Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 8 [2] January 2019 : 130-135

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD
Global Impact Factor 0.876
Universal Impact Factor 0.9804
NAAS Rating 4.95

ORIGINAL ARTICLE **OPEN ACCESS**

Effect of Quercetin Administration and Exercise on Plasma Cytokine Levels in Rats with STZ Induced Diabetes

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ABSTRACT
In this study, it was aimed to determine the effects of preventive quercetin administration and exercise on plasma cytokine (IL-1, TNF-α, IL-6, and IL-10) levels in rats with streptozotocin (STZ) induced experimental diabetes. 32 adult male Wistar Albino rats of similar liveweight were used in the study. Animals used in the study were assigned into 6 groups containing an equal number of rats as the Control group (C), Quercetin group (Q), Exercise group (E), Diabetes group (D), Diabetes + Quercetin group (DQ), and Diabetes + Exercise group (DE). A single dose of intraperitoneal (i.p.) 60 mg/kg STZ was injected into the rats in the D, DQ, and DE groups. 15 mg/kg live body weight per day quercetin was injected i.p. throughout the trial into the rats in the Q and DQ groups after the development of diabetes. On the other hand, the rats in E and DE groups were given blocks of swimming exercises during the experiment. The levels of IL-1, TNF-α, IL-6, and IL-10 were determined in the blood samples collected from the rats at the end of the trial. In group D; IL-1, TNF-α, and IL-6 levels were significantly increased but the levels of IL-10 decreased ($p < 0.05$). In the groups where quercetin and exercise were given to the rats, the levels of these parameters were observed to approach the values observed in the control group. In conclusion; in the rats with STZ induced diabetes, it was determined that the administration of quercetin and the practice of regular swimming exercises improved the untoward consequences favorably in the parameters examined in the study.
Keywords: *Cytokines,Diabetes Mellitus, Exercise, Quercetin, Rat*

Received 12.08.2018 Revised 22.10.2018 Accepted 16.12.2018

INTRODUCTION

Diabetes Mellitus (DM) is currently a major health issue with a life-long duration. It develops due to the insufficient secretion of insulin from the pancreatic β cells and/or due to the impairment of the insulin response of respective tissues. The disease is characterized by hyperglycemia, glycosuria, polyuria, polydipsia, polyphagia, ketosis, acidosis, and dehydration. DM is a chronic metabolic disease adversely affecting the carbohydrate, fat, and protein metabolisms and is associated with a high morbidity and mortality during its course. Regular treatment and monitoring of the patient is required, however, the lifespan and the quality of life of the patient are adversely affected due to the acute and chronic complications associated with the disease [1,2,3].

Cytokines are substances in glycoprotein structure involved in the immune system regulation and in the inflammatory processes. Furthermore, they serve as messengers in the intracellular interactions. Cytokines can be secreted by several various cell types [4,5].

Metabolic syndrome is a disorder that affects all tissues and systems unfavorably. It is comprised of several components including insulin resistance, diabetes mellitus, dyslipidemia, obesity, hypertension, coronary artery disease, non-alcoholic fatty liver, and endothelial dysfunction, all of which triggering each other individually. It is a major risk and threat for the well-being of the individuals and for the public health by impairing the quality of life and decreasing the lifespan. Modification of inflammatory-mediated cytokine responses appears to be a good target for the prevention and treatment of DM and metabolic syndrome [6]. Pharmacological treatment of diabetes is based on hypoglycemic drugs and insulin. Due to the side effects of these therapeutic agents, interest in herbal and synthetic treatment methods is on the

rise today [1]. It has been suggested that antioxidants may be used as an adjunct to the medical treatment in regulating the impaired glycemic balance in uncontrolled diabetes [7,8,9].
Quercetin (3,3', 4',5,7-pentahydroxyflavone) is the most potent radical scavenger flavonol and it has been reported that it suppresses inflammation due to its antioxidant properties by strengthening the endogenous antioxidant defense systems [10]. A diet rich in quercetin has been suggested to reduce the risk of diabetes [11]. Quercetin is suggested to be an antidiabetic mainly with regards to its anti-inflammatory and antioxidant effects observed in diabetes models as the oxidative stress and inflammation are the major conditions playing a role in the development and prognosis of diabetes [12]. It is observed that the levels of TNF-α, IL-1β, IL-6, IL-8, and MCP-1 (monocyte chemoattractant protein-1) are decreased after quercetin administration in diabetic individuals [13].
The positive effects of exercise on human health are one of the well-recognized facts currently. Exercise helps prevent cardiovascular diseases, chronic respiratory diseases, obesity, cancer, osteoporosis, diabetes mellitus, and psychological disorders [14]. The degree of the effect of exercise on the immune system functions depends on several variables including its frequency, duration, severity, and the individual's physical fitness [15,16,17]. It has been reported that regular aerobic exercise in diabetic patients improves blood glucose regulation, enhances the sensitivity of the cells to insulin, lowers the levels of the lipids, and facilitates the weight loss, improving the cardiovascular system functions and metabolic control [18,19,20]. Physical exercises have been shown to increase the IL-6 levels in normal individuals and in individuals with Type-I diabetes [21,22]. The changes in the levels of IL-6 vary according to the duration and intensity of exercise [22]. It was reported that resistance training at 3 to 9-day intervals in patients with Type-I diabetes increased the IL-6 levels with improvements in hyperglycemia consequently [23]. It has been suggested that regular resistance exercises recommended for type-I diabetes [24,25] and the alterations in IL-6 levels associated with these work-outs facilitate the metabolic functions by providing a balance between the glucose production and uptake [26,27,28].
In this study, it was aimed to determine the effects of quercetin administration and exercise on the levels of some of the plasma cytokines (IL-1, TNF-α, IL-6, and IL-10) in rats with streptozotocine (STZ) induced experimental diabetes.

