ORIGINAL ARTICLE

# Serum and urinary leptin and ghrelin in children with nephrotic syndrome

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**Abstract**

**OBJECTIVE:** The aim of the present study was to evaluate the serum and urinary levels of leptin and ghrelin in children with primary idiopathic nephrotic syndrome (NS), to compare these results between patients during the relapse and remission phase and to evaluate the possible role of leptin and ghrelin in the pathogenesis of NS.

**PATIENTS AND METHODS:** Forty-nine children with primary idiopathic NS (25 children with relapse and 24 children in remission), who were followed up at the Pediatric Nephrology Unit, enrolled. Twenty-eight age- and sex-matched healthy children served as controls. Serum and urinary leptin levels were determined by immunoenzymatic ELISA, and serum and urinary ghrelin levels were determined by the RIA method.

**RESULTS:** The serum leptin levels were significantly lower in the children with NS during the relapse phase than in the children with NS during remission or in the controls (1.42±0.34 ng/dl and 3.60±0.70 ng/ml; $p<0.01$, 1.42±0.34 ng/ml and 5.27±4.67 ng/ml; $p<0.001$, respectively). The urinary leptin excretion levels were significantly higher in the relapse group than in the controls (0.40±0.11 ng/ml and 0.12±0.06 ng/ml, $p<0.01$, respectively). The serum ghrelin levels were similar between the study groups ($p>0.05$). The urinary ghrelin excretion levels were significantly higher in the relapse group than in the remission group and the controls (965.0 pg/ml [93–3711] and 679.7 pg/ml [93–3783], $p<0.05$; 965.0 pg/ml [93–3711] and 387.7 pg/ml [114–1214], $p<0.001$, respectively). The urinary ghrelin levels were also significantly higher in the remission group than in the controls (679.7 pg/ml [93–3783] and 387.7 pg/ml [114–1214]), $p<0.01$, respectively). The serum leptin levels were positively correlated with the serum albumin levels (r=0.440, $p<0.05$) and were negatively correlated with the serum triglyceride levels during the relapse phase. The urinary leptin and ghrelin levels were positively correlated with proteinuria in the relapse group.

**CONCLUSIONS:** We propose that leptin plays a role in the pathophysiology of NS and is associated with proteinuria, hypoproteinemia and hyperlipidemia. The significant urinary excretion of ghrelin in children with NS is possibly due to underlying pathophysiological changes, and normal serum ghrelin levels might be associated with an unknown compensatory mechanism.

## INTRODUCTION

Nephrotic syndrome (NS) is a common childhood glomerular disorder that is characterized by heavy proteinuria (urinary protein excretion >40 mg/m$^2$ per hour or spot protein-creatinine ratio >200 mg/mmol), hypoalbuminemia (serum albumin <2.5 g/L), edema and hyperlipidemia. Childhood minimal change nephrotic syndrome (MCNS) may occur at any age but is most common between the ages of 2 and 5 years; these patients respond promptly to corticosteroid therapy with remission of their proteinuria. Although the pathogenesis of idiopathic childhood NS remains unclear, previous studies indicate the role of the immune system (Eddy *et al.* 2003).

Leptin, a polypeptide hormone, is synthesized by adipocytes and functions as a starvation and adiposity signal after binding to its receptor, which is localized primarily in the hypothalamus (Fruhbeck *et al.* 1998; Pelleymounter *et al.* 1995; Zhang *et al.* 1994). Leptin regulates food intake and metabolic/endocrine functions (such as reproduction, glucose homeostasis, and insulin sensitivity) and plays a regulatory role in immunity, inflammation, wound healing, angiogenesis, and hematopoiesis (Fantuzzy & Faggioni 2000; Frank *et al.* 2000). Leptin is primarily (i.e., 80%) cleared by the kidney via glomerular filtration. Serum leptin levels correlate negatively with GFR in patients exhibiting varying degrees of chronic renal failure, and leptin may contribute to the progression of proliferative renal disease (Dotsch *et al.* 2005; Sharma *et al.* 1997).The effects of leptin on the podocyte have yet to be determined. Leptin stimulates the synthesis of type I collagen in mesangial cells, and type 4 collagen in glomerular endothelial cells contributes to extracellular matrix deposition, glomerulosclerosis, and proteinuria (Ballerman 1999). Ghrelin, which is a 28-amino-acid peptide hormone, is predominantly produced by the stomach and promotes the release of growth hormone (Kojima *et al.* 1999). Controversy exists regarding the serum levels of ghrelin during renal disease. A threefold increase in serum ghrelin levels has been demonstrated in patients with end-stage renal disease (Dotsch *et al.* 2005).

