESULTS

Feed and Water Consumption, Body Weight

Induction of diabetes resulted in significant increases in the feed and water consumption (Table 1). Ultimate body weight of diabetic groups were also significantly lower than the control group ($p<0.001$). No significant difference was observed between diabetic groups in terms of ultimate body weight, average feed and water consumption ($p>0.05$).

Plasma Lipids

Our results show that total cholesterol and triglyceride levels of DC and DCC groups were higher than group C (total cholesterol: $p<0.001$, $p=0.008$ for DC and DCC groups, respectively; triglyceride: $p<0.001$ for both groups) but there was no significant difference between the groups in terms of HDL levels ($p>0.05$). In addition, the mean LDL-C level of the group DC was significantly higher than the group C ($p=0.004$), but no significant difference was found between the group DCC and the other groups ($p>0.05$) (Table 2).

Insulin, Paraoxonase1 Activity, Total Antioxidant Status (TAS), Total Oxidant Status (TOS) and Oxidative Stress Index (OSI)

The mean insulin, TAS, PON1 activity levels were significantly lower ($p<0.001$) and TOS, OSI values were significantly higher ($p=0.002$, $p<0.001$, respectively) in the group DC compared to the group C. No significant difference was found between the DCC and other groups in terms of TOS and OSI values, whereas the mean TAS and PON1 activity values of group DCC were significantly higher than the group DC ($p=0.05$, $p=0.044$, respectively). In addition, the mean insulin and PON1 activity levels of group DCC were significantly lower than the group C ($p=0.001$, $p=0.043$) (Table 3).

Table 1. Groups' live body weights at the beginning and end of the experiment, and their mean feed and water consumption during the study period (mean ± SEM, n=8).

	C	DC	DCC
AFI (g/day)	17.9±0.4	22.0±0.6^{a*}	22.0±0.6^{a*}
AWI (mL/day)	41.4±2.1	86±5.1^{a*}	84±5^{a*}
IBW (g)	299.7±3.3	303.5±2.7	310.6±3.2
UBW (g)	351.6±3.2	229.9±3.8^{a*}	232.6±3.6^{a*}

AFI; average food intake, AWI; average water intake, IBW; initial body weight, UBW; ultimate body weight. [a] Significantly different from group C. [a](p<0.001).*

Table 2. Groups' mean TC, TG, HDL-C and LDL-C values (mg/dL) at the end of the experiment (mean ± SEM, n=8).

	C	DC	DCC
TC	78.9±4.2	122.5±7.3^{a*}	114.1±8.3^{a}
TG	78.4±5.4	198.4±13.1^{a*}	174.4±14.3^{a*}
HDL-C	33.2±2.9	24.9±2.1	29.5±3.1
LDL-C	37.7±3.2	56.4±4.0^{a}	50±3.6

[a]Significantly different from group C. [a](p<0.05), [a](p<0.001).*

Table 3. Groups' mean insulin (pg/mL), TAS (mmol/L), TOS (µmol/L), PON1 activity (U/L) and OSI levels (AU) at the end of the experiment (mean ± SEM, n=8).

	C	DC	DCC
Insulin	198.2±5.4	137.6±5.9^{a*}	140.2±6.6^{a*}
TAS	1.66±0.09	1.07±0.07^{a*}	1.38±0.07^{b}
TOS	5.53±0.62	10.73±0.96^{a}	8.77±1
PON1	14.3±1.3	4.7±0.5^{a*}	9.5±1^{a,b}
OSI	0.33±0.03	1.07±0.17^{a*}	0.67±0.11

[a]Significantly different from group C. [b]Significantly different from group DC. [a,b] (p<0.05), [a] (p<0.001).*

DISCUSSION

Feed and Water Consumption, Weight Loss

Polyphagia and polydipsia are among the most important signs and symptoms of DM. In the presence of diabetes elevated rate of gluconeogenesis and lipolysis in order to meet the energy needed by cells causes weight loss. In addition, loss of energy due to glucose excretion in urine is the other cause of weight loss. The results show that vitamin C can not adequately protect the live weight of diabetic rats against proteolytic and lipolytic effects of DM. In various studies in the literature, weight loss was noted in STZ-induced diabetic rats (13,14) and the findings obtained in this study are consistent with the literature data.

Insulin and Lipid Profile

Increased serum total cholesterol, LDL cholesterol and triglyceride levels in diabetes are caused by changes in lipoprotein lipase and hepatic lipase activities due to insulin deficiency or insensitivity. Besides hypercholesterolemia and hypertriglyceridemia, other characteristics of diabetic dyslipidemia is decrease in HDL-C concentration. The findings of the changes in plasma total cholesterol, triglyceride and LDL cholesterol levels of the group DC are consistent with similar studies in the literature (15,16). Decreased lipoprotein lipase and hepatic triglyceride lipase activities resulting from decreased insulin level are thought to be responsible for this condition.

