PhD thesis

Investigations of additional cardio-metabolic biomarkers in patients with different BMI categories and kidney function

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Pécs

2011

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List of abbreviations

BMI	Body mass index
BP	Blood pressure
BU	Bergmeyer unit
CRP	C-reactive protein
DTNB	5,5'-dithiobis 2 nitrobenzoic acid
FIZZ	Found in inflammatory zones protein
FPG	Fasting plasma glucose
GSH	Reduced glutathion
HbA_{1C}	Hemoglobin A_{1c}
HDL-C	High density lipoprotein-cholesterol
HDPS	Hemodialysed patients
HOMA-IR	Homeostasis model assessment insulin resistance
IDF	International Diabetes Federation
IL-6	Interleukin-6
IR	Insulin resistance
Kt/V	Dialysis efficiency
LDL-C	Low density lipoprotein-cholesterol
MDA	Malonyldialdehyde
NEFA	Non-esterified fatty acids
PAP	para-Aminophenasol
PKI	Individuals with preserved kidney function
PON1	Paraoxonase 1
RBP-4	Retinol binding protein-4
sE-Selectin	Soluble E-Selectin
TBA	Thiobarbituric acid
TBARS	Thiobarbituric acid reactive substances
TCA	Trichlor acid
TG	Triglyceride

TNF-α	Tumor necrosis factor alpha
WAT	White adipose tissue

Summary

Introduction

Oxidative stress is enhanced in both metabolic syndrome and hemodialysed patients (HDPS). HDL-bound paraoxonase 1 (PON1) enzyme protects lipoproteins from oxidation. However, PON1 activity is reduced in both diabetes mellitus and kidney failure. Altered levels adipokines, e.g. leptin, adiponectin, and resistin as well as cytokines, e.g. interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) secreted by adipose tissue may contribute to abdominal obesity related insulin resistance (IR), inflammation and atherosclerosis, as well as to decreased PON1 activity. Adiponectin e.g. correlates positively and independently from other factors with PON1 activity, while negatively with C-reactive protein (CRP) and malonyldialdehyde (MDA) suggesting a role in the alleviation of oxidative stress.

Soluble E-selectin as a marker of endothelium inflammation shows a direct association with IR. In kidney failure, its severity is related both with PON1 activity and MDA level. However, in chronic renal diseases adiponectin has a controversial role. By some investigations, its level seems to be directly related to the risk of the cardiovascular events according to a paradoxical role of adiponectin in chronic renal diseases that may contribute to the explanation of a “reverse epidemiology”.

Aims of the present work

To investigate of the role of adipokines in modifying metabolic syndrome, serum PON1 activity, endothelium activation, and increased oxidative stress in two patient’s group, in (i) kidney failure and (ii) those with preserved kidney function but having various degrees of obesity.

Methods

The investigations were carried out in two different patient’s groups , in 70 HDPS and in 74 individuals with preserved kidney function (50 obese, and 24 healthy ones). Among others, anthropometric parameters, systolic and

diastolic blood pressures were measured and the IR index calculation was based on homeostasis model assessment (HOMA-IR). Adiponectin, sE-selectin, resistin and leptin were measured by ELISA, while activities of PON1 and catalase, level of non-esterified fatty acids (NEFA), as well as measures of lipid peroxidation, e.g. reduced glutathion (GSH), MDA level were determined using spectrophotometric methods.

Results

In the haemodialysed patient's body mass index (BMI), waist, albumin, CRP, triglyceride and HOMA-IR were significantly higher in the lower adiponectin subgroup, while dialysis efficiency and HDL-C were significantly lower. According to these, adiponectin level correlated positively with dialysis efficiency and HDL-C, while negatively with BMI, waist, albumin, fibrinogen, CRP, HOMA-IR and triglyceride levels. Multiple regression analyses showed that not only BMI and HOMA-IR were independent negative predictors of serum adiponectin level, but also the albumin level that is a marker of nutrition. Soluble E-Selectin inversely and independently correlated with the age, while GSH positively with HDL-C.

In individuals with preserved kidney function, HOMA-IR was correlated positively with BMI, waist circumference, serum NEFA, leptin, IL-6 and TNF-α levels, while negatively with adiponectin, without significant association to resistin. Leptin, and in lesser degree IL-6 and adiponectin were significant predictors of HOMA-IR. Resistin level was higher in the controls than among the obese subjects, and correlated negatively with BMI, waist circumference, serum leptin, NEFA levels, systolic BP, HbA_{1C} and MDA, while positively but not independently with PON1 activity. Beside MDA, PON1 activities were also negatively correlated with BMI, waist circumference, systolic BP, levels of HbA_{1C}, insulin and HOMA-IR, and correlated positively with concentrations of HDL-C. Of these variables, BMI and MDA were independent predictors of PON1 activity.

Conclusions and future perspectives

In kidney failure, in contrast to normal renal function, higher adiponectin levels have no correlation with PON1 activity or the sE-selectin level. However, adiponectin shows associations with dialysis efficiency, and similar to individuals with preserved kidney function, traits of metabolic syndrome. In addition to BMI and HOMA-IR, the serum albumin concentration is also one of the independent negative predictors of the serum adiponectin level. Collectively, these findings may add details to the understanding of the role that adiponectin plays in the chronic renal disease related to "reverse epidemiology."

In individuals with preserved kidney function, although insulin resistance has association with many of the investigated parameters, of these only serum level of leptin and to a lesser degree IL-6 and adiponectin are independent determinants of the severity of insulin resistance. Moreover, even together explain they only a minority of variance of insulin resistance. Resistin showed a positive, although not independent correlation with serum PON1, and a negative correlation with numerous parameters of the metabolic syndrome (i.e. adiposity, blood pressure, levels of leptin, NEFA, HbA_{1C}, and lipid peroxidation).

Introduction

High density lipoprotein has antioxidative characteristics in which one of its associated enzymes, paraoxonase 1 (PON1), plays an outstanding role protecting lipoproteins from oxidative modification (Getz et al. 2004, Watson et al. 1995, Rosenblat et al. 2006, Mackness et al. 2004). PON1 activity is reduced, among others, in diabetes mellitus (Mackness et al. 1991; Abbott et al. 1995), ischemic cardiac disease (Mackness et al. 2003), and kidney failure (Paragh et al. 1998, Schiavonet al. 2002, Dirican et al. 2004).

The International Diabetes Federation (IDF), when established the new definition of metabolic syndrome, also suggested several other additional metabolic criteria for research, e.g. adipose tissue biomarkers, atherogenic dyslipidemia (beyond elevated triglyceride and low HDL-C), insulin resistance, vascular dysregulation (beyond elevated blood pressure), and proinflammatory state (Alberti et al. 2005).

De Caterina et al. (2001) in a study with hypertensive patients found that the soluble E-Selectin (sE-selectin) was positively correlated with age and low density lipoprotein-cholesterol (LDL-C). Miller et al. (2006) demonstrated that the level of sE-selectin which is a marker of inflammatory activation in the endothelium correlated positively with body mass index (BMI) even if data were corrected for age, sex, race, smoking habits, blood pressure, serum levels of lipids and insulin. In healthy, non diabetic, normotensive individuals a direct association between insulin resistance and sE-Selectin was obtained; independently form age, sex, BMI, and lipoprotein levels (Chen et al. 1999). Intra-abdominal adiposity and insulin resistance are also closely related. Adipose tissue secreted adipokines seem to play an important role in the regulation of metabolic and inflammatory processes related to abdominal obesity, and therefore in the insulin resistance (Staiger et al. 2005, Yudkin et al. 2007). However, it remains uncertain whether abdominal obesity directly promotes

generalized insulin resistance, or serves only as a marker for this. Of the adipokines, leptin and adiponectin are secreted by adipocytes, while resistin, in humans mostly by macrophages. In individuals without infection, white adipose tissue (WAT), especially the intra-abdominal one, is also a main source of plasma pool of classical cytokines i.e. IL-6 and TNF-α that may contribute to obesity-related insulin resistance (Marette et al. 2002).

Kidney failure and obesity have some overlap as in both conditions are there altered levels of adipokines and inflammatory markers, as well as decreased PON1 activity. Based on the anti-atherosclerotic effect of adiponectin, an inverse correlation has been demonstrated in various populations with one of the soluble adhesion molecules, sE-selectin (Krakoff et al. 2003, Mantzoros et al. 2005, Kantartzis et al. 2006). In addition, with the high cardiovascular risk of HDPS, an elevated serum level of sE-selectin has been demonstrated in this population, probably due to both inadequate clearance, and enhanced synthesis/release (Bonomini et al. 1998).

Adiponectin, a 29 kDa protein, is the most abundant adipose tissue-derived protein in human plasma. Adiponectin has insulin sensitizing, anti-inflammatory, and anti-atherosclerotic properties (Staiger et al. 2005, Yudkin et al. 2007). According to it, the plasma concentration of adiponectin negatively correlates with insulin resistance in various ethnical groups (Weyer et al. 2001, Yamamoto et al. 2002) and its level is lower among obese (Arita et al. 1999, Matsubara et al. 2002, Matsubara et al. 2003), and type 2 diabetic subjects (Weyer et al. 2001, Hotta et al. 2000), especially when is associated with coronary disease (Hotta et al. 2000) and is increasing when excessive body mass is lost (Yang et al. 2001). The adiponectin level shows an inverse correlation with triglyceride level, even after correction for clinical and laboratory parameters (e.g. leptin), while positive correlation with HDL-C (Yamamoto et al. 2002, Tschritter et al. 2003, Matsubara et al. 2002, Cnop et al. 2003, Mantzoros et al. 2005). It is

also known that the adiponectin blocks the monocytes adhesion to endothelium, lowering the endothelial response to inflammatory stimuli (Ouchi et al. 1999). According to this, Krakoff et al. (Krakoff et al. 2003) in Pima Indians found an inverse correlation between adiponectin levels and inflammatory activation of endothelium (i.e. serum adhesion molecules, like soluble E-Selectin). These findings were confirmed in other patient populations (Mantzoros et al. 2005, Kantartzis et al. 2006), although not unequivocally (Schalkwijk et al. 2006). In patients with preserved kidney function, serum adiponectin concentration is correlated with PON1 activity, in addition to HDL-C and triglyceride levels. This relationship was independent from other factors, including HDL-C (Bajnok et al. 2008), a finding that may contribute to the anti-atherosclerotic effect of adiponectin.

Adiponectin has controversial role in chronic renal diseases (Guebre-Egziabher et al. 2007). The adiponectin level is increased in kidney failure and decreased shortly after kidney transplantation (Chudek et al. 2003) suggesting that the kidneys play an important role in adiponectin biodegradation and/or elimination. Furthermore, Guebre-Egziabher et al. (2005) established that adiponectin is more related to metabolic disturbances than to the decline in renal function in chronic kidney disease. Zoccali et al. (2002) demonstrated that the increased adiponectin level is inversely related to the risk of the cardiovascular events in end stage renal disease suggesting that the adiponectin may act as a protective factor against atherosclerosis in this patient population. These data were confirmed by Takemoto et al. (2009) in a Japanese population. In contrast, Menon et al. (2006) reported high, rather than low adiponectin levels are associated with increased mortality in a cohort of patients with chronic kidney failure and suggested further studies to elucidate the underlying mechanisms. Similarly to this latter finding, Schnabel et al. (2008) found a positive association between the serum level of adiponectin and the major cardiovascular events in a long term study carried out in patients with

coronary artery disease. Beige et al. (2009) proposed a paradoxical role of adiponectin in chronic renal diseases according to a reverse epidemiology due to the uremic environment that overwhelms the vascular-protective effect of adiponectin.

