INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Metabolic Syndrome in HD Patients: Association with Body Composition, Nutritional Status, Inflammation and Serum Iron

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Abstract

Objective Insulin resistance and metabolic syndrome (MeS) are common in end-stage renal disease (ESRD) patients on maintenance hemodialysis (HD). Such metabolic and clinical abnormalities may lead to an increased risk for cardiovascular disease.

Methods The study group included 22 well-nourished and 20 middle- to moderate-malnourished, stable ESRD patients, with median dialysis duration of 48 months (IQR 24.5-82.0). To determine nutritional status, body composition, inflammatory biomarkers and the presence of MeS subjective global assessment (SGA), anthropometrical measurements (BMI and waist circumference), bioelectrical impedance analysis (BIA), and biochemical parameters [the levels of serum albumin, cholesterol, HDL-cholesterol, triglyceride, hematocrit, hemoglobin, iron, TIBC, transferrin saturation (TSAT), ferritin, calcium, phosphorus, intact parathormone (i-PTH), TNF-alpha, IL-6 and high sensitivity C-reactive protein (hs-CRP)] were used. All parameters were evaluated by comparisons between two groups, with MeS (Group 2) and without it (Group 1). Logistical regression analysis was used to evaluate the correlation between measured variables and the presence of MeS in HD patients. Independent variables for MeS were identified by backward multivariate regression analysis. To identify the independent predictors for insulin resistance index (HOMA-IR) multivariate regression analysis was conducted, after linear regression analysis.

Results After adjustment for confounding variables, a model consisting of serum levels of iron, transferrin saturation (TSAT), and BMI which accounted for 62% of the variance in MeS, determined only BMI as an independent marker (according to ATP-III criteria). But, serum glucose level, iron, waist and total fat mass accounted for 68% of the variance in MeS, according to IDF critera. Glucose level was an independent predictor. BMI and iron, as independent variables, contributed to 29% of the variance in IR HOMA, the sensitive marker of MeS.

Conclusion The present study demonstrated that serum iron participated together with independent predictors, glucose and BMI, in the pathogenesis of IR and MeS of ESRD patients on maintenance HD.

Key words: end-stage renal disease, metabolic syndrome, SGA score, adipocitokynes TNF-alpha, IL-6, iron

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Introduction

Metabolic syndrome (MeS) (i.e. insulin resistance syndrome) is defined as the clustering of several cardiovascular risk factors in an individual, including impaired glucose tolerance/diabetes, hypertension, dyslipidemia, with an elevated level of triglycerides and a lower level of high density lipoprotein-cholesterol (HDL-cholesterol), visceral obesity and the presence of pro-inflammatory and pro-thrombotic

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state (1-5).

Adipose tissue is now recognized as an immune organ that secretes numerous immunomodulatory factors (6), and seems to be a significant source of inflammatory signals that cause disturbance of the insulin-signaling pathway at relevant sites, such as liver, muscle, and adipose tissue (7, 8). Furthermore, a substantial number of patients with ESRD on dialysis present with the state of chronic low-grade inflammation. The potential causes of inflammation may be related to the loss of kidney function, reduced clearance of inflammatory cytokines, uremia per se or its consequences (increased oxidative or carbonyl stress, accumulation of advanced glycation end products, secondary hyperparathyroidism, vitamin D deficiency and fluid overload) (9-11). Extracorporeal circulation of blood during hemodialysis (HD) may act as a stimulus for an inflammatory response, as well the usage of plasticizers-PTFE grafts and tunneled cuffed catheters or non-biocompatible dialyzer membranes (12).

Absolute or functional iron deficiency in ESRD results from the presence of uremia and chronic inflammation (13). Furthermore, iron requirements are increased in patients treated with recombinant human erythropoietin, due to enhanced erythropoiesis, that often necessitates therapy with intravenous iron. It was shown that the degree of anemia associated with deteriorated tissue oxygenation, could predispose such patients for the development of IR and consequently hyperinsulinemia (14). On the other hand, iron overload, which can be registered in HD patients, synergistically acts with other factors committed to protein catabolism (15). Patruta et al demonstrated impaired neutrophil function among patients treated with parenteral iron even in the absence of overt iron overload (16). Recent randomized studies suggested that higher iron stores influence the insulin action in type 2 diabetes mellitus (T2DM) and even in healthy subjects (17, 18).

