Insulin resistance and chronic inflammation are associated with muscle wasting in end-stage renal disease patients on hemodialysis

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Abstract. Muscle wasting is independent predictor of mortality in end-stage renal disease (ESRD) patients on maintenance hemodialysis (MHD). We investigated the effect of insulin resistance on lean body mass (LBM), and association between insulin resistance, chronic inflammation, and body composition in these patients. We analyzed cross-sectionally body composition, nutritional status and biochemical parameters in 35 non-diabetic ESRD patients who were on MHD. Bioelectrical impedance analysis was performed to quantify body fat, lean body mass and total body water (FAT (%), FAT (kg), LBM (%), LBM (kg) and TBW(%)). The association between LBM (kg) and gender, FAT (kg), high sensitivity C-reactive protein (hs-CRP), and homeostatic model assessment score (HOMA-IR) was recorded. Multiple linear regression analysis using LBM (kg) as dependent variable showed that FAT (kg) ($\beta = 0.563$, $p = 0.05$), HOMA-IR ($\beta = 0.619$, $p = 0.03$), and hs-CRP ($\beta = 0.488$, $p = 0.04$) were independently associated with LBM in males. In females, only FAT (kg) ($\beta = 0.648$, $p = 0.001$) significantly predicted LBM. Those variables explained 37% of variance of LBM (kg) in males, and 44% in females. It seems that insulin resistance participates independently in the pathogenesis of muscle wasting in both sexes, particularly in males. The effect of chronic inflammation was not so strong in females, and this point out that regulation of muscle wasting in female patients probably differs from that in males.

Key words: Insulin resistance — Muscle wasting — Chronic inflammation — End-stage renal disease

Introduction

Insulin plays a pivotal role in regulating body protein metabolism. Insulin deficiency, as seen in untreated type 1 diabetes mellitus (T1DM) is associated with increased skeletal muscle catabolism (Felig et al. 1977) and urinary nitrogen loss. In humans, systemic insulin administration inhibits muscle protein breakdown in patients with T1DM (Pacy et al. 1991) and in healthy subjects (Toffolo et al. 2003). Chow et al. (2006) confirmed that normal physiological levels of insulin inhibit muscle protein breakdown as well as exert stimulatory effect on muscle protein synthesis. Ikizler et al. (1994) demonstrated that hemodialysis (HD) is a catabolic event, decreasing circulating amino acids, accelerating rates of whole body and muscle proteolysis, stimulating muscle release of amino acids, elevating net whole body and muscle protein loss, and increasing energy expenditure.

It is known that complex syndrome of uremia can trigger muscle protein breakdown including metabolic acidosis, decreased insulin action, increased glucocorticoid production, high levels of angiotensin II, and inflammation (Pupim et al. 2005; Song et al. 2005). A common cellular signaling pathway is a decrease in phosphatidylinositol 3-kinase (PI3K) activity. Reduced PI3K-Akt signaling enhances protein breakdown in muscle (Du and Mitch 2005).

In the present study we examined the relationship between insulin resistance, as measured by HOMA-IR, inflam-

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matory marker, as measured by high sensitivity C-reactive protein (hs-CRP), and lean body mass (LBM) of maintenance hemodialysis (MHD) patients.

Materials and Methods

Subjects

The study group included 35 (20 male and 15 female), sex and age-matched, stable (their body weight had been stable for at least 6 months before the study) end-stage renal disease (ESRD) patients on MHD, with median dialysis duration of 48 months (inter quartiles range (IQR) 24.0–82.0). Exclusion criteria were: diabetes mellitus, cardiac failure (NYHA III or IV), acute myocardial infarction and acute infective disorders during 3 months before the inclusion. They were not obese and without severe malnutrition (BMI was between 20 and 30 kg/m^2). Patients were dialyzed with synthetic membranes and a bicarbonate dialysate with 1.25, 1.5 or 1.75 mmol/l calcium according to the serum calcium-phosphate equilibrium and with obligatory use of 1,25-dihydroxy vitamin D3 to control the parathyroid hormone (PTH) levels. The duration of HD was individually tailored (thrice weekly) to control body fluids and blood chemistries and with aim to achieve an adequate dose of dialysis Kt/v > 1.2 (1.46 ± 0.13). Patients regularly did not receive erythropoietin therapy at that time, because health insurance didn't pay it. Antihypertensive drugs were prescribed when necessary to obtain pre-dialysis blood pressure <160/90 mmHg. None of the patients received lipid lowering drugs, β-blockers, L-carnitine or vitamin B_{12} during 3 months before the inclusion. Calcium carbonate ($CaCO_3$) was used to try to obtain pre-dialysis serum phosphate level <2.0 mmol/l. All patients were sedentary (<1 h/week of physical activity), free of alcohol abuse and non-smokers. They maintained their habitual diets (35 kcal/kg b.w., protein intake 1.01–2 g/kg b.w., fats <35% caloric intake) with sodium and potassium restriction. Each patient gave informed written consent to participate in the study, which was approved by the Institutional Ethic Committee.

