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Visceral Adipose Tissue is Associated with Insulin Resistance in Hemodialyzed Patients

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: It has not been definitively established which factors affect insulin resistance (IR) and whether dialysis decreases IR. The aim of this study was to investigate factors that may have an influence on homeostasis model assessment (HOMA-IR) in hemodialyzed patients (HDpts) and to compare IR between HDpts and healthy subjects.

Material/Methods: We examined 33 HDpts and paired 33 subjects of the control group, matched for sex, age, and BMI. We analyzed concentrations of insulin, glucose, leptin, resistin, and total and high-molecular-weight adiponectin (HMWad) in serum. Using computed tomography in HDpts, we evaluated visceral adipose tissue (VAT), concentrations of visfatin, CRP, and IL-6.

Results: HOMA-IR (median, 1.3 *vs.* 1.4, P=0.19), insulin (median 6.8 *vs.* 6.0 µIU/mL, P=0.7), glucose (79 mg/dL *vs.* 93 mg/dL, P=0.001). IR in HDpts is dependent on VAT (r=0.36, P=0.04) and this relationship is stronger than the relationship of BMI and IR (r=0.3, P=0.1). In HDpts we found higher concentrations of leptin (P=0.001) and resistin (P<0.001), with no relation to IR. HMWad and its percentage in relation to total adiponectin are higher in HDpts (P=0.03 and P<0.001, respectively).

Conclusions: HOMA-IR in HDpts does not differ from the control group. In HDpts it depends on the quantity of VAT and this relationship is stronger than with BMI. In HDpts leptin and resistin do not influence IR. HMWad and its percentage in total adiponectin are significantly higher in HDpts.

MeSH Keywords: **Adiponectin • Hemodialysis Solutions • Insulin Resistance • Intra-Abdominal Fat • Leptin**

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Background

In end-stage renal disease (ESRD) mortality is several times higher than in the general population. Cardiovascular diseases cause over half of all deaths. Insulin resistance (IR) is listed among the non-traditional risk factors involved in cardiovascular diseases [1,2]. In our previous work concerning this subject, we showed that HOMA β-cell function is strongly correlated with HOMA-IR in HDpts. We also showed that in non-diabetic ESRD HDpts, HOMA indices and Disposition Index may be important models in interpretation of glucose metabolism disorders. This work concerned the same patients. We present the remaining results of the work [3].

The etiology of IR accompanying renal failure is multifactorial. It is derived from disturbances associated with uremic environment. A major role is attributed to the function of adipose tissue, especially visceral [2,4]. Elevated concentrations of adipocytokines, related primarily to the lack of their elimination, contribute to the development of malnutrition, cachexia, atherosclerosis, and severity of inflammation, and also play a role in the pathogenesis of IR [5]. In the population of patients with stages 3–5 chronic kidney disease (CKD) it was demonstrated that leptin was a strong predictor of IR assessed by HOMA-IR [6]. Uremic environment and associated risk factors of cardiovascular diseases have an advantage over a protective activity of elevated concentrations of adiponectin [7]. Axelsson et al. showed that resistin concentration in patients with CKD positively correlates with inflammatory markers and is not associated with insulin resistance after adjustment for GFR [8]. Many studies of patients with CKD before the era of renal replacement therapy confirm the existence of elevated IR [9]. The data considering dialyzed patients are inconclusive. Kobayashi et al. showed that the initiation of hemodialysis (HD) and peritoneal dialysis had an effect of reducing IR [10].

The aim of this study was to measure the impact of the factors that may influence homeostasis model assessment (HOMA-IR) in hemodialyzed patients (HDpts) and to compare IR between HDpts and subjects without renal failure, matched for sex, age, and BMI. We also compared the concentrations of adipocytokines in both groups to assess the factors that may have a potential impact on the value of HOMA-IR, with a particular focus on the concentration of adipocytokines, selected inflammation markers, and quantity of visceral adipose tissue (VAT) as measured by computed tomography (CT).

