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INFLUENCE OF LYCOPENE ADMINISTRATION ON NEOPTERIN, MYELOPEROXIDASE AND GAMMA GLUTAMYL TRANSFERASE IN DIABETIC RATS

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ABSTRACT

In this study, it was aimed to investigate the influence of lycopene administration on serum Neopterin (NEO), Myeleperoxidase (MPO) and Gamma glutamil tramsferase (GGT) activity in rats with experimentally induced diabetes.

Male Wistar-Albino rats aged 7-8 weeks and weighing 250-300 gr were used in the study. Rats were randomly allocated to four groups as control, lycopene, diabetes and diabetes -lycopene with 7 rats in each. 45 mg/kg streptozotocin (STZ) prepared in cold citrate buffer was applied via intraperitoneal route in order to induce experimental diabetes. Lycopene was prepared in corn oil and administered via peroral route through gavage in the dose of 10 mg/kg daily in lycopene and DL groups. Blood samples were taken into serum tubes from the hearts of the rats under general anesthesia at the end of 28 days of test period. Blood samples were centrifuged and serum was obtained. Neopterin, MPO and GGT activities were determined in serum samples.

The lowest neopterin level was detected in control group ($p<0.001$). The highest neopterin level was obtained in diabetes group, neopterin level of lycopene group was lower than that of diabetes group however a statistically significant difefrence was not detected. Neopterin level of DL group was found lower than that of diabetes and lycopene groups and this decrease was statistically significant ($p<0.001$). MPO level was found the lowest in diabetes group compared to other groups ($p<0.001$). MPO level of control group was found statistically significantly higher than that of lycopene and DL group ($p<0.001$). No statistically significant difference was observed between groups with regard to CRP levels. GGT activity was the highest in diabetes group and the lowest in DL group ($p<0.001$).

In conclusion, inflammation markers, neopterin and GGT were low in the groups which received lycopene. These findings suggest that lycopene may be useful for prevention of the complications of diabetes and related inflammation.

KEYWORDS:
Diabetes mellitus, Rat, Lycopene, Neopterin, Myeloperxidase, Gamma glutamyl transferase,

INTRODUCTION

Diabetes mellitus (DM) is a chronic and progressive disease characterized by carbohydrate, protein and lipid metabolism disorders and hyperglycemia [1]. DM is a chronic metabolic disease which develops as the result of absolute absence of insülin or relatively decreased insulin effect leads to death due to acute complications, reduces quality of life due to chronic complications, characterized by carbohydrate, protein and fat metablism disorders [2].

Lycopene is a ceratinoid which is found most in human plasma. Lycopene which is a potent antioxidant is also a vitamin which has anti-inflammatory and anticancer properties [3].

Lycopene shows an antioxidant activity as the result of binding of double bonds with uncoupled electrons. It protects lipids from peroxidation injury in high concentrations [4].

The association between neopterin production and immune activation was proven and a strong association was shown between neopterin levels and severity and progression of diseases [5, 6]. Neopterin and derivatives are synthesized from GTP via guanosine triphpsphate (GTP) cyclohydrolase I in vivo. GTP cyclohydrolase activity is increased by IFN-γ most [7, 8].

Neopterin was found high in body fluids in infections, autoimmune diseases, malignities, allograft rejections, cardiac and renal insufficiencies, coronary artery diseases and myocardial infarction in many clinical and experimental studies [9].

Type 1 diabetes is accepted as an insulin-dependent chronic autoimmune disease. Neopterin concentrations were detected high in newly diagnosed Type 1 DM patients compared to control group. Neopterin levels are similar in Type 2 DM patients and control group [9].

Under the light of these data, neopterin measurement was reported to be sensitive for determining disease activity and prognosis in autoimmune diseases [6]. Myeloperioxidase (MPO) enzyme is one

of the major granule proteins and a heme protein which consists 5% of total neutrophil protein. Combination of superioxide production and MPO release give a widespread and unique oxidative potential of neutrophil. Hydrogen peroxide which is formed by dismutation of superoxide uses oxidize halides to form hypohalous acid through a reaction catalysed by MPO. Chloride is the most proper substrate in physiologic concentrations [10]. DM is known to affect MPO acitivity, although low [11].

