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The Effects of Acute and Chronic Hyperglycemia on Serum Paraoxonase Activity

[Akut ve Kronik Hipergliseminin Serum Paraoksanaz Üzerine Etkileri]

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ABSTRACT

Objectives: Paraoxonase (PON1) is a high density lipoprotein bound serum esterase that is synthesized by the liver which has ability to metabolize lipid peroxides hence playing an important role in protection against atherosclerosis. Our aim was to evaluate the effect of acute and chronic hyperglycemia on PON1 activity in order to clarify the effect of glucose homeostasis. Besides, the relation of hemoglobin A_{1c} with triglyceride, total cholesterol, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol and PON1/high density lipoprotein-cholesterol ratios which play role in the development of atherosclerosis was also evaluated.

Design and methods: Chronic effects were investigated in Type 2 diabetes patients (n=290) divided into three groups according to their HbA_{1c} levels (group 1: <7%, group 2: 7-8.9%, group 3: ≥9%). Oral glucose tolerance test applied 192 subjects were evaluated for acute effects.

Results: No significant difference was observed in PON1 activities between the groups ($p>0.05$) and there was no correlation between PON1 activity, PON1/HDL-C ratio and HbA_{1c}. PON1 activities decreased during OGTT ($p<0.05$) and were insignificantly lower in the subjects with normal glucose tolerance.

Conclusion: Our findings indicate that although there is a tendency of lowered PON1 activity in long term hyperglycemia, the difference was not significant between different HbA_{1c} levels. However, acute hyperglycemia leads to significant decreases in PON1 activity.

Conflict of interest: Authors did not declare any conflict of interest.

Key words: Paraoxonase-1; hemoglobin A_{1c} protein; glucose; diabetes mellitus; hyperglycemia

ÖZET

Amaç: Paraoksonaz (PON1) karaciğerde sentezlenen, yüksek dansiteli lipoproteinlere bağlı bir serum esteraz olup, lipid peroksitleri metabolize etme yeteneği ile ateroskleroza karşı korunmada önemli bir rol oynar. Bu çalışmada, glukoz hemostazının etkisini ortaya koymak amacıyla akut ve kronik hipergliseminin paraoksonaz-1 aktivitesine etkisinin değerlendirilmesi amaçlandı. Ayrıca ateroskleroz oluşumunda rol oynayan trigliserid, total kolesterol, düşük dansiteli lipoprotein-kolesterol, yüksek dansiteli lipoprotein-kolesterol, paraoksonaz-1/yüksek dansiteli lipoprotein-kolesterol oranlarının diyabetli hastalarda hemoglobin A_{1c} düzeyleri ile ilişkisi değerlendirildi.

Gereç ve yöntemler: Kronik etkiler, hemoglobin A_{1c} düzeylerine göre üç gruba ayrılan (grup1: <%7, grup 2: %7-8.9, grup 3>%9) Tip 2 diabetes mellitus hastasında (n=290) araştırıldı. Akut etkiler ise oral glukoz tolerans testi uygulanan 192 kişide değerlendirildi.

Bulgular: Gruplar arasında paraoksonaz-1 aktiviteleri açısından anlamlı bir fark bulunmadı ($p>0.05$). Paraoksonaz-1 aktivitesi ile paraoksonaz-1/yüksek dansiteli lipoprotein-kolesterol oranı arasında bir korelasyon yoktu. Oral glukoz tolerans testi esnasında paraoksonaz-1 aktiviteleri azalırken ($p<0.05$) normal glukoz toleranslı olanlarda anlamlı olmayan bir düşüklük vardı.

Sonuç: Bulgularımız, uzun dönemli hiperglisemide paraoksonaz-1 aktivitesinin azalma eğiliminde olmasına rağmen, farklı hemoglobin A_{1c} düzeyleri arasında anlamlı bir fark olmadığını gösterdi. Ancak akut hiperglisemi paraoksonaz-1 aktivitesinde anlamlı azalmaya sebep oldu.

Çıkar çatışması: Yazarlar herhangi bir çıkar çatışması bildirmemişlerdir.

Anahtar kelimeler: Paraoksonaz-1; hemoglobin A_{1c} protein; glukoz; diabetes mellitus; hiperglisemi

Introduction:

Paraoxonase (PON1) hydrolyzes aromatic carboxylic acid esters, organophosphorus insecticides and nerve gases and is in close association with high density lipoproteins (HDL) in human plasma [1,2]. It also has the ability to metabolize lipid peroxides in low density lipoproteins hence playing an important role in protection against atherosclerosis [2-5]. PON1 was shown to be reduced in some chronic diseases such as diabetes and chronic renal failure. In diabetes mellitus (DM) there were 16.7% and 19.2% reductions in serum PON1 activity and concentration [1,6-9]. This decrease in serum PON1 activity may be one of the factors contributing to the increased incidence of premature atherosclerosis associated with diabetes [1,9].