Material and Methods

The study included 33 patients with ESRD treated with repeated hemodialysis (HD) in the Department of Nephrology, Dialysis, and Internal Diseases, Medical University of Warsaw and affiliations. The cause of ESRD in 15 patients was chronic glomerulonephritis, in 6 polycystic kidney disease, in 3 hypertensive nephrosclerosis, and in 2 chronic pyelonephritis. The cause of ESRD in remaining 7 patients was not determined. The control group consisted of 33 subjects without renal failure, matched for sex, age and BMI. The study was approved by Bioethics Committee of the Medical University of Warsaw on June 20th 2006. Criteria for exclusion from the study were: diabetes, active inflammatory and autoimmune disease, cancer, history of cardiovascular events in the past 3 months, hormonal therapy, alcoholism. Blood samples were collected in fasting state, after at least an 8-hour period without food, in hemodialyzed patients (HDpts) in the morning on a day without dialysis, in the middle of the week. In HDpts, we evaluated the concentrations of glucose, insulin, adipocytokines (leptin, resistin, total and high-molecular-weight adiponectin (HMWad), visfatin, CRP, IL-6 in serum. In the control group, the concentrations of glucose, insulin and adipocytokines (leptin, resistin, adiponectin- total and HMWad) in serum were assessed. In HDpts CT assessing VAT of abdominal cavity was performed.

Glucose concentration was measured using a hexokinase method (Glucose HK Gen.3). Insulin concentration was measured using Immunotech IRMA kit.

HOMA-IR was calculated using the formula:
HOMA-IR = [insulin in serum (μIU/ml) × glucose in serum (mg/dl)]/405

Visfatin was measured with Phoenix Pharmaceuticals Inc. competitive immunoenzymatic test. Total adiponectin and HMWad was measured with ALPCO Diagnostics sandwich immunoenzymatic test (EIA) intended for the quantitative evaluation of adiponectin isoforms. IL-6 was measured with R & D Systems sandwich immunoenzymatic test.

CT was performed using a General Electric 16-slice Light Speed Pro system. Parameters of the X-ray flux were 140 kV and 200 mA and the time of exposure to X-rays was 0.5 sec. The study was performed in the axial plane, assessing the layer thickness of 10 mm. Scanning position was located at the height of the navel. The resulting images were evaluated in the range of 400 Hounsfield units (HU). VAT was assessed by manual analysis, outlining the area with density corresponding to adipose tissue (range from –190 to –30 HU). The evaluation concerned intraperitoneal adipose tissue, retroperitoneal adipose tissue was not assessed. In the evaluation of abdominal adipose tissue the values from the outlined areas were added to each other.

Average values for paired data (HD group *vs.* control group) were compared using the non-parametric Wilcoxon test. The statistical significance of the relationships of tested parameters in HD patients with selected variables was examined using

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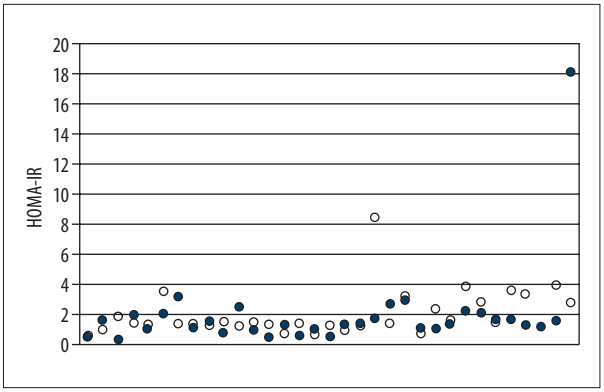

Figure 1. HOMA-IR in individual HD-CG pairs arranged according to increasing BMI in HD group (● HD, ○ CG).