Some studies found negative correlation between serum adiponectin and the level of oxidative stress which is increased in both metabolic syndrome (Katsuki et al. 2006, Lim et al. 2007), and HDPS (Valentini et al. 2008, Chugh et al. 2000, Atamer et al. 2008), in whom this is further exacerbated by the haemodialysis itself (Loughrey et al. 1994). Lim et al. (2007) searching for relationship between plasma levels of adiponectin and markers of inflammation and oxidative stress demonstrated that plasma adiponectin was significantly and negatively correlated with serum CRP and plasma MDA levels. These relationships were independent from other factors, suggesting that adiponectin may alleviate oxidative stress (Lim et al. 2007).

There is a strong positive correlation between serum leptin concentration and insulin resistance (Matsubara et al. 2002 , Mantzoros et al. 1999, Matsubara et al. 2003). However, in animal models leptin shows significant insulin sensitizing effect: co-administration of recombinant leptin and adiponectin, where both adipokines were essential for the appropriate insulin sensitization, could reverse the severe insulin resistance of lipoatrophic mice (Yamauchi et al. 2001). According to it, leptin therapy improved glycemic control and decreased triglyceride levels in lypodystrophic patients, too (Petersen et al. 2002). This raises the possibility that hyperleptinemia is a marker of those processes that result in insulin resistance, but leptin itself may have insulin sensitizing effect. However, leptin has been shown to be involved in the stimulation of sympathetic activity, endothelial production of endothelin-1 and reactive oxygen species, proinflammatory immune response, migration, and proliferation of vascular smooth muscle cells, and calcification of vascular cells (Kougias et al. 2005) that contribute to the insulin resistance,

hypertension and atherosclerosis. Furthermore, leptin shows inverse association with PON1 in obese individuals with preserved kidney function (Ferretti et al. 2005). However, since in patients with kidney failure in whom hyperleptinemia is typically present, high leptin level was not associated with decreased PON1 activity, leptin is probably not responsible for the low PON1 activity in this patient population (Varga et al. 2006).

Resistin as a member of family of cysteine-rich secretory proteins called resistin-like molecules or FIZZ (found in inflammatory zones) proteins is secreted by adipocytes in rodents. In rodents, exogenous administration of resistin induces hepatic insulin resistance (Rajala et al. 2003). However, in humans, resistin is secreted mostly by macrophages (Fain et al. 2003, Yang et al. 2003, Patel et al. 2003, Kaser et al. 2003, Lu et al. 2002, Reilly et al. 2005) and behaves as an inflammatory protein (Reilly et al. 2005). Most of the work in humans (Reilly et al. 2005, Azuma et al. 2003, Lee et al. 2003, Degawa-Yamauchi et al. 2003), but with some exceptions (Silha et al. 2003, Chen et al. 2005), detected no correlation between serum levels of resistin and insulin resistance. The relationship of obesity and serum levels of resistin is not clear. There are reports of positive association between resistin and markers of adiposity (Azuma et al. 2003, Degawa-Yamauchi et al. 2003, Yannakoulia et al. 2003, Volarova de Courten et al. 2004, Fujinami et al. 2004), while other studies found no association (Reilly et al. 2005, Lee et al. 2003; Silha et al. 2003, McTernan et al. 2003, Seow et al. 2004, Savage et al. 2001, Pfutzner et al. 2003, Hegele et al. 2003, Fehmann et al. 2002). Li et al (2006) demonstrated that resistin is positively associated with visfatin, another adipokine that has a decreased level in diabetic patients. Chen et al. (2005) found a negative correlation between HDL-C and serum levels of resistin, but only in men. Therefore, the exact relation of resistin and metabolic syndrome, a cluster of metabolic and inflammatory features, is uncertain. However, in humans, most of the works (Reilly et al. 2005, Azuma et al. 2003, Lee et al. 2003, Degawa-Yamauchi et al. 2003), with some exceptions (Silha et al. 2003, Chen et al.

2005), detected no correlation between serum level of resistin and insulin resistance.

In contrast to the clear inverse correlation between leptin level and PON1 among individuals with normal kidney function, the association of serum levels of resistin with PON1 has been unclear.

In patients undergoing hemodialysis, the levels of CRP (Costa et al. 2008, Goicoechea et al. 2008, Bolton et al. 2001), and fibrinogen were higher (Goicoechea et al. 2008, Kaysen et al. 2003, Bolton et al. 2001). Both of them were independent predictors of all-cause and cardiovascular mortality by multivariate Cox regression analysis providing prognostic information in chronic kidney disease patients (Goicoechea et al. 2008, Zoccali et al. 2003). Fibrinogen level also positively correlated with CRP in these patients (Kim et al. 2005, Kaysen et al. 2003). Furthermore, Kaysen et al (2003) also found that fibrinogen level was directly related to albumin and age suggesting a hypothesis that fibrinogen secretion, in the acute phase response, is regulated, at least in part by factors that also increase albumin synthesis.

Investigating the relationship between nutritional status (i.e. serum albumin concentration) and CRP in haemodialysis patients, Tirmenstajn-Janković et al. (2007) could demonstrate by univariate analysis that fibrinogen and CRP were associated with malnutrition. In a multiple regression model they also found that, beside BMI, CRP was also an independent variable of serum albumin concentration.

Oxidative stress is also high in chronic dialysis patients (Dirican et al. 2007, Durak et al. 2004, Paul et al. 1993, Lukoseviciene et al. 2003, Chugh et al. 2000, Mimić-Oka et al. 1999, Loughrey et al. 1994, Atamer et al. 2008, Valentini et al. 2008) which is further exacerbated by hemodialysis treatment itself (Loughrey et al. 1994), as evidenced by increased lipid peroxidation, i.e. elevated MDA and low antioxidant levels, i.e. decreased glutathione peroxidase. Level of MDA is significantly increased with the severity of kidney dysfunction (Mimić-Oka et al. 1999). MDA levels were

also associated with PON1 activity suggesting that patient with chronic kidney disease exhibits an oxidant-antioxidant imbalance related to high levels of atherosclerotic risk factors (Atamer et al. 2008). Furthermore, MDA level not only correlates positively with the duration of haemodialysis program (Valentini et al. 2008), but the survival was independently predicted by it (Scott et al. 2003). Actually, Miler et al. (2006) found MDA level being the best marker for risk estimation of cardiovascular events in long-term dialyzed patients.

In opposite to MDA levels, studies measuring GSH as another marker of oxidative stress gave conflicting result in HDPS. Chugh et al. (2000) found decreased, while Valentini et al. (2008), in opposite, elevated GSH levels. In comparison with healthy subjects Paul et al. (1993) showed significantly lower glutathione peroxidase activity among these patients with an inverse correlation between MDA and GSH suggesting the existence of a mainly intracellular oxidizing stress.

Regarding the catalase in HDPS, some authors demonstrated decreased (Lukoseviciene et al. 2003, Mimić-Oka et al. 1999), others increased activity compared to controls (Fatouros et al. 2008), while Atamer et al. (2008) found no difference among these patients.

Aims

Aims of the studies were to investigate the role of adipokines in modifying metabolic syndrome beyond anthropometric, glycemic characteristics, or blood pressure, including HDL-C (i.e. PON1 activity) as well as endothelial functions (i.e. markers of lipid peroxidation and proinflammatory state), and insulin resistance. For this purpose two different patient patient's groups were chosen. The first was a group of patients with kidney failure, in whom both leptin and adiponectin levels are higher than in normal population. The second group was recruited from a patient's group with preserved kidney function (PKI) and a high range of BMI in whom leptin levels are supposed to be increased, while adiponectin decreased proportional to BMI elevation.

Aim 1. To test if the uremic hyperadiponectinemia has protective effects on the following vascular abnormalities:

i) decreased serum PON1 activity

ii) inflammatory activation of the endothelium

iii) enhanced oxidative stress

Aim 2. Semi-quantitatively determine the impacts of serum NEFA, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), leptin, adiponectin and resistin levels on insulin resistance measured by homeostasis model assessment (HOMA-IR).

Aim 3. To examine the association of serum levels of resistin as an adipose tissue biomarker with

i) serum PON1 activity

ii) parameters of metabolic syndrome (beyond the blood pressure, anthropometric or glycemic characteristics, including insulin resistance, serum levels of leptin, NEFA, and a marker of lipid peroxidation).

Methods

Participants

The study was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association and approved by the Local Ethics Committee. Subjects participated in the studies gave written informed consent.

The investigations were carried out in two different patient's groups. The first was a hemodialysed patient's group (HDPS). The main characteristics of 70 HDPS are discussed in the Section of Results, **Table 1**. Eighteen of HDPS had polycystic kidney disease, 13 diabetic nephropathy, 12 glomerulonephritis, 11 pyelonephritis, 8 ischemic renal disease, 4 idiopathic kidney atrophy, 2 nephrotic syndrome and 2 had earlier nephrectomy. Fifty one of the HDPS took antihypertensive medication, and 19 had diabetes. The form of hemodialysed treatment was hemodiafiltration in every patient, except two of them in whom high flux hemodialysis treatment alone could be applied. Kt/V (dialysis efficiency) was calculated by the use of Kt/V = - ln (R 0.03-0.075 x UF/W) equation, where R = ratio of blood urea concentration measured after and before dialysis, UF = volume of ultrafiltrate (l), W = body weight after dialysis (kg). Mean (lower/upper quartile) HD time of patients was 38 (16.7 / 62.7) months. Blood specimens for investigations were obtained before the dialysis sessions.

The second patient's group consisted of 74 individuals (50 obese patients and 24 healthy volunteers) with preserved kidney function (PKI) and a wide range of BMI (ranged from 20 to 62 kg/m^2) of whom 3 age- and sex-matched BMI groups were formed, in order to magnify the impact of obesity on the investigated parameters.

The obese individuals (30 female and 20 male) were ambulatory overweight-obese participants (body mass index, BMI exceeding 28 kg/m^2), aged 35.7 ± 10.9; 18-55 years who were randomly selected from

18-65 year old Caucasian people attending Obesity Clinic. BMI ranged from 28 to 62 kg/m^2 among these subjects. All of them were in good general condition. The recruitment of participants was performed so that two similar size BMI groups were formed, BMI ≥40 and BMI between 28 and 39.9 kg/m^2, respectively. Twenty-three patients had hypertension. One of the women was in postmenopausal state (classified by the combination of age and lack of periods for more than 6 months). None of the patients involved in the study had evidence of liver disease defined as alanine aminotransferase or aspartate aminotransferase >1.5 times the upper limit of normal range, thyroid disorders, and infectious diseases or significant inflammation for 3 months prior to study, malignancy, coronary artery disease, blood pressure >160/100 mmHg, cerebral vascular disease, smoking, triglyceride levels higher than 4.5 mmol/L, alcoholism, drug dependence, pregnancy or lactation, anticoagulant, lipid lowering, glucocorticoid, oral contraceptive or sex hormone replacement medication.

