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Aleksandra Radosz, Anna Obuchowicz

An assessment of renal function by neutrophil lipocalin and cystatin C in obese adolescents with or without obesity-induced hypertension

Ocena funkcji nerek z uwzględnieniem stężeń lipokaliny neutrofilowej i cystatyny C u nastolatków otyłych z nadciśnieniem tętniczym indukowanym otyłością lub bez niego

Faculty of Health Sciences in Katowice, Medical University of Silesia in Katowice, Katowice, Poland
Correspondence: Aleksandra Radosz, Department of Paediatrics in Bytom, Specialist Hospital No. 2, Batorego 15, 41-902 Bytom, Poland, e-mail: aradosz@sum.edu.pl

ORCID iDs
1. Aleksandra Radosz https://orcid.org/0000-0003-4668-5992
2. Anna Obuchowicz https://orcid.org/0000-0002-8725-5406

Abstract

Introduction: Obesity and hypertension are associated with organ complications, including kidney diseases. It is necessary to search for the methods of early detection of these complications. **Aim:** The aim of the study was to assess renal function in obese adolescents, based on lipocalin-2 and cystatin C levels in relation to creatinine, estimated glomerular filtration rate and leptin levels. **Materials and methods:** The study included 76 children aged 11–17 years, with obesity or with obesity and obesity-induced hypertension or normosthenic children with tension headaches (control group). Renal function was assessed based on serum creatinine and estimated glomerular filtration rate (Schwartz equation). Plasma and urine lipocalin-2, serum cystatin C and leptin levels were determined by ELISA. **Results:** Renal function assessed by creatinine level and estimated glomerular filtration rate was normal in all patients, but mean creatinine levels were significantly higher and estimated glomerular filtration rate was significantly lower in the study groups compared to controls. No significant differences were found in plasma and urine lipocalin-2 levels. Mean cystatin C level was significantly higher in the obese group. We have found a weak positive correlation between plasma lipocalin-2 and creatinine levels and its weak negative correlation with estimated glomerular filtration rate, as well as a positive correlation for leptin and cystatin C levels in the obese group. **Conclusion:** The role of plasma and urine lipocalin-2 and serum cystatin C in the assessment of renal function in obese adolescents with or without obesity-induced hypertension is ambiguous. The relationship between cystatin C and leptin levels in obese children also requires further research.

Keywords: obesity, lipocalin-2, cystatin C, kidney function, adolescents

Streszczenie

Wstęp: Otyłość i nadciśnienie tętnicze powodują powikłania narządowe, w tym nerkowe. Należy poszukiwać metod ich wczesnego wykrywania. **Cel:** Celem pracy było określenie funkcji nerek nastolatków otyłych przy wykorzystaniu stężeń lipokaliny 2 i cystatyny C w odniesieniu do stężenia kreatyniny i szacunkowego wskaźnika przesączania kłębuszkowego oraz do stężeń leptyny. **Materiał i metody:** Do badania zakwalifikowano 76 dzieci w wieku 11–17 lat, otyłych lub otyłych z nadciśnieniem tętniczym indukowanym otyłością lub normostenicznych z rozpoznaniem napięciowych bólów głowy (grupa kontrolna). Czynność nerek oceniano na podstawie stężenia kreatyniny w surowicy, szacunkowego wskaźnika przesączania kłębuszkowego obliczonego wg wzoru Schwartza. Metodą ELISA oznaczono stężenia lipokaliny 2 w osoczu i w moczu oraz cystatyny C i leptyny w surowicy. **Wyniki:** Funkcja nerek oceniona na podstawie stężenia kreatyniny i szacunkowego wskaźnika przesączania kłębuszkowego była prawidłowa u wszystkich badanych, ale średnie stężenia kreatyniny były znamiennie wyższe, a wartości szacunkowego wskaźnika przesączania kłębuszkowego znamiennie niższe w grupach badanych niż w grupie kontrolnej. Różnice stężeń lipokaliny 2 w osoczu i w moczu były nieznamienne. Średnie stężenie cystatyny C było znamiennie wyższe w grupie dzieci otyłych. Wykazano słabe korelacje stężeń lipokaliny 2 w osoczu: dodatnie ze stężeniem kreatyniny i ujemne z szacunkowym wskaźnikiem przesączania kłębuszkowego oraz dodatnią korelację stężeń leptyny i cystatyny C w grupie dzieci otyłych. **Wniosek:** Znaczenie badania stężeń lipokaliny 2 w osoczu i w moczu oraz cystatyny C w surowicy w ocenie funkcji nerek nastolatków otyłych z nadciśnieniem tętniczym indukowanym otyłością lub bez niego nie jest jednoznaczne. Dalszych badań wymagają też zależności stężeń cystatyny C i leptyny u dzieci otyłych.