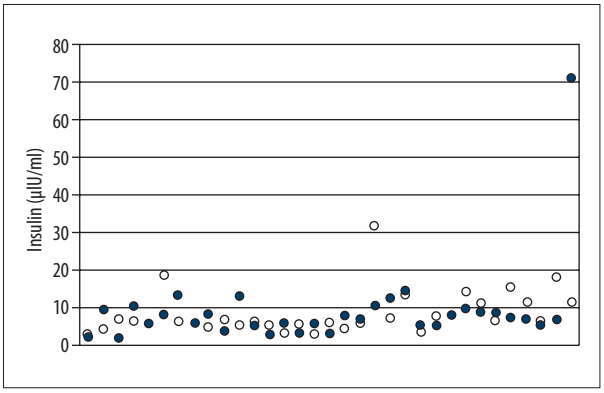

Figure 2. Insulin concentrations in individual HD-CG pairs arranged according to increasing BMI in HD group (● HD, ○ CG).

Spearman's rank correlation coefficient. To analyze the linear trend of parameters tested by tertiles of selected categorized independent variables we used analysis of variance test for linear trend. If the assumption of normal distribution was not met, a logarithmic transformation of the tested parameter was performed. Significance level was α=0.05.

Results

The study consisted of 33 pairs of patients: 33 patients with ESRD treated with repeated HD and 33 subjects without kidney failure, matched for sex, age, and BMI, constituting the control group (CG). Each group consisted of 24 men (72.7%) and 9 women (27.3%). The average age of HDpts was 61±14 years and 61±11 years in the control group. Average BMI in the HD group was 27.1±5.2 kg/m^2, in the control group 27.0±6.2 kg/m^2.

In both groups we evaluated and compared HOMA-IR, concentrations of glucose, insulin, and adipocytokines: leptin, resistin, total adiponectin, HMWad. The percentage of this adiponectin was assessed in relationship with total adiponectin (%HMWad) in serum.

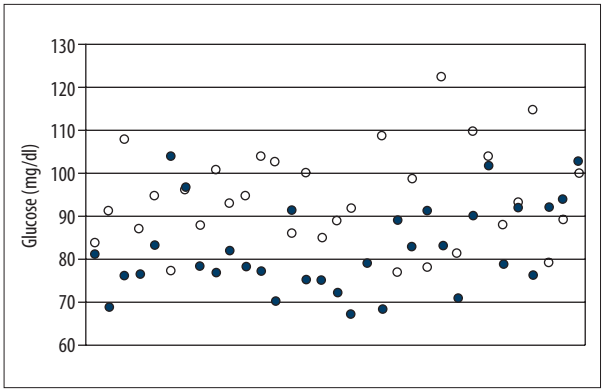

Figure 3. Glucose concentrations in individual HD-CG pairs arranged according to increasing BMI in HD group (● HD, ○ CG).

Our study showed that there is no statistically significant difference in HOMA-IR between the groups (median of HOMA-IR in the HD group was 1.3 and in the control group 1.4, *P*=0.189, Figure 1). Insulin concentrations in both groups did not differ significantly as well (median of insulin concentration in the HD group was 6,8 µIU/mL, in the control group 6.0 µIU/mL *P*=0.698, Figure 2). Glucose concentrations were significantly lower in HDpts than in the control group (median of glucose concentration in the HD group was 79 mg/dL, in the control group 93 mg/dL, *P*=0.001, Figure 3).

Comparison of the individual adipocytokine concentrations in both groups showed significantly higher leptin and resistin concentrations (median of leptin concentration in the HD group was 12.78 mg/L, in the control group 5.96 mg/L, *P*=0.001 and median of resistin concentration in the HD group was 15.90 mg/L, in the control group 5.06 mg/L, *P*<0.001). There were no statistically significant differences between the groups in terms of total adiponectin concentrations (median of adiponectin concentration in the HD group was 1.64 mg/L, in the control group 1.20 mg/L, *P*=0.264). Concentrations of HMWad and its percentage in total adiponectin (% HMWad) differed significantly between the groups (median of HMWad concentration in the HD group was 0.97 mg/L, in the control group 0.60 mg/L, *P*=0.032 and median of%HMWad concentration in the HD group was 56.78, in the control group 42.48, *P*<0.001). Data on the parameters in HDpts compared with the control group are presented in Table 1.