Thus, it is possible that the presence of obesity, chronic inflammation, anemia and inadequate iron stores can implicate the pathogenesis of IR state and MeS in maintenance HD patients. Thus, we hypothesized that iron overload not only participates in inflammation and/or malnutrition but also in insulin action in the long-term HD patients.

Subjects

The study group included 22 well nourished and 20 middle- to moderate-malnourished, sex- and age-matched, stable (their body weight had been stable for at least 6 months before the study) ESRF patients, 22 males (52.30%) and 20 females (47.70%), on maintenance HD. The primary causes of end-stage renal disease were glomerular disease, chronic pyelonephritis, polycystic renal disease, urolithiasis and hypoplastic kidney in 9, 6, 3, 2 and one patient, respectively.

Median dialysis duration was 48 months (IQR 24.5-82.0). The only one severely-malnourished patient was excluded. The patients were dialized through biocompatible dialyzer membranes with AVF at the Hemodialysis Unit of Zemun Clinical Hospital. Exclusion study criteria included history of diabetes mellitus, cardiac failure (NYHA III-IV), acute or chronic infective disorders and immunosuppressive therapy. All patients were sedentary (<1 h/wk of physical activity), free of alcohol abuse and non-smokers. Throughout the study period, the patients continuously received their regular treatments (e.g. antihypertensive therapy, phosphate-binding therapy, i.v. iron, and vitmin B, C and D supplementation), with no regular epoietin adminisitration. All patients were determined to require i.v. iron therapy for either absolute or relative iron deficiency (transferrin saturation <0.20 and/or serum ferritin <100 ng/ml) and the total dose of i.v. iron therapy was less then 1,000 mg over 6 months. The patients with ferritin levels >1,000 ng/ml were excluded. There was no evidence of active infection in the patients during the study period. This study was approved by the Institutional Ethic Committee and written consent for study participation was obtained from each patient.

Materials and methods

To determine the nutritional status, body composition and the presence of inflammation of HD patients, the following methods were used: Subjective global assessment (SGA); Anthropometric measurements, including body mass index (BMI), and waist circumference were recorded by a standardized protocol (dry weight or post dialysis weight was used (dry weight/height^2) for calculating BMI); Bioelectrical impedance analysis (BIA) was performed to quantify body fat ($FAT_{\%}$; FAT_{kg}; $LBM_{\%}$; $TBW_{\%}$) using a TBF-110 Body Fat Analyser (Tanita, Japan); Biochemical parameters measurements (the levels of serum albumin, cholesterol, HDL-cholesterol, triglyceride, hematocrit, hemoglobin, iron, ferritin, calcium, phosphorus, i-PTH, tumor necrosis factor-alpha (TNF-alpha), inteleukin-6 (IL-6) and hs-CRP. The adequacy of dialysis was judged by Kt/V.

SGA was performed on the basis of the patient's clinical hystory and physical examination. The hystory included any change in body weight within last 6 months (weight loss of <5%, 5-10% or >10%) and any alteration in food intake. Each parameter was graded as A (normal or well nourished), B (mild to moderate malnutrition), or C (severe malnutrition). Each parameter assessed during the physical examination was scored as 0 (normal), 1 (mild), 2 (moderate), or 3 (severe). After processing the data obtained from the hystory and physical examination, the total SGA score was determined by the physician as SGA-A (well nourished), SGA-B (mild to moderate malnutrition) or SGA-C (severe malnutrition). We selected only those patients with SGA-A and SGA-B score, because there was only one severely malnourished patient (scored as SGA-C). All patients with three or more of the following criteria were defined as having the MeS (NCEP ATP-III 2001): 1) abdominal obesity [waist circumference, >102 cm in males, or >88 cm in females], 2) hypertriglyceridemia ($\geq$1.69 mmol/l), 3) low HDL choles-