In later studies, MPO was detected to show its antimicrobial activity by making an inhibitör and killer effect on microorganisms by producing hypochloric acid and other toxic agents in phagolysosomes of neutrophils. MPO realizes its effect on post-translational modification in target molecules by using H2O2 MPO-mediated injury is not limited with microorganisms, HOCl and its derivatives cause a similar injury in host tissue [12, 13].

In this study, it was aimed to investigate the influence of lycopene administration on serum neopterin, CRP, MPO and GGT in rats with experiemnatlly-induced DM.

MATERIALS AND METHODS

Animal. Animal material of the study was obtained from Test Animals Unit of Yüzüncü Yıl University (Van, Turkey). A total of 28 male Wistar albino rats aged approximately 7-8 weeks were used. Initial weight of rats was determined as 220-2500 gr. Rats were kept in cages with animal feed and fresh water ad libitum in rooms with temperature of 22± 2°C in 12 hours light and dark cycle during 4-weeks of test period. Serum samples obtained from the project with number of 2010-SBE-D115 was used in the studySubjects were randomly allocated to 4 groups. The experiments were conducted according to ethical guidelines, and under the supervision of Yuzuncu Yil University Local Ethics Committee of Animal Experiments.

Group I was determined as control group (C) (n=7),

Group II as diabetes group (D) (n=7),

Group III as lycopene group (L) (n=7),

Group IV as diabetes-lycopene group (DL) (n=7).

45 mg/dl of streptozotocin (STZ) was dissolved in cold citrate buffer and applied intraperitoneally in order to create diabetes in the rats. Glucose level was measured in venous blood samples obtained from tail vein 72 hours after STZ injection using Lever Check-TD-22 brand of biosensor glucose test device. The rats whose plasma glucose >250 mg/dl were accepted as diabetic and enrolled in D and DL groups. Lycopene dissolved in 10 mg/dl corn oil was applied to the rats in D and DL groups via peroral gavage for 28 days.

Biochemical Analysis. After the 4-week trial, under ether anesthesia, blood samples were taken from animals from the left ventricle of their hearts, into tubes with anticoagulant and gel.

Determination of the amount of HbA1c was performed in whole blood with a commercial kit (Roche Diagnostics GmbH, D-68298 Mannheim, Germany) and an autoanalyzer (HITACHI-911) on the same day.

Neopterin and Myeloperoxidase levels were measured using rat neopterin ELISA kit (Cusabio Biotech). GGT level was detected using Cobas integra 800 autoanalyser (Roche).

Statistical analysis. Results were expressed as median, mean, standard deviation, minimum and maximum values. Kruskal-Wallis test was used for comparison of groups. Tukey test was used as multicomparison test for determining the different group. Statistical significance was taken as 1% and SPSS statistical package program was used for calculations.

RESULTS

Neoptrin, MPO, CRP and GGT levels of groups are presented in Table 1.

It was seen that HbA1c levels are highest in diabetes group, close to the levels of control group in DL group, significantly higher in lycopene group compared to control and DL groups ($p<0.05$).

Neopterin levels did not show a statistical significance in lycopene (L) and diabetes (D) groups ($p>0,05$). Neopterin level was lowest in control (C) group and the difference was statistically significant ($p<0,05$). Neopterin level of DL group was observed

TABLE 1
HbA1c, neopterin, MPO and GGT levels of rats in control, diabetes, diabeteslycopene and lycopene group

Parameters	n	Groups			
		Control Group (C) X± SEM	Diabetes Group (D) X±SEM	Diyabet+Lycopene (D+L) Group X±SEM	Lycopene Group (L) X±SEM
Neopterin (pmol/ml)	7	14.4 ± 0.08c	34.41 ± 1.79a	25.45 ± 1.56b	34.26 ± 3.08a
MPO (ng/ml)	7	0.82 ± 0.08a	0.47 ± 0.10d	0.62 ± 0.05c	0.78 ± 0.07b
GGT (U/L)	7	1.50 ± 0.1b	3.40 ± 0.26a	0.80 ±0.26d	1.20 ± 0.22c
HbA1c (%)	7	1.67 ± 0.2 b	6.23 ± 0.89a	2.08 ± 0.18b	3.93 ± 0.43c

#: The letters in the same line express statistical difference ($p<0.05$)

to be significantly lower compared to D and L group (p<0,05).