Despite new potential studies of leptin and ghrelin regulation in health and in pediatric chronic renal failure, it is not entirely obvious to what extent this knowledge will influence potential therapeutic options in the field of appetite loss and malnutrition (Dotsch *et al.* 2005). Leptin may play a potential role in the pathogenesis of chronic renal failure and in lipid metabolism (Cohen & Friedman 2004; Trevisan *et al.* 2006). Published data indicate a relationship between the leptin concentration and lipid parameters. Hyperlipidemia, which is an important characteristic of NS in children, is usually observed during the active phase of the disease. However, persisting lipid anomalies during remission have been reported and raise the question regarding other potential factors that affect the development of dyslipidemia (Querfeld 1999). The existence of a link between dyslipidemia and oxidative stress in the pathogenesis of renal damage has been demonstrated by a study in which hyperlipidemia aggravated the glomerulosclerosis (Kojima *et al.* 1999).

To the best of our knowledge, only a limited number of studies have reported the serum and urinary leptin levels during NS; however, no data on the serum and urinary ghrelin levels in NS have been presented (Buyan *et al.* 2003; Ece *et al.* 2004; Merta *et al.* 2003; Ozata *et al.* 2002; Schroth *et al.* 2001; Schroth *et al.* 2003; Wasilewska *et al.* 2005).The relationship between ghrelin and leptin merits some comment because these compounds are antagonistic signals towards energy balance and the inflammation process. The aim of the present study was to determine whether the leptin and ghrelin levels in the serum and urine change in pediatric NS patients during the relapse and remission phase and to evaluate the possible relationship between these parameters and the pathogenesis of the disease.

## PATIENTS AND METHODS

In this study, 49 pediatric NS patients (25 children in relapse and 24 children in remission) with NS were studied. The serum C3, C4, anti-nuclear antibodies, anti-DNA antibodies, and anti-nuclear cytoplasmic antibodies were within normal limits. Based on the proteinuria, the NS patients were divided into two groups: the relapse group and the remission group. The children with proteinuria (i.e., urinary protein level exceeding 1 g/m$^2$ of body surface area per day) were assigned to the relapse group. Children were excluded if they had conditions associated with NS and secondary NS. The control group consisted of 28 age- and sex-matched healthy children. The trial was approved by the appropriate local ethical committee of Eskisehir Osmangazi University, and informed written consent was obtained from the individuals with parental responsibility (2005/299).

All of the NS subjects and controls were evaluated by anthropometric measurements that included the weight and body mass index (BMI). The body mass index was calculated using the formula: weight (kg) / height$^2$ (m$^2$). Age, weight, height and BMI were similar between the NS subjects and the controls ($p$>0.05). Serum blood urea nitrogen, creatinine, total protein, albumin, total cholesterol, triglyceride, HDL-C, LDL-C, VLDL-C, Lp(a), ApoA1, and Apo B levels were determined by enzymatic assay (Roche Diagnostic Kits) using a BM HITACHI 717/7150 modular autoanalyzer. The serum LDL-C and VLDL-C values were estimated by the formula of Friedewald *et al.* The twenty-four-hour urinary protein excretion was determined using a Roche/Hitachi 912 modular autoanalyzer. Blood and urine samples for the leptin and ghrelin assays were obtained between 10.00 and 12.00 hours from all of the subjects and kept at –70 °C until the time of the hormone assay. The serum and urinary leptin concentrations were deter-

mined by ELISA using a commercially available kit (LINCO-Human Leptin Elisa Kit). The serum and urinary ghrelin concentrations were determined by ELISA using another commercially available kit (LINCO Total Ghrelin RIA kit).