terol [<1.02mmol/l in males, or <1.29 mmol/l in females], 4) high blood pressure (≥130/85 mm Hg), and 5) high fasting glucose (≥5.6 mmol/l). The International Diabetes Federation (IDF) carried out a new definition with suggestion that the key element is central obesity [increased waist circumference (population specific) ≥94 cm for men, or ≥80 cm for women, plus any 2 of the following: lipids TG ≥1.7 mmol/l or on TG Rx; HDL-C <1.03 mmol/l in men or < 1.29 mmol/l in women or on HDL-C Rx; blood pressure ≥ 130 mm Hg systolic or ≥85 mm Hg diastolic or on hypertension Rx; glucose ≥5.6 mmol/l (including diabetes)].

Laboratory measurements, the levels of glucose, triglyceride, total cholesterol, HDL-cholesterol, albumin, calcium, phosphorus, hemoglobin and iron were assessed with a convential autoanalyzer, using blood samples obtained midweek, after overnight fasting and immediately prior to dialysis. The haematocrit was measured by centrifugation. Serum ferritin was measured using an immunoradiometric assay. The levels of i-PTH were assessed by immunoradiometric assay (CIS-Bio) and plasma insulin levels were measured using a radioimmunoassay method (INEP Zemun, Belgrade). IL-6 and TNF-alpha concentrations were measured in duplicate by Immunotech IL-6 immunoassays and Immunotech TNF-alpha immunoassays (Beckman Counter™). hs-CRP was measured by the Olympus (LATEX) assay on an Olympus AU 400 analyzer. Insulin resistance index was calculated from fasting insulin and glucose concentrations using the Homeostatic Model Assessment score (HOMA-IR) (19).

Statistical analysis. Before statistical analysis, the Kolmogorov-Smirnov test was used to assess the normal distribution of the variances. Descriptive variables are presented as mean ± SD or as median and inter-quartiles range (IQR), depending on whether the distribution was normal or skewed. The values of HOMA-IR, adipokines, triglycerides, iron, ferritin, total fat %, CRP, TNF-alpha, IL-6 and i-PTH were log transformed to achieve a normal distribution. Comparisons between two groups were performed using one-way analysis of variance. Mann-Whitney test was used to determine the cases where variables values were not normally distributed. Logistical regression analysis was used to evaluate the correlation between measured variables and the presence of MeS, and backward multivariate regression analysis was performed to assess the variables independently related to MeS, according to both criteria (ATP-III and IDF). The potentially independent variables included in the analysis were age, sex, dialysis efficacy (Kt/V), markers of nutritional status and body composition, iron, TSAT, phosphorus, inflammatory markers and i-PTH levels. All p values were based on a two-sided test of statistical significance. Significance was accepted at the level of $p<0.05$. Statistical analyses were performed with statistical package *SPSS for Windows 8.0* (Chicago, IL).

Results

The clinical characteristics of the study patients are shown in Table 1. There were no differences regarding age, gender, dialyasis efficacy, albumin, lean body mass, SGA score, iron, ferritin, phosphorus, i-PTH, total body fat, and cytokines (TNF-alpha, IL-6 and hs-CRP) between the two groups. Serum levels of glucose, triglycerides, total-cholesterol/HDL-cholesterol, and calculated HOMA-IR were significantly higher (data not presented), and TSAT was lower in group 2 patients, according to ATP-III criteria. As we expected, the levels of glucose, triglycerides, total-cholesterol/HDL-cholesterol (data not presented), calculated HOMA-IR and total fat mass were significantly higher in patients with MeS, according to stronger IDF criteria.

