Srčnožilna umrljivost in mikrovnetje pri trebušno debelih hemodializnih bolnikih

Cardiovascular mortality and microinflammation in abdominal obese hemodialysis patients

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Izvleček

Namen: *Trebušno maščevje ima pomembne provnetne lastnosti in predstavlja vir različnih vnetnih posrednikov. Z ozirom na dejstvo, da so pri hemodializnih (HD) bolnikih povišane koncentracije nekaterih vnetnih posrednikov, bi lahko imelo trebušno maščevje pomembno vlogo v patogenezi mikrovnetja, ki je dokazano povezano s pospešeno aterosklerozo. Namen naše raziskave je bil določiti vpliv mikrovnetja na srčnožilno umrljivost trebušno debelih HD bolnikov.*

Metode: *V raziskavo smo vključili enainsedemdeset HD bolnikov (povprečna starost 59.3 ± 12.8 let). Izmerili smo jim obseg pasu in trebušno debelost opredelili skladno s priporočili Mednarodnega združenja za sladkorno bolezen (International Diabetes Federation). Določili smo serumske koncentracije lipidov (trigliceridi, HDL in LDL holesterol) in vnetnih posrednikov*

Abstract

Purpose: *Abdominal adipose tissue has important inflammatory properties and is a source of various inflammatory mediators. Given that concentrations of some inflammatory mediators are high among hemodialysis (HD) patients, abdominal obesity may play an important role in the pathogenesis of microinflammation which is known to be associated with accelerated atherosclerosis. The aim of our study was to determine the impact of microinflammation on cardiovascular (CV) mortality in abdominal obese HD patients.*

Methods: *Seventy–one HD patients (mean age 59.3 ± 12.8 years) were included in our study. Waist circumference (WAC) was measured and abdominal obesity was defined according to the International Diabetes Federation. Serum levels of lipids (triglycerides, high density li-*

(interlevkin 6, tumor nekrozni dejavnik–alfa, žilnocelična adhezivna molekula–1 (VCAM–1), medcelična adhezivna molekula–1 (ICAM–1)). Bolnike smo spremljali od dneva določitve vnetnih posrednikov (november 2003) do njihove smrti oziroma do 10. novembra 2009.

Rezultati: *Povprečna vrednost obsega pasu je bila za moške 97.6 ± 16.1 cm in 92.2 ± 15.9 cm za ženske. Trebušno debelost smo ugotovili pri 62% vključenih bolnikih. S Coxovo regresijsko analizo smo ugotovili, da sta vnetna posrednika VCAM–1 ($p<0.031$) in ICAM–1 ($p<0.024$) napovednika srčnožilne umrljivosti pri trebušno debelih HD bolnikih. Četudi smo v omenjeno analizo vključili starost in ostale znane dejavnike tveganja za razvoj ateroskleroze (arterijska hipertenzija, kajenje, HDL in LDL holesterol, trigliceridi) sta oba vnetna posrednika ostala napovednika srčnožilne umrljivosti.*

Zaključek: *Rezultati naše raziskave potrjujejo povezanost mikrovnetja in srčnožilne umrljivosti pri trebušno debelih HD bolnikih.*

poproteins (HDL) cholesterol, low density lipoproteins (LDL) cholesterol) and inflammatory mediators (interleukin–6, tumor necrosis factor–alpha, vascular cellular adhesion molecule–1 (VCAM–1), intercellular adhesion molecule–1 (ICAM–1)) were measured. Patients were observed from the date of measurement (November 2003) of inflammatory mediators until their death or to 10th of November 2009.

Results: *The mean WAC value for men was 97.6 ± 16.1 cm, and for women 92.2 ± 15.9 cm. Abdominal obesity was found in 62% of the enrolled patients. Cox regression analysis showed that the inflammatory mediators VCAM–1 ($p<0.031$) and ICAM–1 ($p<0.024$) were predictors of CV mortality in abdominal obese HD patients. Both inflammatory mediators remained predictors of CV mortality if age and other known risk factors for atherosclerosis (arterial hypertension, smoking, HDL and LDL cholesterol and triglycerides) were included in the analysis.*

Conclusion: *The results of our study indicate that microinflammation is associated with CV mortality in abdominal obese HD patients.*

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with end–stage renal disease (ESRD) on renal replacement therapy (1). Compared with the general population, the cardiovascular (CV) mortality rate may be increased by 15– to 30–fold in patients with ESRD (2). The fundamental reason for the majority of CVD in these patients is atherosclerosis (1,3). The pathogenesis of atherosclerosis in hemodialysis (HD) patients is complex and involves several risk factors. The traditional risk factors for CVD (age, hypertension, hypercholesterolemia, diabetes, sedentary lifestyle and smoking) only partly explain these high morbidity and mortality rates; additional non–traditional risk factors such as microinflammation appear to play a role (4–8).