All of the analyses were performed using the SPSS 13.0 software package (Chicago, IL, USA). Parametric data are expressed as the mean±SD, as the comparison of the data was performed using Student's independent-samples t-test. In all of the analyses, a $p$-value <0.05 was accepted as statistically significant. Because the urinary ghrelin levels were not normally distributed, the Mann-Whitney-U test was used for the comparison. The correlation analysis was performed using Pearson's correlation test. The $p$-values of <0.05 were considered significant.

## RESULTS

The present study investigated 49 pediatric NS patients (18 girls and 31 boys; 25 children in relapse and 24 children in remission) who were between the ages of 25 and 204 months and diagnosed in the Pediatric Nephrology Unit of the Eskisehir Osmangazi University Faculty of Medicine. The control group consisted of 28 healthy children (13 girls and 15 boys) between 27 and 196 months of age. The systolic blood pressure levels were significantly higher in the NS patients than in the controls (105.5±9.5 mmHg and 99.8±9.2 mmHg, $p$<0.05), unlike the diastolic blood pressure ($p$>0.05).

The 24-hour urinary protein excretion was higher in the relapse group than in the remission group and controls (106.4±20.7 mg/m$^2$/h and 3.73±0.38 mg/m$^2$/h, $p$<0.0001; 106.4±20.7 mg/m$^2$/h and 2.14±0.22 mg/m$^2$/h, $p$<0.0001, respectively). The 24-hour urinary protein excretion was similar between the remission group and the controls ($p$>0.05). The serum total protein levels were significantly lower in the NS subjects in the relapse group than in the remission group and controls (4.43±1.0 g/dl and 6.83±0.6 g/dl, $p$<0.001; 4.43±1.0 g/dl and 7.56±0.4 g/dl, $p$<0.001, respectively). The serum total protein levels were significantly lower in the remission group than in the controls (6.83±0.6 g/dl and 7.56±0.4 g/dl, $p$<0.001). The serum albumin levels were significantly lower in the relapse group than in the remission and control groups (2.04±0.9 g/dl and 4.12±0.41 g/dl, $p$<0.001; 2.04±0.9 g/dl and 4.67±0.31 g/dl, $p$<0.001, respectively). The serum albumin levels were significantly lower in the remission group than in the controls (4.12±0.41 g/dl and 4.67±0.31 g/dl, $p$<0.001). The spot urinary protein creatinine ratio was significantly higher in the relapse group than in the remission group and controls (6.06±1.09 g/dl and 0.18±0.03 g/dl, $p$<0.0001; 6.06±1.09 g/dl and 0.10±0.01 g/dl, $p$<0.0001, respectively), whereas no significant difference was found between the remission group and the controls ($p$>0.05) (Table 1).

The serum triglyceride levels were significantly higher in the relapse group than in the remission group and controls (287.2±201.2 mg/dl and 144.5±84.6 mg/dl, $p$<0.001; 287.2±201.2 mg/dl and 76.6±26.7 mg/dl, $p$<0.001, respectively). The serum triglyceride levels were also significantly higher in the remission group than in the controls (144.5±84.6 mg/dl and 76.6±26.7 mg/dl, $p$<0.001). The serum total cholesterol levels were significantly higher in the relapse group than the remission group and controls (394.4±135.7 mg/dl and 198.2±61.7 mg/dl, $p$<0.001; 394.4±135.7 mg/dl and 133.0±26.7 mg/dl, $p$<0.001, respectively). The serum total cholesterol levels were also significantly higher in the

