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Serum paraoxonase activity and oxidative stress in patients with adult nephrotic syndrome

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ABSTRACT

Objective: It has been shown that low paraoxonase-1 (PON1) activity is associated with a risk of an early development of atherosclerosis. In the present study, we investigated serum paraoxonase, and arylesterase activities and oxidative stress in patients with adult nephrotic syndrome (NS). In addition, we examined the relationship between these measurements and atherosclerosis.
Methods: Twenty-one patients with NS and 21 healthy controls were enrolled in the study. Serum basal and salt-stimulated paraoxonase activities, arylesterase activity, lipid hydroperoxide (LOOH) and total thiol (SH) levels were measured.
Results: Serum basal and salt-stimulated paraoxonase activities, arylesterase activity and total SH levels were significantly lower in patients with NS than in controls ($p < 0.05$, $p < 0.05$, $p < 0.01$ and $p < 0.05$, respectively), whereas LOOH levels were significantly higher ($p < 0.05$). Serum LOOH levels were significantly correlated with total-SH levels in patients with NS ($r = -0.467$; $p < 0.01$). Moreover, proteinuria levels were significantly correlated with serum LOOH levels ($r = 0.397$; $p < 0.01$), whereas no correlation was found among serum paraoxonase activity, arylesterase activity and total-SH levels in NS patients ($p > 0.05$).
Conclusions: We concluded that oxidative stress is increased, while serum PON1 activity is decreased in patients with adult NS. In addition, these results indicate that lower PON1 activity is associated with an oxidant–antioxidant imbalance that may contribute to atherosclerosis in adult patients with NS.

1. Introduction

Nephrotic syndrome (NS) is characterized by excessive proteinuria, hypoalbuminemia, edema and hyperlipidemia [1]. In some experimental and clinical trials, NS was shown to be associated with increased oxidative stress [2–4]. Many factors have been shown to induce proteinuria in experimental models [5,6]. One possible explanation for the development of proteinuria is oxidative damage to glomerular cells [7]. Oxidative damage by free radicals has been implicated in kidney injury, especially in NS. Furthermore, previous studies have shown that oxidative damage to glomerular cells is significantly correlated with the course and prognosis of NS [7,8].

Many risk factors such as hypertension, cigarette smoking, diabetes, hyperlipidemia and hypercoagulability play a role in the development of atherosclerosis [9]. On the other hand, hyperlipidemia, increased lipid oxidation reactions, and defects in antioxidant status may lead to glomerulosclerosis and the progression of glomerular disease in NS [10]. It has also been shown that high levels of low density lipoprotein cholesterol (LDL-C) in NS are associated with a risk of early atherosclerosis development [11].

Reactive oxygen species (ROS) are normally deactivated by enzymatic and nonenzymatic antioxidant systems. Plasma contains various antioxidant molecules, and albumin is the major circulating antioxidant in both plasma and serum [12]. In addition, the most important extracellular enzymes that are involved in this process are paraoxonases, including the high-density lipoprotein cholesterol (HDL-C)-associated enzyme paraoxonase-1 (PON1) in serum. PON1 is a 354 amino acid calcium-dependent esterase with a molecular mass of approximately 45 kDa [13]. The oxidative modification of LDL-C has been shown to play an important role in the pathogenesis of atherosclerosis [14]. Serum PON1 plays an essential role in protection against atherosclerosis by preventing the oxidative modification of serum lipoproteins, which is a crucial step in atherogenesis [15]. Indeed, higher serum PON1 enzyme activity has an important role in the prevention of atherosclerosis [16]. In

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addition, in human serum PON1 contributes to the antiatherogenic effect of HDL-C, and its activity is inversely correlated with oxidative stress [17,18]. PON1 has also been shown to hydrolyze specific oxidized lipids [17,19].

It has been suggested that increased oxidative stress can lead to reduced PON1 activity, which is closely related to atherosclerosis [19,20]. Several studies found that serum PON1 activity was reduced in patients with pediatric NS [21–23]. To the best of our knowledge, PON1 activity in the serum of patients with adult NS has not been previously investigated.

In the present study, we measured serum paraoxonase and arylesterase activities, and lipid hydroperoxide (LOOH) and total thiol (SH) levels along with lipid parameters in patients with adult NS. In addition, we examined the relationship between these measurements and atherosclerosis.

2. Methods

2.1. Subjects

In this prospective study, 21 patients with NS (10 females and 11 males) and 21 healthy controls (12 females, 9 males) were enrolled.

A diagnosis of NS was confirmed in the patients according to the following general criteria: proteinuria >3.5 g/1.73 m^2/24 h, hypoalbuminemia <2.5 gr/dl, edema, hyperlipidemia, and no current systemic disease.

