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# Lipid metabolism and renal function markers in obese adolescents

## Gospodarka lipidowa a markery funkcji nerek u otyłych nastolatków

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**Abstract**

**Aim of the study:** To investigate the relationship of renal function markers and lipid metabolism parameters in obese adolescents.

**Material and methods:** The study comprised 76 children aged 11–17 years, hospitalised due to: obesity (group I – 19 children) or obesity accompanied by obesity-induced hypertension (group II – 30 children) or normosthenic children with a diagnosed tension headaches (control group – 27 children). A subgroup with metabolic syndrome (MS – 16 children) was also separated. Renal function was assessed on the basis of: serum creatinine concentration, glomerular filtration rate estimated using Schwartz eqation (eGFR), determination of plasma and urinary neutrophil gelatinase-associated lipocalin and cystatin C. On the basis of statistical analysis, it was checked whether renal function markers depend on lipid metabolism parameters.

**Results:** In the study groups mean creatinine concentrations were significantly higher and eGFR values significantly lower than in the control group, but they remained within norm. Differences in plasma and urinary neutrophil gelatinase-associated lipocalin concentrations were not significant. Mean cystatin C concentrations were significantly higher in the group of obese children. Multiple linear regression analysis showed that the most important predictor was: LDL-C for urinary neutrophil gelatinase-associated lipocalin ($R2 = 0.42$) and TG for eGFR ($R2 = 0.44$) concentrations in group I; cholesterol for creatinine concentrations in MS group ($R2 = 0.44$).

**Conclusions:** Renal function of the obese adolescents included in the study was normal and the associations with lipid metabolism were poorly expressed.

**Key words:**
obesity, neutrophil gelatinase-associated lipocalin, cystatin C, lipidogram, adolescents.

**Streszczenie**

**Cel pracy:** Zbadanie zależności wskaźników funkcji nerek i parametrów gospodarki lipidowej u otyłych nastolatków.

**Materiał i metody:** Badaniami objęto 76 dzieci w wieku 11–17 lat, hospitalizowanych z powodu: otyłości (grupa I – 19 dzieci) lub otyłości z towarzyszącym nadciśnieniem tętniczym indukowanym otyłością (grupa II – 30 dzieci) lub normostenicznych z rozpoznaniem napięciowych bólów głowy ( grupa kontrolna – 27 dzieci). Wydzielono podgrupę z zespołem metabolicznym (MS – 16 dzieci). Czynność nerek oceniono na podstawie: stężeń kreatyniny oraz cystatyny C w surowicy, oszacowanego przy użyciu wzoru Schwartza przesączania kłębuszkowego u dzieci (eGFR), oznaczenia stężenia związanej z żelatynazą neutrofilową lipokaliny (NGAL) w osoczu i w moczu. Na podstawie analizy statystycznej sprawdzono, czy parametry funkcji nerek pozostają w zależności od parametrów gospodarki lipidowej.

**Wyniki:** Średnie stężeń kreatyniny były znamiennie większe, a wartości eGFR znamiennie mniejsze w grupach badanych niż w kontrolnej, ale mieściły się w granicach norm. Różnice stężeń związanej z żelatynazą neutrofilową lipokaliny w osoczu i w moczu były nieznamienne. Średnie stężenie cystatyny C było znamiennie większe w grupie I. Analiza regresji liniowej wielorakiej wykazała, że najważniejszym predyktorem były stężenia LDL-C dla stężeń związanej z żelatynazą neutrofilową lipokaliny w moczu ($R2 = 0,42$) i TG dla eGFR ($R2 = 0,44$) w grupie I, a w grupie z MS stężenie cholesterolu dla stężenia kreatyniny ($R2 = 0,44$).

**Wnioski:** Funkcja nerek otyłych nastolatków objętych badaniem była prawidłowa, a jej związki z gospodarką lipidową słabo wyrażone.

