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Effect of *Allium Cepa* on Paraoxonase 1 Activity and Oxidative Stress in Streptozotocin Induced Diabetic Rats

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Abstract The protective role of Paraoxonase 1 (PON1) enzyme against oxidative stress has not yet been fully elucidated. In some studies, it was suggested that low PON1 activity observed in diabetic cases may be due to increased susceptibility to lipid peroxidation and it is important to identify the changes in PON1 activity level in the as a result of the consumption of foods with antioxidant activity. This study was carried out to determine the changes in PON1 activity value and oxidative stress-related parameters to be resulted by onion which shows an antioxidant activity. It was also aimed to examine the changes to be brought to the functional activity of onion by the heat treatment applied to it. 32 male rats were divided into 4 groups as Group C and Group DC fed with a standard rat diet, Group DLO fed with a diet supplemented with 5% lyophilized onion powder, and Group DFO fed with a diet supplemented with 5% oven-dried onion powder. The rats in the groups were fed for 8 weeks. The rats in Group DC, Group DFO, and Group DLO were induced diabetes by a single dose STZ injection (45 mg/kg). Total Antioxidant Status (TAS) and PON1 activity levels of the Group DLO were significantly higher ($p<0.05$, $p<0.001$, respectively) and the Total Oxidant Status (TOS) and Oxidative Stress Index (OSI) values were significantly lower than of the DC group ($p>0.05$). TAS, TOS, PON1 activity levels and OSI values of Group DC and Group DFO were not significantly different ($p>0.05$). Group DLO had lower TOS level, higher PON1 activity level and OSI value than Group DFO ($p<0.05$). Although the findings show that onion may be effective in elevating PON1 activity levels and reducing diabetes-related oxidative stress, heat treatment applied to onion adversely affects these functional effects of it.

Keywords: *paraoxonase, total antioxidant status, total oxidant status, oxidative stress index*

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1. Introduction

In diabetes which is a chronic metabolic disease characterized by hyperglycemia, where the organism cannot utilize carbohydrates, fat, and protein due to insulin secretion or defects in its effects [1], the production of reactive oxidant species (ROS) causing oxidative damage due to long-term hyperglycemia is elevated [2]. Increased reactive oxidant species have an important role in the pathogenesis of diabetic complications. Endogenous antioxidants cannot balance reactive oxygen species [3] while reactive oxygen species in healthy individuals are controlled by enzymatic (superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase enzymes) and non-enzymatic antioxidants (vitamins A, C, and E, and glutathione). For this reason, diabetic antioxidants can be used to treat the adverse effects of free radicals [4]. There is sufficient evidence that onion, which contains many phytochemical substances such as carotenoids, flavonoids, minerals, phenolics, phytoestrogens, terpenoids, vitamins, anthocyanins, and amino acids [5], has protective effects against oxidative stress by increasing the levels of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) [6,7] and lowering the bioactive aldehyde levels formed by degradation of lipid hydroperoxides [8,9] in the presence of diabetes. However, no *in vivo* study conducted to determine how heat treatment affects the antioxidant activity of onion has been found in the literature. In *in vitro* studies, it was found that secondary compounds content which is thought to have a role in the functional effects of onion and garlic and their antioxidant capacities were reduced as a result of heat treatment and different cooking techniques [10,11].

It is important not only following up the free radicals and oxidative stress parameters, which are thought to be critical in the emergence of secondary complications, it is important to follow up Paraoxonase-1 (PON1) enzyme as well. It was reported that PON1 enzyme activity, which protects HDL and LDL from oxidation by neutralizing the atherogenic effects of lipid peroxides, was reduced in the presence of diabetes and such a reduction might be due to reduced antioxidant capacity [12] and increased oxidative stress [13]. Although PON1 enzyme activity known to be

protective against atherosclerosis [14] is increased by onion consumption [15], there are limited studies on this topic. Therefore, the purpose of this study was to determine the changes in total antioxidant status (TAS), total oxidant status (TOS) and PON1 activity levels to be resulted by onion which shows an antioxidant activity. It was also aimed to examine the changes to be brought to the functional activity of onion by the heat treatment applied to it.