Many previously published studies have discussed the role of microinflammation in patients with chronic renal failure, but the causes of the inflammatory response in these patients remain unclear (9). Increased inflammatory mediators have been attributed to increased oxidative stress, acidosis, heart failure, and the accumulation of proinflammatory cytokines and other agents normally cleared by the kidney. Thus, causes of microinflammation may include comorbidities, oxidative stress, infections and HD–related factors that depend on membrane biocompatibility and the dialysate (9,10). Another possible cause is obesity, which is associated with a chronic inflammatory response (11–14).

White adipose tissue has been recognized as an active participant in numerous physiological and pathophysiological processes (12). It has important endocrine functions because it secretes various factors,

the so–called adipokines (i.e. interleukin–6 (IL–6), tumor necrosis factor–alpha (TNF–α), leptin, resistin, etc.). In obesity the production of adipokines by adipose tissue is increased (14). However, as a prognostic factor for CVD, the distribution of body fat is more important than the amount of fat because not all white adipose tissue is equally hormonally active. The most active is abdominal (central, visceral) fat (14,15), which plays an important role in the development of atherosclerosis (11). The most frequently studied proinflammatory cytokines among the secreted adipokines are IL–6 and TNF–α (12). The TNF–α mediates gene expression in endothelial cells, whose protein products are involved in the expression of selective adhesion molecules. Moreover, TNF–α facilitates activation and recruitment of inflammatory cells, as well as IL–6. Additionally, IL–6 stimulates liver synthesis of acute phase proteins, especially CRP (C–reactive protein) and fibrinogen (12,16). Endothelial dysfunction/injury has a pivotal role in atherogenesis and results in altered homeostatic properties of the endothelium that leads to increased permeability, procoagulant properties and increased adhesiveness of leukocytes and platelets. Various vasoactive molecules, cytokines and growth factors are released which induce an inflammatory response (16,17). An important event in atherogenesis is the adhesion of circulating leukocytes to the vascular endothelial cells and subsequent transendothelial migration, which is mediated by interaction of leukocyte surface receptors with their ligands expressed on the surface of endothelial cells. Those ligands are selective adhesion molecules which are expressed in response to proinflammatory cytokines, i.e. TNF–α and IL–6. The adhesion molecules vascular cellular adhesion molecule–1 (VCAM–1), intercellular adhesion molecule–1 (ICAM–1) and E–selectin have been detected by immunohistochemistry in human atherosclerotic lesions, and their expression was found to be correlated with intimal infiltration by T–lymphocytes and monocytes/macrophages (18).

Considering the proinflammatory effect of inflammatory mediators secreted by abdominal adipose tissue and their role in atherogenesis, abdominal obesity plays an important role in the pathogenesis of microinflammation, which is known to be associated with accelerated atherosclerosis. The aim of our study was to determine the impact of microinflammation on CV mortality in abdominal obese HD patients.

MATHERIAL AND METHODS

In total, 71 HD patients, 39 (55%) males and 32 (45%) females, were included in our study. The patients' mean age was 59.3 ± 12.8 years, ranging from 22 to 78 years. The mean duration of HD treatment was 59.7 ± 50.4 months, ranging from 1 to 199 months. All patients received HD three times a week for 4.2 ± 0.5 hours per session. Only conventional HD with bicarbonate dialysate was used. The quality of the water was checked regularly against prescribed standards. The HD patients were divided into abdominal obese and abdominal non–obese individuals. According to the International Diabetes Federation, abdominal obesity was defined as a waist circumference (WAC) at least 94 cm for men and 80 cm for women. The WAC was measured in centimeters using a tape measure placed midway between the lower rib margin and the iliac crest in the horizontal plane, with the participants standing, before an HD session. Systolic and diastolic blood pressures were measured routinely, before and after each dialysis procedure, using a standard mercury sphygmomanometer. The results are reported as the average of the measurements made during one month. Hypertension was defined as an average measured blood pressure ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic, or if the patient received treatment for hypertension. Information on smoking habits was obtained by questionnaire, and the HD patients were divided in two subgroups on this basis: smokers (present or former) and non–smokers. The concentrations of serum lipids (triglycerides, HDL and LDL cholesterol) were measured by standard laboratory methods. Serum levels of IL–6 and TNF–α were measured by a chemiluminescence method (Immulite 1000; DPC, Los Angeles, USA) and serum levels of VCAM–1 and ICAM–1 were measured using a spectrophotometric method (R&D Systems, Minneapolis, MN, USA).