By logistical regression analysis we evaluated the correlation between measured variables and MeS in the entire HD patient group. After adjustment for age, sex and t/V, the association between the MeS and other variables (serum iron, TSAT and BMI) explained 62% of variation of the presence of MeS, and only BMI (p=.03) was independent factor predicting MeS (ATP-III) in HD patients (Table 2). In logistical regression analysis performed according to IDF criteria, after adjustment for age, sex and Kt/V, the levels of glucose, iron, waist circumference and total fat mass explained 68% of variation of the presence on MeS, but only glucose level (p=.02) was an independent predictor (Table 2a). HOMA-IR, separately, correlated significantly with BMI, lean body mass (LBM), serum phosphorus and iron (Table 3). To determine the independent factors for the HOMA-IR, we then performed multivariate analysis, including the abovementioned variables in a model. That explained 29% of variation of the HOMA-IR index. Only BMI (β=.558, p=.01) and iron (β=.561, p=.04) were independent factors predicting the HOMA-IR in long-term HD patients (Table 4). To further clarify a relative weighing of these independent factors to the IR index, we did a stepwise regression analysis. We found that BMI was the strongest independent factor for the HOMA-IR (β=.440, p=.01) (Table 5).

Discussion

The present study supports the hypothesis that MeS is presented in the vast majority of non-diabetic HD patients. We have also shown that the patients with MeS did not differ significantly for BMI, total body fat, abdominal fat, muscle mass and the prevalence of malnutrition (SGA score). However, nutritional status, estimated through BMI, was responsible for the presence of MeS. This finding confirms the statement that in addition to waist circumference, which determined MeS, BMI is the powerful predictor of MeS. A similar finding indicating that the likelihood of MeS increases with an increasing BMI value, regardless of waist circumference in the metabolic syndrome definition, was reported by St-Onge et al for both sexes (20). Where IDF definition of MeS was introduced, the prevalence of MeS was higher, as a consequence of stronger criteria. The present findings suggest, according to the IDF definition, that glucose level is independent predictor of MeS, in non-obese

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Table 1. Clinical Data of Study HD Patients

variable	HD patients without MeS (Group 1)	HD patients with MeS* (Group 2)	Significanse (p)
Number $_{n}$	20	22(52.4%)	0.55
	15	27(64.2%)	0.08
Gender $_{male\ (\%)}$	55	54	0.87
	73	44	0.07
Age $_{year}$	55(41-60)	59(52-64)	0.09
	56.0(49.0-60.0)	57.5 (47.5-64.5)	0.51
Dialysis duration $_{mo}$	51(24-82)	43(27-91)	0.86
	69(24-111)	41(24-60)	0.30
Kt/V	1.29±0.15	1.22±0.17	0.74
	1.28±0.12	1.26±0.18	0.35
Phosphorus	1.42±0.37	1.31±0.36	0.45
	1.37±0.28	1.36±0.41	0.91
Hg $_{g/l}$	90.50(74.50-97.75)	95.00(84.00-110.00)	0.28
	88.00(74.00±102.75)	94.50(83.50-103.50)	0.46
Ht	0.27(0.22-0.30)	0.29(0.25-0.34)	0.28
	0.27(0.22-0.30)	0.28(0.24-0.31)	0.38
Iron $_{\mu g/l}$	14.65±6.55	15.25±6.43	0.69
	16.44±7.06	15.32±5.48	0.18
TIBC $_{\mu g/l}$	32.14±7.83	38.37±5.98	0.71
	35.23±6.27	35.05±8.37	0.95
Transferrin saturation	48.52±22.77	38.58±11.63	**0.02**
(TSAT=Fe/TIBC)	46.58±23.56	40.94±13.16	0.27
Ferritin $_{\mu g/l}$	494.00(171.00-930.00)	449.00(287.25-886.90)	0.83
	487.65(262.00-930.50)	443.00(102.00-886.60)	0.45
Leukocytes $_{n}$	5.9(4.8-7.5)	5.6(5.0-6.6)	0.68
	6.3(5.0-7.9)	5.5(4.9-6.5)	0.15
Albumin $_{g/l}$	33.27±2.76	32.70±3.45	0.47
	33.22±2.17	31.45±3.43	0.08
SGA $_{A\ (\%)}$	50	60	0.52
	34.79	65.21	0.89
BMI $_{kg/m2}$	21.18±2.30	23.31±3.30	0.78
	21.24±3.31	22.70±2.70	0.13
waist $_{cm}$	83.00±12.51	87.05±12.60	0.45
	83.53±9.22	88.11±10.05	0.15
HOMA-IR	3.67(1.20-6.11)	11.49(9.12-17.05)	0.002
	2.56(1.69-4.44)	6.95(5.07-10.81)	0.01
FAT$_{kg}$	10.40(6.27-13.42)	11.30(7.4-23.50)	0.21
	6.5(5.3-11.00)	12.05(9.05-20.47)	0.02
LBM $_{\%}$	46.40(40.00-57.62)	52.40(43.60-60.80)	0.28
	55.00(45.70-61.10)	45.90(37.57-58.60)	0.11
hs-CRP$_{mg/l}$	3.06(0.79-6.00)	3.67(1.73-15.35)	0.14
	2.62(0.21-4.30)	3.58(1.7-9.80)	0.09
TNF alpha $_{pg/ml}$	2.09(0.85-2.78)	2.05(0.77-2.97)	0.99
	2.31(1.24-2.80)	1.96(0.37-3.02)	0.30
IL6 $_{pg/ml}$	2.40(2.05-2.94)	2.45(2.00-2.93)	0.86
	3.24(1.15-9.60)	2.60(0.96-7.80)	0.29
i-PTH $_{pg/dl}$	261.00(11.33-905.25)	197.55(61.97-611.75)	0.98
	197.55(11.32-739.42)	261.15(48.25-836.25)	0.95