Twenty-four age- and sex-matched healthy volunteers (14 and 10 women and men, respectively) with BMI: 20-24.9 (mean 22.4 ± 1.7) kg/m^2, and mean age of 38.4 (± 9.9; 26-58) years served as a control group. Healthy state was defined as without known major disease and/or complaints, a blood pressure less than 140/90 mmHg, normal laboratory tests, including renal and liver function, fasting plasma glucose levels. None of them (i) had hyperlipidemia, or (ii) took medication at the time of the study.

Height and weight were measured while the subjects wore indoor clothes and shoes. BMI was calculated as weight (kg)/ [height (m)] ^{2}. The waist measurement was taken in standing position as the narrowest circumference midway between the lower border of the ribs and upper border of the iliac crest. Systolic and diastolic blood pressures (BP) were measured twice with the subject in the sitting position after resting for at least 5 min using a quality approved automatic electronic sphygmomanometer.

Metabolic syndrome was defined according to the IDF criteria (Alberti): waist circumference ≥94 cm for Europid men and ≥80cm for Europid women, plus any two of the following four factors:

• raised TG level: ≥1.7 mmol/L, or specific treatment for this lipid abnormality

• reduced HDL-C: <1.03 mmol/L in males and <1.29 mmol/L in females, or specific treatment for this lipid abnormality

• raised blood pressure: systolic BP ≥130 or diastolic BP ≥85 mmHg, or treatment of previously diagnosed hypertension

• raised fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes

Biochemical analyses

For routine automated laboratory analyses Cobas Integra 700 Autoanalyzer was used (Roche, Schwitzerland), applying hexokinase method for serum glucose, uricase-PAP method for uric acid, cholesterol esterase/oxidase-PAP method for total cholesterol (TC), glycerol-phosphate-oxidase-PAP method for triglyceride (TG) determination. High-density lipoprotein cholesterol (HDL-C) was measured by direct method. Low-density lipoprotein cholesterol (LDL-C) level was estimated using the Friedewald's formula. Concentrations of albumin and high sensitivity CRP were measured by turbidimetric immunoassay (Roche Cobas Integra), parathormone and insulin by electro-chemiluminescence immunoassay (Roche Elecsys), fibrinogen by Clauss Derived Fibrinogen assay (Sysmex CA 5000 Coagulation analyzer). HbA_{1C} (%) was measured by high-performance liquid chromatography (Bio-Rad Laboratories, Inc., Hercules, CA, USA). The insulin resistance index calculation was based on homeostasis model assessment (HOMA-IR) (Matthews et al. 1985). Serum concentration of adiponectin, and sE-selectin were measured by commercially available sandwich enzyme immunoassays (Quantikine, R&D Systems, Minneapolis, MN, USA). The adiponectin measurement

had intra- and interassay CV ranging from 2.5 to 4.7%, and from 6.8 to 6.9%.

PON1 activity was characterized with using either paraoxone or phenylacetate as a substrate. In the assay using paraoxone, the PON1 activity was determined as described earlier (Paragh et al. 1998). The increase in the absorbance was measured in the Hewlett-Packard 8453 UV-Visible spectrophotometer at 412 nm, and at 25°C due to the formation of 4-nitrophenol after the addition of 50 µl serum to 1 ml Tris/HCl buffer (100 mmol/L, pH 8.0) containing 2 mmol/L $CaCl_2$, and 5.5 mmol/L paraoxone (O,O-diethyl-O-p-nitrophenylphosphate; Sigma). Enzymatic activity was calculated using the molar extinction coefficient of 17,100 M^{-1} cm^{-1}. One unit of paraoxonase activity was defined as 1 nmol of 4-nitrophenol formed per minute under the above assay conditions. The intra-, and inter-assay coefficients of variation in PON1 activities were <3%.

In the assay using phenylacetate this substrate was applied in 1 mmol/l concentration. The reaction was made in 20 mmol/l Tris/HCl pH 8.0 and the increase of absorbance according to the addition of the serum was read at 270 nm using a Hewlett-Packard 8453 UV-Visible spectrophotometer. Blanks were included to correct the spontaneous hydrolysis of substrate. Enzyme activity was calculated using a molar extinction coefficient of 1310 M^{-1} cm^{-1}. One unit (U) is defined as 1 µmol substrate hydrolyzed per minute. The intra-, and inter-assay coefficients of variation were <3% in the tests.

The phenotypic distribution of PON1 was determined by the dual substrate method (Smolen et al. 1991) according to as we have already described (Seres et al. 2004). During this assay, the ratio of salt-stimulated paraoxonase to the hydrolysis of phenylacetate was used to assign individuals to one of the three possible phenotypes. Cut-off values between phenotypes were as follows: ratio <3.0 for AA, ratio between 3.0 and 7 for AB and ratio >7.0 for BB phenotype. In the salt-stimulated paraoxonase

measurement the increase in the absorbance was measured with the Hewlett-Packard 8453 UV-Visible spectrophotometer at 412 nm, and at 25 °C due to the formation of 4-nitrophenol after the addition of 50 µl serum to 1 ml Tris/HCl buffer (100 mmol/L, pH 8.0) containing 2 mmol/L $CaCl_2$, 1 mol/L NaCl and 5.5 mmol/L paraoxone (*O*,*O*-diethyl-O-*p*-nitrophenylphosphate; Sigma). Enzymatic activity was calculated using the molar extinction coefficient of 17,100 M^{-1} cm^{-1}. One unit of paraoxonase activity was defined as 1 nmol of 4-nitrophenol formed per minute under the above assay conditions.

Lipid peroxidation was evaluated by the following measurements.

In case of plasma levels of MDA or thiobarbituric acid reactive substances (TBARS) basically the Matkovics method was used: whole blood was precipitated with a mixture of TCA and TBA and boiled, and the supernatant was measured by photometric at 532 nm expressing the results in nmol/ml (Placer et al. 1966). In PKPS a butanol extraction was applied before the photometric measurement (Galli et al. 2001).

For the determination of blood GSH level, at first TCA was added, and then DTNB (5,5'-dithiobis 2 nitrobenzoic acid [Serva 20735]) to the supernatant of a low-temperature centrifugation. Photometric measurement was done at 412 nm expressing the results of GSH in nmol/ml (Sedlak et al. 1968).

During the determination of catalase enzyme activity from blood the decrease of peroxide concentration was detected at 240 nm (U.V. spectrophotometry on Perkin-Elmer Spectrophotometer) getting the results in BU/ml, where 1 BU means 1 g peroxide destruction per minute.

The plasma concentration of non-esterified fatty acid (NEFA) was measured by optimized enzymatic colorimetric assay (Roche Diagnostics Gmbh, Penzberg, Germany). Serum concentration of resistin was measured by sandwich enzyme immunoassays (BioVendor Laboratory Medicine, Inc., Brno, Czech Republic) that had intra- and interassay CVs ranging from 2.8 to 3.4%, and from 5.1 to 6.9%, respectively. Plasma

concentration of leptin was measured by competitive enzyme immunoassay (WAK-Chemie Medical GMBH, Bad Soden, Germany) that had intra- and interassay CV ranging from 4.2 to 5.4%, and from 3.6 to 8.6%, respectively, and 95 percent concordance with radio-immunoassay.

Statistical analysis

Statistical analyses were performed using the SPSS 11.0 software (SPSS, Inc., Chicago, IL, USA). Normality of distribution of data was tested by Kolmogorov-Smirnov test. Non-normally distributed parameters were transformed logarithmically to correct their skewed distributions.

Differences across paired HDPS subgroups were tested with Student's *t* test. Differences between anthropometry and laboratory characteristics across various BMI groups in the PKI were tested with Bonferroni corrected one-way ANOVA and to assess the difference in metabolic syndrome among the various BMI groups Chi-Square tests were applied. Similarity of gender and age distributions of the three predefined BMI subgroups in PKI was verified by two-way ANOVA with Bonferroni and Scheffe post hoc tests and the differences between anthropometry and laboratory characteristics across various BMI, and PON1 phenotype groups were tested with one-way ANOVA. Furthermore, three-way ANOVA was performed to see the impact of age, sex and BMI category on resistin levels. Patients were classified into age quartiles for the test. To assess the difference in the distribution of PON1 phenotypes and metabolic syndrome among the various BMI groups, Chi-Square tests were applied. Univariate correlations were assessed by Pearson's test, while multivariate ones by backward multiple regression analyses. During the latter we tried to avoid the inclusion of too closely linked variables (e.g. waist beside BMI, or HDL-C beside triglyceride or HOMA-IR) that might have neutralized each others' effects.

Data were expressed as means ± S.D. in case of normal distribution, and median (lower/upper quartile) in case of non-normal distribution. Values of $P < 0.05$ were considered statistically significant.

Results

Studies on hemodialysed patients (HDPS)

Subgroup analyses.

The patient's group has been divided into subgroups, according to median values of (i) adiponectin (**Table 1**), and (ii) HOMA-IR (**Table 2**).