At the time of blood sampling none of the enrolled patients had an ongoing bacterial or viral infection. Patients were observed from the date of measurement of inflammatory markers and serum lipid levels (November 2003) until their death, or to 10th of November 2009.

A Cox regression model was used to assess the influence of inflammatory mediators on CV outcomes. The statistical analysis was performed using SPSS for Windows, version 19.0.1 (SPSS Inc, Chicago, IL). All data are presented as mean ± SD. A relationship was considered statistically significant at p less than 0.05.

The study was carried out in accordance with the guidelines of the Declaration of Helsinki. Informed consent was obtained from each participant.

RESULTS

The mean WAC value for all patients was 95.2 ± 16.2 cm (range 72–138 cm); for men it was 97.6 ± 6.1 cm (range 75–135 cm) and for women 92.2 ± 15.9 cm (range 72–138 cm). Abdominal obesity was found in 62% of the enrolled patients, 20 (51.2%) men and 24 (75%) women. In total, 70.5% of the abdominal obese patients (and 77.8% of the non–obese) had arterial hypertension and 22.7% of the abdominal obese patients (22.2% of the non–obese) were smokers. Thirty–five (49.3%) of the patients were receiving statin therapy. The basic characteristics of the enrolled patients are presented in Table 1. We confirmed increased serum values of inflammatory mediators in the HD patients (both abdominal obese and abdominal non–obese), except for the IL–6 values. No statistically significant differences in the values of inflammatory mediators between abdominal obese HD patients and abdominal non–obese HD patients were found (IL–6: p=0.44; TNF–α: p=0.489; VCAM–1: p=0.258; ICAM–1: p=0.186).

During the observation period (2200 days), 28 abdominal obese HD patients died as a result of a CV event.

Using Cox regression analysis, the inflammatory mediators VCAM–1 (p<0.031) and ICAM–1 (p<0.024) were found to be predictors of CV mortality in abdominal obese HD patients, and VCAM–1 (p<0.012) was a predictor of CV mortality in abdominal non–obese HD patients. No statistically significant relationships were found between CV mortality and the serum levels of IL–6 and TNF–α. Using adjusted Cox regression analysis, where age and other known risk factors for atherosclerosis (arterial hypertension, smoking, triglycerides, HDL and LDL cholesterol) were included in the statistical analysis, both adhesion molecules still remained predictors of CV mortality in abdominal obese HD patients (VCAM–1: p<0.010; ICAM–1: p<0.016), but not in the group of abdominal non–obese HD patients (VCAM–1: p<0.165; ICAM–1: p<0.657). Additionally, triglycerides (p<0.001) were predictors of CV mortality in the abdominal obese HD patients in the adjusted model.

DISCUSSION

The accumulated data support the idea that atherosclerosis results from chronic microinflammation in the intima of arteries, which is caused by an immune reaction to autoantigens at the endothelial level (7,17,19). It is known that atherosclerosis is accelerated in HD patients, and several studies have shown that the serum values of proinflammatory cytokines are increased in uremic patients predialysis, as well as in patients undergoing dialysis (20). Therefore, these cytokines may be potential pathogenic mediators in the development of atherosclerotic lesions, and may play a role in accelerating vessel pathology (21). Given that abdominal adipose tissue is known to be a source of various inflammatory mediators, abdominal obesity may play an important role in the pathogenesis of microinflammation, and may also accelerate atherosclerosis and CV events in HD patients with abdominal obesity.

The results of our study confirmed the presence of increased serum values of inflammatory mediators in HD patients, with the exception of IL–6. However, no statistically significant differences were found in the

Table 1: *Abbreviations: HD: hemodialysis; WAC: waist circumference; IL–6: interleukin 6; VCAM–1: vascular cellular adhesion molecule 1; ICAM–1: intercellular adhesion molecule 1; TNF–α: tumor necrosis factor alpha; TG: triglycerides; HDL: high density lipoproteins; LDL: low density lipoproteins; SD: standard deviation.*