MATERIAL AND METHODS

32 adult male Wistar Albino rats of similar live weight were used in the study. Animals used in the study were assigned into 6 groups containing equal number of rats as the Control group (C), Quercetin group (Q), Exercise group (E), Diabetes group (D), Diabetes + Quercetin group (DQ), and Diabetes + Exercise group (DE). The rats were housed in plastic rat cages in the experimental animal unit at 23 ± 2 ^{o}C at room temperature and in a 50±10% humidified environment at a 12/12 night/day light cycle and they were fed ad-libitum with a standard rat diet. Rats were provided ad libitum access to water (~ 50 ml/day/rat) to be refreshed daily. The rats in the (D), (DQ), and (DE) groups were administered a single dose intraperitoneal (i.p.) injection of 60 mg/kg STZ (Sigma S0130-1G) dissolved in 0.1 M citrate buffer (pH: 4.5). Then, 72 hours later than the STZ administration, the fasting blood glucose levels were measured with a glucose meter (PlusMED) in the capillary blood taken from the tip of the tail to check if diabetes occurred. Animals with blood glucose levels of 250 mg/dl or over were considered diabetic. After the development of diabetes, 15 mg/kg live body weight/day Quercetin (Sigma Q4951) was injected intraperitoneally into the rats in the Q and DQ groups throughout the study. During the 4-week trial period, the rats in the (E) and (DE) groups were given a 30-minute swimming exercise per day, 5 days a week. The study has continued for 4 weeks after diabetes developed.
At the end of the study, blood samples, taken from the rats in all groups with cardiac puncture under general anesthesia (thiopental anesthesia, 40 mg/kg), were collected into anticoagulant (EDTA) containing laboratory tubes in adequate amounts. After collecting the blood samples, the rats were sacrificed by cervical dislocation under anesthesia.The blood samples were centrifuged (Hermle Z380) and the plasma of these samples was separated and stored at-80 ^{0}C until the time of analysis. The levels of IL-1, TNF-α, IL-6, and IL-10 levels were measured in these plasma samples in a Siemens CentaurXP Immunoassay System device, using commercial kits (Siemens) in compliance with the product information. At the end of the study, an analysis of variance was performed with Duncan's Multiple Range test in the SPSS 22.0 software for the statistical analysis of the data and to determine the significance of the differences between the groups.

RESULT

In this study, the data collected during the trial are presented in Table 1.

TABLE 1. THE EFFECT OF QUERCETIN ADMINISTRATION AND EXERCISE ON PLASMA IL-1, TNF-A, IL-6 AND IL-10 LEVELS IN THE RATS WITH EXPERIMENTALLY INDUCED DIABETES (X±SEM, N=8)

Parameters	C	Q	E	D	DQ	DE
IL-1 (pg/ml)	27.13±3.09^{c}	25.52±3.19^{c}	27.82±2.45^{c}	62.28±4.70^{a}	39.43±3.80^{b}	40.32±3.52^{b}
TNF-α (pg/ml)	63.90±5.58^{b}	66.17±6.05^{b}	69.79±4.21^{b}	134.91±31.55^{a}	84.97±5.81^{b}	91.06±7.68^{b}
IL-6 (pg/mL)	30.51±4.02^{c}	35.57±2.49^{c}	42.11±4.0^{c}	100.47±9.10^{a}	72.11±6.11^{b}	80.98±4.60^{b}
IL-10 (pg/mL)	59.04±4.15^{a}	58.00±2.71^{a}	57.09±3.99^{a}	29.61 ± 4.03^{b}	48.97±4.97^{a}	47.32±4.99^{a}

a,b,c: The difference between the mean values is significant if the same parameter on the same line is labelled with a different letter ($p < 0.05$).

In the group D, the levels of IL-1, TNF-α, and IL-6 were significantly higher compared to the other groups ($p < 0.05$). After the administration of quercetin and exercise, it was observed that the levels of these parameters in the diabetic group approached to the levels measured in the groups C, Q, and E. On the other hand, the levels of IL10 significantly decreased in the group D compared to the other groups ($p<0.05$).

