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Obesity indices and adipokines in non-diabetic obese patients with early stages of chronic kidney disease

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Background: The aim of this study was to estimate obesity parameters: waist circumference (WC), waist-to-hip ratio (WHR), weight-to-height ratio (WHtR), visceral adiposity index (VAI), body adiposity index (BAI), and serum adipokines (leptin, adiponectin, resistin) and their associations with estimated glomerular filtration rate (eGFR), serum creatinine, and microalbuminuria (MA) in patients with early stages of CKD and in non-CKD obese patients.

Material/Methods: 67 non-diabetic obese (BMI ≥30 mg/kg^2) out-clinic patients (25 males, 42 females), aged from 36.5 to 64 years were divided into 2 groups: Group A (n=15) – patients with early stages of CKD (eGFR between 30 and 60 ml/min/1.73 m^2 or with MA >20 mg/l in morning urine sample independently from GFR) and Group B – patients without chronic CKD (n=52).

Results: In Group A compared to Group B, BAI and leptin were higher (42.2±7.1 *vs.* 37.5±7.0; p<0.05 and 51.8±26.7 ng/mL *vs.* 35.3±24.9 ng/mL; p<0.05; respectively) and negative correlations occurred between eGFR and BAI (r=–0.709; p=0.003), leptin (r=–0.68; p=0.005), and resistin (r=–0.528; p<0.05). In Group B, negative correlations occurred between creatinine and VAI (r=–0.332; p<0.05), BAI (r=–0.619; p<0.0001), leptin (r=–0.676; p<0.0001), and adiponectin (r=–0.423; p=0.002), and between eGFR and resistin (r=–0.276; p<0.05).

Conclusions: BAI may be a valuable obesity parameter as a predictor of early stages of CKD in patients with obesity. Leptin may be an important pathogenic factor in obese patients with early stages of CKD. Resistin is associated with eGFR in obese patients, independently of CKD.

Key words: adipokines • chronic kidney disease • obesity

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Background

Obesity is a growing health problem. It has been postulated that it may also be a risk factor of development of chronic kidney disease (CKD), independently of hypertension, diabetes, and pre-existing renal disease [1,2]. Obesity often coexists with hypertension, which may lead to nephropathy. Nevertheless, data about the renal consequences of obesity and development of chronic renal disease are controversial. Some authors state that obesity is an important but potentially reversible risk factor for development of CKD, whereas others did not observe any association between obesity and worsening of renal function [1–10]. Obesity is weakly associated with early stages of kidney disease, but this relationship is much stronger in patients with end-stage kidney disease [4]. Moreover, obesity may influence progression to kidney failure in patients with early stages of kidney disease [4–6].

Typical hemodynamic renal consequences of non-diabetic obesity include hyperfiltration, increased effective renal plasma flow (ERPF), and glomerular filtration rate (GFR) [1,4,6,11]. It was suggested that the high GFR in very obese patients might result from an increase in transcapillary hydraulic pressure difference [1]. Other renal effects of obesity include increased glomerular capillary wall tension and podocyte stress, which together with hyperfiltration, lead to chronic glomerular overload and injury [4].

Obese subjects may have structural kidney changes such as increased kidney weight and glomerular planar surface, mesangial expansion, and podocyte injury [6]. Additionally, obesity leads to glomerulomegaly, segmental glomerulosclerosis, and obesity-related glomerulopathy [6,7,11]. Obesity may increase risk of graft loss in kidney transplant recipients and occurrence of renal cell carcinoma and nephrolithiasis [6]. On the other hand, obesity is associated with a survival advantage in patients with end-stage renal disease (ESRD) undergoing hemodialysis [6].

Insulin resistance, which often coexists with obesity (especially with central obesity) may play an important role in progression of CKD in obese patients [1,12]. Insulin resistance has been positively correlated with GFR and ERPF [1,12].

Obesity is proposed as a possible risk factor of MA, especially in patients with hypertension and diabetes [2]. Obesity may also be associated with progression of existing proteinuria in CKD patients [2,6]. Some authors suggest that obesity may also be harmful to the kidneys in subjects without history of hypertension, diabetes, or pre-existing renal disease [2]. In contrast, other investigators, taking age into consideration, did not observe any negative consequences of obesity for GFR compared to non-obese subjects [3].