MPO level was lowest in group D and the difference was statistically significant (p<0,05). MPO level was found statistically significantly higher in Grup C compared to Group L and DL (p<0.05). MPO level was detected higher in group L compared to Group DL and D (p<0.001).

GGT level was the highest in Group D and the difference was statistically significant (p<0.05). The lowest GGT level was detected in group DL and a statistically significant difference was observed when compared with Group C and L (p<0.05). GGT level was found statistically significantly low in Group L when compared to control group (p<0.05).

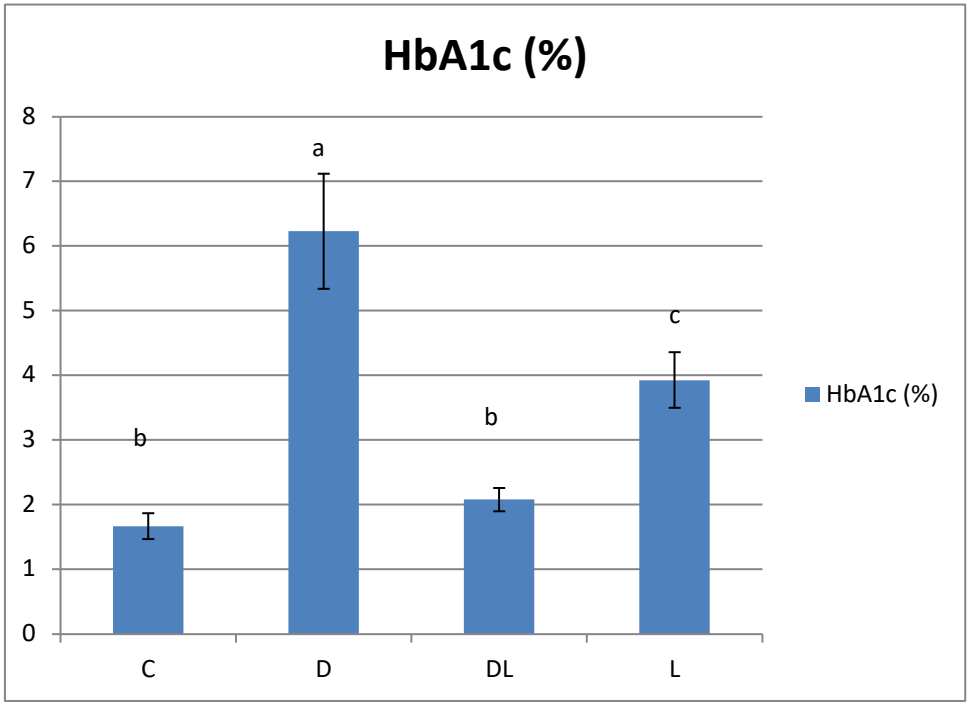

FIGURE 1
The level of HbA1c in groups.

C: Control group; D: Diabetes group; DL: Diyabet+Lycopene group; L: Lycopene group. Different letters to express statistical significance