**Tab. 1.** Laboratory features, including the lipid parameters, in the study groups.

| | Relapse (n=25) | Remission (n=24) | Control (n=28) | $p$-value |
|---|---|---|---|---|
| Proteinuria (mg/m$^2$/h) | 106.4±20.7 | 3.73±0.38 | 2.14±0.22 | ***p1*<0.0001** ***p2*<0.0001** *p3*>0.05 |
| Total protein (g/dl) | 4.43±1.0 | 6.83±0.6 | 7.56±0.4 | ***p1*<0.001** ***p2*<0.001** ***p3*<0.001** |
| Albumin (g/dl) | 2.04±0.9 | 4.12±0.41 | 4.67±0.31 | ***p1*<0.001** ***p2*<0.001** ***p3*<0.001** |
| Spot urinary protein/ creatinine ratio | 6.06±1.09 | 0.18±0.03 | 0.10±0.01 | ***p1*<0.0001** ***p2*<0.0001** *p3*>0.05 |
| TG (mg/dl) | 287.2±201.2 | 144.5±84.6 | 76.6±26.7 | ***p1*<0.001** ***p2*<0.001** ***p3*<0.001** |
| TC (mg/dl) | 394.4±135.7 | 198.2±61.7 | 133.0±26.7 | ***p1*<0.001** ***p2*<0.001** ***p3*<0.001** |
| HDL-C (mg/dl) | 63.0±21.3 | 59.9±13.0 | 55.8±11.1 | *p1*>0.05 *p2*>0.05 *p3*>0.05 |
| VLDL-C (mg/dl) | 58.4±39.9 | 31.3±19.0 | 15.3±4.05 | ***p1*<0.01** ***p2*<0.001** ***p3*<0.001** |
| LDL-C (mg/dl) | 249.8±114.7 | 105.2±67.0 | 61.5±21.6 | ***p1*<0.001** ***p2*<0.001** ***p3*<0.01** |
| ApoA1 (mg/dl) | 178.1±48.6 | 148.0±30.5 | 141.6±27.4 | ***p1*<0.05** ***p2*<0.01** *p3*>0.05 |
| Apo B (mg/dl) | 169.0±90.0 | 102.1±59.7 | 84.2±11.7 | ***p1*<0.01** ***p2*<0.001** *p3*>0.05 |
| Lp (a) (mg/dl) | 122.7±34.6 | 12.4±9.28 | 19.0±11.0 | ***p1*<0.05** ***p2*<0.05** *p3*>0.05 |

***p1***; relapse *vs.* remission, ***p2;*** relapse *vs.* controls, ***p3***; remission *vs.* controls

remission group than in the controls (198.2±61.7 mg/dl and 133.0±26.7 mg/dl, $p<0.001$). The serum HDL-C levels were similar among the study groups ($p>0.05$) (Table 1). The serum VLDL-C and LDL-C levels were significantly higher in the relapse group than in the remission group and controls, and the serum VLDL-C and LDL levels were significantly higher in the remission group than in the controls (31.3±19.0 mg/dl and 15.3±4.05 mg/dl, $p<0.001$). The serum apoA1, apoB, and Lpa levels were higher in the relapse group than in the remission group and controls.

The serum leptin levels were lower in the NS patients in the relapse phase than in the remission group and controls (1.42±0.34 ng/dl and 3.60±0.70 ng/ml, $p<0.01$; 1.42±0.34 ng/ml and 5.27±4.67 ng/ml, $p<0.001$, respectively). The serum leptin levels were similar between the remission group and the controls ($p>0.05$) (Table 2). The urinary leptin excretion was higher in the relapse and remission groups than in the controls (0.40±0.11 ng/ml and 0.12±0.06 ng/ml, $p<0.01$; 0.59±0.18 ng/ml and 0.12±0.06 ng/ml, $p<0.05$, respectively), whereas these values were similar between the relapse and remission groups (Table 2).

The serum ghrelin levels were similar between the NS patients during the relapse or remission phase and the controls ($p>0.05$) (Table 2). Urinary ghrelin excretion were significantly higher in both relapse and remission group than the controls (965.0 pg/ml (93–3711) and 679.7 pg/ml (93–3783); $p<0.05$, 965.0 pg/ml (93–3711) and 387.7 pg/ml (114–1214); $p<0.001$). Urinary ghrelin excretion were significantly higher in the remission group than the controls (679.7 pg/ml (93–3783) and 387.7 pg/ml (114–1214), $p<0.01$). In the relapse group, the serum leptin levels were positively correlated with the serum albumin levels (r=0.440, $p<0.05$).