It was suggested that in the pathogenesis of obesity-related glomerulopathy, one should also consider adipokines, especially leptin and adiponectin [4,7,8,11]. Increased leptin levels in obese subjects may contribute to proteinuria and glomerulosclerosis [8]. It was found that leptin, by stimulation of the synthesis of type 1 collagen in mesangial cells and also type 4 collagen in glomerular endothelial cells, contributes to their deposition in extracellular matrix and could consequently lead to glomerulosclerosis and proteinuria [8]. Some authors have observed an association between adiponectin and urine albumin excretion [4,8]. Adiponectin, via receptors on podocytes, may play a role in podocyte morphology and/or function [4]. In mice without adiponectin expression, there was observed effacement of podocyte foot processes and proteinuria [4]. It was recently shown that circulating resistin is strongly associated with GFR and inflammatory biomarkers in patients with CKD [13].

Classical obesity parameters or indices include body mass index (BMI), waist-to-hip ratio (WHR) and waist circumference (WC). Some authors have proposed these obesity indices as possible determinants of risk of CKD; however, there are controversies among them as to which of these parameters is a better predictor of CKD [4–6,14,15]. For example, a positive correlation was found between BMI and GFR and filtration fraction, as well as with MA in obese subjects [4,6]. Other authors, however, did not observe any significant relationships between BMI and GFR or incidents of CKD in obese patients [9,16,21]. However, results obtained from the Framingham Offspring Cohort and the Hypertension Detection and Follow-Up Program indicate an association between BMI and increased risk of new onset of CKD [5[. Moreover, some authors prefer WC, while others support WHR as a determinant of risk of CKD [9,16–18].

Recently, some newer obesity indices were proposed for better description of obesity, such as waist-to-height ratio (WHtR), visceral adiposity index (VAI), and body adiposity index (BAI); however, their clinical usefulness in determining CKD risk in obese subjects is unknown [14,17,19–21].

The aim of this study was to determine relationships between renal parameters such as serum creatinine concentration, eGFR (by GFR-MDRD [Modification of Diet in Renal Disease]), MA, and urinary albumin concentration (UAC), and both classical and newer obesity parameters and indices, as well as with serum levels of leptin, adiponectin, resistin, insulin, and insulin resistance by HOMA-IR in obese non-CKD and CKD patients.

Material and Methods

Sixty-seven adult, non-diabetic, obese (BMI ≥30 mg/kg^2), outclinic patients of both sexes (25 males, 42 females), aged from

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36.5 to 64 years, were enrolled in the study. Patients were consecutively recruited to the study between the 1 June and 15 December 2010.

Patients with psychiatric disorders, pregnancy, cancer, stroke, severe hepatic or renal diseases, and acute cardiovascular events or with history of abdominal surgery that could have an impact on abdominal fat distribution, were excluded from the study.

Subjects were divided into 2 basic groups: A – patients with early stages of CKD (30 ml/min/1.73 m^2 <eGFR <60 ml/min/1.73 m^2 or with microalbuminuria (MA) >20 mg/l in morning urine sample independently from GFR) (n=15); and B – patients without CKD (n=52).

After taking the medical history, all the subjects had their blood pressure and pulse measured 3 times after a 10 min rest with an OMRON M4 Plus automated device on the left upper arm and results were averaged. Serum glucose concentrations were measured by the glucose hexokinase enzymatic assay (Olympus Beckman Coulter, Switzerland) and serum levels of creatinine, serum urea nitrogen, and serum albumins concentrations to calculate eGFR according to the GFR-MDRD 6-variable equation formula:

$$170 \times SCr^{-0.999} \times\_age^{-0.176} \times\_SUN^{-0.170} \times\_SAlb^{+0.318} \times (0.762 \text{ female}) \times (1.180 \text{ black});$$

where: SCr-serum creatinine concentration (mg/dl), SUN-serum urea nitrogen (mg/dl), SAlb-serum albumin concentration g/dl [22].

Adiponectin, leptin, resistin, and insulin were estimated by using an ELISA method (DRG Instruments GmbH, Marburg, Germany) in fasting venous blood samples. Urinary albumin concentrations were estimated in morning urine samples obtained from the patients. Serum levels of triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) were also measured to calculate VAI. The homeostasis model assessment of insulin-resistance (HOMA-IR) index was used to estimate insulin resistance. HOMA-IR was calculated according to the following formula: fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5 [23]. HOMA-IR index higher than 2.5 was acknowledged as significant for insulin resistance.