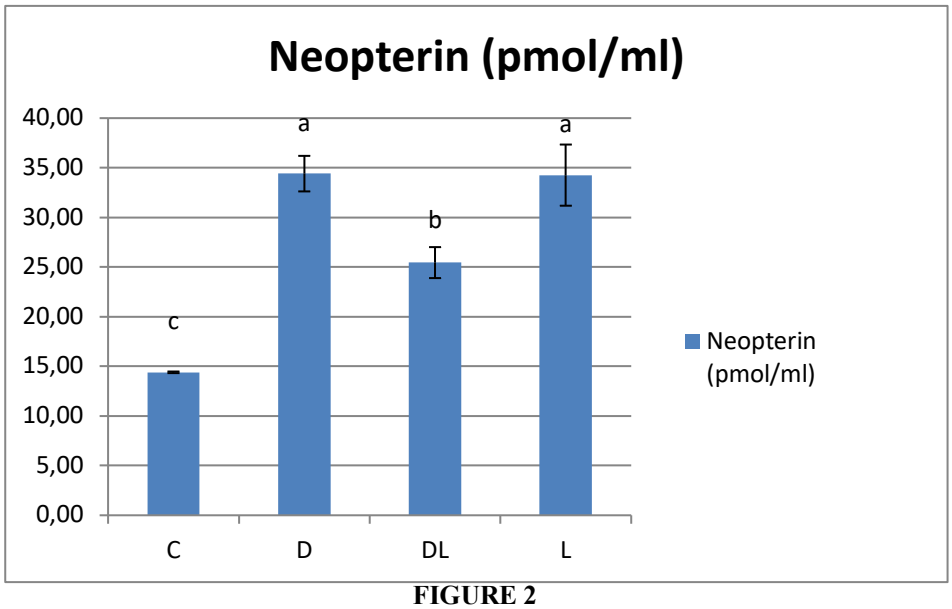

FIGURE 2
The level of Neopterin in groups

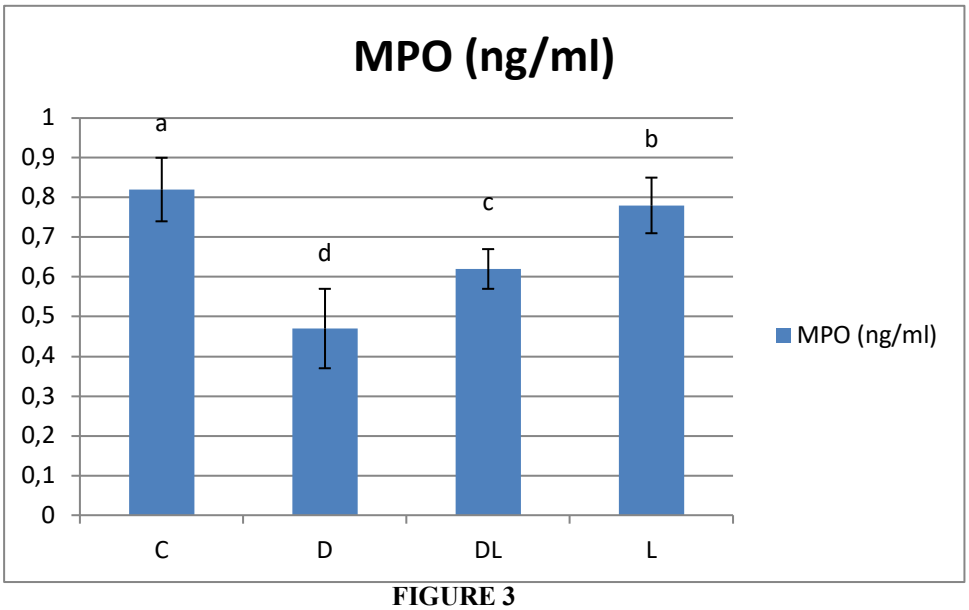

FIGURE 3
The level of MPO in groups

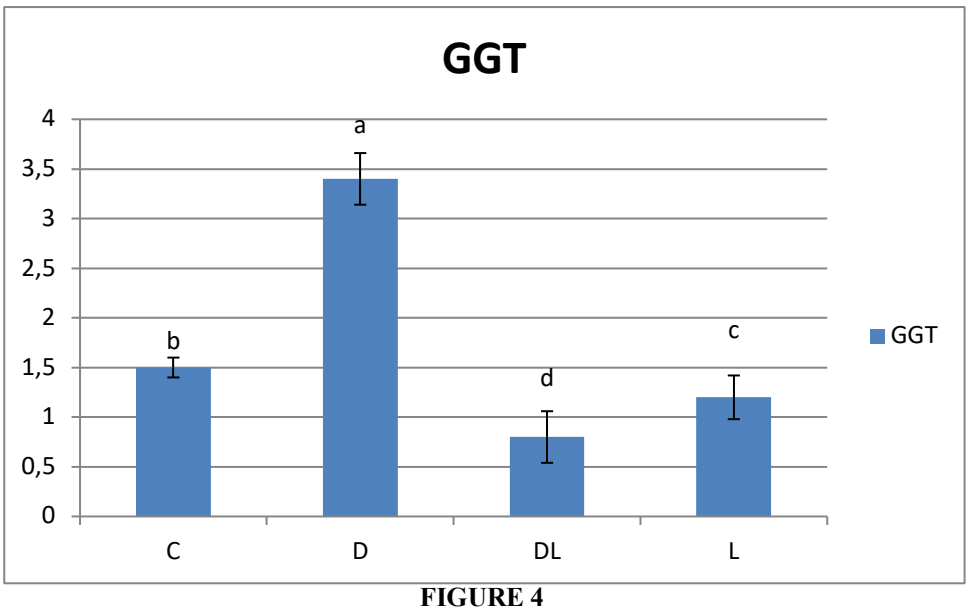

FIGURE 4
The level of GGT in groups

DISCUSSION

Susceptibility to infections increases in diabetic patients. Particularly impaired neutrophil functions are accused for the increase in susceptibility to infections in various studies [14].

Influences of lycopene have been investigated in many studies with regard to its antioxidant effect for prevention of the effects of free oxygen radicals. Antioxidant activity achieved by lycopene mediates prevention of various oxidative injuries, toxicity and other diseases. Therefore lycopene, a ceratinoid, is a more effective antioxidant against biologic effects and contributes to cell and tissue recovery both in vivo and in vitro [15]. Lycopene was reported to may have antioxidant effects in treatment of chronic diseases like cancer, cardiovascular diseases, osteoporosis and diabetes [16].

Pennathur et al. [17] showed that lycopene could have protective effects against cardiovascular diseases, prostate cancer, respiratory and gastro-intestinal system diseases. Lycopene is an anti-inflammatory agent. Lycopene inhibits activation of NF-kB and thereby decreases the expression of inflammatory cytokines like IL-6 and IL-8 [18]. Ghavipour et al. [18] observed that tomato juice reduces serum concentrations of IL-6 and IL-8 in their study investigating the influences of tomato consumption on levels of inflammatory biomarkers (IL-6, IL-8, hCRP and TNF- α) in overweight and obese women.

Neopterin activation is increased by interferon