Methods

The study was cross-sectionally designated. 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 BMI and waist circumference, which were recorded by a standardized protocol (dry weight or post dialysis weight was used for calculating BMI); bioelectrical impedance analysis was performed to quantify body fat (FAT (%), FAT (kg)), LBM (%), LBM (kg), total body water (TBW (%)) using a body fat analyser TBF-110 (Tanita, Japan); biochemical parameters measurements (levels of serum albumin, hemoglobin, ferritin, i-PTH, TNF-α, IL-6, hs-CRP, glucose and insulin). The blood samples were also taken for the determination of the red blood cell phospholipids fatty acids composition. SGA is a clinical method for evaluating nutritional status, including history, symptoms, and physical parameters. The history used in the SGA focuses on 5 areas: body weight, dietary intake, gastrointestinal symptoms, functional capacity, and disease state. The percentage of body weight lost in the previous 6 months is characterized as mild (<5%), moderate (5–10%), or severe (>10%). Dietary intake is classified as normal or abnormal as judged by a change in intake and whether the current diet is nutritionally adequate. The presence of persistent gastrointestinal symptoms such as anorexia, nausea, vomiting, diarrhea, and abdominal pain for at least 2 weeks is recorded. In addition to the medical history, there is also a physical examination, which is noted as normal, mild, moderate, or severe alterations. The loss of subcutaneous fat is evaluated in the triceps region and the midaxillary line at the level of the lower ribs. These measurements are not precise but are merely a subjective impression of the degree of subcutaneous tissue loss. The second feature is muscle wasting in the temporal areas and in the deltoids and quadriceps, as determined by loss of bulk and tone detectable by palpation. A neurologic deficit will interfere with this assessment. The presence of edema in the ankle and sacral regions and the presence of ascites are noted. Coexisting disease such as heart failure will modify the weight placed on the finding of edema. The findings of the history and physical examination are used to categorize patients as having very mild malnutrition to being well nourished (SGA-A score), having moderate or suspected malnutrition (SGA-B score) , or having severe malnutrition (SGA-C score). Fluid shifts or ascites must be considered when interpreting changes in body weight. Laboratory measurements, the level of glucose, albumin, hemoglobin and iron were assessed with a convential autoanalyzer, using blood samples obtained midweek, after overnight fasting and immediately prior to dialysis. Serum ferritin was measured using an imunoradiometric assay. The levels of i-PTH were assessed using immunoradiometric assay (CIS-Bio) and plasma insulin levels were measured using a radioimmunoassay method (INEP Zemun, Belgrade). IL-6 and TNF-α concentrations were measured in duplicate by Immunotech IL-6 immunoassays and Immunotech TNF-α immunoassays (Beckman Counter^{TM}). hs-CRP was measured by the Olympus (Latex) assay on the Olympus AU 400 analyzer. Insulin resistance index was calculated from fasting insulin and glucose concentration using HOMA-IR (Matthews et al. 1985).

Statistical analysis

Before statistical analysis, normal distribution of the variances was evaluated using the Kolmogorov-Smirnov test. Descriptive results are expressed as mean ± SD or as median and IQR, depending on whether the distribution was normal or skewed. The values of insulin, HOMA-IR, hs-CRP, and i-PTH were log transformed to achieve a normal distribution. The Pearson's correlation and simple regression analysis were used to evaluate the association between measured variables and LBM (kg). Demographic characteristics (age and sex), serum albumin and creatinine concentrations were considered as potential confounders of the relation between LBM (kg) measures and markers of insulin resistance, inflammation and body composition. 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 the SSPS statistical package, version 15 (SPSS, Chicago, IL).

Table 1. Baseline demographic, nutritional characteristics and body composition

Variable	Male	Female	p
Sex	20 (57.14%)	15 (38.86%)	0.40
Age (years)	55.74 ± 13.11	54.11 ± 10.76	0.54
Duration of HD (years)	60 (34–28)	39 (23.50–67)	0.21
Kt/v	1.26 ± 0.18	1.38 ± 0.23	0.62
Body weight (kg)	67.08 ± 8.43	58.93 ± 9.10	0.60
BMI (kg/m^2)	21.40 ± 2.92	23.35 ± 2.91	0.58
Waist (cm)	87.30 ± 8.51	85.7 ± 11.52	0.16
FAT (kg)	8.99 ± 5.81	17.6 ± 8.47	0.01
LBM (kg)	39.08 ± 18.92	24.51 ± 5.49	0.04
SGA-A (%)	9 (39)	11 (75)	0.03

Values are presented as mean ± SD for normally distributed data, median and IQR for non-normally distributed data, and percentages as appropriate. HD, hemodialysis; Kt/v, number used to quantify hemodialysis adequacy; BMI, body mass index; FAT, fat mass; LBM, lean body mass; SGA-A (%), subjective global assassement-A group.