2. Materials and Methods

2.1. Preparation of Onion Powder and Rat Diets

After separating the head and stem parts of the onions provided from a local market in Ankara, the shells were peeled off and diced using a ceramic knife. Some of the diced onions was firstly placed in a freezer (Operon, South Korea) and stored at -78°C for 24 hours, and then transferred into a lyophilizator and dried at -76°C under 200 mTorr engine pressure. The remaining diced onions was directly placed in a furnace (Vestel AFB-1004, Turkey) and dried at +80°C using its fruit-dry mode. The onion powders obtained were pelleted by adding 5% to standard rat diet.

Table 1. Essential nutrients and vitamin contents of the standart diet

Ingredients	Standart diet
Protein (%)	23
Oil (%)	5.5
Cellulose (%)	3.5
NDF* (%)	11
ADF** (%)	3.7
Lizin (%)	1.05
Metionin (%)	0.55
Sistin (%)	0.45
Vitamin A IU/kg	18000
Vitamin D IU/kg	3500
Vitamin E mg/kg	70
Onion powder*** (%)	0/5

*Neutral detergent fibre, **Acid-detergent fibre, *** C ve DC groups were fed with standard rat diet (onion free), DLO and DFO groups were fed with 5% onion suplemented diet.

2.2. Animals and Experimental Induction of Diabetes

Thirty-two male wistar-albino rats aged 3-4 months, weighted 280-330 g and obtained from the Experimental Animals and Research Laboratory at Ankara University were used in the study. The animals were housed in the cages under standard conditions. (12:12 h light dark cycle, 50% relative humidity at 21 °C). After the adaptation period, the rats were randomly divided into 4 groups as 8 rats in each group, and then Streptozotocin (Sigma-Aldrich, USA) with a dose of 45 mg/kg body weight in 0.1 M citrate buffer (pH: 4.5) was injected intraperitoneally into 24 rats to be induced experimental diabetes. Seven days after the injection, the fasting blood glucose (FBG) measurements were taken by drawing blood from their tail veins after 12 hours of fasting, and using a glucometer (Accu-Chek Performa Nano, Turkey); accordingly the rats with FBG values exceeding 250 mg/dL were considered diabetic. Then, for the following 8 weeks, the groups C and DC were fed with standard rat diet, the DLO group was fed with rat diet including 5% onion powder (dried at -76°C in lyophilizator), and the DFO group was fed with rat diet including 5% onion powder (dried at +80 °C in furnace) (Table 1). At the end of 8 weeks, the rats were anesthetized after 12 hour of fasting, using an injection of 10 mg/kg Xylazine and 70 mg/kg Ketamine HCl, and then they were sacrificed taking 5-7 mL of intracardiac blood. The rat bloods obtained were centrifuged and the TAS, TOS and PON1 activity levels were checked.

2.3. Measurement of TAS

Total Antioxidant Capacity measurements of serum samples were determined using the Total Antioxidant Status kit (Rel Assay Diagnostics, Turkey) according to the method developed by Erel (16). In this method, the antioxidative effect of the sample against the potent free radical reactions, which is initiated by the produced hydroxyl radical, is measured. The results are expressed as mmol Trolox Eq/L.

2.4. Measurement of TOS

Total Oxidant Capacity measurements of serum samples were determined using the Total Oxidant Status kit (Rel Assay Diagnostics, Turkey) according to the method developed by Erel (17). The colour intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules present in the sample. The assay is calibrated with hydrogen peroxide (H_2O_2) and the results are expressed as μmol H_2O_2 Eq/L.

2.5. Measurement of PON1 Activity Level

Paraoxonase (PON1) enzyme levels of serum samples were measured using the Rel Assay Diagnostics kit. The measurement principle is based on the fact that Paraoxonase enzyme in the sample hydrolyzes the paraoxon substrate in the reaction medium. Absorbance was measured at 412 nm. The results were given in U/L. For PON activity, enzyme activity which converts 1 μmol paraoxon to P-nitrophenol in 1 minute was defined as Unit (U).