All the study participants underwent measurements of their body mass (BM), height, and waist (measured at a level midway between the lowest rib and the iliac crest) and hip (widest diameter over the greater trochanters) circumferences to calculate obesity indices as follows:

1) body mass index:
BMI = weight/height^2 (kg/m^2);
2) waist-to-hip ratio:
WHR = waist circumference (cm)/hip circumference (cm);
3) waist-to-height ratio:
WHtR = waist (cm)/height (cm),
normally ranges from 0.46 to 0.62 [14];
4) visceral adiposity index VAI for:

$$\text{Males} = \left(\frac{WC}{39.68+(1.88\times BMI)}\right)\times\left(\frac{TGs}{1.03}\right)\times\left(\frac{1.31}{HDL\text{-}C}\right)$$

$$\text{Females} = \left(\frac{WC}{36.58+(1.89\times BMI)}\right)\times\left(\frac{TGs}{0.81}\right)\times\left(\frac{1.52}{HDL\text{-}C}\right)$$

normal value = 1 in healthy non-obese subjects with normal adipose distribution and normal TG and HDL-C levels [19];
5) body adiposity index, which is approximately equal to the percentage of body fat for adult men and women of differing ethnicities;

$$BAI = \frac{\text{Hip circumference}}{\text{Height (cm)}^{1.5}} - 18$$

where hip circumference is measured in cm [20].

The study protocol was approved by the local Bioethics Committee and informed consent was obtained from all the patients.

Statistical analysis

Results are expressed as mean ± standard deviation (SD) or proportions (%) in the brackets. For some data, median (Me) and interquartile range (IQR) – from lower (25%) quartile (LQ) to upper quartile (UQ) – were applied as appropriate for description of results. Standard Student t test for the comparison of data showing no departures from normality (according to the Shapiro-Wilk test), and the non-parametric Mann-Whitney U test for the remaining variables were used. Non-parametric analysis of variance (Kruskal-Wallis test) and the post hoc all-pairwise comparisons Conover-Inman tests were used for data that departed from normality. Chi-square tests were used for comparison of categorical variables and Fisher's exact test was applied when appropriate. Spearman's rank correlation (r) was used to assess simple associations. P values <0.05 were considered as statistically significant.

Results

The 2 compared groups did not significantly differ in age, sex, and concomitant diseases (Table 1). Patients with CKD more often received diuretics compared to non-CKD patients (80.0% *vs.* 48.1%, p<0.05) and there were no significant differences in other treatments between compared groups (Table 1).

In Group A, mean eGFR was lower compared to Group B (64.1±14.9 ml/min/1.73 m^2 *vs.* 74.2±10.4 ml/min/1.73 m^2; p<0.01), MA occurred more often (33.3% *vs.* 1.9%; p<0.01), and

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Table 1. Clinical characteristics of obese CKD and non-CKD patients.

Clinical data	Group A (CKD) N=15 n (%)	A (non-CKD) N=52 n (%)	Statistical significance p
Males	3 (20.0%)	22 (42.3%)	NS
Age (years)	60.0±11.6	54.9±11.6	p=0.07
Hypertension	14 (93.3%)	41 (78.8%)	NS
Ischemic heart disease	4 (26.7%)	17 (32.7%)	NS
Myocardial infarct	1 (6.7%)	7 (13.5%)	NS
Cardiac failure	8 (53.3%)	17 (32.7%)	NS
Stroke	1 (6.7%)	2 (3.8%)	NS
IFG /IGT	10 (66.7%)	29 (55.8%)	NS
Asthma/COPD	0	5 (9.6%)	NS
Hepatic failure	2 (13.3%)	10 (19.2%)	NS
Hyperuricemia/gout	5 (33.3%)	17 (32.7%)	NS
Hyperlipidemia	14 (93.3%)	48 (92.3%)	NS
Statins	10 (66.7%)	26 (50%)	NS
Fibrates	0	6 (11.5%)	NS
ASA	3 (20%)	13 (25%)	NS
ACEI	11 (73.3%)	35 (67.3%)	NS
ARB	3 (20.0%)	14 (26.9%)	NS
Diuretics	12 (80.0%)	25 (48.1%)	p<0.05
CCA	5 (33.3%)	14 (26.9%)	NS
BB	7 (46.7%)	17 (32.7%)	NS
Spironolactone	5 (33.3%)	14 (25.0%)	NS
ARA	2 (13.3%)	5 (9.6%)	NS

CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; IFG – impaired fasting glucose; IGT – impaired glucose tolerance; ASA – acetylsalicylic acid; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin II receptor antagonist; CCA – calcium channel antagonist; BB – β-adrenergic receptor blocker; ARA – α_1-adrenergic receptor antagonist; NS – not significant.

median UAC was higher than in group B [9.5(1.5–32.7) mg/L *vs.* 2.6(1.5–8.9) mg/L; p<0.05] (Table 2). In patients with CKD, we noted significantly higher mean BAI (42.2±7.1 *vs.* 37.5±7.0; p<0.05) and mean serum leptin concentration (51.8±26.7 ng/mL *vs.* 35.3±24.9 ng/mL; p<0.05) (Table 2). Adiponectin mean serum level was also higher in Group A than in Group B (22.5±14.9 ng/mL *vs.* 15.6±9.9 ng/mL; p=0.055), but was on the border of statistical significance (Table 2).

In Group A, we observed negative correlations between eGFR and BAI (r=–0.709; p=0.003), and serum concentrations of both leptin (r=–0.68; p=0.005) and resistin (r=–0.528; p<0.05) (Table 3). We also found a negative correlation between adiponectin serum levels and UAC (r=–0.504; p=0.056), but this was on the border of statistical significance (Table 3).

In Group B, a positive correlation occurred between serum creatinine concentrations and WHR (r=0.45; p= 0.001) (Table 4). We also observed positive correlations between eGFR and insulin serum levels (r=0.315; p<0.05), HOMA-IR (r=0.34; p<0.05), as well as with VAI (r=0.302; p<0.05) (Table 4). UAC positively correlated with BMI (r=0.322; p<0.05) (Table 4). Negative correlations occurred between serum creatinine levels and VAI (r=–0.332; p<0.05) and BAI (r=–0.619; p<0.0001), as well as with serum concentrations of leptin (r=–0.676; p<0.0001) and adiponectin (r=–0.423; p=0.002) (Table 4). We also observed

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Table 2. Results obtained in both groups of patients.

Parameters	Group A (n=15)	Group B (N=52)	Statistical significance p
Males	3 (20.0%)	22 (42.3%)	NS
Age (years)	60.0±11.6	54.9±11.6	NS
SBP mmHg	138.4±16.9	136.0±17.4	NS
DBP mmHg	82.7±10.3	86.4±8.6	NS
HR min^{-1}	74.3±11.1	75.8±9.5	NS
Serum creatinine µmol/l	94.7±10.5	88.6±14.0	NS
Serum urea mmol/l	6.3±1.8	5.8±1.6	NS
eGFR ml/min/1.73 m^2	64.1±14.9	74.2±10.4	p<0.01
Albuminuria	5 (33.3%)	1 (1.9%)	p<0.01
UAC mg/l	9.5 (1.5–32.7)	2.6 (1.5–8.9)	p<0.05
Isosthenuria	2 (13.3%)	5 (9.6%)	NS
Serum glucose mmol/l	5.8±0.6	5.7±0.5	NS
Serum insulin µU/ml	13.2±8.4	15.0±8.3	NS
HOMA-IR	3.4±2.2	3.9±2.4	NS
BM kg	94.7±11.5	99.7±18.0	NS
WC cm	111.6±8.2	111.6±11.9	NS
WHR	0.93±0.07	0.95±0.08	NS
WHtR	0.70±0.05	0.67±0.07	NS
BMI kg/m^2	37.0±3.8	35.9±4.7	NS
BAI	42.2±7.1	37.5±7.0	p<0.05
VAI	2.0±1.6	2.1±0.9	NS
Serum adiponectin ng/mL	22.5±14.9	15.6±9.9	p=0.055
Serum leptin ng/mL	51.8±26.7	35.3±24.9	p<0.05
Serum resistin ng/mL	0.96±0.37	1.01±0.34	NS

SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; BM – body mass; UAC – urinary albumin concentration; NS – not significant.

a negative correlation between eGFR and resistin serum levels (r=–0.276; p<0.05) in this group (Table 4).