Data are presented as the mean ± SD and as the median and interquartiles range (IQR), for variables with the skewed distribution.

MeS* (according to ATP-III or IDF criteria).The data in second rows are according to IDF criteria.

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Table 2a. Logistic Regression Analysis (Method Backward Stepwise) of Relationships between MeS and Characteristics of HD Patients

variable	B (standardized coefficients)	p-values
iron	0.403	0.06
TSAT	-12.694	0.08
BMI	0.329	0.03

Adjusted R^2= 0.62

Table 2b. Logistic Regression Analysis (Method Backward Stepwise) of Relationships between MeS (IDF criteria) and Characteristics of HD Patients

variable	B (standardized coefficients)	p-values
glucose	1.845	0.02
waist	0.367	0.06
$FAT_{kg\ log}$	0.317	0.07
iron	0.133	0.09

Adjusted R^2=0.68

Table 3. Correlation Coefficient (Pearson's *r*) between HOMA-IR and Demographic, Metabolic, Nutritional and Inflammatory Markers

	Pearson's *r*	P_{values}
variables		
age	0.002	0.99
Kt/V	0.036	0.89
phosphorus	0.384	**0.02**
hemoglobin	0.068	0.73
Iron	0.467	0.03
TSAT	0.341	0.12
$Ferritin_{log}$	0.033	0.79
albumin	-0.154	0.37
Lean body mass %	-0.379	**0.01**
waist	0.320	0.05
BMI	0.366	**0.01**
$FAT_{kg\ log}$	0.285	0.07
CRP_{log}	0.123	0.43
$TNF\text{-}alpha_{log}$	0.147	0.18
$IL\text{-}6_{log}$	0.196	0.25
PTH_{log}	0.128	0.47
Le	-0.153	0.37

HD patients. Visceral adiposity, as well as total obesity participated in the pathogenesis of MeS in the present patients, but not as independent predictors. It can be accepted that in addition to visceral adiposity, systemic low grade inflammation affects the pathogenesis of the metabolic syndrome or T2DM (6, 8). The levels of inflammatory cytokines, or adipokynes, TNF-alpha and IL-6, have been detected in significant amounts in patients with either IR syndrome or diabetes (17-23). The mechanisms responsible for IR produced by chronic inflammation in skeletal muscle, liver, fat and vascular smooth muscle cells might be related to activation of serine/treonine phosphorylation cascades that lead to activation of nuclear factor-kB, and to serine phosphorylation of elements of insulin receptor signaling system, especially IRS-1 (24). We found almost the same high levels of circulating TNF-alpha, and IL-6, in both groups, without a significant correlation with markers of adiposity. That observation did not support the contribution of adipose tissue for systemic inflammatory responses in HD patients. However, it is well known that only about 10% of the total IL-6 appears to be produced exclusively by fat cells (23). Chronic inflammatory diseases, particularly ESRD, are associated with an increase of iron stores, or ferritin levels (15, 25). We also showed the serum iron levels, which were correlated with ferritin and inflammatory cytokine levels, were associated with the presence of MeS in our HD patients.