In DM, patients are prone to chronic exposure to high levels of glucose. One of the consequences of long term exposure to glucose is the non-enzymatic glycation of proteins which is monitored by HbA_{1c} in clinical settings. Besides hemoglobin, apolipoproteins are also susceptible to non-enzymatic glycation. This may disrupt lipoprotein functions and may contribute to vascular damage [10]. There is also increasing evidence suggesting that PON1 activity is affected by meals, but this postprandial modulation is mostly attributed to the fat content [11].

The aim of the current study was to determine the effects of acute and chronic hyperglycemia, which was not evaluated at the same time before, on serum PON1 levels in order to understand whether the glycemic state influence PON1 levels and alter the enzyme activity.

Methods

To evaluate the effects of chronic hyperglycemia; 86 male and 204 female (n= 290) type 2 diabetic patients who applied to our laboratory for HbA_{1c} analysis were recruited. Patients taking lipid lowering drugs and who have co-existing chronic diseases were excluded. Cigarette smoking, hypertension, body mass index (BMI) were also noted. Three groups were formed according to their HbA_{1c} levels: Group1: <7%, Group2: 7-8.9% and Group3: ≥9%, and considered as good, moderate and poor glycemic control, respectively.

After an overnight fasting, venous blood samples were collected between 9:00 and 10:00 a.m., into 4 mL tubes (Vacuette, Greiner bio-one, Austria) containing lithium heparin for HbA_{1c} measurements and into 8 mL plain tubes (Vacuette, Greiner bio-one, Austria) with serum separator for PON1 and routine biochemical tests. Blood in the plain tubes was allowed to clot for 20 minutes at room temperature. Serum was obtained by low-speed centrifugation, and fasting glucose, total cholesterol, triglyceride, HDL-cholesterol (HDL-C) were analyzed by routine laboratory methods at an automatic analyzer (Olympus AU 5223, Japan) with dedicated commercial kits. LDL-cholesterol (LDL-C) was calculated using Friedewald formula. Aliquots for PON1 analysis were stored at –80°C until analysis.

Serum PON1 levels were determined by the method of Reiner et al [12] using paraoxon as substrate and measuring formation of paranitrophenol at 450nm. The method was applied on an autoanalyzer (Modular DP, Roche Diagnostics, Germany). The within-run CV was determined to be 0.7% (n=20). The between-run CV was not evaluated, since all reactives were prepared freshly and all samples were analyzed on the same run. To adjust PON1 activity according to circulating HDL and minimize the influence of HDL, PON1/HDL ratio was calculated by dividing PON1 activity (in U/L) with HDL−C (in mmol/L) [7]. Lithium heparin plasma specimens were kept at room temperature and the HbA_{1c} analysis were performed on the same day with an immunoturbidimetric method using the Modular DP analyzer (Roche Diagnostics, Germany) with the commercially available kits (HbA_{1c} II, Tina-quant, Roche Diagnostics, Germany).

To evaluate the effects of acute hyperglycemia on PON1 activity; 61 male and 131 female patients (n= 192) who applied to our laboratory for OGTT were included in the study. OGTT was performed as described by WHO. After an overnight fasting, 75 g glucose was given in 300 mL water and 0, 1 and 2-hour blood samples were taken into 8 mL plain tubes (Vacuette, Greiner Bio-one, Austria) with serum separator. Serum separation, glucose and PON1 analyses were done as described above. Subjects with 2nd hour post-challenge glucose concentration <7.8 mmol/L were considered as normal glucose tolerance (NGT) (Group I; n=128). Diabetic patients and patients with impaired glucose tolerance having 2nd hour post-challenge glucose concentration ≥7.8 mmol/L were grouped together (Group II; n=64).

The study was approved by the hospital Ethics Committee and carried out in accordance with the principles of the declaration of Helsinki. Written informed consent was obtained from all participating subjects.

All statistical analyses were performed by statistical package for social sciences (SPSS, version 11.0 for Windows, Chicago, IL, USA). Normally distributed data were expressed as mean±SD; one-way ANOVA and independent samples t-test were used to compare group means. Non-normally distributed data were expressed as median with interquartile range (IQR), Wilcoxon signed ranks test and Mann-Whitney U test were applied to compare the groups. The Spearman correlation coefficient (r) was used to test the relationship between the variables.