Table 1. Anthropometric and selected laboratory characteristics in the whole studied patient's group and the two adiponectin subgroups of HDPS (adiponectin >, or ≤compared to median 17.6 value, respectively)

	Total patient's group	Adiponectin >17.6	Adiponectin ≤17.6
N	70	35	35
Age (y)[a]	56.2 ± 11.5	55.8 ± 12.5	56.5 ± 10.5
Female / male	37 / 33	19 / 16	18 / 17
BMI (kg/m^2)[a]	26.4 ± 5.7	24.1 ± 4.3	28.7 ± 6***
Waist (cm)[a]	99.8 ± 15.9	93 ± 13.3	106.5 ± 15.6***
Diabetes	19	6	13
Dialysis efficiency (Kt/V)[a]	1.58 ± 0.26	1.66 ± 0.22	1.51 ± 0.28*
HD time (months)[b]	38 (16.7 / 62.7)	38 (17 / 65)	36 (16 / 55)
Systolic BP (mmHg)[a]	126.9 ± 16.8	126 ± 13.5	128 ± 19.7
Diastolic BP (mmHg)[b]	79 (70 / 91)	77 (69 / 86)	81 (70 / 93)
Creatinine (μmol/l)[b]	692.5 (619.3 / 854.5)	688 (606 / 938)	697 (627 / 846)
Albumin (g/L)[a]	39.3 ± 3.9	38.3 ± 4.1	40.3 ± 3.5*
CRP (mg/L)[b]	7.9 (3.5 / 14.1)	7.5 (1.5 / 11.1)	8.6 (5 / 14.2)*
Fibrinogen (g/L)[a]	4.2 ± 1.1	3.9 ± 1.2	4.4 ± 0.9
sE-Selectin (ng/mL)[a]	38.7 ± 15.9	38.5 ± 17.4	38.8 ± 14.6
Plasma glucose (mmol/l)[b]	5.5 (5 / 6.7)	5.5 (4.8 / 6.4)	5.4 (5.1 / 7.7)
HOMA-IR ($mU{\cdot}mmol/L^2$)[b]	3.5 (1.9 / 7.9)	2.5 (1.2 / 5.6)	5.5 (2.8 / 11)**
Triglyceride (mmol/l)[a]	1.9 ± 0.9	1.7 ± 0.8	2.3 ± 0.9**
Total cholesterol (mmol/l)[a]	4.6 ± 0.9	4.6 ± 0.9	4.5 ± 1.1
HDL-C (mmol/l)[b]	0.90 (0.8 / 1.2)	1.0 (0.9 / 1.2)	0.85 (0.78 / 1)**
LDL-C (mmol/l)[a]	3.1 ± 0.9	3.1 ± 0.8	3.2 ± 0.9
Parathormone (pmol/l)[b]	29.9 (14.5 / 59.3)	41.1 (16.3 / 66.5)	27.0 (10.3 / 46.6)
Adiponectin (μg/mL)[b]	17.6 (13.4 / 27.6)	27.4 (21.0 / 47.2)	13.4 (11.0 / 15.2)***
PON1 activity (U/L)[b]	51.2 (35.1 / 119.2)	50.4 (33.6 / 121.0)	52.6 (36.6 / 118.4)
MDA (nmol/mL)[b]	94.6 (84.9/107.1)	94.9 (85 / 104.4)	94.9 (84.3 / 109.3)
GSH (nmol/mL)[b]	120.8 (105.3/134.4)	118.4 (102 / 133.6)	128.2 (108.2 / 134.8)
Catalase (BE/ml)[b]	94 (73.1/128)	94 (73.1 / 135.8)	94 (83.6 / 125.4)
Total peroxidase (μmol/l)[b]	121.8 (68.2/215)	112.6 (68.2 / 265.9)	134 (67.8 / 208.5)

[a]: Normal distribution, data are mean ± SD. [b]:Non-normal distribution, data are median (lower/upper quartile).
Significant differences between the adiponectin subgroups: *: P <0.05; **: P <0.01; ***: P <0.001.
Abbreviation: BP: blood pressure.

Table 2. Anthropometric and laboratory characteristics of two HOMA-IR subgroups in HDPS (HOMA-IR ≤, or >compared to median 3.6 value, respectively)

	HOMA-IR ≤3.6	HOMA-IR >3.6
N	35	35
Age (y)[a]	54.5 ± 11.4	57.7 ± 11.6
Female / male (n/n)	21 / 14	16 / 19
BMI (kg/m^2)[a]	24.3 ± 3.9**	28.4 ± 6.5
Waist (cm)[a]	93.4 ± 12.3***	105.9 ± 16.8
Diabetes (n)	4**	15
Dialysis efficiency (Kt/V)[a]	1.67 ± 0.21**	1.51 ± 0.27
HD time (months)[b]	38 (12 / 69)	37 (16.7 / 51.2)
Systolic BP (mmHg)[a]	127.7 ± 16.5	126.2 ± 17.6
Diastolic BP (mmHg)[b]	76 (68 / 85)	82 (71 / 95)
Creatinine (μmol/l)[b]	673 (614 / 811)	758 (617 / 913)
Albumin (g/L)[a]	39.9 ± 4	38.6 ± 3.7
CRP (mg/L)[b]	5.2 (1.7 / 9.9)**	9.4 (5.1 / 22)
Fibrinogen (g/L)[a]	4.2 ± 0.9	4.1 ± 1.2
sE-Selectin (ng/ml)[a]	39.9 ± 19.8	37.5 ± 11.3
Plasma glucose (mM)[b]	5.1 (4.8 / 5.5)***	6.7 (5.6 / 8)
HOMA-IR (mU·mmol/L^2)[b]	1.9 (1.1 2.8/)***	7.9 (5.6 / 11)
Triglyceride (mmol/l)[a]	1.7 ± 0.8**	2.2 ± 0.9
Total cholesterol (mmol/l)[a]	4.7 ± 0.9	4.4 ± 1.1
HDL-C (mmol/l)[b]	1.0 (0.8 / 1.3)***	0.8 (0.7 / 0.9)
LDL-C (mmol/l)[a]	3.2 ± 0.8	3.0 ± 0.9
Parathormone (pmol/l)[b]	28.9 (19.0 / 65.5)	31.4 (9.6 / 59.5)
Adiponectin (μg/mL)[b]	20.6 (16.2 / 30.4)**	14.8 (11.0 / 22.2)
PON1 activity (U/L)[b]	55.6 (35.1 / 117)	46.8 (34.3 / 127.2)
MDA (nmol/mL)[b]	96.1 (86.5 / 109.8)	94.3 (84.3 / 103.6)
GSH (nmol/mL)[b]	125.9 (106.3 / 134.3)	118.9(105.2 / 142.5)
Catalase (BE/mL)[b]	94 (86.5 / 109.7)	99.3 (73.2 / 135.9)
Total peroxidase (μmol/L)[b]	138 (69.6 / 209.8)	109.1 (62.2 / 266)

[a]: Normal distribution, data are mean ± SD. [b]:Non-normal distribution, data are median (lower / upper quartile).
Significant differences between the HOMA-IR subgroups: *: P <0.05; **: P <0.01; ***: P <0.001.
Abbreviation: BP: blood pressure.

The following investigated characteristics were significantly higher in the lower adiponectin subgroup: BMI, waist, albumin, CRP, HOMA-IR, and triglyceride; while dialysis efficiency and HDL-C were significantly lower. In the more insulin resistant group, the BMI, waist circumference, diabetes incidence, CRP, glucose, and triglyceride were significantly higher, while the dialysis efficiency, HDL-C, and adiponectin were significantly lower.

Among the diabetic patients (n = 19) the dialysis efficiency and HD time were lower as compared to the non-diabetic groups (n = 51): Kt/V: 1.44 ± 0.22 vs. 1.64 ± 0.25, P <0.01, and 32 (7 / 40) vs. 39 (19 / 69) months, P <0.05, respectively.

Univariate correlations.

The following parameters had to be transformed logarithmically to approximate normal distributions: HD time, diastolic blood pressure, creatinine, CRP, plasma glucose, HOMA-IR, HDL-C, parathormone, adiponectin, and PON1 activity. Pearson's correlations between selected variables with special interest are demonstrated in **Table 3**.

Table 3. Pearson's correlation coefficients of adiponectin and PON1 with selected variables in HDPS

	Adiponectin	PON1	sE-Selectin
Age[a]	0.021	0.044	-0.40**
BMI [a]	-0.439***	-0.074	-0.02
Waist[a]	-0.471***	-0.003	-0.02
Dialysis efficiency[a]	0.351**	0.111	0.01
HD time[b]	-0.047	0.067	-0.218
Systolic BP[a]	-0.059	0.226	-0.04
Diastolic BP[b]	-0.106	0.125	0.05
Creatinine[b]	-0.183	0.096	0.187
Albumin[a]	-0.338**	0.027	0.233
CRP[b]	-0.278*	-0.076	0.115
Fibrinogen[a]	-0.290*	-0.031	0.004
sE-Selectin[a]	-0.060	0.126	-
Plasma glucose[b]	-0.109	0.084	-0.097
HOMA-IR[b]	-0.375***	-0.050	0.003
Triglyceride[a]	-0.359**	-0.006	0.06
Total cholesterol[a]	0.180	-0.045	0.017
HDL-C[b]	0.501***	0.055	0.09
LDL-C[a]	0.090	-0.077	-0.05
Parathormone[b]	0.036	0.082	-0.048
Adiponectin[b]	-	0.011	-0.06
PON1 activity[b]	-0.03	-	0.12

[a]: Normal distribution. [b]:Non-normal distribution.
*: P <0.05; **: P <0.01; ***: P <0,001.
Abbreviation: BP: blood pressure.

Adiponectin level was correlated positively with dialysis efficiency, and HDL-C, while negatively with BMI, waist, albumin, CRP, fibrinogen, HOMA-IR, and triglyceride levels. PON1 activity did not have any significant association with the investigated parameters. The level of sE-Selectin showed an inverse correlation only with the age.

Correlation pattern of dialysis efficiency was very similar: positive one with HDL-C ($R = 0.46$, $P < 0.001$), while negative with BMI ($R = -0.51$, $P < 0.001$), waist ($R = -0.49$, $P < 0.001$), CRP ($R = -0.32$, $P < 0.01$), fibrinogen ($R = -0.30$, $P < 0.05$), and HOMA-IR ($R = -0.33$, $P < 0.01$), but did not show association with albumin ($R = 0{,}02$, $P = 0.88$) (data not shown in table). Trends of correlations were similar in both diabetic and non-diabetic subgroups.

Pearson's correlations between oxidative stress markers and selected variables with special interest are demonstrated in **Table 4**.

Table 4. The Pearson's correlations of oxidative stress markers with other parameters.

	MDA	GSH	Catalase	Total peroxidase
Age[a]	0.08	-0.09	-0.17	0.17
BMI[a]	0.05	-0.15	0.04	0.01
Waist[a]	0.03	-0.08	0.006	0.07
Dialysis efficiency[a]	0.03	0.004	0.1	0.05
Systolic BP[a]	-0.001	-0.3*	0.004	0.06
Diastolic BP[b]	-0.03	-0.24*	0.131	0.06
sE-Selectin[a]	-0.006	-0.05	0.14	0.09
HOMA-IR[b]	-0.016	-0.09	-0.01	-0.001
Triglyceride[a]	0.1	-0.12	0.21	-0.09
HDL-C[b]	-0.1	0.25*	-0.16	0.08
LDL-C[a]	-0.1	0.2	-0.08	0.09
Adiponectin[b]	-0.15	0.06	-0.1	0.08
MDA[b]	-	-0.14	0.29*	-0.08
GSH[b]	-0.14	-	-0.08	-0.18
Catalase[b]	0.29*	-0.08	-	0.05
Total peroxidase[b]	-0.08	-0.18	0.05	-

[a]: Normal distribution. [b]:Non-normal distribution.
*: $P < 0.05$
Abbreviation: BP: blood pressure.

Only the level of GSH had significant association, as was expected, a positive one with HDL-C, and a negative one with blood pressure. Analyzing the inner correlations of oxidative stress markers we found significant correlations between the catalase and MDA.

Multivariate correlations.

The independent predictors of adiponectin level were tested in multiple regression models (**Table 5**). At first, two less adjusted models (Model 1 and 2) were constructed in which, beside the albumin, the impact of age, sex, and BMI were tested. In Model 3 CRP was also included, while in the more fully adjusted model, Model 4, HOMA-IR, as a parameter of metabolic syndrome, too. Of the selected anthropometric and laboratory variables, the correlations with adiponectin level were independent in case of BMI, albumin concentration and HOMA-IR (but not CRP). Investigating the independent predictors of sE-Selectin, of the selected anthropometric, blood pressure and laboratory variables only age turned out being significant (**Table 6**).