Słowa kluczowe: otyłość, lipokalina 2, cystatyna C, funkcja nerek, nastolatki

INTRODUCTION

Hypertension (HT), overweight and obesity, and even the metabolic syndrome affect an increasing percentage of paediatric population. In Poland, over 20% of pubertal children and over 10% of preschool children are overweight[1]. Complications of obesity, such as hepatic steatosis, HT, type 2 diabetes and cancer, are important causes of mortality in adults. Since many obese children and adolescents are expected to be obese in adulthood, early detection of organ complications of obesity, including renal complications, is an important goal of contemporary paediatrics. It has been shown that long-term obesity is a significant risk factor for end-stage kidney disease[2]. HT, which is very common among adults, has its onset already during adolescence in many cases. About 30% of obese individuals have obesity-induced HT. Hyperleptinaemia and hyperinsulinism in obese individuals activate the sympathetic nervous system, and stimulate the renin–angiotensin–aldosterone system, leading to sodium retention. Vascular damage and endothelial dysfunction occur, increasing vascular resistance. This leads to HT[1]. Neutrophil gelatinase-associated lipocalin-2 (NGAL) is an acute phase 25 kDa glycoprotein. It is secreted by e.g. neutrophils, renal tubular cells, bone marrow and adipose tissue. It plays a role in apoptosis, fatty acid transport, and inflammatory processes[3]. Chronic inflammation, which is caused by multiple pro-inflammatory cytokines stimulated by metabolic stress, plays a major role in the pathogenesis of obesity and its complications. Animal studies have shown upregulated NGAL expression mediated by the tumour necrosis factor alpha (TNF-α), interferon gamma (INF-γ) or insulin[3]. A rapid early increase in urine NGAL levels is seen in acute kidney damage, therefore, this parameter has been recognised as a marker of kidney function in these conditions for several years now[4]. There are reports indicating a relationship between NGAL and obesity and its metabolic complications in adults[5]. The possible association between other adipokines and NGAL also needs to be considered. It seems that such correlations can be expected for leptin. Apart from playing an important role in appetite modulation, it is a multidirectional protein involved in metabolic reactions. Leptin promotes, among others, chronic inflammation. It activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κβ) and TNF-α, which are important for stimulating NGAL synthesis. Leptin receptors have been found, among others, on immune cells[6]. Leptin is also involved in regulating blood pressure[7]. Serum creatinine and estimated glomerular filtration rate (eGFR), calculated in children with the Schwartz formula, are the primary indicators of kidney function in medical practice. Serum cystatin C level is also used to assess eGFR, as it is the resultant of the synthesis of this protein and the rate of its excretion by the kidneys. Cystatin C is a protease inhibitor produced in all human cells. It is not absorbed, but entirely filtered in the glomeruli. In contrast to creatinine, cystatin C levels are not affected by diet[8]. In adolescents, obesity does not induce changes in the kidneys that would meet the criteria for acute kidney injury or chronic kidney disease. The possibility of identifying biomarkers of early renal dysfunction would be important for both exploratory and clinical reasons. Literature data indicate that, e.g., NGAL may be such a biomarker[9].

The aim of the study was to assess renal function in obese adolescents with or without obesity-induced HT based on serum creatinine and cystatin C levels, eGFR, plasma and urine NGAL levels, as well as to determine the relationship between these parameters and serum leptin levels.