2.6. Calculation of OSI

While OSI, which refers to the percentage value of the ratio of TOS levels to TAS levels, was calculated, the mmol value in TAS level was converted to μmol value as in the TOS test. The results were expressed as "arbitrary unit" (AU) and calculated according to the following formula (17).

$$OSI = \frac{TOS, \mu\text{mol } H_2O_2 \text{ Eq / L}}{\text{TAS, mmol Trolox Eq / L} X10}.$$

2.7. Statistical Analysis

Using Statistical Package for the Social Sciences (SPSS) version 18.0 (SPSS Inc., Chicago, IL, USA) software, the data were statistically analyzed by one-way ANOVA. Results are expressed as mean±SE for groups of eight animals each. Statistical significance was considered at $p<0.05$.

3. Results

3.1. TAS and TOS Levels

The mean values and statistical analyzes of TAS, TOS and PON1 activity levels of the four groups in the study are as shown in Table 2. It was found that TAS levels of Group C and Group DC fed with standard diet were significantly reduced in the presence of diabetes ($p<0.001$), but TOS levels were significantly elevated ($p<0.01$). While the mean TAS level of the group fed with lyophilized onion powder was found to be significantly higher ($p<0.05$) and TOS level of it was significantly lower ($p<0.05$) when compared to the Group DC, no statistically significant difference was found between the Group DFO and Group DC in terms of these parameters ($p>0.05$).

3.2. PON1 Activity Level

The difference between the Group C and Group DC was statistically significant ($p<0.001$) while the highest value was found in the Group C and the lowest value was in the Group DC (Table 2). Mean PON1 activity values of the Group DLO were found to be significantly higher than those of the Group DC ($p<0.001$), but there was no statistically significant difference between the Group DFO and Group DC in terms of the mean PON1 activity values ($p>0.05$).

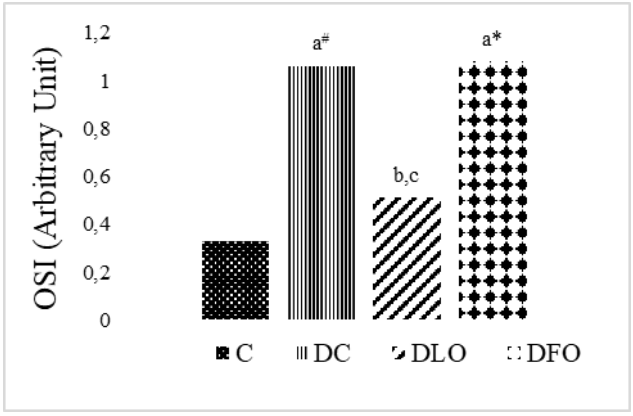
Table 2. Groups' mean TAS, TOS and PON1 activity levels at the end of the experiment

Group[1]	C	DC	DLO	DFO
TAS (mmol trolox eqv./L)	1,7±0,1	1,1±0,1^{a*}	1,4±0,1^{b}	1,1±0,1 ^{a*}
TOS (μmol/L H_2O_2 eqv./L)	5,5±0,6	10,7±1,0$^{a\#}$	7,0±0,8^{b,c}	11,4±1,0^{a*}
PON1 (U/L)	14,3±1,3	4,7±0,5^{a*}	12,2±1,7^{b*,c}	7,4±0,9$^{a\#}$

[1]C, Normal rats fed standart diet; DC, Diabetic rats fed standart diet; DLO, Diabetic rats fed standart diet plus %5 lyophilized onion powder; DFO, Diabetic rats fed standart diet plus %5 baked onion powder.
^{a}Significantly different from Group C. ^{b}Significantly different from Group DC. ^{c}Significantly different from Group DFO. ^{b,c} ($p<0.05$), $^{a\#}$ ($p<0.01$), ^{a*,b*} ($p<0.001$).

