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# ENDOTHELIAL DYSFUNCTION IS ASSOCIATED WITH VISFATIN AND OXIDATIVE STRESS IN HEMODIALYSIS PATIENTS

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**Abstract:** Background: Endothelial dysfunction (ED) is marker of atherosclerosis in chronic renal failure. In uremia, visfatin was associated with inflammation and endothelial dysfunction. Materials and methods: We evaluated 32 chronic hemodialysis patients (group 1), divided in 2 subgroups (with and without diabetes mellitus) and 20 volunteers-control group (group 2). Plasma visfatin, endothelial-dependent flow-mediated vasodilatation and nitroglycerin-induced endothelium independent vasodilatation (NMD) were assessed for all groups. Malondialdehyde (MDA), hemoglobin, Kt/V, parathormone, C-reactive protein (CRP), albumin, ferritin, transferin saturation, cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol, calcium, phosphorus and body mass index (BMI) were determined in group 1. Results: FMD (p=0.02) and NMD (p=0.01) were significantly higher in group 2 than in group 1. In group 1, FMD negatively correlated with visfatin (p=0.007) and MDA (=0.03) and positively correlated with LDL-cholesterol (p=0.0007). BMI, CRP and HDL-cholesterol were significantly higher (p=0.009, =0.001, =0.01 respectively) in diabetes patients compared to patients with no diabetes, while NMD, albumin and calcium were significantly lower (p=0.04, =0.003, =0.04 respectively). Conclusions: Endothelial dysfunction, measured by FMD, is increased in HD patients compared to controls and is associated with visfatin and oxidative stress. Diabetes mellitus is associated with NMD, but it does not influence FMD and visfatin, even if inflammation is enhanced in these patients.

**Keywords:** endothelial dysfunction, flow mediated dilatation, visfatin, hemodialysis, diabetes mellitus

## INTRODUCTION

Excessive incidence of atherosclerosis and cardiovascular mortality in hemodialysis (HD) patients was observed years ago (Lindner et al., 1974) and this has not changed since then. Uremia is associated with endothelial dysfunction (ED) and impaired bioavailability of nitric oxide upon shear stress-induced stimulation of the endothelium (Kari et al., 1997). Endothelial dysfunction may work as a trigger for the accelerated atherosclerosis in patients with chronic renal failure. Systemic inflammation and oxidative stress seem to contribute to endothelial dysfunction in chronic kidney disease (CKD) patients (Del Vecchio et al., 2011; Recio-Mayoral et al., 2011).

Adipose tissue has been described as a hormonally active organ with a role in the pathogenesis of cardiovascular complications seen in uremia (Axelsson et al., 2008). Some adipokines appear to work as modulators of vascular injury (Wang et al., 2006) and inflammation (Takami et al., 2001). Associations between adipokines and ED have been demonstrated in chronic kidney disease (CKD) (Malyszko et al., 2004).

Visfatin, also known as nicotinamide phosphoribosyltransferase (NAMPT), is an adipokine that was first described in 2005 by Fukuhara et al., who found that visfatin was correlated with visceral fat mass and has an insulin mimetic activity. Visfatin might be influenced by renal function (Yilmaz et al., 2008) and in uraemia, it was associated with inflammation and markers of endothelial damage (IL-6, ICAM, CD164 and VCAM-1) (Axelsson et al., 2007; Malyszko et al., 2010), but also with altered flow mediated dilatation (Yang et al., 2007). Contradictory results were reported regarding visfatin's association with body fat mass and diabetes in patients on maintenance dialysis (Chen et al., 2006; Haider et al., 2006; Pagano et al., 2006).

The aim of this study was to assess endothelial dysfunction, measured by flow mediated dilatation

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(FMD), in patients on maintenance HD and to correlate it with diabetes and markers of inflammation, oxidative stress, anemia, lipid profile and calcium phosphorus metabolism. Also, we determined visfatin levels in these patients and we investigated its relationship with ED.

## MATERIALS AND METHODS

A prospective, transversal and observational study was performed in a single dialysis unit. A total of 32 patients undergoing hemodialysis 3 times a week were included in the study (62.3±15.7 years; duration of HD 2.0±1.4 years; 23 men and 9 women) (group 1). We used as exclusion criteria infections and malignancies. Group 1 was divided in 2 subgroups: 17 patients with diabetes mellitus (66.67±6.47 years, duration of HD 1.5± 0.9 years; 12 men and 5 women)(subgroup A) and 15 patients without diabetes mellitus (58.00±14.84 years, duration of HD 2.6±2.2 years, 11 men and 4 women)(subgroup B). Twenty volunteers served as matched controls (41.2±7.32 years, 9 men and 11 women)(group 2). The dialysis program of the patients was 4 hours 3 times per week using polyamide hollow-fibres membranes (Gambro AB, Stockholm, Sweden) and bicarbonate dialysis. The informed consent of all patients and controls was obtained and the study was approved by the Ethics Committee of our unit.