Analysis of relationship between IR and the individual parameters in HDpts demonstrated that IR assessed by HOMA-IR showed no association with BMI (*r*=0.296, *P*=0.094). Statistical significance was observed in the analysis of BMI linear trend (P=0.034). It was shown that there was a statistically significant correlation between the quantity of VAT measured by CT (CTvisc) and HOMA-IR (*r*=0.363, *P*=0.038), also in the analysis of CTvisc linear trend (P = 0.016). HOMA-IR medians in tertile groups of visceral tissue quantity are presented in Figure 4.

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Table 1. Parameters studied in HD pts and control group.

	HD group			Control group			p-value*
	Mean ±SD	Median	Range	Mean ±SD	Median	Range	
HOMA-IR	1.95±2.98	1.32	0.31–18.09	1.99±1.54	1.40	0.57–8.49	0.189
Insulin, µIU/mL	9.04±11.60	6.84	1.64–71.13	8.37±5.91	5.97	2.73–31.56	0.698
Glucose, mg/dL	82.42±10.35	79.00	67–104	93.88±11.56	93.00	77–123	0.001
Leptin, mg/L	21.29±16.86	12.78	0.59–52.68	10.75±11.79	5.96	0.21–48.38	0.001
Resistin, mg/L	18.33±7.32	15.90	8.65–39.24	5.48±2.20	5.06	2.75–14.73	<0.001
Adiponectin, mg/L	1.65±0.85	1.64	0.22–3.50	1.61±1.20	1.20	0.35–5.91	0.264
HMW, mg/L	0.94±0.56	0.97	0.00–2.42	0.72±0.65	0.60	0.02–2.94	0.032
%HMW, %	53.48±16.63	56.78	0.00–81.79	41.09±16.29	42.48	5.71–83.44	<0.001
LAR	22.03±34.28	8.19	0.25–179.68	10.51±12.24	4.80	0.21–45.02	0.058

* Wilcoxon test. HOMA-IR – homeostasis model assessment; HMW – high molecular weight adiponectin; %HMW – percentage of high molecular weight to total adiponectin; LAR – leptin: adiponectin ratio. Conversion factors to SI units are as follows: for insulin – 6.94, glucose – 0.0555.

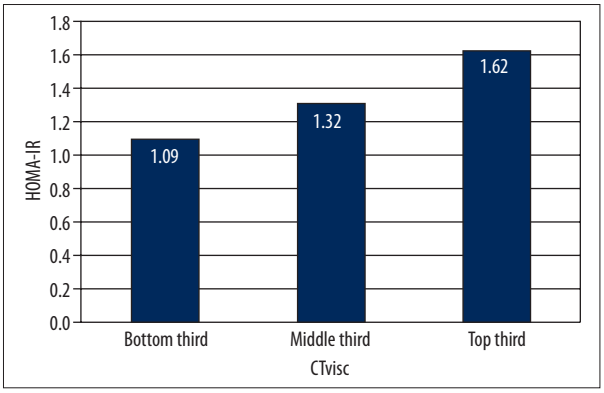

Figure 4. HOMA-IR medians in tertile groups of visceral tissue quantity (CTvisc).

Evaluation of the relationship between the adipocytokine concentrations and VAT quantity showed a significant correlation of VAT quantity with leptin (r=0.553, *P*=0.001) and resistin concentrations (r=0.386, *P*=0.027). The direction of the correlation of adiponectin with the VAT quantity was negative but not statistically significant (r=–0.294, *P*=0.097) and similar to the concentration of HMW (r=–0.100, *P*=0.579). There was no relationship of HMW percentage (r=0.136, *P*=0.449) and visfatin concentrations (r=0.009, *P*=0.960) with VAT quantity. Analysis of the relationship of adipocytokine concentration with inflammatory state showed the presence of significant correlation between visfatin (41.02±27.36 mg/L) and CRP(12.95±18.30 mg/L) concentrations (r=0.421, *P*=0.015). There was no significant correlation between IL-6 concentration (9.68±9.58 pg/mL) and tested cytokines.