3.3. Oxidative Stress Index (OSI)

According to oxidative stress calculation (Figure 1), OSI values of the Group DC and Group DFO are higher than of the Group C and the difference is statistically significant ($p<0.01$). There was no significant difference between the Group DLO and Group C ($p>0.05$). OSI value of the Group DLO was found to be significantly lower than of the Group DC and Group DFO ($p<0.05$).



^{a}Significantly different from Group C. ^{b}Significantly different from Group DC. ^{c}Significantly different from Group DFO. ^{b,c} ($p<0.05$), $^{a\#}$ ($p<0.01$), ^{a*} ($p<0.001$).

Figure 1. Effects of supplementation of onion on the oxidative stress index (Arbitrary Unit)

4. Discussion

4.1. Effects on Oxidative Stress

Diabetes Mellitus is a chronic metabolic disorder as well as an increased oxidative stress. In the meantime, the production of reactive oxidant species (ROS), which leads to oxidative damage due to long-lasting hyperglycemia, increases. In addition, prolonged hyperglycemia leads to progressive glycation of certain antioxidant enzymes and consequently reduction in their activities. Similar to this study, it was observed that TAS levels were reduced and TOS levels were elevated in rats with STZ-induced diabetes, and the results obtained in this study are compatible with these results [18,19]. In some studies, MDA levels were examined as markers of lipid peroxidation and it was concluded that MDA levels were elevated in diabetic rats [20,21,22]. In the same studies, the antioxidant capacity was evaluated by examining GSH, SOD, and CAT levels and it was found that the values of these parameters were reduced in diabetic rats.

Onion is an antioxidant thanks to its sulfurous compounds and flavonoids such as quercetin. Azuma et al. [23] found that the plasma TBARS levels of diabetic rats fed with a diet supplemented with lyophilized onion (6%) were lower than those fed with a standard rat diet. In another study, the plasma MDA levels of rats fed with a diet supplemented with 3% lyophilized onion were lower than those fed with a standard rat diet [8]. The plasma MDA and TBARS levels were reduced and antioxidant enzyme levels were elevated in some studies in which onion extracts or onion juice were administered as oral gavage [9,24,25]. It was also determined that TBARS levels were lowered with the administration of the extraction of essential oils within onion as oral gavage [26]. It was found out that antioxidant enzyme levels (SOD, CAT, GSH) were elevated and MDA levels were reduced with the administration of quercetin alone, which is among the

bioactive compounds thought to be effective in the antioxidant effect of onion [27]. It was concluded that S-Methyl Cysteine, which is among the sulfurous compounds thought to play a role in the antioxidant activity, increased the antioxidant capacity when administered alone [28].

In this study, lyophilized onion powder significantly increased the antioxidant capacity, but reduced the oxidant capacity. On the other hand, there was no statistically significant effect of the oven-dried onion powder on the TAS and TOS levels, and no *in vivo* study was found in the literature in which the effects of heat-treated onion forms on oxidative stress were evaluated. *In vitro* studies revealed that heat treatments applied to nutrients with high quercetin content and sulfurous compounds, such as onion and garlic, reduced the quercetin content [10] and the antioxidant activity [11]. As a result, it is considered that reduced amounts of sulfurous compound and quercetin due to applied heat treatments is thought to be a role in the absence of statistically significant effect of thermal onion powder on the TAS and TOS levels, whereas the data in the literature reveal that lyophilized onion has positive effects on these levels.