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Table 4. Multivariate Regression Analysis of Relationships between HOMA-IR and Characteristics of HD Patients

variable	B (standardized coefficients)	p-values
BMI	0.525	0.008
iron	0.457	0.02

Adjusted R^2=0.29

Table 5. Backward Stepwise Regression Analysis of Relationships between HOMA-IR and Characteristics of HD Patients

variable	B (standardized coefficients)	p-values
BMI	0.440	0.01

Adjusted R^2=0.20

More precisely, serum iron correlated with HOMA-IR, which could be used as a surrogate of insulin resistance. Furthermore, iron was an independent predictor of the insulin resistance index in our participants. Previous studies showed that a high ferritin level in ESRD patients represents an inflammatory marker rather than a high level of iron stores (23). As we did not register the patients with ferritin levels >1,000 μg/l, we excluded the presence of iron overload. The high serum iron and ferritin levels detected in the HD patients can also result from ineffective utilization of iron stores, because they were off the recombinant human erythropoietin treatment. It is noteworthy that administration of iron significantly enhances the RBC response after erythropoietin therapy in HD patients (25). Igaki et al proposed the idea of an individual target hemoglobin concentration, tailored for the clinical condition of each HD patients, bearing in mind an insulin resistant state as a consequence of anemia (14). The present data revealed the need for a lower dose of parenteral iron to be administrated to patients with MeS.

Multiple logistic regression analysis identified three factors responsible for the presence of MeS (ATP-III), where serum iron and TSAT participated, but not independently, and only BMI was an independent predictor. According to the IDF criteria, the iron level participated in the pathogenesis of MeS, also. By the same analysis, we confirmed that, in addition to BMI, iron participated as an independent predictor for calculated IR index. Our finding that serum iron is independently related with HOMA-IR, supports the statement of Drucke et al that accelerated atherosclerosis could also be a consequence of iron therapy, due to its pro-oxidant properties, in ESRD patients (26). However, it is likely that correction of anemia, with regular treatment with erythropoietin and an adjusted dose of intravenous iron, may decrease the level of serum iron and consequent inflammation. Furthermore, a decrease of IR could be expected. The level of i-PTH did not differ between the patients and we did not find a significant association between the presence of secondary hyperparathyroidism and IR. However, adequate treatment of hyperparathyroidism could suppress the level of IL6 in HD patients (27).

The present results suggest that the increase of peripheral insulin resistance in ESRD patients on HD could be associated with chronic inflammatory response, where the serum iron plays a role as one of the components, which is in agreement with the study that showed that complete correction of anemia, with a high dose of parenteral iron, did not improve cardiovascular outcomes in HD patients (15). The role of nutritional status in the development of periferal IR agreed with the other studies (6, 28). Because of its cross-sectional design, our study allows just to identify the association, but not its cause. In addition to this limitation, another limitation is the absence of obese study patients.

In conclusion, chronic inflammation with a high serum iron and low transerrin saturation, participates in the pathogenesis of MeS (insulin resistance) in ESRD patients on maintenance HD, together with BMI or glucose level, as independent predictors. Visceral and total fat represent another predictors, according to IDF criteria. It seems that reduced chronic inflammation with lowering of the serum iron level, and individually adjusted treatment of anemia, under-the-control intravenous iron and/or blood transfusion with regular erythropoietin therapy, may restore insulin sensitivity in such patients.

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