Discussion

The results of our study suggest that BAI is the only obesity index that is significantly different between compared groups. This result may suggest that greater accumulation of body fat may distinguish obese patients with CKD from those without CKD. Moreover, we found a negative correlation between BAI and eGFR in obese subjects with CKD, which confirms this suggestion. However, we did not observe any significant correlation between BAI and serum creatinine, which could be connected with lack of significant difference between serum creatinine in the compared groups. Is has been postulated that in CKD-patients GFR-MDRD is a more sensitive index of renal failure than serum creatinine [22,24]. Therefore, we did not find a significant correlation between BAI and serum creatinine in this group of patients. However, the highly significant correlation between BAI and serum creatinine in non-CKD patients might result from better sensitivity of serum creatinine than eGFR for estimation of renal sufficiency in this patient group, as has been suggested by other authors [24]. Some authors suggest that MDRD formula may be better method for estimation of renal function in elderly patients than in subjects younger than

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Table 3. Correlations between estimated parameters in group A.

Patients with CKD N=15	Serum creatinine µmol/l	eGFR ml/min/1.73 m²	UAC mg/l
SBP mmHg	0.239 NS	–0.044 NS	0.174 NS
DBP mmHg	0.503 P=0.067	–0.126 NS	–0.013 NS
Serum insulin µU/mL	0.377 NS	0.129 NS	0.393 NS
HOMA-IR	0.420 NS	–0.124 NS	0.279 NS
BMI kg/m²	0.090 NS	–0.247 NS	0.129 NS
WC cm	–0.066 NS	0.185 NS	0.390 NS
WHR	–0.273 NS	0.662 p=0.007	0.286 NS
WHtR	0.113 NS	–0.237 NS	0.074 NS
VAI	0.153 NS	0.156 NS	0.379 NS
BAI	0.246 NS	–0.709 p=0.003	–0.389 NS
Serum leptin ng/mL	0.106 NS	–0.680 p=0.005	–0.307 NS
Serum adiponectin ng/mL	0.354 NS	–0.401 NS	–0.504 p=0.056
Serum resistin ng/mL	0.343 NS	–0.528 p<0.05	–0.018 NS

Data are expressed as r – Spearman's rank correlation with statistical significance p.

65 years [25,26]. We also could not exclude that differences in sex, age, and serum albumin concentration in both compared groups might have affected the obtained results.

The usefulness of BAI in estimation of body fat in non-dialyzed CKD patients was suggested by Silva et al. [21]. Nevertheless, we did not find any published data on the association between eGFR and BAI. In obese patients without CKD, BAI correlated negatively with serum creatinine concentrations but not with eGFR. Based on the results obtained in our study, it is difficult to explain this discrepancy. It is well known that eGFR based on GFR-MDRD, but not on the Cockcroft-Gault formula, is a more objective parameter to describe renal function in obese patients with CKD compared to those without CKD [6,22]. We also cannot exclude differences in muscle mass or the impact of age- and sex-dependent differences in calculating eGFR by the MDRD formula; however, differences in age, sex, and BMI did not reach statistical significance in our study. Gerchman et al. observed a positive correlation between BMI and creatinine clearance, independently of body fat distribution and gender in nondiabetic subjects [15]. In contrast, Noori et al., in a population-based cohort study, observed an association between abdominal obesity and risk of development of CKD and suggested that baseline WC was a better predictor of CKD than WHR and BMI [16].

We found an association between BMI and UAC, but only in non-CKD obese patients. Data about the relationship between BMI and MA are controversial. Some authors also observed a significant correlation between albumin urinary excretion rate and BMI in obese patients without renal complications [27]. In another study, based on non-diabetic and non-CKD patients with overweight or obesity, an association between BMI and MA was found [28]. Moreover, the results of logistic regression analysis indicated BMI as a predictor of MA in this population, independently from age and sex [28]. Ferris et al. also found an association between MA and BMI, but only in patients with BMI ≥35 kg/m² [29]. In contrast, Chang et al. did not find any significant relationship between BMI and MA in healthy, normotensive, euglycemic Korean men and suggested that only

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Table 4. Correlations between estimated parameters in group B.