Results

The baseline characteristics of the 35 patients, 20 men and 15 women, on MHD, who completed the study, are presented in Table 1. The two groups (men and women) were with similar age and BMI, but women, as expected, had more FAT (kg), and smaller amount of LBM (kg), than men (Table 1). On the opposite, according to SGA assessment the majority of men were mild to moderate malnourished (69%), then women (25%). Biochemical parameters, as albumin, creatinine, glucose, insulin and inflammatory markers: hs-CRP, TNF-α, IL-6 and fibrinogen, did not differ between groups. Despite exclusion of patients with diabetes mellitus and obesity, the median (interquartile range) HOMA-IR score was 9.25 (6.45–12.32) and 12.11 (6.45–17.05), respectively (Table 2). We recorded strong association between IL6 and FAT (kg) ($r = 0.462$, $p = 0.04$), only in women, and association between TNF-α and FAT (kg) ($r = 0.331$, $p = 0.08$) was with borderline significance, for these patients. By linear regression analysis we evaluated the correlation between measured variables and LBM (kg) in the both groups. LBM (kg) correlated significantly with sex, age, BMI, FAT (kg), hs-CRP, fibrinogen, albumin, creatinine and HOMA-IR (data are not showed).

To determine the independent factors responsible for LBM (kg), for both sexes, respectively, we performed multivariate analysis, including the abovementioned variables in a model. After adjustment for age, Kt/v, fibrinogen, serum albumin and creatinine, the association between the LBM

Table 2. Basaline biochemical analysis of study patients

Variable	Male	Female	p
Serum albumin (g/l)	32.21 ± 13.63	32.56 ± 2.58	0.25
Serum hs-CRP (mg/l)	3.53 (1.42–12.8)	3.62 (0.84–7.14)	0.65
Serum TNF-α (pg/ml)	2.30 (1.24–2.82)	2.04(0.37–2.80)	0.24
Serum IL-6 (pg/ml)	3.23 (1.06–9.60)	1.60 (1.15–5.04)	0.37
Serum fibrinogen (g/l)	3.40 ± 0.60	3.02 ± 0.69	0.65
i-PTH (pg/ml)	454.40 (96.92–905.25)	172.55 (7.95–423.22)	0.17
Serum creatinine (μmol/l)	328.34 ± 38.60	253.20 ± 41.32	0.09
Serum glucose (mmol/l)	5.58 ± 11.21	5.54 ± 1.03	0.35
Serum insulin (mU/l)	34.20 (26.80–43.00)	55.10 (28.10–69.90)	0.25
HOMA-IR	9.25 (6.45–12.32)	12.11 (6.45–17.05)	0.30

Values are presented as mean ± SD for normally distributed data, median and IQR for non-normally distributed data.

(kg) and independent variables (FAT (kg), HOMA-IR and hs-CRP) explained 37% of variation of LBM in men (Table 3). The similar association was established in women, where the same independent predictors (FAT (kg), HOMA IR and hs-CRP) predicting LBM (kg) (hs-CRP with borderline significance), indicating an even stronger association, and explained 44% of variation of LBM (Table 4).

Table 3. Association between LBM and FAT, insulin resistance and hs-CRP in males

Variable	β	*p*
FAT (kg)	0.563	0.05
HOMA-IR	–0.619	0.03
hs-CRP	–0.488	0.04

Adjusted $R^2 = 0.37$, $p = 0.04$.

Table 4. Association between LMB and FAT, insulin resistance and hs-CRP in females

Variable	β	*p*
FAT (kg)	0.648	0.001
HOMA-IR	–0.496	0.05
hs-CRP	–0.341	0.06

Adjusted $R^2 = 0.44$, $p = 0.01$.