**Tab. 2.** Serum leptin and ghrelin levels and urinary leptin and ghrelin excretion.

| | Relapse (n=25) | Remission (n=24) | Control (n=28) | *p*-value |
|---|---|---|---|---|
| Serum leptin levels (ng/ml) | 1.42 ± 0.34 | 3.60 ± 0.70 | 5.27 ± 4.67 | ***p1*<0.01**<br>***p2*<0.001**<br>*p3*>0.05 |
| Urinary leptin excretion (ng/ml) | 0.40 ± 0.11 | 0.59 ± 0.18 | 0.12 ± 0.06 | *p1*>0.05<br>***p2*<0.01**<br>***p3*<0.05** |
| Serum ghrelin levels (pg/ml) | 678.2 ± 67.2 | 559.0 ± 65.4 | 607.3 ± 338.8 | *p1*>0.05<br>*p2*>0.05<br>*p3*>0.05 |
| Urinary ghrelin excretion (pg/ml) | 965.0 (93-3711) | 679.7 (93-3783) | 387.7 (114-1214) | ***p1*<0.05**<br>***p2*<0.001**<br>***p3*<0.01** |

***p1***: relapse *vs.* remission; ***p2***: relapse *vs.* control; ***p3***: remission *vs.* control; *Data are presented as the mean ±SD, except for the urinary ghrelin excretion, which is presented as the median (minimum-maximum).

In the relapse group, the serum leptin levels were negatively correlated with the serum triglyceride levels (r=0.439, $p<0.05$). The serum triglyceride levels were negatively correlated with the serum albumin levels in the relapse group (r=–0.512, $p<0.01$). The serum leptin levels were positively correlated with the urinary leptin excretion (r=0.470, $p<0.05$). In the control group, the serum leptin levels were negatively correlated with the serum ghrelin levels (r=–0.413, $p<0.05$), serum triglyceride levels (r=–0.485, $p<0.05$) and serum VLDL-C levels (r=–0.487, $p<0.05$) and were positively correlated with the serum TC levels (r=0.374, $p<0.05$).

In the relapse group, the urinary leptin excretion was positively correlated with the presence of proteinuria (r=0.719, $p<0.001$). In the remission group, the urinary leptin excretion levels were not correlated with any of the studied parameters ($p>0.05$). The urinary leptin excretion levels were positively correlated with the serum TG levels (r=0.477, $p<0.05$) and serum VLDL-C levels (r=0.479, $p<0.01$) in the healthy children.

In the relapse group, the serum ghrelin levels were positively correlated with the serum LDL-C levels (r=0.491, $p<0.05$). The serum ghrelin levels were positively correlated with urinary protein excretion (r=0.409, $p<0.05$) and serum LDL-C levels (r=0.445, $p<0.05$). In the control group, the serum ghrelin levels were negatively correlated with the serum HDL-C levels (r=–0.439, $p<0.05$) and serum ApoB levels (r=–0.409, $p<0.05$). In the relapse group, the urinary ghrelin levels were positively correlated with urinary protein excretion (r=0.637, $p<0.01$). In the remission group, the urinary ghrelin levels were positively correlated with the serum albumin levels (r=0.486, $p<0.05$), serum TG levels (r=0.485, $p<0.05$) and serum LDL-C levels (r=0.485, $p<0.05$). In the control group, the serum ghrelin levels were negatively correlated with the serum leptin levels (r=–0.413, $p<0.05$).