γ (IFN- γ) [9]. IFN-γ production increases when T lymphocytes are stimulated by specific antigens and this condition leads to elevated neopterin levels. The conditions where T lymphocytes are activated, mainly viral infections, change neopterin level [19]. Cellular immune events are known to contribute to the pathogenesis of autoimmune diseases. T cell activation and significant elevation of IFN-γ levels enable the increase in neopterin in early stages of autoimmune diseases and thereby showing the activity and degree of autoimmune diseases as a marker [20].

Type 1 diabetes mellitus is accepted as an insulin-dependent chronic autoimmune disease. Neopterin concentration was detected higher in newly diagnosed type 1 DM patients compared to control group. However it was found to be similar in type 2 DM patients and control group [9]. As the result of these data, neopterin level measurement was reported to be useful in determining disease activity and prognosis in autoimmune diseases [6]. Monocyte macrophages play an important role in inflammatory response in diabetic patients [21]. Monocyte activation was shown to increase in type 1 DM patients compared to non-diabetics [22, 23].

Neopterin was shown to increase the production of chloride species and the oxidative potential of reactive oxygen in immuno-competent cells. It was also found to inhibit neopterin, xanthin oxidase and NADPH oxidase activity. Therefore neopterin may directly be included in the steps leading to oxidative stress [24]. Melicharova et al. [25] compared urinary neopterin level in patients with diabetes and diabetic foot and could not find a correlation between urinary neopterin levels. Bodlaaj et al. [26] could not find a difference between serum neopterin levels in diabetic and non-diabetic patients in their study conducted with the end stage renal failure patients.

Neopterin was reported as a marker of the complications and progression of DM [27]. In invitro studies, a few antioxidant compounds could slow neopterin production in mononuclear cells of peripheral blood. Antioxidant compounds suppress in vivo Th1 type immunity and neopterin production [28]. Neopterin is used as a senstive biomarker in immunemediated response of Th-1 type cells [29].