Patients without CKD N=52	Serum creatinine µmol/l	eGFR ml/min/1.73 m²	UAC mg/l
SBP mmHg	–0.112 NS	–0.092 NS	–0.044 NS
DBP mmHg	0.024 NS	–0.016 NS	–0.068 NS
Serum insulin µU/mL	–0.208 NS	0.315 p<0.05	0.029 NS
HOMA-IR	–0.197 NS	0.340 p<0.05	0.016 NS
BMI kg/m2	–0.171 NS	0.190 NS	0.322 p<0.05
WC cm	0.117 NS	0.248 p=0.076	0.237 NS
WHR	0.450 p=0.001	0.200 NS	–0.001 NS
WHtR	–0.183 NS	0.111 NS	0.249 NS
VAI	–0.332 p<0.05	0.302 p<0.05	0.071 NS
BAI	–0.619 P<0.0001	0.102 NS	0.177 NS
Serum leptin ng/mL	–0.676 P<0.0001	0.093 NS	–0.090 NS
Serum adiponectin ng/mL	–0.423 p=0.002	–0.139 NS	–0.007 NS
Serum resistin ng/mL	0.205 NS	–0.276 p<0.05	0.037 NS

Data are expressed as r – Spearman's rank correlation with statistical significance p.

WC and systolic blood pressure (SBP) were independent predictors of MA [30]. These observations were supported by results from the multinational, multicenter large population study conducted by Thoenes et al. on over 20 000 hypertensive outpatients from 26 countries [31]. The authors, based on the results of multivariate analysis, indicated that WC, but not BMI, was independently associated with MA [31].

Data about the relationship between obesity anthropometric parameters or indices and renal function estimated by serum creatinine or eGFR are controversial. Noori et al., based on results obtained from a cohort study on non-CKD adult subjects, observed a stronger association between GFR and WC than with WHR and BMI [16]. Gerchman et al. suggest that BMI is a better independent determinant of creatinine clearance in nondiabetic subjects than body fat distribution [15]. However, Løkkegaard et al. did not find any correlation between BMI and GFR in obese patients [27]. Elsayed et al., in both creatinine- and GFR-based models, found that WHR, but not BMI, is associated with increased risk of incidents of CKD and mortality [17]. Burton et al., based on eGFR calculation, suggest that CKD risk is independently associated with higher WC and BMI, but not WHR, in non-diabetic patients [18]. The results of our study indicate that central obesity parameters such as WHR and VAI compared to BMI may be related to kidney function described by serum creatinine or eGFR. However, the relationships both central obesity parameters with serum creatinine are opposite. We suggest that this discrepancy might result from a more compound VAI formula, which includes serum TG and HDL-C concentrations; differences in this parameters as well as in hypolipemic treatment, especially with fibrates, might have impact on obtained results. The results obtained from our and other studies indicate the complex relationship between obesity and renal function as well as the risk of CKD [1–10,32,33]. The data obtained from different studies are still controversial and need further verification.

Higher mean serum leptin concentration observed in obese CKD patients and the negative correlation between serum leptin concentrations and eGFR indicate that this adipokine may be

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involved in the pathogenesis of CKD in these patients, as was previously suggested by other authors [8,34]. We also found an association between serum leptin and serum creatinine in the non-CKD group. We suggest that lack of significant correlation between serum leptin concentration in CKD patients might result from the small size of this group. As mentioned above for CKD patients, eGFR, especially calculated according GFR-MDRD formula, is a better parameter to estimate renal function than serum creatinine concentration [24]. Shankar et al. reported that higher plasma leptin concentrations were associated with CKD after adjusting for other factors such as age, sex, race/ethnicity, BMI, diabetes, hypertension, and serum cholesterol [34]. It should be taken into consideration that leptin is eliminated mainly via the kidneys [35]. Therefore elevated serum leptin levels may result from impaired renal clearance as well as from increased synthesis of this hormone [35]. It has also been suggested that in obese patients leptin may play a role in pathogenesis of obesity-related glomerulopathy [35]. Results from animal studies indicate that leptin induces proliferation of glomerular endothelial cells, enhances glomerular TGF-β1 expression and increases collagen type I, and IV mRNA synthesis [8,35,36]. These actions of leptin may lead to focal glomerulosclerosis, glomerular and mesangial glucose uptake, and proteinuria [7,8,35]. Leptin may also be indirectly involved in kidney injury via central sympathetic activation, which results in elevation of blood pressure and in tachycardia [32,35]. Some authors have suggested that both excessive hyperleptinemia and deficiency of adiponectin in obese patients may directly stimulate the renin-angiotensin-aldosterone system, which may contribute to proteinuria and CKD [32].