4.2. Effects on PON1 Activity

While PON1 activity levels may vary depending on many genetic and environmental influences, one of the most important factors is oxidative stress, which is caused by increased lipid and protein oxidant products and reduced levels of antioxidant enzymes and vitamins. It was found out that PON1 activity levels were reduced when oxidative stress was increased due to increased lipid and protein oxidant products and reduced levels of antioxidant enzymes and vitamins [29]. For example, it was revealed that smokers and people with metabolic syndrome, diabetic individuals had lower PON1 enzyme activity compared to control group [30,31,32]. There are a number of studies on the relationship between PON1 enzyme activity, which neutralizes the atherogenic effects of lipid peroxides and protects HDL and LDL from oxidation, and diabetes. In the vast majority of these studies, PON1 enzyme activity was reported to be lower in diabetic individuals than in healthy ones [12,31,33]. Tartan et al. [34] found that patients with Type 2 DM and coronary artery disease who experienced a short duration of diabetes had higher PON1 activity than those who experienced a longer duration of diabetes. Similar to this study, it was concluded that PON1 activity levels in experimental STZ-induced diabetic rats were significantly lower than normal rats, and the results obtained in this study are compatible with these results [35,36].

The studies on the effects of onion on PON1 activity are limited and studies of Jaiswal and Rizvi [15] revealed that PON1 activity levels were elevated with the administration of onion extracts. Administration of quercetin, which is believed to play a role in the functional activity of onion, is also associated with a significant increase in PON1 enzyme activity in rats [37]. In this study, it was also found that lyophilized onion powder significantly increased PON1 enzyme activity, whereas the oven-dried onion powder had no statistically significant effect. It was observed that PON1 activity levels were elevated when the antioxidant capacity was increased but the oxidant capacity was decreased.

5. Conclusion

Oxidative stress, which is thought to play an important role in diabetic micro and macrovascular complications, can be dealt with daily diets with foods known to have an antioxidant activity such as onions. However, inappropriate preparation and cooking techniques applied to these foods may cause the loss of the functional activity of them. As a matter of fact, it was proven that lyophilized onion powder significantly increased PON1 activity levels and could be protective against oxidative stress. There was no statistically significant effect of oven-dried onion powder on TAS, TOS, and PON1 activity levels. It is important to evaluate similar changes to be appeared in the functional activity of similar foods that are consumed extensively but prepared with different preparation and cooking methods. Medical nutrition therapy, one of the cornerstones of diabetes treatment, can benefit from the outcomes of such studies.

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Conflict of Interests

The author declares that there is no conflict of interests.

References

[1] American Diabetes Association, "Diagnosis and classification of diabetes mellitus'', *Diabetes care*, 37(1). 81-90. 2014.

[2] Asmat, U., Abad, K. and Ismail, K, "Diabetes mellitus and oxidative stress—a concise review", *Saudi Pharmaceutical Journal*, 24(5). 547-553. 2016.

[3] Hamamcıoglu, A.C, "The Role of Oxidative Stress and Antioxidants in Diabetes Mellitus", *Turkish Journal of Diabetes and Obesity*, 1(1). 7-13. 2017.

[4] Vincent, A.M., Russell, J.W., Low, P. and Feldman, E.L, "Oxidative stress in the pathogenesis of diabetic neuropathy", *Endocrine reviews*, 25(4). 612-628. 2004.

[5] Ouyang, H., Hou, K., Peng, W., Liu, Z. and Deng, H, "Antioxidant and Xanthine Oxidase Inhibitory Activities of Total Polyphenols from Onion", *Saudi Journal of Biological Sciences*. 2017. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S1319562X17302152. [Accessed Sept. 18, 2018].

[6] Ogunmodede, O.S., Saalu, L.C., Ogunlade, B., Akunna, G.G. and Oyewopo, A.O, "An Evaluation of the Hypoglycemic, Antioxidant and Hepatoprotective Potentials of Onion (Allium cepa L.) on Alloxan-induced Diabetic Rabbits", *International journal of pharmacology*, 8(1). 21-29. 2012.

[7] Pal, M., Roy, U.K., Datta, S., Ghosh, T., Harlalka, S. and Biswas, L, "Onion peel extracts ameliorate oxidative stress in Streptozotocin-induced diabetic rats", *Serbian Journal of Experimental and Clinical Research*, 14(3). 101-108. 2013.