We analyzed the relationship between IR and the hormones secreted by VAT. It was found that the relationship between HOMA-IR and leptin concentration was statistically significant (*r*=0.470, *P*=0.006). The relationship between IR measured by HOMA-IR and inflammatory state expressed by CRP concentration was of borderline of statistical significance (*r*=0.336, *P*=0.056). The relationship between HOMA-IR and IL-6 showed no statistical significance (r=0.294, P=0.102).

Discussion

Not all studies confirm that IR markers increased in CKD escalate with a decrease in GFR. Our previous work, based on the partial results of the same clinical work, showed no difference in insulin resistance measured by HOMA-IR in non-diabetic HDpts and healthy subjects. It demonstrated the usefulness of HOMA-IR and Disposition Index in the interpretation of carbohydrate disorders in HDpts [3]. The current work examines the factors influencing insulin resistance in this group of patients. Decreased sensitivity to insulin exists already in the early stages of CKD, when a significant renal failure is not found. Conclusions from the studies conducted in patients with various stages of CKD suggest that IR markers in the more advanced stages of CKD do not always differ significantly from those in the early stages [11,12]. In HDpts we found no statistically significant difference in IR compared with subjects without renal failure (Figure 1), these partial results were also presented in the previous work [3]. There was no statistically significant difference in the level of insulinemia between the two examined groups as well (Figure 2). It should be noted

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that glycemia (the second parameter taken into account in the calculation of HOMA-IR) differed significantly, with the values higher in patients without renal failure (Figure 3). However, the significance of this parameter did not influence the differences in HOMA-IR between the groups.

Interpretation of the causes of significantly lower glycemia in HDpts is difficult. Mak et al. in his work on insulin concentrations in CKD note that patients with ESRD are characterized by a rather mild hyperglycemia in fasting state and impaired glucose tolerance in stress testing, although some researchers represent different views [13]. In the work on hypoglycemia in patients with renal failure Arem et al. stress that hypoglycemia in patients with ESRD is quite frequent which is caused by cachexia, impaired renal gluconeogenesis, deficiency of glucogenic amino acids - precursors for gluconeogenesis and production of counterregulatory hormones [14].

Our results do not support the hypothesis that in hemodialyzed patients with ESRD IR is higher than in the general population. The results obtained indicate that replacement therapy, by reducing the disturbances associated with advanced renal failure, can reduce IR, which is consistent with the work by Kabayashi et al. [10]. Beneficial effects of renal replacement therapy in order to reduce IR are confirmed by the work of Minguez et al, who found that HOMA-IR in HDpts showed a negative correlation with Kt/V marker demonstrating the adequacy of dialysis [15]. Trirogoff et al. assessed IR using HOMA-IR in patients with stages 3 and 4 of CKD, finding no significant differences compared with the control group [16].

Many studies confirmed higher levels of adipocytokine concentrations in renal failure, especially for ESRD, resulting from impaired renal elimination [17,18]. In our study we found no significant differences in adiponectin concentrations between the groups. Data from the literature indicate higher concentrations of this adipokine in patients with renal failure [7,19]. In the present study the results comparing the concentration of HMWad and its percentage (% HMWad) in total adiponectin between the two groups showed no significant differences in total adiponectin concentrations while the concentrations of HMWad and its percentage in total adiponectin were significantly higher in dialyzed patients (Table 1). Shen et al. also showed a higher concentration of HMWad in renal failure and interpreted this as a compensatory mechanism designed to reduce the metabolic disturbances associated with uremia [20].

Odamaki et al. evaluated the quantity of VAT by CT in HDpts and in subjects without renal failure, showing that after adjustment for BMI visceral adipose tissue in HDpts was relatively higher [21].