Table 5. Multiple regression analysis for adiponectin as a dependent variable

	Model 1 (R^2 = 0.222)			Model 2 (R^2 = 0.325)		
Variable	*β*	*t*	*P*	*β*	*t*	*P*
Age	0.149	1.323	0.19	0.075	0.694	0.49
Sex	-0.104	-0.953	0.344	-0.061	-0.59	0.557
BMI	**-0.476**	**-4.242**	**0.001**	**-0.468**	**-4.448**	**0.001**
Albumin	**-**	**-**	**-**	**-0.331**	**-3.149**	**0.002**
CRP	-	-	-	-	-	-
HOMA-IR	-	-	-	-	-	-

	Model 3 (R^2 = 0.354)			Model 4 (R^2 = 0.396)		
Variable	*B*	*t*	*P*	*β*	*t*	*P*
Age	0.068	0.635	0.528	0.095	0.897	0.373
Sex	-0.073	-0.718	0.476	-0.044	-0.437	0.664
BMI	**-0.421**	**-3.917**	**0.001**	**-0.358**	**-3.281**	**0.002**
Albumin	**-0.331**	**-3.194**	**0.002**	**-0.333**	**-3.271**	**0.002**
CRP	-0.179	-1.716	0.091	-0.122	-1.152	0.254
HOMA-IR				**-0.238**	**-2.163**	**0.034**

Significant values are indicated in bold; *β* is standardized regression coefficient

Table 6. Multiple regression analysis for sE-Selectin as a dependent variable in HD group

	Model (R^2 = *0.212)*		
Variable	*β*	*t*	*P*
Age	**-0.403**	**-3.601**	**0.001**
Sex	0.096	0.820	0.415
BMI	0.086	0.74	0.462
Systolic BP	-0.088	-0.76	0.45
Kt/V	0.116	1.041	0.302
Adiponectin	-0.02	-0.15	0.881
PON1	0.116	1.034	0.305

Significant value indicated in bold; *β* is standardized regression coefficient.
Abbreviation: BP: blood pressure.

In other models we also investigated the dialysis efficiency as a variable, but this was not an independent predictor of adiponectin when BMI was also included in the model, beside age and gender (data not shown).

Studies on individuals with preserved kidney function (PKI)

Subgroup analyses.

Anthropometric and laboratory characteristics of the second patient patient's group divided by BMI categories and genders are shown in **Table 7** and **8**.

Table 7. Anthropometric and selected laboratory characteristics in individuals with preserved kidney function

BMI	**≥40**	**28 - 39.9**	**20 - 24.9**
N	25	25	24
Age (y)[a]	37.0 ± 10.4	37.1 ± 11.4	38.4 ± 9.9
Female/Male (n/n)	15/10	15/10	14/10
BMI (kg/m^2)[a]	45.8 ± 5.3*†	34.0 ± 2.8*†	22.4 ± 1.7
Waist (cm)[a]	128.5 ± 17.9*†	108.3 ± 11.6*†	79 ± 7.5
Systolic BP (mmHg)[a]	137 ± 10.6*	137 ± 14.8*	112 ± 10.8
Diastolic BP (mmHg)[a]	86 ± 10.0*	85 ± 7.8*	71 ± 8.0
Plasma glucose (mmol/l)[b]	5.5 (4.7/5.6)*	5.1 (4.8/5.3)*	4.4 (4/4.7)
HbA_{1C} (%)[b]	5.6 (5.4/6.2)	5.6 (5.4/5.9)	5.45 (5.3/5.7)
Plasma insulin (mU/l)[b]	23.7 (19.0/27.7)	17.3 (14.5/30.6)	16.4 (14.9/20.0)
HOMA-IR (mU·mmol/l^2)[b]	5.16 (3.9/6.7)*	3.92 (3.1/7.2)	3.22 (2.64/4.14)
Uric acid (µmol/l)[a]	338 ± 104*	328 ± 72	250 ± 64
Triglyceride (mmol/l)[b]	1.70 (1.1/2.3)*	1.47 (1.2/1.9)*	0.89 (0.72/1.26)
Total cholesterol (mmol/l)[b]	5.38 (4.6/5.7)	5.40 (5.0/5.75)	4.86 (4.3/4.5)
HDL-C (mmol/l)[a]	1.17 ± 0.24*	1.23 ± 0.28*	1.7 ± 0.53
LDL-C (mmol/l)[b]	3.30 (2.9/3.7)*	3.40 (2.9/3.5)*	2.74 (2.2/3.35)
NEFA (mmol/l)[a]	0.48 ± 0.19*	0.53 ± 0.22*	0.26 ± 0.14
TBARS (µmol/l)[b]	1.23 (1.2/1.5)*	1.18 (1.1/1.3)*	0.27 (0.21/0.36)
Adiponectin (µg/ml)[b]	4.4 (3.4/6.75)*	7.44 (4.45/10.3)*	11.5 (8,4/14.5)
PON1 activity (U/l)[b]	62.9 (57/72)*	63.5 (54/91)*	100.3 (77/113)
IL-6 (pg/ml)[b]	2.88 (1.78/5.17)*	1.77 (1.1/3,27)*	0.27 (0.15/0.47)
TNF-α (pg/ml)[b]	0.29 (0/1.61)*	0.30 (0/1.97)*	0.22 (0.15/0.46)
Leptin (ng/ml)[b]	40.4 (20.6/64.3)*	37.15 (19.8/55.8)*	2.55 (1.38/3.58)
Resistin (ng/ml)[b]	7.9 (6.3/9.7)*	7.4 (6.2/8.8)*	9.3 (7.7/12.9)*

[a]: Normal distribution, data are mean ± SD. [b]:Non-normal distribution, data are median (lower / upper quartile).
*: Significant differences between normal and obese BMI group; †: significant differences between the 2 obese groups
Abbreviation: BP: blood pressure.

Among overweight-obese subjects the BMI had a wide range, from 28 to 62 kg/m^2 with a mean of 40.6 ± 7.35 kg/m^2. Age and male/female ratio did not differ among BMI subgroups. Although the female participants in the whole study patient's group were significantly older than males (39.8 ± 10,4 vs. 34.1 ± 9,8 years), interaction between the anthropometric factors was not

significant. According to data from literature, HDL-C and leptin levels were higher among women than in men.

The following parameters were significantly higher in at least one of the obese groups as compared to normal controls: systolic and diastolic blood pressure, fasting plasma glucose, HOMA-IR, uric acid, triglyceride, LDL-C, NEFA, TBARS, IL-6, TNF-α and leptin levels, while HDL-C, PON1 activity and adiponectin level were significantly lower.

Table 8. Anthropometric and selected laboratory characteristics in individuals with preserved kidney function according to genders

	Total	**Women**	**Men**
N	74	44	30
Age (y)[a]	37.5 ± 10.5	39.8 ± 10.4[*]	34.1 ± 9,8
BMI (kg/m^2)[a]	34.7 ± 10.5	34.3 ± 10.2	35.3 ± 11.1
Waist (cm)[a]	106.4 ± 24.4	100.1 ± 21.5	114.6 ± 26.5
Systolic BP (mmHg)[a]	128 ± 16.9	126 ± 17.0	131 ± 16.1
Diastolic BP (mmHg)[a]	80 ± 10.7	79 ± 11.0	82.5 ± 9.8
Plasma glucose (mmol/l)[b]	4.8 (4.4/5.2)	4.9 (4.3/5.2)	4.8 (4.5/5.2)
HbA_{1C} (%)[b]	5.6 (5.3/5.8)	5.5 (5.3/5.8)	5.6 (5.3/6.1)
Plasma insulin (mU/l)[b]	19.0 (14.8/31.1)	20.2 (14.9/31.0)	18.2 (14.7/32.5)
HOMA-IR (mU·mmol/l^2)[b]	4.03 (2.9/6.9)	4.18 (2.9/7.1)	3.93 (2.95/6.7)
Uric acid (µmol/lM)[a]	307 ± 91.5	270 ± 75	306 ± 88
Triglyceride (mmol/l)[b]	1.33 (0.9/1.9)	1.26 (0.9/1.9)	1.42 (0.96/2.01)
Total cholesterol (mmol/l)[b]	5.30 (4.5/5.6)	5.40 (4.6/5.6)	5.23 (4.4/5.5)
HDL-C (mmol/l)[a]	1.36 ± 0.43	1.48 ± 0.50[*]	1.18 ± 0.23
LDL-C (mmol/l)[b]	3.20 (2.8/3.6)	3.20 (2.7/3.6)	3.29 (2.8/3.5)
NEFA (mmol/l)[a]	0.43 ± 0.22	0.44 ± 0.22	0.40 ± 0.21
TBARS (µmol/l)[b]	1.10 (0.3/1.5)	1.05 (0.28/1.5)	1.16 (0.29/1.68)
Adiponectin (µg/ml)[b]	7.28 (4.14/11.29)	7.78 (4.53/12.35)	5.95 (3.19/9.85)
PON1 activity (U/l)[b]	74.1 (58/101)	74.1 (58/99)	74.3 (58/101)
IL-6 (pg/ml)[b]	0.26 (0.26/2.92)	1.36 (0.19/3.49)	1.27 (0.28/2.58)
TNF- (pg/ml)[b]	0.24 (0/1.01)	0.24 (0/1.04)	0.25 (0.06/0.87)
Leptin (ng/ml)[b]	20.5 (3.6/46.7)	23.5 (5.5/49.1)[*]	15.8 (1.68/40.8)
Resistin (ng/ml)[b]	8.3 (6.7/10.3)	8.5 (7.0/10.4)	7.8 (6.7/9.4)

[a]: Normal distribution, data are mean ± SD. [b]:Non-normal distribution, data are median (lower / upper quartile).
[*]: Significantly higher among women than in men
Abbreviation: BP: blood pressure.

Resistin level was higher in the controls than among the obese subjects, without difference between the obese subgroups (7.9; 6.3/9.7 vs. 7.4; 6.2/8.8). Impact of BMI categories on the resistin level remained significant even

after adjustments for age, and gender. The concentrations of resistin were similar in the 3 groups of PON1 phenotypes, and there was no significant difference in the distribution of PON1 phenotypes among the 3 BMI groups of subjects.

Univariate correlations.

The following parameters had to be transformed logarithmically to approximate normal distributions: fasting plasma glucose, HbA1C, fasting plasma insulin, HOMA-IR triglyceride, total and LDL-C, NEFA, TBARS, PON1 activity, IL-6, TNF-α, leptin, and adiponectin.

Pearson's correlation analyses of HOMA-IR are shown in **Table 9**. In summarizing: HOMA-IR was correlated positively with BMI, waist circumference, serum NEFA, leptin, IL-6 and TNF-α levels, while negatively with adiponectin, with no significant association to resistin.