Findings about the effects of vitamin C on insulin secretion, insulin resistance and diabetic dyslipidemia are inconsistent. In a study conducted with 84 individuals with type 2 diabetes, it was reported that vitamin C intake (1000 mg) for 6 weeks significantly decreased FBG, triglyceride and LDL levels, while there was no statistically significant effect on total cholesterol, HDL and insulin levels (17). With the intake of 500 mg vitamin C for 3 months, HDL cholesterol levels significantly increased but no significant changes were observed in triglyceride, total cholesterol, LDL cholesterol and FBG values in type 2 diabetic individuals (18). In a similar study, supplementing type 2 diabetic individuals with the same dose of vitamin C for the same time period has no significant effect on the levels of FBG, HDL and triglycerides, while LDL cholesterol and total cholesterol levels significantly decreased (19). In an another study it was reported that diabetic rats supplemented with vitamin C intragastrically (60 mg/kg) had higher HDL levels than diabetic rats without vitamin C supplementation and there was no significant difference in FBG, total cholesterol, triglyceride, VLDL and LDL levels between the groups (20). According to findings of this study, vitamin C supplementation at a dose of 200 mg/kg (rat bait) has no statistically effect on insulin, LDL cholesterol, total cholesterol and HDL cholesterol and these results are consistent with the results obtained by Uslu (2013). It is thought that contradictions between the findings in literature data are result from differences in methodology (application tecnique, duration, dose etc.) of studies.

Oxidative Stress

The production of reactive oxidant species (ROS), which causes oxidative damage due to long-term hyperglycemia in diabetes, increases and the oxidative balance deteriorates in favor of oxidants. Different methods have been used to evaluate oxidative stress and antioxidant capacity in diabetes. In various studies, malondialdehyde (MDA) levels were observed as indicators of lipid peroxidation and it was noted that MDA levels increased in diabetic rats. On the other hand, antioxidant capacity was evaluated with superoxide dismutase (SOD), glutathione (GSH) and catalase (CAT) levels in the same studies and it was stated that these parameters decreased in diabetic rats (15,21). In the evaluation of oxidative stress and antioxidant status in recent years, TOS and TAS levels are measured instead of these parameters. In addition, the measurement of TAS level may give more valuable information than the individual measurement of aforementioned antioxidants. In the studies conducted in this context, it was observed that TOS levels increased and TAS levels decreased in the presence of diabetes, and the results obtained in this study were consistent (22).

In various studies it has been reported that vitamin C has potent effectiveness in increasing GSH and plasma antioxidant capacity and decreasing lipid peroxidation (23,24). Contrary to these results, it was concluded that vitamin C had no effect on TAS and TOS levels in diabetic rats (20). According to the results of similar studies effects of vitamin C on oxidative stress may vary depending on the differences of vitamin C adminastiration (duration, dose, application way). As a result, according to the data in the literature and the results obtained from this study, it is possible to suggest that vitamin C may be protective against impaired oxidant-antioxidant balance in the presence of diabetes.

PON1 Activity

Paraoxonase 1 (PON1) is an antioxidizing enzyme that protects HDL and LDL against oxidation with contributing to the hydrolysis of lipid peroxides into oxidized lipoproteins and PON1 activity levels may change depending on many environmental and genetic factors. The main factor is oxidative stress which downregulates serum PON1 expression due to the changes in the redox status. There are many studies about the association of PON1 enzyme activity with diabetes, and the majority of these studies have reported that PON1 enzyme activity is lower in diabetic subjects than in healthy subjects (25,26). Tartan et al. (2007) also reported that patients with a shorter duration of diabetes had higher PON1 activity than patients with a longer duration of diabetes (27). When the results were compared with similar studies in the literature, it was concluded that PON1 activity levels in normal rats were significantly higher than in diabetic rats and these results were consistent with the results obtained in the study.

Vitamin C has been found to be effective in increasing PON1 activity levels. Jarvik et al. (2002) reported that PON1 activity was increased by the administration of vitamin C in combination with vitamin E (28). In a study conducted by Ferretti et al. (2008), after supplementing with vitamin C (500 mg/3 times a week) to hemodialysis patients for 6 months, the mean value of PON1 activity was found significantly higher and lipid hydroperoxide level was significantly lower in the vitamin C supplemented group (29). According to the results obtained from the study, the increase in Paraoxonase enzyme activity was observed with vitamin C supplementation and the results were consistent with the literature.

CONCLUSION

Exogenous antioxidant support in diabetes has a crucial role in preventing the complications related to the disease. Vitamin C supplementation increased the antioxidant capacity in diabetic rats. In addition, PON1 activity which has antioxidant and antiatherogenic activity also increased with vitamin C supplementation. Meeting the daily requirement of vitamin C of diabetic individuals can be effective in improving the prognosis of the disease. Researches which aims to investigate hypoglycemic and hypolipidemic activity of vitamin C with different techniques and methodologies may be useful.

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