A renal biopsy was performed in all of the patients with NS. The etiologies of the patients with NS were as follows: membranous glomerulonephritis MGN ($n = 9$), focal segmental glomerulosclerosis (FSGS) ($n = 6$) and membranoproliferative glomerulonephritis (MPGN) ($n = 6$). The average follow-up period for the patients with NS was 26.1 ± 14.5 months. All of the patients were receiving immuno suppressive therapy.

Most of the patients were receiving angiotensin-converting enzyme inhibitors or angiotensin-II type 1 receptor blockers. None of the patients received nonsteroidal antiinflammatory drugs, albumin or a blood transfusion within the 1-month period prior to the study. The patients with NS were not receiving antioxidant vitamin supplements (e.g. vitamin E or C). Two of the patients were receiving statin treatment.

The control group consisted of 21 healthy subjects (without a history of chronic or recurrent disease). The subjects in the control group were asymptomatic with an unremarkable medical history and a normal physical examination. None of the control subjects were receiving statin treatment or antioxidant vitamin supplements including vitamin E or C.

The study protocol was conducted in accordance with the Helsinki Declaration as revised in 1989 and was approved by the local ethics committee. All subjects were informed about the study and the written consent was obtained from each one.

2.2. Exclusion criteria

The exclusion criteria included a history of alcohol abuse, habitual smoking, intravenous drug abuse, pregnancy, antioxidant supplements, an active infection, diabetes mellitus, liver or pulmonary disease, rheumatoid arthritis and coronary artery disease.

2.3. Blood samples

Blood samples were obtained following an overnight fasting period. Blood samples were collected into empty tubes and immediately stored at 4 °C. The serum fraction was then separated from the cells by centrifugation at 3000 rpm for 10 min, after which the lipid parameters were measured immediately. The remaining serum portions were stored at −80 °C for no longer than 6 months [24] and used for measuring PON1 activity, LOOH and total SH levels.

2.4. Measurement of paraoxonase and arylesterase activities

Paraoxonase and arylesterase activities were measured using paraoxon and phenyl acetate substrates, respectively [25]. Paraoxonase activity is expressed as U/L of serum. One unit of arylesterase activity is defined as 1 μmol of phenol generated/min and is expressed as kU/L of serum [26]. The phenotype distribution of PON1 was determined in the presence of 1 mol/L NaCl (salt-stimulated paraoxonase). The ratio of the salt-stimulated paraoxonase activity to the arylesterase activity was used to assign individual subjects to one of the three phenotypes [25].

2.5. Measurement of lipid hydroperoxide levels

Serum LOOH levels were measured with the ferrous ion oxidation–xylenol orange assay as previously described [27].

2.6. Measurement of total thiol levels

Total serum SH levels were measured according to the method of Ellman as modified by Hu et al. [28].

2.7. Other parameters

The levels of triglycerides (TG), total cholesterol (TC), HDL-C and LDL-C were determined using commercially available assay kits (Abbott®) with an autoanalyzer (Aeroset®, Abbott®).

Serum creatinine and albumin levels were determined by an autoanalyzer (Aeroset®, Abbott®, Germany) using commercially available assay kits (Abbott®).

Proteinuria levels were measured by the turbidimetric method using an automatic analyzer (Aeroset®, Abbott®). Proteinuria was defined as a urinary protein excretion rate >150 mg/24 h. Nephrotic proteinuria was defined as an excretion rate that exceeded >3.5 g/24 h.

GFR (glomerular filtration rate) (ml/min) was obtained by the following formula: urine creatinine (mg/dl) × (urine volume in 24 h (ml))/(Plasma creatinine (mg/dl)) × 1440.

2.8. Statistical analysis

The results are expressed as the mean ± standard deviation. Nonparametric continuous variables were compared by the Mann–Whitney *U*-test. Parametric variables were compared using the Student's *t*-test. For examining the impact of independent variables on proteinuria levels, a linear regression analysis was performed. A Pearson correlation analysis was used to determine the association between levels of proteinuria, and PON1 activity, total SH groups and LOOH levels. Differences were considered to be statistically significant when the p value was less than 0.05. The data were analyzed using the SPSS® for Windows computing program (Version 11.0).

3. Results

The demographic characteristics of the subjects with NS and controls are presented in Table 1. There were no statistically significant differences between the NS patients and controls with respect to age, gender and body mass index ($p > 0.05$). Moreover, there were no statistically significant differences between the NS patients and controls with respect to heart rate, systolic and diastolic blood pressure ($p > 0.05$). The GFR was slightly higher in patients with NS than

Table 1
Demographic characteristics of the two groups in this study.