MATERIALS AND METHODS

The research was conducted after obtaining the approval of the Bioethics Committee of the Medical University of Silesia (Resolution No. KNW/0022/KB1/15/12 of February 7, 2012).

Patients of the Department of Paediatrics aged 11–17 years, who were diagnosed with obesity (OB group: 19 children – 3 boys and 16 girls) or obesity with obesity-induced HT (OB-HT group: 30 children – 18 boys and 12 girls) were included in the analysis. The age-matched control group (27 children – 7 boys and 20 girls) consisted of non-HT patients from the same Department, but with normal somatic parameters, who were hospitalised for tension headaches (induced by emotional stress or associated with incorrect body position when using electronic devices for a long time). Informed written consent to participate in the study was obtained from parents and study participants over the age of 13 years. Diagnostic workup was performed, allowing to exclude secondary obesity and causes of HT other than those induced by obesity in the study groups, and to diagnose tension headaches in the control group. Other acute and chronic diseases were excluded in all patients. The mean age was: in group I 14.9 ± 1.99 years, in group II 14.5 ± 2.44 years, in control group 13.9 ± 1.93 years. Among all obese children, girls accounted for 57% and boys for 43%. The same percentages were 74% and 26% in the control group, respectively. Girls predominated in the OB group (84% vs. 40%) compared to the OB-HT group. After an overnight fasting, in addition to the tests related to hospital stay, serum cystatin C and leptin levels, plasma and urine NGAL (BioVendor reagent, Czech Republic) were assayed using the enzyme-linked immunosorbent assay (ELISA). Additionally, for the study serum creatinine levels were used (Cobas Integra) and estimated glomerular filtration rate (eGFR) was assessed using the Schwartz formula (0.413 × height [cm] / blood creatinine [mg/dL]). Body mass, height and body mass index (BMI) were referred to Polish reference values for sex and age[10]. BMI values exceeded the 97th percentile in OB and OB-HT patients, and were between the 10th and 85th percentile in the control group. Blood pressure was assessed daily in the morning using sphygmomanometer with pressure cuff

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matched to the patient's arm size. The children with suspected HT had 24-hour blood pressure measurement with Oscar2 ABPM (SunTech) – the measurements were taken every 20 minutes during the day and every 30 minutes during the night. HT was diagnosed based on blood pressure norms for Polish children[11] and the recommendations of the Polish Society of Paediatric Nephrology[12]. HT was diagnosed in all patients in the OB-HT group. Statistical analysis was performed using the R System version 4.2.1 in the RStudio environment. The compliance of the data distribution with normal distribution was verified using the Shapiro–Wilk *W* test, and since the distribution was not normal, non-parametric tests were used in the statistical analysis: Kruskal–Wallis test with post hoc analysis and Spearman's rank correlation test for results in individual groups and in combined groups to increase the power of the statistical test. Multiple linear regression was used to assess the simultaneous impact of all independent variables (age, gender, BMI, leptin levels) on dependent variables (urine NGAL, plasma NGAL, cystatin C, creatinine levels and eGFR). Coefficients of determination were calculated. A $p < 0.05$ was considered statistically significant for the study. Differences in creatinine level and eGFR between boys and girls were insignificant. Differences in urine and plasma NGAL and cystatin C levels between girls and boys in the analysed groups were also insignificant. Therefore, the results were assessed holistically, regardless of gender division.

RESULTS

The mean levels of the tested compounds and eGFR in individual groups, as well as the statistical comparison of the results are presented in Tab. 1.

Renal function assessed by serum creatinine and eGFR was within the generally accepted range in all patients. However, statistical comparison showed significant differences in mean creatinine levels and eGFR values in the OB and OB-HT groups vs. the control group, with worse findings in the study groups. Significantly higher mean serum cystatin C levels were observed in the OB group compared to controls, as well as leptin levels in both study groups vs. the control group and in the OB group vs. the OB-HT group. Statistical analysis showed no significant differences for NGAL levels (Tab. 1).