[8] Babu, P.S. and Srinivasan, K, "Influence of dietary capsaicin and onion on the metabolic abnormalities associated with streptozotocin

induced diabetes mellitus", *Molecular and cellular biochemistry*, 175(1-2). 49-57. 1997.

[9] El-Demerdash, F.M., Yousef, M.I. and Abou El-Naga, N.I, "Biochemical study on the hypoglycemic effects of onion and garlic in alloxan-induced diabetic rats", *Food and Chemical Toxicology*, 43(1). 57-63. 2005.

[10] Harris, S., Brunton, N., Tiwari, U. and Cummins, E, "Human exposure modelling of quercetin in onions (Allium cepa L.) following thermal processing", *Food chemistry*, 187. 135-139. 2015.

[11] Locatelli, D.A., Nazareno, M.A., Fusari, C.M. and Camargo, A.B, "Cooked garlic and antioxidant activity: correlation with organosulfur compound composition", *Food chemistry*, 220. 219-224. 2017.

[12] Kalmar, T., Seres, I., Balogh, Z., Kaplar, M., Winkler, G., and Paragh, G, "Correlation between the activities of lipoprotein lipase and paraoxonase in type 2 diabetes mellitus", *Diabetes & metabolism*, 31(6), 574-580. 2005.

[13] Mackness, B., Durrington, P., Boulton, A., Hine, D. and Mackness, M, "Serum paraoxonase activity in patients with type 1 diabetes compared to healthy controls", *European Journal of Clinical Investigation*, 32(4). 259-264. 2002.

[14] Durrington, P., Mackness, B., and Mackness, M, "Paraoxonase and atherosclerosis", *Arteriosclerosis, thrombosis, and vascular biology*, 21(4). 473-480. 2001.

[15] Jaiswal, N., and Rizvi, S.I, "Onion extract (Allium cepa L.), quercetin and catechin up‐regulate paraoxonase 1 activity with concomitant protection against low‐density lipoprotein oxidation in male Wistar rats subjected to oxidative stress", *Journal of the Science of Food and Agriculture*, 94(13). 2752-2757. 2014.

[16] Erel, O, "A novel automated direct measurement method for total antioxidant capacity using a new generation, more stable ABTS radical cation", *Clinical biochemistry*, 37(4). 277-285. 2004.

[17] Erel, O, "A new automated colorimetric method for measuring total oxidant status", *Clinical biochemistry*, 38(12). 1103-1111. 2005.

[18] Atilla, G, "Protective effects of chromium and Trigonella foenum-graecum (Fenugreek) on oxidative stress, diabet and TNF-alfa level in streptozotocin-induced diabetic rats," *Physiology Thesis*. 2014.

[19] Ünsal, C. and Ünsal, H. "The Effects of Swimming Exercise on Lipid Profile and Oxidant-Antioxidant Status in Type I Diabetic Rats", *Fırat University Medical Journal of Health Sciences,* 30(3). 119-123. 2016.

[20] Madhuri, K. and Naik. PR, "Ameliorative effect of borneol, a natural bicyclic monoterpene against hyperglycemia, hyperlipidemia and oxidative stress in streptozotocin-induced diabetic Wistar rats", *Biomedicine & Pharmacotherapy*, 96. 336-347. 2017.

[21] Samarghandıan, S., Borjı A., Delkhosh, M.B. and Samini, F, "Safranal treatment improves hyperglycemia, hyperlipidemia and oxidative stress in streptozotocin-induced diabetic rats", *Journal of Pharmacy & Pharmaceutical Sciences*, 16(2). 352-362. 2013.

[22] Vuppalapatı, L., Velayudam, R., Ahamed, K.N., Cherukurı, S. and Kesavan, B.R, "The protective effect of dietary flavonoid fraction from Acanthophora spicifera on streptozotocin induced oxidative stress in diabetic rats", *Food Science and Human Wellness*, 5(2). 57-64. 2016.