Table 9. Pearson's correlation coefficients of HOMA-IR with selected variables

	HOMA-IR
BMI[a]	0.30[*]
Waist[a]	0.34[**]
NEFA[a]	0.34[**]
Leptin[b]	0.53[†]
Resistin[b]	-0.15
Adiponectin[b]	-0.42[***]
IL-6[b]	0.27[*]
TNF-α[b]	0.30[*]

[a]: Normal distribution. [b]:Non-normal distribution.
[*]: P <0.05; [**]: P <0.01; [***]: P <0.001; [†]: P <0.0001

Pearson's univariate correlation analyses of serum levels of resistin for the whole patient's group, as well as separately for men and women are shown in **Table 10,** while as scatter plots with selected variables in **Figures 1** and **2**.

Resistin correlated negatively with BMI, waist circumference, serum leptin and NEFA levels, systolic BP, HbA_1C, and MDA, and correlated positively

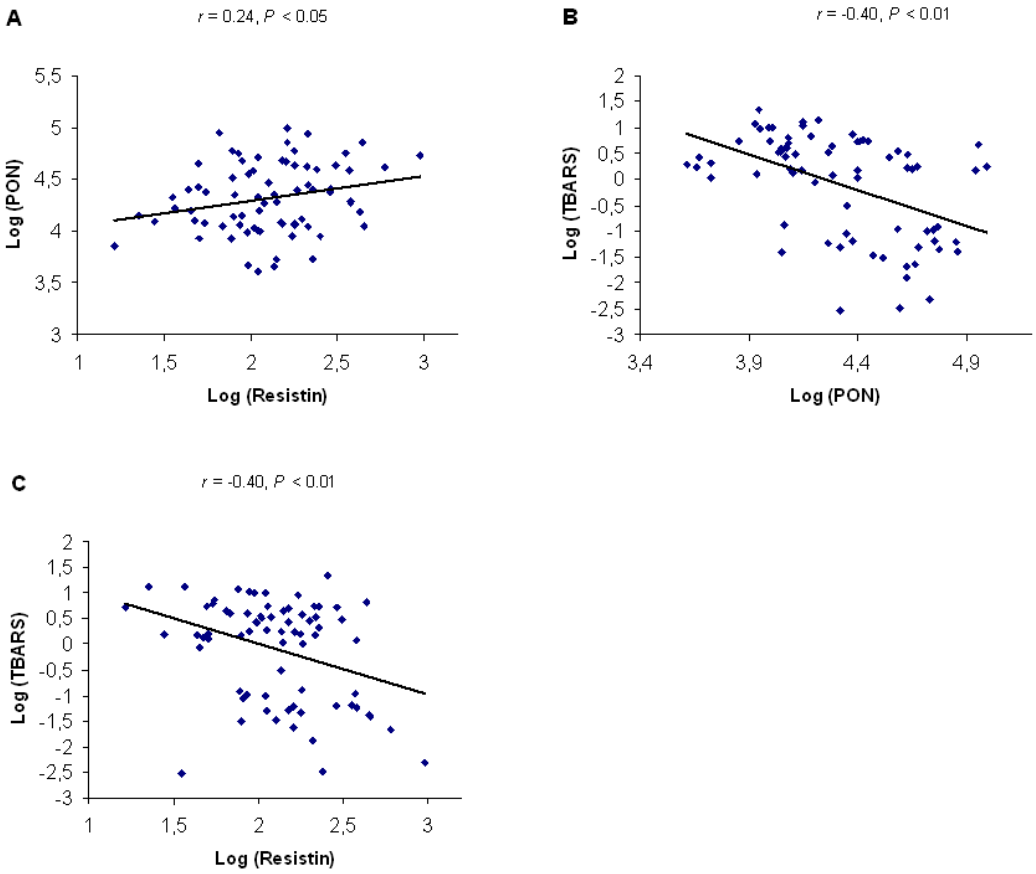
with PON1 activity. No association was found between concentrations of resistin and the following parameters: diastolic BP, levels of uric acid, glucose, insulin, HOMA-IR, triglyceride, total cholesterol, LDL-C, HDL-C. Beside MDA, PON1 activities were also negatively correlated with BMI ($r = -0.39$, $P < 0.01$), waist circumference ($r = -0.42$, $P < 0.001$), systolic BP ($r = -0.32$, $P < 0.01$), levels of HbA1C, ($r = -0.31$, $P < 0.05$), insulin ($r = -0.24$, $P < 0.05$), and HOMA-IR ($r = -0.25$, $P < 0.05$), and correlated positively with concentrations of HDL-C ($r = 0.28$, $P < 0.05$).

Table 10. Pearson's correlation coefficients for the serum resistin concentrations in the whole patient's group and in both sexes separately.

	Total	**Women**	**Men**
Age[a]	0.01	-0.10	0.08
BMI[a]	-0.27*	-0.29	-0.24
Waist[a]	-0.28*	-0.31*	-0.18
Systolic BP[a]	-0.28*	-0.27	-0.24
Diastolic BP[a]	-0.08	-0.06	-0.06
Plasma glucose[b]	-0.13	-0.13	-0.13
HbA_{1C}[b]	-0.26*	-0.41*	-0.09
Plasma insulin[b]	-0.14	-0.10	-0.20
HOMA-IR[b]	-0.15	-0.11	-0.21
Uric acid[a]	-0.08	-0.07	0.09
Triglyceride[b]	-0.05	0.02	-0.12
Total cholesterol[b]	0.02	-0.03	0.01
HDL-C[a]	-0.04	-0.08	-0.23
LDL-C[b]	0.04	0.04	0.08
NEFA[b]	-0.23*	-0.29*	-0.20
TBARS[b]	-0.40**	-0.38*	-0.43*
Adiponectin[b]	0.09	0.04	0.09
PON1 activity[b]	0.24*	0.20	0.33*
IL-6[b]	-0.24*	-0.26	-0.21
TNF-α[b]	-0.14	-0.16	-0.12
Leptin[b]	-0.28*	-0.27	-0.37*

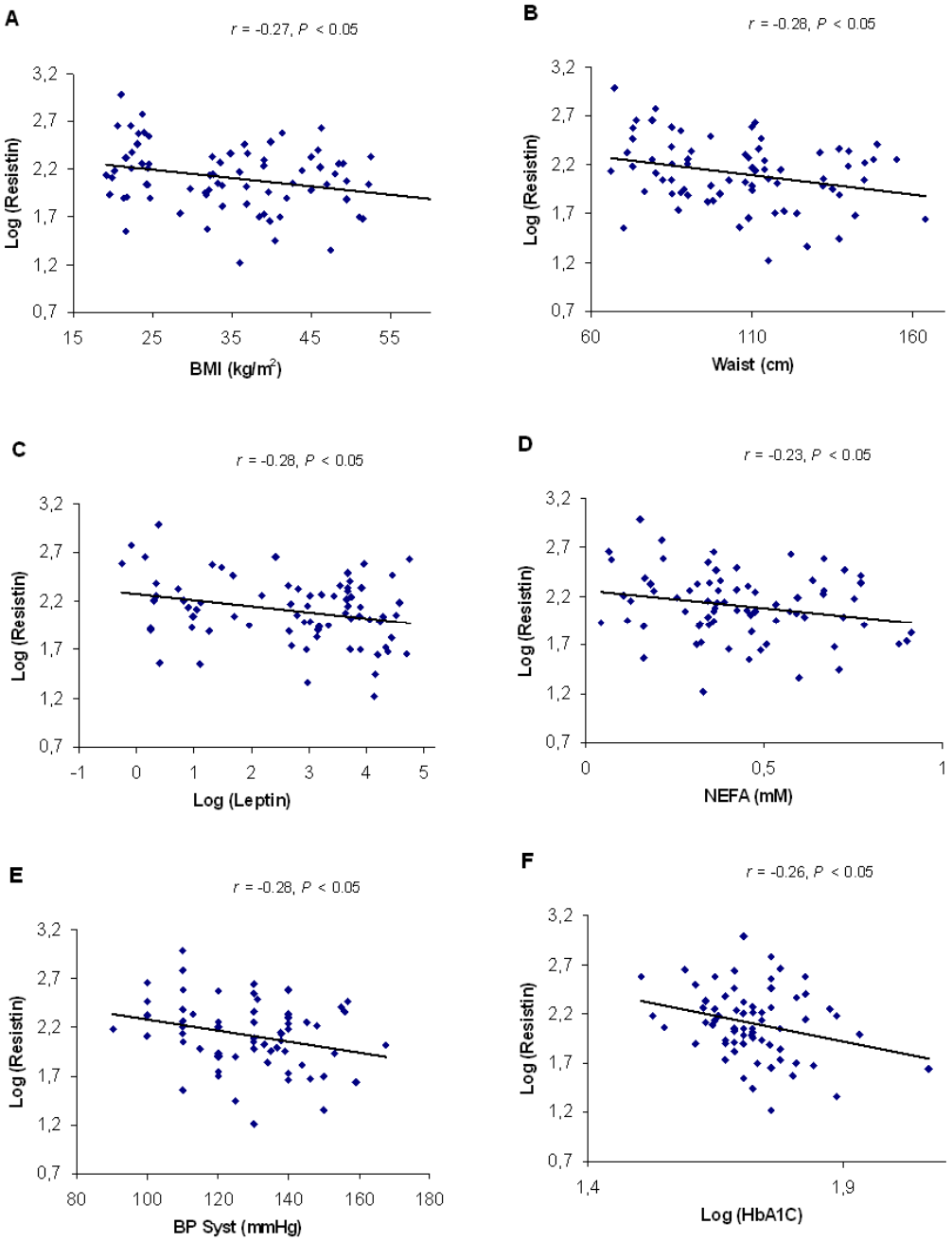
[a]: Normal distribution. [b]:Non-normal distribution.
*: $P < 0.05$; **: $P < 0.01$
Abbreviation: BP: blood pressure.

Figure 1. Relationships between levels of resistin, TBARS and PON1 activity.



Log-transformed resistin is related directly to log-transformed PON1 (A), and inversely to log-transformed TBARS (C). Log-transformed TBARS is related inversely to log-transformed PON1 (B).

Figure 2. Relationships between serum levels of resistin and selected variables.



Log-transformed concentrations of resistin are correlated inversely with BMI (A), waist circumference (B), levels of log-transformed leptin (C), and non-esterified fatty acid levels (D), systolic blood pressure (E), and log-transformed HbA1C (F).

Multivariate correlations.

It was in multiple regression analyses tested whether NEFA, or any of adipokines were independent predictors of HOMA-IR, in addition to the basic anthropometric characteristics (**Table 11**). Two models were constructed with either BMI, or waist circumference. In both models leptin, and in lesser degree IL-6 were significant predictors of HOMA-IR.

However, adiponectin was a significant predictor of HOMA-IR only in Model 1. When BMI was replaced by waist circumference in the regression model (Model 2), adiponectin ceased being an independent variable. These parameters together explained only 35-36% of variance of HOMA-IR. During the multivariate tests the association between IL-6 and HOMA-IR was negative, in opposite to the univariate analysis, where this was positive.