**Key words:**
otyłość, lipokalina związana z żelatynazą neutrofilową, cystatyna C, lipidogram, nastolatki.

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## Introduction

Obesity, prevalence of which is increasing worldwide in both adults and children, has proven impact on development of type 2 diabetes, hypertension, and chronic cardiovascular disease [1]. It also causes haemodynamic and histological changes in kidneys and is considered an important cause of chronic kidney disease (CKD) in adults. Importantly, obesity from early childhood can result in early onset of CKD [1, 2]. Vivante *et al*. found that the risk of end-stage renal disease (ESRD) in obese 17-year-olds is 2.4 times higher over a follow-up of 25 years than in non-obese subjects [3]. The relationship between obesity and CKD is not explained in detail. Potential mechanisms of this relationship include co-existence of haemodynamic factors (including glomerular hyperfiltration, increased sodium reabsorption, increased sympathetic nervous system activity and RAAS activity), metabolic influences (including abnormal lipid metabolism, adipokine dysregulation, insulin resistance, oxidative stress) and lipid nephrotoxicity [2]. Dysregulation of fatty acid and cholesterol metabolism increases accumulation of triglycerides in kidneys, leading to abnormalities in renal structure and function [3]. A study of Polish children aged 6–14 years old with overweight and obesity showed prevalence of lipid disorders at the level of 38.2% among girls and 40.5% among boys [4]. The most common abnormality was reduced HDL cholesterol (HDL-C) concentration and elevated LDL cholesterol (LDL-C) concentration [4]. It should also be noted that 7.1% of 14-year-olds in the European population meet the criteria for diagnosis of the metabolic syndrome [5]. In the context of the considered influence of lipid metabolism on renal function in obese adults and significant prevalence of dyslipidaemia in overweight children, it would be appropriate to investigate the relationship of renal function markers of these children with lipid metabolism parameters. The basic parameters used to assess renal function are creatinine and eGFR (estimated glomerular filtration rate), calculated in children using the Schwartz equation. Taking into account the fact indicated in the literature that serum creatinine concentrations in obese children are mostly normal [6] other renal function biomarkers should be considered in assessment of their renal function. Among them, the literature emphasises importance of checking concentrations of neutrophil gelatinase-associated lipocalin (*NGAL*) and cystatin C [7, 8]. These are mentioned as markers of acute kidney injury [7] and markers of kidney disease in obese children [8]. NGAL is a glycoprotein, belonging to the acute phase proteins, secreted, among others, by neutrophils, renal tubular cells, bone marrow and adipose tissue. In diagnosing of acute kidney injury, determination of urinary NGAL has a specificity of 76% and a sensitivity of 77% [9]. Some reports show relationship of NGAL concentrations with obesity and its metabolic complications in adults [10]. Cystatin C is a protease inhibitor produced in all human cells. It is filtrated entirely in the glomeruli and not reabsorbed; and diet does not affect its concentrations [8].

Due to the potential relationship of CKD with abnormal lipid metabolism, renal function markers need to be related to lipid metabolism markers, including concentrations of non-HDL-C, representing all atherogenic lipoproteins.

## Aim of the study

This study aims at evaluating the relationship between renal function markers (serum creatinine and cystatin C concentrations, eGFR levels and NGAL concentrations in plasma and urine) and lipid metabolism parameters (serum concentrations of total cholesterol, its fractions and triglycerides) in obese adolescents.

## Material and methods

The study was approved by the Bioethics Committee of the Silesian Medical University (Resolution No. KNW/0022/KB1/15/12 of 07.02.2012). Informed written consent to participate in the study was given by parents and study subjects aged over 13 years old.

The study included 76 patients of the Department of Paediatrics, aged 11–17 years old, qualified after the diagnostic procedure. The following groups were established: group I, adolescents with primary obesity (19 children, including 16 girls and 3 boys), group II, adolescents with primary obesity and obesity-induced hypertension (30 children – 12 girls and 18 boys) and an equal-aged, normosthenic control group (27 children – 20 girls and 7 boys). The patients in the control group were diagnosed with tension headaches (emotional or caused by inappropriate body position when handling electronic equipment). Apart from the aforementioned disorders, no other acute or chronic diseases were found in the children included in the study. Carbohydrate metabolism disorders were excluded- in all subjects fasting glycemia, postprandial glycemia or results of glucose tolerance test were within the normal ranges. Group II included children with newly diagnosed obesity-induced hypertension (HT) untreated before. The characteristic features of the groups included in the study were as follows: the mean age of the patients in the groups was: I – 14.9 ±1,99 years, group II – 14.5 ±2,44 years, control group – 13.9 ±1,93 years. The sex structure was as follows: among all obese children, girls accounted for 57% and boys for 43% of the subjects; in the control group, girls accounted for 74% and boys for 26% of the subjects. Comparing group I and II, girls predominated (84% vs. 40%). Based on the International Diabetes Federation [11] criteria on diagnosis of metabolic syndrome (MS), the study subjects comprised a group of 16 children with MS (37,7% of all included in the study obese children). In all subjects, biochemical diagnostic tests were performed after overnight fasting. For the purposes of the study we used following laboratory results: creatinine concentrations, total cholesterol (TC), LDL-C, HDL-C and triglyceride (TG) concentrations (all determinations in hospital laboratory, the Cobas Integra). The non-HDL concentration was calculated. eGFR values were calculated, using the Schwartz equation: 0.413 × height [cm] /blood creatinine concentration [mg/dl]. Concentrations of individual lipoprotein and triglyceride fractions were categorised as normal, borderline, high using the guidelines by the National Heart, Lung and Blood Institute [12]. Concentrations of serum cystatin C, plasma NGAL and urinary NGAL were determined by ELISA (reagents from Biovendor,