Results of other clinical studies indicate that serum adiponectin levels fall with obesity [8,32,37]. Nevertheless, we observed higher adiponectin serum levels in obese CKD patients than in obese non-CKD subjects, and its negative correlation with urinary albumin concentration, although both were on the border of statistical significance. Adiponectin also negatively correlated with serum creatinine, but only in the non-CKD patient group. We suggest that this may indicate a possible role of this adipokine in pathogenesis of obesity-related CKD. We suppose that lack of significant correlation between serum adiponectin and creatinine concentrations in CKD patients might result from the small size of this group. Increased adipokine blood levels in patients with renal dysfunction have also been reported by other authors [32]. In lean children with chronic renal failure, increased serum adiponectin was associated with decreased creatinine clearance [38]. However, the results of other clinical studies indicate hypoadiponectinemia as a link with MA in hypertensive patients [8]. In our study, we also observed a negative correlation between serum adiponectin and UAC in obese CKD patients, but this was on the border of statistical significance. Nevertheless, this observation may confirm the results of a previous study conducted by Yano et al., who found an inverse association between serum adiponectin and low-grade albuminuria in obese nondiabetic patients [39].

We observed a negative correlation between serum resistin and eGFR, both in CKD and non-CKD patients. Axelsson et al. reported markedly elevated plasma resistin levels in patients with renal function impairment [13]. The authors also demonstrated that circulating resistin levels are strongly associated with both GFR and inflammatory markers in patients with CKD [13]. In our study, serum resistin concentration was a little lower in CKD patients, but this difference was not statistical significant. We suggest that it might result from the small size of this patient group and the early stage of kidney injury. The kidneys are probably the main pathway of resistin elimination [13]. In contrast to leptin and adiponectin, resistin appears not to be related to visceral and total fat mass in CKD patients [13]. Increased serum resistin in both obese and CKD patients and the association between this adipokine and declined renal function and inflammatory biomarkers were reported by other authors [32,36].

We observed a relationship between serum insulin, HOMA-IR, and eGFR in non-CKD obese patients. It was well documented that insulin resistance is associated with obesity, especially with visceral obesity [12,33,40–43]. It was suggested that hyperinsulinemia and insulin resistance could induce glomerular hypertrophy, directly or indirectly, by stimulation of the insulin-like growth factor-1 receptor [33]. Insulin resistance is also associated with MA [12]; therefore, some authors have suggested that insulin resistance might be a link between obesity and CKD [12,33]. Nevertheless, other investigators did not observe any associations between insulin resistance and GFR in CKD patients [43–45]. These results are also in agreement with our observations in the CKD group.

Our study has several limitations. The most important limitation was the small sizes of the compared groups, especially for the CKD patient group. Some results did reach the border of statistical significance and we cannot exclude that in larger groups they would become significant. Because of the small size of the subject population, we also could not divide both groups according to sex and age. The results of our previous studies and those from other authors indicate that serum leptin and adiponectin, as well as some obesity indices such as WC, WHR, and BAI, are sex-dependent in obese patients [35,39,40]. We could not estimate differences in muscle mass, which might have an impact on serum creatinine and eGFR. Sex and age are important demographic parameters for estimation of eGFR, especially for MDRD formula. We cannot exclude the impact of age differences between the groups on estimated renal parameters, although this difference was only on the border of statistical significance. Nevertheless, in larger groups of subjects this difference could become significant. The limitations of our pilot study lead us to carefully formulated conclusions. Further

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detailed studies based on larger groups of patients should be conducted to conclusively address these topics.

Conclusions

BAI may be a valuable obesity parameter as a predictor of early stages of CKD in patients with obesity. Leptin may be an important pathogenic factor in obese patients with early stages of CKD. Resistin is associated with eGFR in obese patients, independently of CKD.

Statement

The authors declare no conflicts of interest with respect to this study.

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