Results

Effects of chronic hyperglycemia

Clinical characteristics of patient groups are summarized in Table 1. The mean age and BMI were not different between three groups (p>0.05). Serum PON1 levels showed a large variability ranging from 5 U/L to 167 U/L in the whole study group. Minimum PON1 levels were

9 U/L, 9 U/L and 5 U/L, while maximum PON1 levels were 167 U/L, 148 U/L and 131 U/L in groups 1, 2 and 3, respectively. No significant difference was obtained in PON1 levels between the groups ($p>0.05$). Although PON1/HDL-C ratio was observed to decrease as the HbA_{1c} levels rise, the difference between the groups was not significant (Table 1).

There was no correlation between PON1 activity, PON1/HDL-C ratio and HbA_{1c}, plasma glucose.

Male (n=86) and female (n=204) patients, hypertensive (n=143) and normotensive (n=147), smoking (n=99) and non smoking patients (n=191), patients with BMI≥30 (n=112) and BMI<30 (n=178) were also compared and no significant difference was observed between PON1 activities and PON1/HDL ratio ($p>0.05$) (Table 1)

Effects of acute hyperglycemia

PON1 activity decreased significantly during OGTT. Fasting PON1 activity was higher than both 1st and 2nd hour activities. The change in serum glucose levels and PON1 activity during OGTT are demonstrated in Table 2.

Table 1. Demographic and biochemical parameters of patients grouped according to HbA_{1c} levels. Data are presented as mean±SD, except for PON1 activity which is depicted as median with IQR.

	≤ 6.9 % **(n= 119)**	**7.0 – 8.9 %** **(n= 99)**	**≥ 9.0 %** **(n= 72)**
Age (years)	52 ± 11	54 ± 11	55 ± 10
BMI (kg/m²)	30 ± 6	29 ± 5	28 ± 5
***Glucose** (mmol/L)	8.1 ± 2.8 [ab]	11.2 ± 4[c]	14.3 ± 4.3
***T.Cholesterol** (mmol/L)	5.0± 0.8[d]	5.2 ± 0.8	5.3 ± 1
***Triglycerides** (mmol/L)	1.46 ± 0.7	1.65 ± 0.8	1.67 ± 1.1
***LDL-C** (mmol/L)	3.1 ± 0.8	3.2 ± 0.8	3.3 ± 0.8
***HDL-C** (mmol/L)	1.18 ± 0.3	1.18 ± 0.3	1.2 ± 0.3
PON1 (U/L)	41.5 [19.75-74.25]	43 [21-64]	25.5 [18.25-66]
PON1/HDL	44.7 ± 31.8	41.2 ± 27.1	36.6 ± 27.8

* Conversion factors for Glucose (mg/dL) = mmol/L / 0,0555, for T. Cholesterol, LDL-C and HDL-C (mg/dL) = mmol/L / 0,0259, and for Triglycerides (mg/dL) = mmol/L / 0,0113.

[a] **≤ 6.9 %** vs **7.0 – 8.9 %** (p=0.000)
[b] **≤ 6.9 %** vs **≥ 9.0 %** (p=0.000)
[c] **7.0 – 8.9 %** vs **≥ 9.0 %** (p=0.000)
[d] **≤ 6.9 %** vs **≥ 9.0 %** (p=0.033)

Table 2. Glucose and PON1 levels in OGTT subjects. Glucose levels are presented as mean±SD, PON1 activity depicted as median with IQR.

	Fasting	1st hour	2nd hour
Whole Group (n=192)			
Glucose (mmol/L)*	5.8±0.7[*,#]	9.9±2.8[§]	7.0±2.2
PON1 (U/L)	63 [28-100][*,#]	61[25-97]	61[25-98]
Group I (n=128)			
*Glucose (mmol/L)	5.5±0.7[a,*,#]	8.7±2.2[a, §]	5.8±1.1[a]
PON1 (U/L)	55[28-96]	51[26-92]	53[26-91]
Group II (n=64)			
*Glucose (mmol/L)	6.3±0.7[*,#]	12.4±2.2[§]	9.5±1.5
PON1(U/L)	86[25-109][*,#]	80[24-106]	79[24-107]

[*]Conversion factor for Glucose (mg/dL) = mmol/L / 0,0555,
[a]Group 1 vs Group 2 ($p<0.05$)
^Fasting vs 1st hour (p=0.000)
[#]Fasting vs 2nd hour (p=0.000)
[§]1st hour vs 2nd hour ($p< 0.001$)

Discussion

It has been repeatedly shown that PON1 activity is decreased in both Type 1 and Type 2 DM [1,6,7]. There may be several reasons for this decrease, but the most probable is the non-enzymatic glycation of Apo A1, HDL and PON1 due to the high levels of blood glucose [13]. In *in vitro* experiments, Hedrick et al. have exposed purified HDL and PON1 at 25 mM glucose for 1 week and Ferretti et al. have incubated purified HDL and PON1 in different glucose concentrations (0, 50 and 100 mM) for different time periods (24, 48 and 72 hours) and they both observed decrements in HDL-PON1 activities up to 50% [13,14]. These studies clearly proved that both proteins are affected from high concentrations of glucose, and probably are glycated and oxidized in these conditions. But in this experimental circumstances, it is not easy to draw conclusions about *in vivo* conditions, because glucose concentrations that are used are very high and non−physiological. Similarly, the correlation of the decrease in PON1 activity with exposure time cannot be extrapolated to *in vivo* conditions, since this magnitude of high glucose levels if seen in diabetic patients are transient and do not last long.