Discussion

The current study demonstrated that insulin resistance, together with total fat mass and chronic inflammation measured by hs-CRP could be independent predictor for LBM in non-diabetic chronic dialysis patients. Chevalier et al. (2005) has demonstrated the presence of insulin resistance and enhanced whole-body protein catabolism in young healthy obese women compared to lean women during the post-absorptive state. Although, our patients were not obese, men and women, separately, have many reasons for the presence of insulin resistance including acidosis, chronic inflammation, anemia, higher level of serum iron and iron stores (Rašić-Milutinović et al. 2000, 2007a,b, 2008). We studied non-obese middle-aged and older ESRD patients where many factors including acidosis, inflammation, and dialysis itself are known to influence visceral protein stores. Our results indicate that in the absence of diabetes, or obesity (BMI < 30), insulin resistance is evident in the HD patients and inversely correlates with LBM, a relationship that persists even after adjustment for fat mass and chronic inflammation. That association is stronger in male patients.

Many studies have attempted to explain the loss of protein stores, and especially the loss of muscle mass in ESRD patients. Siew et al. (2007) concluded that insulin resistance significantly contributes to the enhanced muscle protein catabolism observed in MHD patients. Investigations by tracer kinetic models and insulin clamp techniques in healthy individuals have detailed that it remains the blunting of proteolysis rather than enhanced protein synthesis is net protein anabolic effect of insulin in the post-absorptive state (Gelfand and Barrett 1987; Chow et al. 2006). The increase in muscle protein degradation in uremia and most other catabolic disease states is mostly due to programmed activation of the ubiquitin-proteasome system (UPS) (Rajan and Mitch 2008). The underlying mechanism demonstrated by Du and Mitch (2005) appears to be suppression of insulin receptor substrate-1-associated phosphatidylinositol 3-kinase activity resulting in stimulation of the UPS *via* caspase-3. The present results underline an independent role of insulin resistance in muscle protein metabolism, and in agreement with the findings of other authors, that have shown the contribution of insulin resistance to muscle atrophy in HD patients, through defects in insulin receptor signaling (Lee et al. 2007) independently of total fat mass.

It is generally accepted that obesity produces insulin resistance, through the induction of peripheral disruption of insulin signaling pathways by increasing the level of circulating free fatty acids (FFA) and inflammatory mediators. As the largest endocrine organ, adipose tissue is able to regulate various biological processes through adipose-derived signaling proteins termed adipokines (Chaldakov et al. 2003), insulin sensitivity, feeding behavior and the sequestration of FFA as triglycerides also being targeted (Guilherme et al. 2008). Evidence based from humans as well as animal models shows that increased concentrations of inflammatory markers are associated with insulin resistance and reduction in lean mass (Garcia-Martinez et al. 1993; Mayer-Davis et al. 1998). We showed that plasma concentrations of hs-CRP were inversely associated with muscle mass, significantly only in men on HD. Our results confirm data from previous studies demonstrating a relation between BMI and total fat mass and markers of inflammation in ESRD patients (Stenvinkel et al. 1999). Based on these observations, we hypothesized that insulin resistance significantly contributes to the enhanced muscle protein catabolism observed in MHD patients, particularly men. Male patients were significantly mild to moderate malnourished (61%), with lower total fat mass and LBM, but without any differences for peripheral insulin resistance compared to women. That emphasize that the association between insulin resistance and LBM remained significant, independently of fat mass, in male group. In female group, the association between insulin resistance and LBM is weaker, and total fat mass is strongest independent predictors for LBM. Inflammatory cytokines of female patients, particularly IL-6, correlated with insulin resistance, and total

fat and we could explain its effect more as those of adipokines. Obviously, some of cytokines appear negative effect on LBM indirectly, by potentiating insulin resistance. Wang et al. (2006) have recently demonstrated in an animal model that the enhanced muscle proteolysis associated with insulin resistance appears to be reversible with the administration of the peroxisome proliferator-activated receptor-gama agonist Rosiglitazone. These results need to be extended to human studies. However, the reduction of insulin resistance by supplemented n-3 PUFAs in ESRD patients (Rasic-Milutinovic et al. 2007) may contribute to muscle wasting. Kato et al. (2003) found significantly higher prevalence of cardiovascular (63 vs. 25%) and pulmonary deaths (30 vs. 0%) in men on regular HD, with lower limb/trunk lean mass (LTLM) ratio, and he revealed that reduced LTLM ratios were significant determinants of 5 year mortality in men. Kalantar-Zadeh et al. (2004) examined the predictability of markers of the malnutrition-inflammation complex syndrome (MIS) in HD patients and concluded that MIS score and CRP were the only variables to have statistically significant associations with mortality and hospitalization.

Our results should be interpreted with some limitations. At first, the cross-sectional design of the study did not allow us to investigate the cause-effect relation between markers of insulin resistance, inflammation and body-composition measures.

In conclusion, it has been observed that ESRD patients on MHD are at risk for a progressive loss in LBM not entirely accounted for by inadequate nutrient intake alone. The results of this study indicate that insulin resistance and inflammation in ESRD may be an important contributor to protein wasting that represents a novel target for intervention.

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