Table 11. Multiple regression analysis for HOMA-IR as a dependent variable

	Model 1 ($R^2 = 0.361$)				Model 2 ($R^2 = 0.354$)			
Variable	*β*	*t*	*P*	*%*	*β*	*t*	*P*	*%*
Age	0.041	0.293	0.771	<1.0	-0.056	-0.366	0.716	<1.0
Sex	-0.1	-0.713	0.48	<1.0	-0.025	-0.120	0.905	<1.0
BMI	-0.347	-1.254	0.217	1.4	-	-	-	-
Waist	-	-	-	-	0.027	0.078	0.938	<1.0
NEFA	-0.430	-0.339	0.735	<1.0	0.087	0.483	0.632	<1.0
Leptin	**0.720**	**3.756**	**0.001**	**20.2**	**0.769**	**2.392**	**0.022**	**21.6**
Resistin	0.012	0.086	0.932	<1.0	0.039	0.257	0.799	<1.0
Adiponectin	**-0.268**	**-1.962**	**0.045**	**4.9**	-0.260	-1.502	0.142	4.6
IL-6	**-0.534**	**-2.654**	**0.011**	**7.6**	**-0.555**	**-2.069**	**0.046**	**6.7**
TNF-α	-0.027	-0.151	0.880	<1.0	-0.091	0.435	0.667	<1.0

Significant value indicated in bold; *β* is standardized regression coefficient

This discrepancy was further analyzed in another model, in which, beside basic anthropometric characteristics, only IL-6 was included (**Table 12**). In this test only the BMI was a significant predictor. However, the entire explaining power of this model for HOMA-IR was low (14%).

Table 12. Multiple regression analysis for HOMA-IR as a dependent variable

	Model (R^2 = *0138)*		
Variable	*β*	*t*	*P*
Age	-0.052	-0.441	0.661
Sex	-0.003	-0.028	0.978
BMI	**0.364**	**3.129**	**0.003**
IL-6	-0.092	-0.447	0.656

Significant value indicated in bold; *β* is standardized regression coefficient

To test if the association of resistin with PON1 existing in the univariate analysis were independent of anthropometric and other laboratory parameters, we carried out multiple regression analyses with PON1 as the dependent variable (**Table 13**). At first, two less adjusted models (Model 1 and 2) were constructed in which, besides resistin, the impact of age, sex, and BMI were tested. In Model 2 HDL-C was also included, since PON1 is associated to a subfraction of HDL-C. In these models only BMI turned out being an independent predictor of PON1, explaining 12.6% of the variance of PON1. We also constructed a more completely adjusted model (Model 3), applying parameters that are related either to metabolic syndrome (systolic blood pressure, HDL-C, HOMA-IR), and/or lipid peroxidation (LDL-C and MDA). The reason for including these latter two parameters was that higher level cholesterol concentration and lipid peroxidation are related to enhanced inactivation of PON1 in an interaction between lipid peroxides and the sulfhydryl groups of the enzyme (Aviram). In the larger model (Model 3) BMI ceased being a significant independent variable of PON1 and of the investigated parameters only MDA proved to be a predictor of PON1 showing that of the partly related variables, MDA and BMI, variance of PON1 is explained better by the MDA than by BMI. However, even MDA explained only 2% of variance of PON1.

Table 13. Multiple regression analyses for PON-1 as a dependent variable

	Model 1 (R^2 = 0.20)			Model 2 (R^2 = 0.21)		
Variable	*β*	*t*	*P*	*β*	*t*	*P*
Age	0.08	0.67	0.50	0.04	0.34	0.73
Sex	-0.09	-0.79	0.44	-0.14	-1.22	0.23
BMI	**-0.42**	**-3.87**	**<0.001**	**-0.42**	**-3.87**	**<0.001**
Systolic BP	-	-	-	-	-	-
HOMA-IR	-	-	-	-	-	-
LDL-C	-	-	-	-	-	-
HDL-C	-	-	-	0.11	0.82	0.42
TBARS	-	-	-	-	-	-
Resistin	0.14	1.22	0.23	0.14	1.22	0.23

	Model 3 (R^2 = 0.22)		
Variable	*β*	*t*	*P*
Age	0.05	0.37	0.71
Sex	-0.04	-0.27	0.79
BMI	0.11	0.39	0.70
Systolic BP	-0.07	-0.35	0.73
HOMA-IR	-0.23	-1.54	0.13
LDL-C	-0.06	-0.42	0.68
HDL-C	0.06	0.34	0.74
TBARS	**-0.41**	**-3.2**	**0.002**
Resistin	0.11	0.78	0.44

Significant value indicated in bold; *β* is standardized regression coefficient.

Discussion

In individuals with normal renal function, adiponectin has a positive and independent correlation with the antioxidant PON1, an enzyme protecting lipoproteins from lipid peroxidation (Bajnok et al. 2008), yet an inverse relationship with sE-selectin, a marker of inflammatory activation of the endothelium (Krakoff et al. 2003, Mantzoros et al. 2005, Kantartzis et al. 2006). In accordance with investigations made in renal failure patients (Huang et al. 2004, Stenvinkel et al. 2004, Lee et al. 2004), we found a clear inverse correlation between adiponectin and acute phase proteins (CRP and fibrinogen) produced primarily or exclusively by the liver. However, in our study adiponectin was not associated either with sE-selectin, or PON1 activity. The latter finding may suggest that the uremia-related elevated adiponectin level has no protective effect on the PON1 activity, which is typically decreased in these patients (Paragh et al. 1998, Schiavon et al. 2002, Dirican et al. 2004).

The following mild, but statistically significant differences could be demonstrated in the higher as compared to the lower adiponectin subgroup; the albumin level was mildly lower, while the dialysis efficiency was higher. The latter finding existed in the less insulin resistant subgroup as well. The adiponectin concentration also had an inverse relationship with the serum albumin level.

Many known pathophysiologic pathways of metabolic syndrome can be demonstrated in kidney failure; abdominal obesity, atherogenic dyslipidemia, and elevation of acute phase proteins are more pronounced in the lower adiponectin and the insulin resistant subgroups of HDPS compared to the respective counterparts. Furthermore, the adiponectin level was lower in the more insulin resistant subgroup and the lower adiponectin subgroup was more insulin resistant. These findings support previous results (Takemoto et al. 2009, Huang et al.2004, Diez et al. 2005) that showed negative correlation between adiponectin concentration and

measures of adiposity, dyslipidemia, and insulin resistance, even in renal failure.

Our multiple regression analyses showed that not only BMI and HOMA-IR were independent negative predictors of serum adiponectin level, but also the albumin level a marker of nutrition. Therefore, the inverse relationship between adiponectin and albumin may be an aspect of the pathomechanism existing in the background of chronic renal disease related to the "reverse epidemiology" of adiponectin (Beige et al. 2009).

Adiponectin had also associations with dialysis efficiency and, similarly to individuals with preserved kidney function, traits of metabolic syndrome. In opposite to our observations, Huang et al. (Huang et al. 2004) did not find association between dialysis efficiency and the adiponectin level in hemodialysis patients. This discrepancy may be related to the small number of investigated patient's group (n = 28 vs. n = 70 of our study). The possible relationship between the serum adiponectin concentration and dialysis efficiency is not simply due to the enhanced clearance of adiponectin during HD sessions, since the large molecular weight of adiponectin is minimally removed by dialysis (Beige et al. 2009, Huang et al. 2004). However, this association between the adiponectin level and dialysis efficiency was not an independent one in a simple regression model that also included BMI. Dialysis efficiency has also shown associations with the metabolic syndrome (a positive association with adiponectin, and a negative association with the measures of adiposity, dyslipidemia, insulin resistance, and acute phase proteins), but not with the serum albumin level. The association between adiponectin and dialysis efficiency has been also shown by Chen et al. (Chen et al. 2008) in chronic peritoneal dialysis patients.

Among the oxidative stress markers only the GSH showed significant correlations with analyzed parameters. As expected, there was a positive association with HDL-C, while negative ones with both systolic and diastolic blood pressure. However, in our patient's group we found no

correlations between the analyzed cardio-metabolic parameters and the total peroxidase, the catalase activity, or MDA concentration.

The limitations of this study were that the investigated patient's group was not large and no healthy control group was included. However, the clinically significant correlations were clearly established, even at this sample size. Moreover, we did not consider it essential to recheck the previously well-documented kidney failure-related alterations of variables, e.g., adiponectin, PON1, and sE-selectin. Furthermore, to reliably demonstrate correlations between PON1 and adiponectin needs a larger patient's group with a wide range of adiponectin (enabled by a wide range of BMI). A potential shortcoming of our study was that the various isoforms of adiponectin were not investigated, so it cannot be excluded that a high molecular weight form of adiponectin might be correlated with PON1.

In the current concept of metabolic syndrome the adipose tissue secreted products, adipokines and NEFA play pivotal roles. We tested the association of insulin resistance to levels of these humoral factors, in addition to basic anthropometric characteristics. As expected by previous studies, in univariate analyses insulin resistance was correlated positively with obesity, levels of serum NEFA (Koutsari et al. 2006), leptin (Matsubara et al. 2002, Matsubara et al. 2003), IL-6 and TNF-α (Marette et al. 2002), while negatively with adiponectin serum concentration (Weyer et al. 2001, Yamamoto et al. 2002), with no significant association to resistin (Reilly et al. 2005, Azuma et al. 2003, Lee et al. 2003, Degawa-Yamauchi et al. 2003). In line with these findings, HOMA-IR, NEFA, leptin IL-6 and TNF-α level were significantly higher, while adiponectin level was significantly lower in obese people as compared to normal controls, without significant difference in respect of resistin.

At this point we were interested if there was a hierarchy between the adipokines and NEFA in the determination of insulin resistance. Matsubara et al. earlier found both leptin and adiponectin were significant

determinants of HOMA-IR (Matsubara et al. 2003); however, the measure of their relative contribution to the insulin resistance was not established. Furthermore, in a combined multivariate model, we also tested the influence of other adipokines on HOMA-IR as a dependent variable. The investigated parameters on the whole explained only a minor part of the variance of insulin resistance showing that other factors also play pivotal roles in the determination of its degree. On HOMA-IR leptin had the highest influence of the adipokines, while IL-6 and adiponectin had minor ones, and TNF-α, resistin, NEFA or BMI were not significant independent predictors of this. Since abdominal adiposity measured by waist circumference is regarded as a better predictor of cardio-vascular and diabetes related risk than BMI (Yusuf et al. 2005), during the multivariate analyses we also tested waist circumference as a predictor, instead of BMI. However, neither waist circumference had significant predictive power for the insulin resistance in a model that also contained the adipokines.