To evaluate the long term effects of glucose and the effects of non-enzymatic glycation on PON1 activity in an *in vivo* setting, enzyme activity in patients with different levels of HbA_{1c} can be evaluated, since HbA_{1c} is a good indicator of glycemic control and non-enzymatic glycation in diabetics. In the present study, the lowest median PON1 activity was observed in the patients with the highest HbA_{1c} level which is ≥9%. PON1/HDL-C ratio also gradually decreased as the HbA_{1c} levels increased. It seems that PON1 activity decreases as the glycemic control deteriorates, but these changes were not significant in our study. This may be explained by the high inter−individual biological variability of PON1 activity. Richter et al. [15] proclaimed that up to 13−fold, while Playfer et al. [16] proclaimed that up to 40−folds difference may exist between individuals and they explained this wide inter-individual difference by phenotypic variation of PON1 [6]. In our results, although there was a considerable difference in enzyme activity and in PON1/HDL-C ratio between the groups, this cannot be pointed out statistically, probably because of the wide distribution of the values.

Observed lower PON1/HDL-C ratio−although not statistically significant-cannot be explained only by HDL-C, since HDL-C levels were almost same in all 3 groups. This decreased ratio is probably due to other factors that lead to decrease in PON1 enzyme activity in diabetics with poor glycemic control. Kopprasch et al. proposed that in diabetic patients glycoxidation and/or lipoxidation processes may cause conformational changes both in HDL and the enzyme itself and these changes may lead to alteration of enzyme activity. They also stated that compositional changes may result in the destabilization of the enzyme [6].

In this study, we did not find a correlation between PON1 activity and HbA_{1c} levels and plasma glucose. Our findings are similar to those of Ferretti et al. [17], Sozmen et al. [18] and Kordonouri et al. [19]. They also did not find any correlation between PON1 activity and HbA_{1c} levels. Kordonouri et al. proposed that this may be the result of difference in turn-over rates of PON1 and HbA1c. They stated that although there is no data on PON1 turnover rate it may be similar to that of HDL, which is only limited to days [19].

OGTT was chosen as an *in vivo* model for investigating the effects of acute hyperglycemia on PON1 activity. We observed a significant decrement in PON1 activity during OGTT. Our results support the effects of glucose on postprandial modulation of PON1 activity. Beer et al. demonstrated PON1 decrease after ingestion of high fat−high carbohydrate meal [11]. They showed that PON1 mass returned to baseline levels after 4 hours which corresponds to the time period for removal of triglycerides from blood. Several studies [20,21] claim that the acute decrease of PON1 activity after meals is due to postprandial hyperlipidemia, especially saturated fatty acids, but our results suggest that the postprandial decrease in PON1 activity may be due to glucose per se. There is no data on individual PON1 activity change during OGTT. PON1 activity measurements during OGTT were used to compare the difference between normoglycemic and impaired glucose tolerance groups grouped according to the results of the test. So we propose that enzyme activity change during OGTT encountered in the present study is due to glucose or hormonal changes, since during OGTT there is no change in the triglyceride or lipid levels which were suggested as responsible for postprandial modulation of PON1 activity.

In order to evaluate the change in PON1 activity in the early stage of diabetes or the pre-diabetic state, the OGTT subjects were divided according to OGTT results. The investigation of PON1 activities in patients identified as either impaired glucose tolerance or diabetic during the OGTT revealed higher but not statistically significant results compared the NGT group, although we have presumed the opposite. Similarly Kopprash et al. and van den Berg et al. also found higher but not statistically significant PON1 activity in glucose intolerant groups when compared to NGT patient and they concluded that PON1 activity loss is not encountered in the early stages of DM [6,22]. It is postulated that high insulin levels encountered due to insulin resistance at pre−diabetic stages may even lead to higher PON1 activities in non−diabetic and insulin resistant subjects [23]. Although our results also support the tendency that PON1 activity is increased in the early stages of DM, we could not provide statistical significance to this finding.

In conclusion, our data indicate that PON1 activity deteriorates as the glycemic control impairs and interestingly PON1 activity decreases during OGTT. Although it is not clear when PON1 return to its normal activity

during OGTT, we think that the decrease in PON1 activity should be taken into consideration in the therapy of diabetic patients.

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