 

Czech Republic). The values of weight and height measurements and BMI calculations were related to Polish referances values for sex and age [13], as well as values of waist and hip circumferances measurements [14]. In the control group, all children had normal body weight (BMI between the 10th and 85th percentile). In groups I and II, BMI values exceeded the 97th centile in each subject. Arterial blood pressure was measured daily, in the morning hours, with a sphygmomanometer with pressure cuff matched to the patient's arm size. In addition, children with suspected HT had their arterial blood pressure measured 24 hours a day with Oscar2 ABPM (SunTech). Pressure measurements were taken every 20 minutes during the day and every 30 minutes in the night.

HT was diagnosed using the arterial blood pressure references for Polish children [15] and Polish Society for Paediatric Nephrology recommendations [16].

Statistical analysis of the results was performed using R language rev. 4.2.1 in the RStudio environment. Due to the fact that in the study material, differences in creatinine concentrations and creatinine-based eGFR values were non-significant between boys and girls, and that differences in urinary and plasma NGAL and cystatin C concentrations were also non-significant between girls and boys in the groups, the results within the groups were considered as a whole, without taking sex into account. The distribution normality was verified by the Shapiro-Wilk test. Multiple group comparisons were performed using ANOVA or the Kruskal-Wallis test. Post-hoc analysis was performed using Student's *t* or *U* Mann-Whitney multiple comparisons test with Holm-Bonferroni correction, respectively. Comparisons of the two groups were made using the Student's *t*-test or the Mann-Whitney *U* test. The correlation was assessed on the basis of Spearman's rank coefficients. In the analysis, the significance level was set at $p = 0.05$. The simultaneous influence of all independent variables studied (lipid metabolism parameters) on the dependent variables (renal function markers) was assessed, using the multiple linear regression method. Determination coefficients and RMSE (root mean square error) were calculated.

## Results

Statistical analysis of frequency of normal, borderline and high concentrations of lipoproteins and triglycerides showed statistically significant difference only for normal TG concentrations, which were more frequent in the control group ($p < 0.0185$).

Statistical comparison of mean concentrations of TC, HDL-C, LDL-C, non-HDL-C and TG showed statistically significant differences only between the II and the control group for non-HDL-C ($p = 0.036$) and TG ($p = 0.031$). In the control group non-HDL-C and TG concentrations were lower. Assessing lipid metabolism in children with MS in comparison with the control group, we found: statistically significantly lower mean HDL-C concentration ($p < 0.0001$) and significantly higher mean non-HDL-C ($p = 0.0215$) and TG ($p = 0.0001$) concentrations in the MS group (Table I).

Reference of serum creatinine concentrations and eGFR values to generally accepted norms showed that renal function in all children included in the study was normal. Statistical comparison of mean creatinine concentrations ($p = 0.0001$; $p = 0.0008$ respectively) and eGFR ($p = 0.0002$; $p = 0.03$ re-