In our study we found no relationship between insulin resistance and BMI in the group of patients treated with renal replacement therapy and statistical significance was shown only in the analysis of BMI linear trend. CT showed a significant correlation between VAT quantity and IR (Figure 4). This observation suggests that the assessment of VAT is important in HDpts, in whom BMI particularly does not reflect body composition. In HDpts without diabetes Shinohara et al. showed a positive correlation between HOMA-IR and cardiovascular mortality, regardless of BMI. They also suggested that one of the causes of IR in patients with ESRD may be higher adipocytokine concentrations, which could cause “IR without obesity” [2,4,22].

Heimbürger et al. proved that leptin concentration showed a strong positive correlation with the quantity of adipose tissue [23]. In the present work, the concentration of leptin in dialyzed patients also showed a positive correlation with the quantity of VAT assessed by CT at twice the average concentration of this adipokine in serum compared with the control group (Table 1). We also found a positive correlation between the quantity of visceral tissue evaluated by CT and resistin concentration. In our study visfatin concentration does not correlate with the quantity of VAT. Results of the studies on visfatin suggest that it is ubiquitous substance, rather than only associated with the adipose tissue [24]. The correlation of total adiponectin and its HMWad form with the quantity of VAT was not statistically significant, but it had a negative direction, indicating an inverse relationship between these parameters. Tamei et al. observed a strong negative correlation between the quantity of VAT assessed by CT, and the concentration of HMWad in HDpts [25].

Assessing the influence of adipocytokines on IR in the present study we found a statistically significant positive correlation between HOMA-IR and leptin in HDpts. Based on our research it should be concluded that the effect of leptin on IR may be a reflection of the impact of VAT synthesizing leptin. Leptin concentration is a reflection of the visceral tissue quantity and is not associated with IR, if one takes into account that the IR does not differ significantly between the groups of paired patients, while leptin concentrations in HDpts are twice as high. High levels of leptin concentration in ESRD lose their influence on IR. Leptin is “biologically inactive” towards IR, although its correlation with HOMA-IR in HDpts is significant. The observed significance may be due to a strong relationship of leptin concentration with the quantity of VAT, therefore VAT may be significant for the existence of IR. Lack of biological effects of high levels of leptin concentrations on IR in ESRD can be explained referring to the exponential nature of the relationship presented in the work by Stenvinkel et al. [6]. Previous studies indicate an inverse correlation of adiponectin concentration with IR in HDpts [13,18]. Other authors, however, do not confirm these reports. Taskapan et al. believe that there is no relationship of the concentrations of leptin, resistin and adiponectin with HOMA-IR, neither in HDpts nor in patients on peritoneal dialysis and that the concentrations

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of leptin were determinants of lipid disorders, particularly in patients on peritoneal dialysis [17]. Similarly, in the present study we also found no relationship between IR and adiponectin concentration, which applies not only to total adiponectin concentration, but also to the concentration of HMWad and its percentage in total adiponectin.

The behavior of resistin concentration did not confirm the presence of correlation with HOMA-IR. Many results of the studies on the influence of resistin on IR do not confirm that this adipocytokine intensifies it, as it was originally thought [8].

It is believed that chronic inflammation may result in the stimulation of IR by the induction of proinflammatory cytokines. Kursat et al. emphasize a positive correlation between IR and inflammatory state expressed by the value of CRP concentration that occurs in HDpts [26]. A similar conclusion was reached by Borazan et al. proving that CRP concentration was significantly higher in HDpts who have higher HOMA-IR [27]. In this study, the correlation between insulin expressed by HOMA-IR and inflammatory state expressed by CRP concentration is of borderline statistical significance, while there is no relationship between IR and IL-6 concentration.

Conclusions

1. IR measured using HOMA-IR in patients treated with repeated HD does not differ from IR measured by the same method in subjects without renal failure, matched for sex, age and BMI.
2. IR in HDpts is dependent on the quantity of VAT, and this relationship is more important than the influence of BMI on IR.
3. Elevated levels of leptin and resistin concentrations in blood serum of HDpts have no effect on IR.
4. The concentrations of HMWad and its percentage in total adiponectin in serum are significantly higher in HDpts, suggesting that this isoform is a compensating factor which limits its metabolic disturbances accompanying uremia.

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