Parameters	NS ($n=21$)	Control ($n=21$)	p
Age (years)	36 ± 10	33 ± 9	ns
Sex (females/males)	10/11	12/9	ns
Body mass index (kg/m^2)	22.2 ± 2.2	21.2 ± 1.2	ns
Systolic blood pressure (mm Hg)	123 ± 14	120 ± 12	ns
Diastolic blood pressure (mm Hg)	80 ± 10	78 ± 14	ns
Heart rate (min)	86 ± 6	82 ± 8	ns
Proteinuria (mg/24 h)	1167.9 ± 767.3	122.2 ± 68.3	<0.05
GFR (ml/min)	126.1 ± 16.2	121.6 ± 13.9	ns
Albumin (mg/dl)	3.76 ± 0.96	4.54 ± 0.44	<0.05
Creatinine (mg/dl)	0.8 ± 0.2	0.7 ± 0.2	>0.05
TG (mg/dl)	197.4 ± 79.2	105.5 ± 29.6	<0.05
TC (mg/dl)	235.7 ± 64.2	177.1 ± 21.7	<0.05
HDL-C (mg/dl)	41.1 ± 8.2	47.2 ± 9.1	<0.05
LDL-C (mg/dl)	153.2 ± 56.2	108.7 ± 22.4	<0.05

TC: total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; GFR, glomerular filtration rate; NS, nephrotic syndrome; ns: non significant.
Values are mean ± SD.

controls but this was not statistically significant ($p > 0.05$). Furthermore, the average follow-up period for the patients with NS was 26.1 ± 14.5 months (Table 1).

Proteinuria levels were significantly higher in patients with NS than in controls ($p < 0.05$), whereas serum albumin levels were significantly lower in patients with NS than in controls ($p < 0.05$). Serum TG, TC and LDL-C levels were significantly higher in patients with NS compared with controls ($p < 0.05$ for all three parameters), whereas HDL-C levels were significantly lower ($p < 0.05$) (Table 1).

Serum basal/salt-stimulated paraoxonase activities, arylesterase activity and total-SH levels were significantly lower in patients with NS than in controls ($p < 0.05$, $p < 0.05$, $p < 0.01$ and $p < 0.05$, respectively), whereas LOOH levels were significantly higher ($p < 0.05$) (Table 2).

In the NS patients, serum TG, TC, HDL-C and LDL-C levels were not correlated with paraoxonase, arylesterase activities, total-SH and LOOH levels ($p > 0.05$).

Using a Pearson correlation analysis, we found that serum LOOH levels were significantly correlated with total-SH levels in patients with NS ($r = -0.467$, $p < 0.01$). Furthermore, proteinuria levels were significantly correlated with serum LOOH levels ($r = 0.397$, $p < 0.01$), whereas no correlation was found between serum paraoxonase, arylesterase activity and total-SH levels in the NS patients ($p > 0.05$).

The PON1 phenotypes distribution was calculated in two groups. A significant correlation was observed between the PON1 (Q/R) 192 polymorphism distribution in NS patients and controls ($p < 0.05$). However, when patients with NS were divided according to etiological factors, no differences were observed between MGN, FSGS and MPGN with respect to the PON1 (Q/R) 192 polymorphism distribution ($p > 0.05$).

4. Discussion

Our data show, for the first time, that adult NS patients have significantly lower PON1 activity and total SH levels. Moreover, we found that LOOH levels were significantly higher in adult NS patients than in controls. Furthermore, we found a negative correlation between serum LOOH levels and total SH levels in patients with NS. Finally, we found a positive correlation between serum LOOH levels and proteinuria levels in patients with NS.

Table 2
PON1 activity, total thiol and oxidative stress levels in NS patients and controls.

Parameters	NS ($n=21$)	Control ($n=21$)	p
Paraoxonase (U/L)	133.83 ± 47.24	199.83 ± 58.69	<0.05
Salt-stimulated	243.61 ± 114.89	508.46 ± 229.24	<0.05
Arylesterase (kU/L)	148.85 ± 32.05	194.27 ± 44.79	<0.01
LOOH (μmol/L)	11.86 ± 1.75	5.58 ± 1.68	<0.05
Total-SH (mmol L^{-1})	0.33 ± 0.12	0.50 ± 0.05	<0.05

LOOH: lipid hydroperoxide; SH: thiol; NS: nephrotic syndrome.
Values are mean ± SD.

ROS play an important role in the pathophysiological processes of a surprisingly wide variety of clinical and experimental renal diseases [29]. ROS, which are strong oxidants, can also produce proteinuria by injuring to glomerular epithelial cells, through the reduction of the electronegative charge of the glomerular filtration barrier or by other unknown mechanisms [30,31]. It has been suggested that enhanced permeability of the glomerular capillary wall is perhaps influenced by the generation of free radicals [32].