[23] Azuma, K., Minami, Y., Ippoushı, K. and Terao J, "Lowering effects of onion intake on oxidative stress biomarkers in streptozotocin-induced diabetic rats", *Journal of clinical biochemistry and nutrition*, 40(2). 131-140. 2007.

[24] Jung, J.Y., Lim, Y., Moon, M.S., Kim, J.Y. and Kwon O, "Onion peel extracts ameliorate hyperglycemia and insulin resistance in high fat diet/streptozotocin-induced diabetic rats", *Nutrition & metabolism*, 8: 1-18. 2011.

[25] Lee, B., Jung, J.H. and Kim H.S, "Assessment of red onion on antioxidant activity in rat", *Food and chemical toxicology*, 50(11). 3912-3919. 2012.

[26] El-Soud, N. and Khalil, M, "Antioxidative effects of Allium cepa essential oil in streptozotocin induced diabetic rats", *Macedonian Journal of Medical Sciences*, 3(4). 344-351. 2010.

[27] Alam, M.M., Meerza, D. and Naseem, I, "Protective effect of quercetin on hyperglycemia, oxidative stress and DNA damage in alloxan induced type 2 diabetic mice", *Life Sciences*, 109(1). 8-14. 2014.

[28] Senthilkumar, G.P., Thomas, S., Sivaraman, K., Sankar, P. and Bobby, Z, "Study the effect of s-methyl L-cysteine on lipid metabolism in an experimental model of diet induced obesity", *Journal of clinical and diagnostic research: JCDR*, 7(11), 2449-2451. 2013.

[29] Aslan, R, "Evaluation of level of total antioxidant status (TAS), total oxidant status (TOS) and paraoxonase (PON1) in smokers", Master Thesis in Medicine. 2012.

[30] Garin, M.C.B., Kalix, B., Morabia, A. and James, R.W, "Small, dense lipoprotein particles and reduced paraoxonase-1 in patients with the metabolic syndrome", *The Journal of Clinical Endocrinology & Metabolism*, 90(4). 2264-2269. 2005.

[31] Flekac, M., Skrha, J., Zidkova, K., Lacinova, Z. and Hilgertova, J, "Paraoxonase 1 gene polymorphisms and enzyme activities in diabetes mellitus", *Physiological research*, 57(5). 717-726. 2008.

[32] Senti, M., Tomás, M., Anglada, R., Elosua, R., Marrugat, J., Covas, M.I. and Fıtó, M, "Interrelationship of smoking, paraoxonase activity, and leisure time physical activity: a population-based study", *European Journal of Internal Medicine*, 14(3). 178-184. 2003.

[33] Ferrettı, G., Bacchettı, T., Mascıangelo, S. and Pallotta, G, "Lipid peroxidation in hemodialysis patients: effect of vitamin C supplementation", *Clinical biochemistry*, 41(6). 381-386. 2008.

[34] Tartan, Z., Orhan, G., Kasıkçıoğlu, H., Uyarel, H., Ünal, S., Özer, N., Özay, B., Çiloglu, F. and Cam, N, "The role of paraoxonase (PON) enzyme in the extent and severity of the coronary artery disease in type-2 diabetic patients", *Heart and Vessels*, 22(3). 158-164. 2007.

[35] Özgün, E., Özgün, G.S., Eskiocak, S., Yalçın, Ö. and Gökmen S.S, "Effect of L-carnitine on serum paraoxonase, arylesterase and lactonase activities and oxidative status in experimental colitis", *Turkish Journal of Biochemistry*, 38(2). 145-153. 2013.

[36] Parmaksız, İ, "Advanced Glycation End-Products in Complications of Diabetes Mellitus", *Marmara Medical Journal*, 24.141-8. 2011.

[37] Hamidia, Z., Nayeri, H., Vessal, M., Naderi, G. and Boshtam, M, "Myrıcetın, quercetın, kaempferol and galangın all ıncrease serum paraoxonase actıvıty", *Indian Journal of Fundamental and Applied Life Sciences*, 3(1).36-43. 2013.