Aşcı et al. [30] compared urinary and serum neopterin levels between Type 1 and Type 2 diabetic patients. They found serum and urinary neopterin levels higher in diabetic patients, consistently with literature. They recommended that neopterin level could be a useful marker for prediction of the prognosis and activity of the diabetic patients. Lasselin et al. [31] found neopterin level higher in Type 2 DM patients compared to Type 1 DM patients.

In this research, the lowest neopterin level was found in control group. The highest neopterin level was detected in diabetic group. High neopterin level in diabetes group may be an indicator of increased oxidant level in diabetes. Elevated neopterin level shows an activation in immune system. High neopterin level in the group which lycopene was given and not diabetic may arise from lycopene's activating adipose tissue. Reduced neopterin level in diabetic rats which were given lycopene supports the finding that lycopene have some immune-suppressor effect.

MPO is a pro-oxidative enzyme which is released from activated leukocytes and monocyte/macrophages. It produces free radicals and reactive oxygen species when released as a part of natural defense of the host [32]. Antimicrobial activity of MPO leads to injury in endothelium and vessel wall [33]. An elevation is seen in MPO levels in patients with coronary artery diseases [34]. Heilmen et al. [35] found plasma MPO level higher in the patients with type 1 DM compared to control group. Papers are available reporting that MPO activity both increases and decreases in diabetic cases in different tissue and clinical studies [36, 37].

Diabetic patients are highly susceptible to bacterial and fungal infections. DM leads to impairment in inflammatory responses and immunologic functions [38]. Some studies proposed that hyperglycemia leads to neutrophil dysfunction [39]. Ferreira et al. [40] evaluated MPO enzyme activity in peritoneal neutrophils in diabetic rats. They did not find a statistically significant difference in MPO enzyme activity when compared to control group. In the same study, they measured hypochloric acid in order to determine MPO gene expression and MPO activity. MPO gene expression was found high in diabetic group compared to control group and a 40% reduction was detected in hypochloric acid in diabetic group. Uchimura et al. [41] found MPO activity in leukocytes of type 2 diabetic patients lower compared to the controls. Moldeveanu et al. [42] found MPO level high in diabetic group.

In this study, MPO activity was found the highest in control group and the lowest in diabetic group. The elevation in MPO activity in control group was found statistically significant when compared with other groups ($p<0.001$)

Elevations in GGT level in diabetic patients pulled attention in many epidemiologic studies conducted in recent 40 years [43]. The association between serum GGT and poor glycemic control was documented in 1980 [44]. Watkins et al. [45] showed that hepatic GGT activity increased in STZ-induced diabetic rats. Hamden et al. [46] found GGT level significantly high in alloxan-induced diabetic rats compared to control group. GGT was found to elevate in drug use and liver diseases. A significant elevation is reported in plasma GGT level in diabetic rats [47].

In this study, serum GGT activity was found statistically significantly high in diabetic group ($p<0.001$). GGT activity was the lowest in Group DL and there was a statistically significant difference when compared to control and lycopene groups ($p<0.001$). GGT activity of control group was high

in lycopene group and the difference was statistically significant ($p<0.001$).

Ghathi et al. [47] and Shamsi et al. [48] found GGT activity significantly high in STZinduced diabetic rats compared to non-diabetics. They reported that this elevation indicated STZinduced hepatotoxicity. The results of our study are consistent with literature.

Increased GGT level in diabetic rats indicates STZ-induced hepatotoxicity. GGT level may have arisen due to oxidative stress caused by diabetes. Lycopene administration caused decreased GGT activity by reducing oxidative stress in Group DL and it may be stated that this condition has arisen from the antioxidant property of lycopene. Decreased GGT activity particularly in Group DL compared to diabetic group is one of the important results obtained from indicating antioxidant property of lycopene.

It may be stated that decrease in neopterin level in Group DL compared to Group D, elevated MPO activity in group DL compared to diabetic group and very low GGT activity in Group DL compared to diabetic group may be an important indicator of positive and antioxidant effect of lycopene on diabetes. Lycopene is known to be an antioxidant compound which has an important role as free radical scavenger. The results of our study suggest that lycopene may be an effective nutritional factor for prevention of diabetes complications and inflammatory response, this is important as it shows the antiinflammatory effect and further studies are required.

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