Interestingly, we found discrepant associations between IL-6 and HOMA-IR during the uni-, and multivariate analyses: positive one during the univariate, while in multivariate tests, depending on whether in the model beside of basic anthropometric characteristics NEFA and other adipokines were also included either negative one, or neutral. The approach of our study does not seem to be appropriate clarifying the biological background of this finding. However, the reason for this may be related to that curious connection between IL-6 and insulin resistance (Glund et al. 2008, Hoene et al. 2008) that has been recently intensively debated even at the level of basic research (Spangenburg et al. 2007). Namely, IL-6 release from adipose tissue results in a proinflammatory state leading to insulin resistance, while, on the other hand, IL-6 produced by working muscles could enhance glucose disposal, lipolysis and fat oxidation (Hoene et al. 2008).

However, there were limitations of this work. (i) For the assessment of insulin resistance a surrogate marker, the homeostasis model assessment

(HOMA-IR) was used that has some imprecision compared to more sophisticated methods. However, Bonora et al. previously found high correlation between HOMA-IR and the euglycemic - hyperinsulinemic clamp method (r values were around -0,8) in various patient populations, including obese subjects (Bonora et al. 2000). Moreover, the correlation between insulin sensitivity and adiponectin level that Cnop et al found using Bergman's minimal model was very similar to our results (r = 0.375 vs. 0,42) (Cnop et al. 2003). (ii) The investigated population included both sexes and was not too large overall. While in a larger population smaller statistically significant correlations could be detected, the clinical significance of such minor findings would be highly questionable. Therefore, the investigated population seems to be satisfactory in proving our basic observations. (iii) It is known that the peripheral venous concentration of non-esterified fatty acids poorly correlates to its biological effect, since the pivotal effects of NEFA are related to their portal flux. However, the latter cannot be routinely measured. (iv) Other novel adipokines, e.g. visfatin and retinol binding protein-4 (RBP-4) were not investigated. The inclusion of these recently discovered humoral factors might add to the explanation of relation of adipokines and insulin resistance. However, their roles in the determination of insulin resistance are quite uncertain. For instance, although plasma visfatin levels are increased in subjects with the metabolic syndrome (Filippatos et al. 2008), its concentration is not correlated with insulin resistance even in univariate analysis (Oki et al. 2007, Pfutzner et al. 2007, Chen et al. 2007). The association between RBP-4 and insulin resistance is also uncertain: while Kowalska et al. demonstrated that serum RBP4 was inversely related to insulin sensitivity measured by euglycemic hyperinsulinemic clamp test (Kowalska et al. 2008), other authors did not find correlation between RBP-4 and insulin resistance measuring by either a similar test (Promintzer et al. 2007) or HOMA-IR (Silha et al. 2007). Hence, further studies are warranted in this field.

Among our study subjects with a broad range of BMI, we obtained negative association between serum levels of resistin and, beside insulin resistance, some other features of metabolic syndrome, such as BMI, waist circumference, serum levels of leptin, HbA_{1C}, and non-esterified fatty acid, systolic BP, and TBARS. Although these correlations were not too strong, except the one with the TBARS, on the whole were concordant. The fact that fasting plasma glucose was not related to serum levels of resistin may be due to the fact that HbA_{1C} reflects the long-term glycemic burden.

Previous studies are contradictory with respect to the association of serum levels of resistin and obesity. The Mantzoros group found that resistin was correlated positively with body fat mass and negatively with waist to hip ratio in 61 female and 53 male consecutively enrolled healthy Greek students (Yannakoulia et al. 2003). However, the same group found no association between resistin and markers of adiposity, including serum levels of leptin, insulin resistance and levels of lipid in 123 middle-aged women with a higher average and broader range of BMI (mean 30.9 [± 5.5] kg/m^2) (Lee et al. 2003). Azuma et al. demonstrated that serum levels of resistin were significantly higher in 64 young nondiabetic obese subjects taking no medication (BMI 32.9 [± 5.6] kg/m^2) than in 15 lean volunteers, and there was a positive correlation between levels of resistin and BMI when the two groups were combined ($P = 0.35$, $p < 0.01$) (Azuma et al. 2003). Degawa-Yamauchi et al.'s (2003) results for 27 lean and 50 obese (37 women and 13 men, BMI 49.8 [± 1.5] kg/m^2, age 47 [± 1] yr) subjects showed higher serum levels of resistin in the obese subjects (mean ± [SEM] 5.3 [± 0.4] ng/ml; range 1.8-17.9) compared to the lean subjects (3.6 [± 0.4] ng/ml; range 1.5-9.9; $P = 0.001$). Furthermore, they found a significant positive correlation between resistin and BMI ($r = 0.37$, $P = 0.002$) (Degawa-Yamauchi et al. 2003). In a Pima Indian population with a mean body weight of 91 (± 19) kg (range 50-148 kg), circulating levels of resistin were proportional to the degree of adiposity, but not the degree of insulin resistance (Volarova de Courten et al. 2004). Fujinami et al. (2004)

demonstrated a moderate positive correlation between serum levels of resistin and BMI in normal subjects ($r = 0.412$, $P < 0.0003$) and in patients with type 2 diabetes ($r = 0.395$, $P < 0.0001$). However, other investigators (Lee et al. 2003, Silha et al. 2003, McTernan et al. 2003, Seow et al. 2004, Savage et al. 2001, Pfutzner et al. 2003) did not find a correlation of adiposity with serum levels of resistin. Hegele et al. (2003) studied 35 nondiabetic adult Dunnigan-type familial partial lipodystrophy subjects and 51 matched normal first-degree relatives. Compared with the controls, the lipodystrophy subjects had significantly higher plasma levels of insulin and more dyslipidemia, higher mean triglycerides and lower HDL-C cholesterol, significantly higher nonesterified free fatty acids and CRP, and significantly lower leptin and adiponectin than the controls. Subgroup analysis showed that these differences were more pronounced in women. Other biomarkers such as resistin, fibrinogen, and plasminogen activator inhibitor-1 were not di1fferent between groups (Hegele et al. 2003). Plasma levels of resistin were not statistically different, even in individuals with a broad range of BMI, as compared to healthy controls (Fehmann et al. 2002). In a study of inherited risk of coronary atherosclerosis there was no correlation between waist circumference and serum levels of resistin (Reilly et al. 2005).

Another source of discrepancy in our results might be related to technical problems associated with the measurement of resistin. However, Pfutzner et al. (2003) established that three commercially available resistin ELISAs, including the one we used (Biovendor, Brno, Czech Republic) (although it proved to be different with respect to calibration and reference ranges that may be linked to the different antibody specificities), with different target epitopes had passed the standardized technical validation procedure, with inter-assay and intra-assay variability below 10% and 15%, respectively. They concluded that resistin assays showed good technical quality, but the diagnostic value remained still unclear, since no correlation was found between any of the resistin assays and any of the clinical or laboratory

parameters, such as BMI, age, disease duration, triglycerides, LDL, HDL-C, insulin, glucose, and intact proinsulin (Pfutzner et al. 2003). Similarly, in a direct comparison of two ELISAs, including the test we used, Reilly et al. found a high level of correlation ($r = 0.99$, $P < 0.001$) (Reilly et al. 2005).

We also investigated the possible association of serum levels of resistin with activity of the HDL-associated antioxidant enzyme paraoxonase 1 (PON1) (Getz et al. 2004, Watson et al. 1995, Rosenblat et al. 2006). They showed a positive univariate correlation. However, when we tested if the association between resistin and PON1 was independent of anthropometric and other parameters in multiple regression analysis, resistin was not an independent predictor of PON1. Actually, during this multivariate analyses only the negative correlation between PON1 and lipid peroxidation (measured by TBARS) remained significant, and neither the BMI, nor age, gender, systolic BP, HOMA-IR, LDL-C or HDL-C were significant predictors of PON1 activity.

In agreement with the majority of previous work (Azuma et al. 2003, Lee et al. 2003, Degawa-Yamauchi et al. 2003, Chen et al. 2005), we did not find a correlation between serum levels of resistin and insulin resistance itself. Similarly to others' finding, there was no relationship between resistin and LDL-C levels (Lee et al., 2003; Chen et al. 2005, McTernan et al. 2003, Pfutzner et al. 2003). However, we cannot confirm the report by Chen et al. of an association between serum levels of HDL-C and resistin (Chen et al. 2005). In a study of inherited risk of coronary atherosclerosis, serum levels of resistin were correlated negatively with HDL-C but only in women (Reilly et al. 2005).

At the moment, the reason for these conflicting results cannot be properly identified. The broad range of BMI, from 28 kg/m^2 to 62 kg/m^2, with a mean (S.D.) of 40.6 ($\pm$ 7.35) kg/m^2 in our obese patient's group may provide some explanation of the discrepancy between our results and those of other workers.

The finding that some parameters of metabolic syndrome, e.g. diastolic BP, levels of uric acid, glucose, insulin, triglyceride, HDL-C, and HOMA-IR were not related significantly to serum levels of resistin might be because our study patient's group was not large enough to have sufficient statistical power that was otherwise enough for our basic observation, i.e. the significant positive correlation between serum resistin and PON1.

Like Chen et al. (2005), but unlike some previous studies (Lee et al. 2003, Silha et al. 2003, Yannakoulia et al. 2003), we found no significant difference between sexes in the serum levels of resistin.

Conclusions and future perspectives

1. To the best of our knowledge, we investigated first a possible relationship between adiponectin with PON1 and sE-selectin in kidney failure. However, we found no correlation among PON1 activity, sE-selectin and adiponectin levels in this patient's group. Moreover, our findings raise the possibility that - although itself the lower insulin resistance in patients with higher adiponectin levels might be beneficial, even in kidney failure - the condition related to uremic malnutrition marked by the lower serum albumin concentration may be more detrimental. Furthermore, the uremic environment, despite the kidney failure-related hyperadiponectinemia, may overwhelm the protective effect of adiponectin against endothelial dysfunction and low PON1 activity. These findings collectively may add to the understanding of the role that adiponectin plays in the chronic renal disease-related "reverse epidemiology."

2. We applied a combined model containing multiple adipose tissue derived humoral factors to investigate their collective effects on the insulin resistance. Although of the investigated parameters the severity insulin resistance correlated positively with obesity, serum NEFA, leptin, IL-6 and TNF-α, while negatively with adiponectin during univariate analyses, only serum leptin, and in lesser degree IL-6 and adiponectin were independent determinants of insulin resistance. Moreover, even together explain they only a minority of variance of it.

3. Some of our observations related to resistin are also without antecedents in the literature. Although we found no correlation between serum levels of resistin and insulin resistance, resistin was associated negatively with some features of metabolic syndrome, i.e. anthropometric, blood pressure and laboratory (glycemic control, other adipokines, and oxidative stress) characteristics.

4. To the best of our knowledge, our experiment was the first report that investigated the relationship between resistin and PON1.

Acknowledgements

First of all I would like to thanks my supervisors Prof. Gábor L. Kovács for giving me the possibility to work at his institute and Doc. László Bajnok for leading me during my scientific work and for having faith in this project at right and wrong.

I greatly appreciate the technical assistance of Doc. Tamás Kőszegi who helped me during the first steps leading into the laboratory measurements.

At last but not least, I would like to thank all members of Institute of Laboratory Medicine for helping me in this work.

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List of Attila Peti's publications

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