## DISCUSSION

Recent studies have revealed that leptin is primarily cleared by the kidney via glomerular filtration. Urinary leptin is a valid marker of the serum leptin concentration, and thus, this non-invasive assay may be a useful tool for the longitudinal assessment of changes in leptin in children. (Sharma *et al.* 1997). The serum leptin levels are negatively correlated with the GFR in patients with varying degrees of chronic renal failure (Briley & Szczech 2006).The effects of leptin on the podocyte have not yet been determined. Leptin-stimulated synthesis of type I collagen in mesangial cells and type 4 collagen in glomerular endothelial cells contributes to extracellular matrix deposition, glomerulosclerosis, and proteinuria and might contribute to the progression of proliferative renal disease (Ballerman 1999; Dotsch *et al.* 2005). The increased protein filtration in NS increases urinary leptin excretion. However, increased leptin loss in the urine is not always accompanied by a decrease in the

serum leptin levels (Schroth *et al.* 2001, Wasilewska *et al.* 2005). Schroth *et al.* (2001)reported unexpectedly normal serum leptin levels despite significant leptin excretion in children with MCNS. The urinary leptin loss was associated with proteinuria and disappeared after remission. Buyan *et al.* (2003) reported low serum leptin levels with elevated urine leptin concentrations at the onset of MCNS, and the serum leptin levels were negatively correlated with proteinuria. The urinary concentration of leptin in the proteinuric patients was higher than in the patients without proteinuria and in the healthy controls, whereas no significant correlation was found between the urinary leptin levels and proteinuria. Wasilewska *et al.* (2005) reported increased urinary leptin excretion in children with NS accompanied by normal serum leptin levels. After remission, the urinary leptin excretion decreased towards normal levels but was still higher than in the controls. The serum leptin levels in pediatric NS patients before treatment were similar to the controls; after remission of the proteinuria, the serum leptin levels increased but still did not differ from the levels in healthy children. The researchers found a positive linear correlation between the leptin and protein levels in the urine. In our study, the serum leptin levels were lower in the pediatric NS patients in the relapse phase than in the remission group and controls. The serum leptin levels were lower in the remission group than in the control subjects but without a statistically significant difference. The serum leptin levels were positively correlated with the serum albumin levels, while the serum leptin levels were negatively correlated with the serum triglyceride levels. The urinary leptin excretion levels were higher in the relapse and remission groups than in the controls, whereas the levels were similar between the relapse and remission group. Urinary leptin loss persists during the remission period. In our study, we found a positive correlation between the urinary leptin levels and the urinary protein loss. This positive correlation between leptinuria and proteinuria, as well as the persistence of leptinuria during remission highlights the possible role during the disease course. Elevated urinary loss in patients with NS could be explained by two possible mechanisms. According to the first hypothesis, Schroth *et al.* (2001) propose a glomerular loss of the 16 kDa leptin peptide that is independent of the molecular size in patients with proteinuria. Elevated glomerular and urinary leptin levels might accelerate disease proliferation, thereby aggravating glomerulosclerosis and tubular damage, and continuous leptin excretion might be an additional mechanism in the progression of renal failure (Schroth *et al.* 2001). Buyan *et al.* (2003) suggested that both proteinuria and leptinuria are factors associated with progressive renal damage and found increased leptin excretion parallel to increased protein excretion during the relapse phase. Our study results support the premise that elevated urinary leptin levels during the relapse phase might be related to the potential effect of leptin during the pathophysiology. Additional studies investigating the relationship between leptin and renal endothelial and tubular proliferation are required because leptin is the main modulator of renal fibrosis (Ballerman 1999; Briley & Szczech 2006; Wolf *et al.* 1999). The second hypothesis is based on leptin as an inflammation marker and its close relationship with disease activity. Leptin exerts a potential effect that is associated with cytokine activation (i.e., IL-1, IL-8, and TNF) and the direct effect of the hypothalamic receptor (Ballerman 1999; Buyan *et al.* 2003; Ece *et al.* 2004; Wolf *et al.* 1999).