The relationship between NS and atherosclerosis has not yet been fully elucidated, although the high levels of LDL-C that are typically found in NS may give rise to atherosclerosis [11]. Skrzep-Poloczek et al. [11] reported significant disturbances in oxidative stress during NS that lead to increased plasma levels of oxidized LDL and cholesterol oxidation products, which exert cytotoxicity and are well-known to induce atherosclerosis. They suggested that this accumulation of oxidized LDL may constitute an important link between NS and atherosclerosis [11].

LOOHs are by-products of lipid peroxidation and are well-known markers of oxidative stress that are formed from unsaturated phospholipids, glycolipids and cholesterol by peroxidative reactions under oxidative stress [33]. Oxidized LDL is, a membrane-bound cholesterol-derived hydroperoxide and, is the principal form of LOOH that is responsible for the development of oxidative stress [33] and may actively contribute to the progression of atherosclerotic lesions and their resulting complications [34]. PON1 is an antioxidant enzyme because it hydrolyses lipid peroxides in oxidized lipoproteins. Human PON1 has been shown to be mostly responsible for the antioxidant activity of HDL-C [13]. Serum PON1 can destroy active lipids in mildly oxidized LDL and, thus, prevents the induction of inflammatory responses in arterial wall cells [16]. Previous studies have indicated that PON1 can prevent the accumulation of lipid peroxide on LDL [19,35].

The pathogenic mechanisms that underlying the decreased serum PON1 activity in NS patients that observed in the present study are unclear. PON1 is an HDL-associated enzyme, and it has been suggested that reduced serum PON1 activity might be associated with decreased HDL-C levels and/or increased oxidative stress [36]. However, consistent with a previous report [36], we found no correlation between PON1 activity and HDL-C levels. Therefore, we concluded that lower serum PON1 activity could be the result of increased oxidative stress in NS patients [35,36]. Thus, the combination of a decrease in both PON1 activity and total SH levels, and an increase in LOOH levels may play an important role in the pathogenesis of atherosclerosis in patients with NS.

Oxidative stress is associated with cardiovascular diseases [37]. Serum PON1 expression is down-regulated by oxidative stress [19,20]. PON1 may lower the risk of atherosclerosis by destroying proinflammatory molecules that are involved in the initiation and progression of atherosclerotic lesions [38]. Additionally, inverse relationships between reduced PON1 activity and increased oxidative stress in patients with acute coronary syndrome [20] and iron deficiency anemia [35] have been reported.

Although serum PON1 activity was found to be reduced in patients with pediatric NS [21–23], serum PON1 activity in patients with adult NS has not been reported previously investigated. In children, the reduced paraoxonase activity that is caused by a PON1 gene polymorphism may promote focal segmental glomerulosclerosis (FSGS) [21]. Gullulu et al. [22] reported reduced PON1 activity in patients who were treated for glomerulonephritis, and Ece et al. [23] reported decreased PON1 activity in children with steroid-sensitive acute-period idiopathic NS.

PON1 activity is determined genetically. However, various factors – such as diet, lifestyle and environmental factors – can influence PON1 activity. It has been shown that daily moderate alcohol consumption can increase PON1 activity [39]. Degraded cooking oil has been reported to lower serum PON1 levels in humans [40], and smoking has also been shown to decrease serum PON1 activity [41]. On the other hand, PON1 activity is positively correlated with the intake of vitamins C and E in the diet [42].

Decreased PON1 activity under oxidative stress has been primarily attributed to changes in the redox status of the protein's free sulfhydryl groups, as sulfhydryl compounds prevented the inhibition of PON1 activity that is caused by ROS [43]. Free sulfhydryl groups of proteins constitute the primary antioxidant component of serum [12]. It has been shown that total-SH levels are associated with the extent of coronary artery disease [44].

There were several limitations of our study. First, this study is a cross-sectional study design. Second, the number of patients with NS that were enrolled in the study was relatively small. Third, PON1 genotype was not determined in the study population; however, it was reported that serum PON1 activity is a better predictor of the risk for cardiovascular diseases than PON1 genotype [45].

In the light of the findings of this study, we concluded that oxidative stress is increased, while serum PON1 activity is decreased in patients with adult NS. In addition, these results indicate that reduced PON1 activity is associated with an oxidant–antioxidant imbalance that may contribute to atherosclerosis in patients with adult NS. Therefore, the combined use of steroids, antioxidant therapy such as vitamins C and E, and lipid-lowering therapy may decrease the development of atherosclerosis in NS patients. Further studies with larger numbers of patients are needed to confirm the mechanisms underlying the association of low PON1 activity and the development of atherosclerosis in NS patients.

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