Significant positive correlations for leptin and cystatin C levels were found when considering the pooled results for all groups of children ($r = 0.44$; $p = 0.0001$) and children in the OB group ($r = 0.55$; $p = 0.0016$). Other correlations between leptin levels and renal function indices were insignificant. There were weak positive correlations between plasma NGAL and creatinine levels ($r = 0.26$; $p = 0.024$) and negative correlations between plasma NGAL and eGFR level for all paediatric groups ($r = -0.23$; $p = 0.044$). Multiple linear regression analysis demonstrated the key predictors for the analysed dependent factors in the individual groups. This was leptin level for plasma NGAL level ($R^2 = 0.43$; feature importance 1.08), and BMI for cystatin C level ($R^2 = 0.5$; feature importance 1.75) in the OB group. In the OB-HT group, the coefficients of determination were lower. Age ($R^2 = 0.2$; feature importance 0.37) and leptin level ($R^2 = 0.2$; feature importance 0.33) were the most important predictors for plasma NGAL level.

DISCUSSION

As pointed out by Salman et al., the impact of obesity on kidney function in obese children and adolescents is not thoroughly investigated[13]. However, Vivante et al. found in their study in a group of 17-year-olds that overweight and obesity were serious risk factors for end-stage renal disease during a 25-year observation period[2]. Therefore, kidney damage in HT and/or obesity requires early detection and implementation of effective management so that the organ damaged at an early stage of life could retain its adequate function for many years. Apart from creatinine and eGFR, more recent markers of kidney damage, such as cystatin C or NGAL, proved useful in the assessment of acute kidney injury[14]. The possibility of using NGAL in the diagnosis of acute kidney injury both in adults and children,

Group	Plasma creatinine [mg/dL] Mean ± *SD*	eGFR [mL/min/1.73 m²] Mean ± *SD*	Plasma NGAL [ng/mL] Mean ± *SD*	Urine NGAL [ng/mL] Mean ± *SD*	Serum cystatin C [ng/mL] Mean ± *SD*	Serum leptin [ng/dL] Mean ± *SD*
OB $n = 19$	0.83 ± 0.15	86.19 ± 21.9	36.18 ± 33.63	16.88 ± 20.25	2691.46 ± 1262.87	37.08 ± 13.19
OB-HT $n = 30$	0.77 ± 0.13	92.01 ± 13.67	20.39 ± 23.55	11.44 ± 20.36	2229.6 ± 1388.64	25.44 ± 16.42
Controls $n = 27$	0.64 ± 0.11	106.21 ± 21.83	20.91 ± 26.81	26.74 ± 28.18	1905.09 ± 1297.81	8.52 ± 9.52
Statistical comparison*						
OB vs. OB-HT	$p = 0.165$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p = 0.0203$
OB vs. controls	$p = 0.0001$	$p = 0.0002$	$p > 0.05$	$p > 0.05$	$p = 0.0157$	$p = 0.0001$
OB-HT vs. controls	$p = 0.0008$	$p = 0.0269$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p = 0.0001$

OB – obesity; **OB-HT** – obesity – hypertension; **eGFR** – estimated glomerular filtration rate; **NGAL** – neutrophil gelatinase-associated lipocalin.
* Kruskal–Wallis test.

Tab. 1. Kidney function parameters and serum leptin levels in study participants

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e.g. in postoperative intensive care patients in critical condition, has been confirmed[15]. Cystatin C and NGAL are also listed among the biomarkers of obesity-induced kidney disease[8,16–18]. Our study was designed to evaluate the usefulness of these markers for the assessment of kidney function in two different groups of paediatric patients: children with obesity and children with obesity and obesity-induced HT. Since the duration of obesity is an important factor for the development of organ complications, groups of obese adolescents were qualified for the study. In the OB-HT group, these were also children with newly diagnosed and previously untreated obesity-induced HT.

All study participants had normal renal function, as determined by serum creatinine and eGFR. However, statistical comparison showed that both mean creatinine levels (higher) and mean eGFR values (lower) were significantly different in the study groups than in the control group, with worse results in the former. This may indicate a downhill trend in renal function in study participants. Contrary to this study, Salman et al. found no significant differences in creatinine levels in their study in children aged 6–18 years, but noted significantly higher eGFR values in obese children, which they explained by hyperfiltration in the initial phase of kidney damage in this group[13].