DISCUSSION

The development of micro and macrovascular complications and the emergence of systemic disorders including chronic hyperglycemia, dyslipidemia, hypertension, and chronic inflammation are reported in Diabetes Mellitus [29]. It is reported that the hyperglycemia in diabetes triggers a systemic inflammatory condition and the proinflammatory cytokines IL-6 and TNF-α play a key role in this process. It is pointed out that IL-6 mediated reactions are involved in the chronicization of the inflammatory response and they lead to the mononuclear cell infiltration by stimulating the monocyte chemoattractant protein-1 (MCP-1) secretion [30]. Furthermore, the activity of IL-6 in provoking insulin resistance in the hepatocytes and adipose tissue is demonstrated [31,32]. The emergence of proinflammatory factors in the development of microvascular diabetic diseases has gained importance in the studies in the literature. Diabetic nephropathy was also found out to cause inflammation in the experimental rat models and clinical trials [33,34,35,36]. It has been reported that IL-1, IL-6, and TNF-α are important inflammatory cytokines, and their levels are increased in diabetic patients [37]. Hatipoğlu (2011) reported in a study that IL-1β levels decreased significantly while the levels of IL-6 level increased in the diabetic rats compared to the control group ($p < 0.05$) [38]. Yorgancı Koyuer (2005) also found that IL-6 levels significantly increased in diabetics compared to the control group in studies which included patients with type 2 DM [39].

Demir et al. (2015) reported that they observed an increase in the levels of IL-6 and TNF-α after treatment with quercetin in the rats with STZ-induced diabetes. In the quercetin-administered diabetes group, elevated levels of plasma IL-6 and TNF-α decreased to the levels observed in the non-diabetic animals. There were no differences in the levels of the inflammatory cytokines between the non-diabetic rat groups regardless of whether they were treated with quercetin or not [40]. The unchanged levels of IL-6 and TNF-α compared to the control group upon quercetin administration (Q group) suggest that this flavonoid is safe in terms of the homeostatic mechanisms of inflammation. Quercetin appears to have an immunomodulatory effect in a diabetic state rather than acting as an immunosuppressant [40]. Data obtained from this study demonstrate that the levels of IL-1, IL-6, and TNF-α increased in the group D, however, their levels decreased in the quercetin administered group (DQ), approaching to the levels observed in the control groups (C, Q). On the other hand, the levels of IL-10 decreased in the group D but significantly increased in the group DQ ($p<0.05$) (Table1).

Several various cytokines are released in response to small tissue injuries and associated inflammatory reactions after periods of acute exercise [41,42]. It has been observed that acute exercise, IL-1, IL-6, TNF-α, and IL-2 enhances the natural killer cell activity (NKCA). Furthermore, it has been demonstrated that a moderate-intensity endurance exercise-induced favorable effects via the NK/IL-2 system on the NKCA [41]. It is reported that an 8-week endurance exercise program resulted in higher IL-1β and IL-6 protein levels in rats compared to the control group [43]. It has been reported that a long-term acute exercise program increases the levels of IL-6Rm RNA level in the skeletal muscles, increasing the sensitivity of the skeletal muscle to IL-6 [44]. On the other hand, high-intensity physical activities are associated with the reduced levels of plasma IL-6 [45]. Intensive exercise is reported to result in increases in the circulating levels of cytokines, including IL-1, IL-6, TNFαR1-2, IL-8, and MIP-1b [46,47]. There are also reports of an increased natural killer (NK) cell activity, stimulated neutrophil functions, enhanced macrophage

functions, and increased cell number and activities of T and B lymphocytes in the acute phase following a mild to moderate exercise [48,49,50].

Madsen et al. (2015) reported that an 8-week cycling exercise program significantly improved diabetes-associated inflammatory cytokines and free fatty acids in patients with type 2 diabetes and in high-risk individuals for the metabolic syndrome [51]. Hayashino et al. (2013) reported in a study that aerobic exercise therapy in patients with Type 2 diabetes reduced IL-6 levels, suggesting that it can be a potential therapeutic option to improve the abnormalities in the degree of inflammation [52]. In a study investigating the effect of endurance exercise program supporting the expression of the basal muscle IL-6Ra protein in type 2 diabetic rats, 8-week endurance exercise has been reported to increase the levels of IL-6 in diabetic and non-diabetic groups [53]. El-Gohary and Hussien (2015) reported that an 8-week exercise program and quercetin treatment resulted in the improvement of obesity-induced insulin resistance and oxidative stress in rats [54]. In our study, it was determined that the regularly performed swimming exercise significantly reduced the initially increased levels of IL-1, IL-6 and TNFα and increased the initially reduced level of IL-10 in group D, approaching to the levels observed in the groups C and E (Table 1). The results of our study support the findings of the studies discussed in this section.

CONCLUSION

In conclusion, we are of the opinion that certain cytokines such as IL-1, IL-6, IL-10 and TNF-α are associated with insulin resistance and diabetes mellitus and that cytokines may affect the pathogenesis of diabetes mellitus. However, quercetin and regular swimming exercise were found to have favorable effects on the parameters studied in this present trial in STZ-induced diabetes.

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CITATION OF THIS ARTICLE

Gokmen Kilincarslan, Nurcan Donmez. Effect of Quercetin Administration and Exercise on Plasma Cytokine Levels in Rats with STZ Induced Diabetes. Bull. Env. Pharmacol. Life Sci., Vol 8 [2] January 2019: 130-135