**Table I.** Investigated parameters of lipid metabolism in children included in the study

| Group | Total cholesterol (mg/dl) M ±SD | LDL-C (mg/dl) m ±SD | HDL-C (mg/dl) M ±SD | Non-HDL-C (mg/dl) M ±SD | Triglycerides (mg/dl) M ±SD |
|---|---|---|---|---|---|
| I ($n = 19$) | 166.95 ±25.76 | 87.63 ±27.8 | 51.95 ±10.42 | 115 ±22.32 | 103.16 ±29.57 |
| II ($n = 30$) | 167.57 ±27.4 | 103.1 ± 32.54 | 46.98 ±13.24 | 120.59 ±30.82 | 126.8 ±62.73 |
| MS ($n = 16$) | 168.56 ±34.23 | 104.09 ±41.21 | 40.91 ±12.91 | 127.64 ±34.1 | 156.62 ± 65.19 |
| Control group ($n = 27$) | 160.56 ±32.65 | 87.63 ±27.8 | 58.59 ±22.09 | 101.96 ±26.04 | 88.36 ±36.00 |
| Statistical analysis* | | | | | |
| I vs. II | $p > 0.05$ | $p > 0.05$ | $p > 0.05$ | $p > 0.05$ | $p > 0.05$ |
| I vs. control group | $p > 0.05$ | $p > 0.05$ | $p > 0.05$ | $p > 0.05$ | $p > 0.05$ |
| II vs. control group | $p > 0.05$ | $p > 0.05$ | $p > 0.05$ | $p = 0.036$ | $p = 0.03$ |
| MS vs. control group | $p > 0.05$ | $p > 0.05$ | $p < 0.0001$ | $p = 0.0215$ | $p < 0.0001$ |

* Test post-hoc pairwise *t*-test or pairwise Wilcoxon test for unpaired samples with Holm-Bonferroni correction
I – obese children; II – obese children with obesity-induced hypertension; MS – subgroup with metabolic syndrome

**Table II.** Investigated markers of renal function of children included in the study

| Group | Creatinine (serum, mg/dl) M ±SD | eGFR (ml/min/1,73 m$^3$) M ±SD | NGAL (plasma, ng/ml) M ±SD | NGAL (urine, ng/ml) M ±SD | Cystatine C (serum, ng/ml) M ±SD |
|---|---|---|---|---|---|
| I ($n$ = 19) | 0.83 ±0.15 | 86.19 ±21.9 | 36.18 ±33.63 | 16.88 ±20.25 | 2691.46 ±1262.87 |
| II ($n$ = 30) | 0.77 ±0.13 | 92.01 ±13.67 | 20.39 ±23.55 | 11.44 ±20.36 | 2229.6 ±1388.64 |
| MS ($n$ = 16) | 0.74 ±0.12 | 94.74 ±15.03 | 23.61 ±30.28 | 16.08 ±27.17 | 2322.54 ±1541.25 |
| Control group ($n$ = 27) | 0.64 ±0.11 | 106.21 ±21.83 | 20.91 ±26.81 | 26.74 ±28.18 | 1905.09 ±1297.81 |
| Statistical analysis* | | | | | |
| I vs. II | $p$ = 0.165 | $p$ > 0.05 | $p$ > 0.05 | $p$ > 0.05 | $p$ > 0.05 |
| I vs. control group | $p$ = 0.0001 | $p$ = 0.0002 | $p$ > 0.05 | $p$ > 0.05 | $p$ = 0.0157 |
| II vs. control group | $p$ = 0.0008 | $p$ = 0.0269 | $p$ > 0.05 | $p$ > 0.05 | $p$ > 0.05 |
| MS vs. control group | $p$ = 0.0163 | $p$ > 0.05 | $p$ > 0.05 | $p$ > 0.05 | $p$ > 0.05 |

* Test post hoc pairwise *t*-test or pairwise Wilcoxon test for unpaired samples with Holm-Bonferroni correction
I – obese children; II – obese children with obesity-induced hypertension; MS – subgroup with metabolic syndrome; eGFR – estimated glomerular filtration rate; NGAL – neutrophil lipocalin

spectively )values, however, revealed significant differences in these data in groups I and II compared with the control group to the detriment of the study groups. Mean serum cystatin C concentration was also significantly higher in the children from group I than in the control group ($p$ = 0,0157). Differences in creatinine concentration between MS subgroup and the control group were also statistically significant ($p$ = 0.0163). Statistical analysis revealed no significant differences in urine and plasma NGAL concentrations in all included children (Table II).