It should be taken into account that the groups included in this study differed significantly in their mean leptin levels, which were the highest in the OB group. Compared with published studies investigating these relationships, this result indicates the highest amount of adipose tissue in this group[19]. Sönmez et al. showed in their study in children aged 10–18 years that mean leptin levels were significantly lower in the group of obese HT patients than in obese non-HT patients, which the authors explain by the effect of lowering leptin levels by angiotensin converting enzyme inhibitors or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB)[20]. Although our patients in the OB-HT group were not treated, a similar result was obtained. This fact requires further research. Leptin is an important factor in the pathogenesis of HT[7]. Its levels may also be affected by the 24-hour blood pressure profile in children[21]. However, such correlations were not analysed in this study. Hyperleptinaemia has a direct and indirect negative impact on kidney function[22]. It has been suggested that it may be a marker of kidney damage in middle-aged and elderly individuals[23]. However, no correlation was found between leptin levels and eGFR values in children with chronic kidney disease[24]. In the OB group, where the levels of leptin were the highest, they positively correlated with the cystatin C, which may indicate a relationship between hyperleptinaemia and deteriorated renal function, as described above. Multiple regression analysis suggested a relationship between plasma NGAL and leptin in the group of obese children.

So far, the relationship between cystatin C levels and obesity in adolescents has not been fully explored. Huo et al. found some associations between cystatin C and the risk of obesity in healthy adolescents aged 14–17 years[25]. It is believed that these levels are independent of body weight. However, their relationship with leptin levels has not been determined. Murai et al. found a strong relationship between serum cystatin C levels and visceral fat area and epicardial adipose tissue, regardless of other factors, including kidney function, in adults with type 2 diabetes[26]. In this context, the correlation between cystatin C and leptin in the OB group deserves attention and further research. Roos et al. indicate that cystatin C levels are more sensitive than creatinine and have comparable specificity in the assessment of renal dysfunction in adults and children[27]. These compounds were considered in our research. The already cited Salman et al. found no significant differences in mean creatinine and cystatin C levels between obese and healthy children[13]. In our study, however, mean creatinine levels were significantly higher in both study groups, and mean cystatin C levels were significantly higher in the OB group compared controls. According to Bostan Gayret et al., serum cystatin C and urine NGAL are good markers of kidney damage in obese children included in this study[8]. While the difference in the mean cystatin C levels in the OB group and the control group was significant, the mean urine and plasma NGAL levels did not differ significantly between the study groups. Similar urine NGAL findings were obtained by Gul et al. in 10–16-year-old obese or overweight children[16], and by Goknar et al. in obese children[18]. On the other hand, Polidori et al. found both higher mean serum cystatin C and urine NGAL in obese prepubertal children[17]. A study in obese adolescents showed a correlation between eGFR and an increased urinary NGAL[28]. In our patients, although no significant difference was found in mean plasma NGAL levels, the correlation analysis for the combined groups showed weak positive correlations of these levels with creatinine and negative correlations with eGFR. This needs further investigations. The literature also points to the importance of metabolic disorders for urine NGAL, including insulin resistance[29] and dyslipidaemia[16,28]. Varied metabolic status of obese children investigated by different authors may therefore generate different results. An assessment of creatinine and cystatin C levels, for which some significant differences were shown in this research when comparing the study and control groups, seems more useful.

Our study has some limitations. The study groups were relatively small, and there was a male/female disproportion. It was not possible to precisely determine the duration of HT in the OB-HT group, although it was a new diagnosis in all patients, without pharmacotherapy, which should be considered an asset of the study. At the same time, however, the multiplicity of factors influencing the possible presence and intensity of HT in obesity may contribute to the heterogeneity of the group.

CONCLUSIONS

Although creatinine levels and eGFR in obese adolescents with or without obesity-induced HT were within normal

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limits, their mean values in the study groups showed unfavourable differences compared to healthy children and therefore should be periodically monitored. The role of plasma and urinary NGAL and serum cystatin C in assessing kidney function in obese adolescents is not clear and requires long-term research, and so does the relationship between cystatin C and leptin levels in obese children.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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