Leptin's role in the regulation of lipid metabolism has not been completely elucidated. Shimabukuro *et al.* (1997) demonstrated that leptin acts peripherally to inhibit triglyceride synthesis and stimulate lipolysis. Experimental studies have revealed that leptin inhibits the hepatic triglyceride, cholesterol ester and fatty acid synthesis via blockage of the stearoyl-CoA desaturase-1 (SCD-1) enzyme (Cohen & Friedman 2004). Serum triglyceride levels are decreased after leptin replacement therapy in leptin deficient ob/ob mice with hypertriglyceridemia (Breslow *et al.* 1999). Generalized lipodystrophy is a disorder associated with hypoleptinemia, hypertriglyceridemia, and proteinuria; after recruiting patients and treating them with a course of recombinant leptin, researchers determined that the subjects' frequency and severity of proteinuria, as well as their serum lipid levels, decreased (Javor *et al.* 2004). The serum triglyceride levels returned to the normal levels after leptin replacement therapy in children with Berardinelli-Seip congenital lipodystrophy (Beltrand *et al.* 2007). In our study, serum leptin levels were negatively correlated with the serum triglyceride levels. Regarding this result, the decreased urinary leptin excretion, which caused decreased serum leptin levels, might have contributed to the dyslipidemia. The relationship between leptin and lipid metabolism may play a potential role in progressive renal damage. Leptin-stimulated synthesis of type I collagen in mesangial cells and type 4 collagen in glomerular endothelial cells contributes to extracellular matrix deposition, glomerulosclerosis, and proteinuria and might contribute to the progression of proliferative renal disease (Ballerman 1999; Dotsch *et al.* 2005). Hyperlipidemia aggravates the progression of renal disease by oxidative stress. In patients with NS, hypercholesterolemia and triglyceride-rich ApoB lipoproteins potentially affect the progression of renal disease.

The relationship between ghrelin and leptin merits discussion because these compounds are antagonistic signals towards the inflammation process and energy balance (Dixit *et al.* 2004). Ghrelin is a novel hormone that possesses GH-releasing, cardiovascular and metabolic activities. Acylation of the ghrelin peptide is a prerequisite for its biological activity and occurs not only in the stomach but also in the kidney (Kojima *et al.* 1999; Mori *et al.* 2000). In addition, the preproghre-

lin and ghrelin receptor genes are expressed in both the kidney and glomerulus of rodents (Mori *et al.* 2000). These findings indicate that ghrelin performs endocrine and/or paracrine functions in the kidney, which is one of the possible targets for direct ghrelin action. Ghrelin concentrations are influenced by the degree of CRF and the mode of dialysis. In patients with end-stage renal disease, a threefold rise in plasma ghrelin levels has been reported (Yoshimoto *et al.* 2002). In patients with chronic renal failure, the plasma ghrelin concentration is already increased but does not stimulate the appetite. Therefore, chronic renal failure might lead to a certain degree of resistance to ghrelin (Dotsch *et al.* 2005). However, there is little information on the role of ghrelin in various renal diseases and no published data regarding the role of ghrelin in nephrotic syndrome. Our study is the first investigation of the serum and urinary ghrelin levels in nephritic syndrome. In our study, the serum ghrelin levels were similar between the relapse, remission and control groups. The urinary ghrelin excretion level was significantly higher in the pediatric NS patients during the relapse phase than in the NS subjects during remission and in the healthy children. After remission, the urinary ghrelin excretion decreased; however, it remained higher than in the healthy children, similar to the urinary leptin excretion. In the relapse group, the urinary ghrelin excretion was positively correlated with the urinary protein excretion. Therefore, we propose the glomerular loss of ghrelin, which has a lower molecular weight than leptin, in patients with proteinuria.

The proteinuria, elevated urinary leptin excretion and decreased serum leptin levels that were observed during the active disease phase in our study might indicate the possible impact on the pathophysiology of dyslipidemia. Moreover, increased urinary ghrelin excretion and the presence of a positive correlation between urinary protein and ghrelin excretion may be caused by the affected ghrelin metabolism during the NS course or may indicate the possible role of ghrelin in the pathophysiology of the disease. In the present study, we could not determine the exact cause of the altered serum and urinary levels of leptin and ghrelin – whether these events were the results of the pathophysiology of the disease or the direct effect of the pathophysiology or both. Additional *in vivo* and *in vitro* studies of the potential role of leptin and ghrelin in the pathophysiology of NS are necessary.

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