	All HD patients	Abdominal obese HD patients
Number of cases	71	44
Males/Females	39/32	20/24
Age (mean ± SD; years)	59.3 ± 12.8	61.1 ± 10
HD treatment duration (mean ± SD; months)	59.7 ± 50.4	53.5 ± 47.1
WAC (mean ± SD; cm)	95.2 ± 16.2	103.1 ± 15.2
Hypertension (proportion; percentage)	52/71; 73.2	31/44; 70.5
Smoking (proportion; percentage)	16/71; 22.5	10/44; 22.7
On statin therapy (proportion; percentage)	35/71; 49.3	23/44; 52.3
IL–6 (mean ± SD; pg/ml)	4.13±2.63	4.33±2.79
TNF–α (mean ± SD; pg/ml)	10.06±2.82	9.88±3.16
VCAM–1 (mean ± SD; ng/ml)	1172.54±299.11	1140.91±299.11
ICAM–1 (mean ± SD; ng/ml)	239.92±63.34	232.05±57.61
HDL (mean ± SD; mmol/l)	1.19±0.39	1.14±0.34
LDL (mean ± SD; mmol/l)	2.41±0.69	2.5±0.53
TG (mean ± SD; mmol/l)	1.87±0.98	1.99±1.05

values of inflammatory mediators between abdominal obese HD patients and abdominal non–obese HD patients.

In recent years it has become apparent that the microinflammatory process in atherogenesis increases CV morbidity and mortality. Moreover, inflammatory mediators have been reported previously to be predictors of mortality in predialysis and also in HD patients. Stenvinkel et al. showed that elevated serum ICAM–1 concentrations were an independent predictor of mortality in patients predialysis (22). Papagianni et al. demonstrated that serum ICAM–1 concentration was an independent predictor of carotid atherosclerosis (5), and that increased serum concentrations of ICAM–1 and VCAM–1 were associated with CV events among HD patients (6). Furthermore, Panichi et al. and Kalantar–Zadeh et al. found a statistically significant relationship between IL–6 and increased CV mortality in HD patients (19,23). However, none of studies mentioned focused on HD patients with abdominal obesity. The results of our study showed that the adhesion molecules VCAM–1 and ICAM–1 were strong predictors of CV mortality in abdominal obese HD patients in both unadjusted and adjusted Cox regression models (adjusted for age, arterial hypertension, smoking, triglycerides, and HDL and LDL cholesterol). The results support our hypothesis and increase concern about the presence of abdominal obesity in HD patients. Previously, abdominal obesity has been clearly associated with all–cause and CV mortality in the general population, but no such association has been stressed in the HD population (24). On the contrary, several studies of patients undergoing dialysis have noted an inverse association between nutritional status or body mass index (BMI) and mortality in these patients, and have not highlighted the important role of abdominal fat as a source of proinflammatory mediators (25). Unfortunately, recent observations indicate that the association between abdominal obesity and survival of HD patients does not deviate from that observed in the general population (26). Furthermore, Postorino et al. recently published the results of a prospective cohort study of the rela-

tionship between abdominal obesity, determined on the basis of WAC, and all–cause and CV mortality in 537 patients with ESRD (25). The authors found that a large WAC was directly associated with an increased risk of all–cause and CV mortality, whereas BMI was again confirmed as an inverse predictor of these outcomes. As a consequence of the opposing associations of WAC and BMI with death, patients with ESRD who had large waist circumferences but low BMI were at the highest risk of overall and CV mortality, whereas the probability of death appeared to be minimal in patients with high BMI but small WAC (25).

In light of the importance of the effect of obesity on clinical outcomes in HD patients, we divided our study population into abdominal obese and abdominal non–obese HD patients and analyzed the impact of inflammatory mediators on mortality in these two groups. The Cox regression model showed that inflammatory mediators VCAM–1 and ICAM–1 were predictors of CV mortality in our abdominal obese HD patients. Furthermore, in an adjusted Cox regression model with the inclusion of other known risk factors for atherosclerosis (age, arterial hypertension, smoking, triglycerides, HDL and LDL cholesterol), both adhesion molecules (VCAM–1, ICAM–1) still remained predictors of CV mortality. Additionally, triglycerides were found to be predictors of CV mortality in these patients.

Our study has some potential limitations. First, the analysis was performed on only a small population of HD patients, and therefore our findings need to be confirmed in larger studies. Second, the findings of our study, which was based on patients undergoing HD, may not be valid in populations of patients with earlier stages of chronic kidney disease. Third, we performed WAC measurement only once on the patients and therefore we cannot rule out possible changes in WAC due to reduction or increase of abdominal obesity over time. Finally, the CV status of our HD patients before enrollment in the study (including previous CV events such as acute coronary syndrome, stroke, and peripheral arterial disease) was not analyzed.

CONCLUSION

In recent years, systemic microinflammation has been regarded as a cardiovascular risk factor both in the general population and in patients with ESRD. The present study combined knowledge of the importance of abdominal obesity in clinical outcomes in HD patients and of the role of microinflammation in stimulating atherogenesis in this population. The results of the study clearly demonstrate the impact of proinflammatory adhesion molecules on CV mortality in abdominal obese HD patients.

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