Correlation analysis showed no relationship of lipid metabolism parameters with renal function markers. Multivariate linear regression analysis identified the most important lipid predictors for the dependent factors studied (indices of renal function). In group I, it were concentrations of: LDL-C for urinary NGAL (R2 = 0.42; RMSE 14.9), non-HDL-C for creatinine (R2 = 0.4; RMSE 0.11), TG for eGFR values (R2 = 0.44; RMSE 15.9). In MS subgroup the most important predictor for creatinine concentration was cholesterol concentration (R2 = 0.44, RMSE 0.08) and for eGFR values was non-HDL-C concentration (R2 = 0.41, RMSE 11.1). Other determination coefficients were lower.

## Discussion

The relationship of CKD in obese adults with abnormal lipid metabolism markers suggests that the values of renal function markers should be related to lipid metabolism parameters in obese adolescents. Indeed, Jadresic *et al*. [17] and Correia *et al.* [18] draw attention to the need for further discussion on the relationship of childhood obesity with CKD in later life. This study mainly aims at checking whether these lipid parameters may be predictors of early obesity-related nephrological complications. We felt it would be useful to include groups of clinically diverse adolescents with obesity, obesity-induced hypertension and those with the metabolic syndrome. Although the renal function of all children included in the study was normal, mean creatinine concentrations were significantly higher and mean eGFR values significantly lower in groups I and II than in the control group. It may suggest slow progression of renal dysfunction and requires longitudinal studies in accordance with the observations of Vivante *et al*. [3]. In contrast to groups I and II, in the separated subgroup with the metabolic syndrome, the mean eGFR value was not significantly different compared to the control group. It may suggest greater renal filtration in this subgroup. However, there are no signs of hyper-filtration, which is pointed out by Salmon *et al.* in the initial phase of renal damage in obese children [19]. Determination of NGAL concentrations in plasma and urine did not significantly differ in the groups studied, just like in the studies by Goknar *et al*. [20] and Gul *et al.* [21]. However, the latter authors found that urinary NGAL concentrations were higher in children with LDL dyslipidaemia. Maćkowiak-Lewandowicz *et al.* also found that in obese individuals with normal or reduced eGFR, increased concentrations of NGAL in urine together with increase cholesterol, triglycerides and uric acid may be predictors for CKD development [22]. Our material shows that only children in the obese group and in the subgroup with MS had significantly higher concentrations of non-HDL-C and triglycerides than children in the control group. These children should be put under precise

 

medical surveillance. Importance of diagnostics of MS for clinical practice is pointed out by Springwald *et al.* [23]. According to the analysis of presented results of lipid metabolism tests in our patients, we need to take into account that the mean age of the subjects was about 14 years. Data from the literature indicate that LDL-C and triglycerides concentrations may decrease at this age due to puberty [12, 24]. Despite the low values of the determination coefficients, the results of the multiple regression analysis suggest some predictive value of cholesterol concentrations and its fractions for creatinine and urinary and plasma NGAL concentrations. These results need to be confirmed with the inclusion of larger study groups. Discussing the importance of obesity in the development of CKD, Prasad *et al.* [1] and Yim *et al.* [2] point out that children born to obese mothers are at greater risk of developing the disease, which would also need to be included in future studies, rather including adults. Indeed, organ changes associated with obesity increase gradually, and obesity and hyperlipidaemia themselves affect kidneys not only directly, but also by inducing cardiovascular disease [24]. It is noteworthy that for the examined markers of renal function cystatin C serum concentration was significantly higher in group I than in control group. In our another publication (in the press) we connected this fact with significantly higher serum concentration of leptin in this group which correlated positively with cystatin C concentration. Hyperleptynemia has negative impact on kidney function [25] and may result in cystatin C concentration increase in the group I. Cystatin C is considered an earlier and more accurate marker of GFR than creatinine [26]. In our study no significant correlation between this marker of renal function and lipid parameters was observed. This issue needs further study, especially that cystatin C is directly engaged in atheroscelosis [26]. All our results should be confirmed in larger group of patients because the most significant limitation of the study is the small number of subjects included. Another limitation we can point is that analysis of markers correlation with blood pressure was not calculated.

## Conclusions

Kidney function in obese teenagers with or without obesity-induced hypertension or with metabolic syndrom was normal. However attention must be given to the fact, that avarage creatinine concentration in obese children was higher and eGFR was lower than in healthy children. Correlation between biomarkers of kidney function (levels of creatinine, NGAL and cystatin C and value of eGFR) and parameters of lipid metabolism were poorly expressed. Further prospective studies on larger groups of patients are needed to confirm these relations.

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