### General clinical and laboratory measurements

Samples were obtained before dialysis session and stored at -80°C until the analysis. We determined plasma visfatin, plasma malondialdehyde (MDA), body mass index (BMI), C-reactive protein (CRP), albumin, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, ferritin, transferrin saturation, hemoglobin, calcium (Ca), phosphorus (P), parathormone (PTH) and Kt/V in HD patients and visfatin in the control group. Laboratory analysis was made by Synevo laboratory in Cluj Napoca.

Plasma visfatin levels were determined by ELISA method (Human Visfatin ELISA kit, BioVision, Mountain View, California, USA) in the Immunology Department of the Second Pediatric Clinic Cluj Napoca.

Plasma malondialdehyde was measured by fluorimetric method using the thiobarbituric acid test. The plasma was heated in a boiling water bath for 1 h with a solution of 10 mM 2 – thiobarbituric acid in 75 mM K2HPO4, pH 3 solution. The reaction product was extracted in n-butanol after cooling. The MDA was spectrofluorometrically determined in the organic phase using a synchronous technique with excitation at 534 nm and emission at 548 nm. Plasma MDA was assessed in the Oxidative Stress Laboratory within the Physiology Department of the University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj Napoca.

### Vascular assessment

Endothelium-dependent vasodilatation (FMD) and endothelium-independent vasodilatation (NMD) of the brachial artery were assessed using ultrasound examination as described by Celermajer et al in 1992. Measurements were made by a single observer using a GE Logiq 3 ultrasound system (General Electric Company, Fairfield, CT, USA) with a 7.5-MHz probe. The non-fistula arm was used. All vasoactive medications were withheld 24 hours before the procedure. After 15 minutes of rest before the examination started, the brachial artery diameter was assessed 5 cm above the antecubital fossa. Three adjacent measurements were made. A pneumatic tourniquet was inflated to 300 mm Hg with obliteration of the radial pulse. After 4 minutes the cuff was deflated and flow measurements were made at 1 minute and 10 minutes post deflation. After further 15 minutes measurements were repeated and again 3 and 4 minutes after administration of sublingual nitroglycerin 325 μg po. FMD was calculated as the percent change in brachial artery diameter post deflation compared with baseline resting diameters. NMD was calculated as the percent change in brachial artery diameter post nitroglycerin administration compared with baseline resting diameters.

### Statistical analysis

Normally distributed variables were expressed as mean ± SD, while non-normally distributed variables were expressed as median (range). A p-value $<0.05$ was considered to be statistically significant. Independent samples Student's t-test, Wilcoxon's test for independent samples, Pearson test and Spearman test were applied for statistical analysis of the results. All statistical calculations were made using the Rcmdr Version 1.6-0.

## RESULTS AND DISCUSSION

Mean±SD for the normally distributed variables and median (range) for the non-normally distributed variables of the studied parameters in HD patients are represented in Table I. FMD was significantly higher in the control group (14.30±5.53 %) than in group 1 (Fig. 1). Also NMD was significantly increased in control group (20.71±9.18 %) compared to HD patients (Fig. 2). Plasma visfatin levels din not vary significantly between the control group (1.41±1.11 pg/ml) and HD patients group (1.13 (0.00-9.65). In the HD patients group, FMD was negatively correlated with visfatin (rho=-0.53, p=0.007) (Fig. 3) and MDA (rho=-0.42, p=0.03). In this group, there was a



Studia Universitatis „Vasile Goldiş", Seria Ştiinţele Vieţii
Vol. 22, issue 2, 2012, pp. 301-310

positive correlation between FMD and LDL-cholesterol (rho=0.66, p=0.0007), but also between NMD and LDL-cholesterol (rho=0.65, p=0.002). Visfatin was negatively associated with NMD in group 1 (rho=-0.38, p=0.04) (Fig. 4). We found no other significant relationship between FMD, NMD and visfatin on one hand and the other studied parameters on the other hand.

Body mass index, CRP and HDL-cholesterol were significantly higher (p=0.009, =0.001, =0.01 respectively) in subgroup A compared to subgroup B, while NMD, albumin and calcium were significantly lower (p=0.04, =0.003, =0.04 respectively) (Table I). There was no other statistically significant variation between the 2 subgroups.

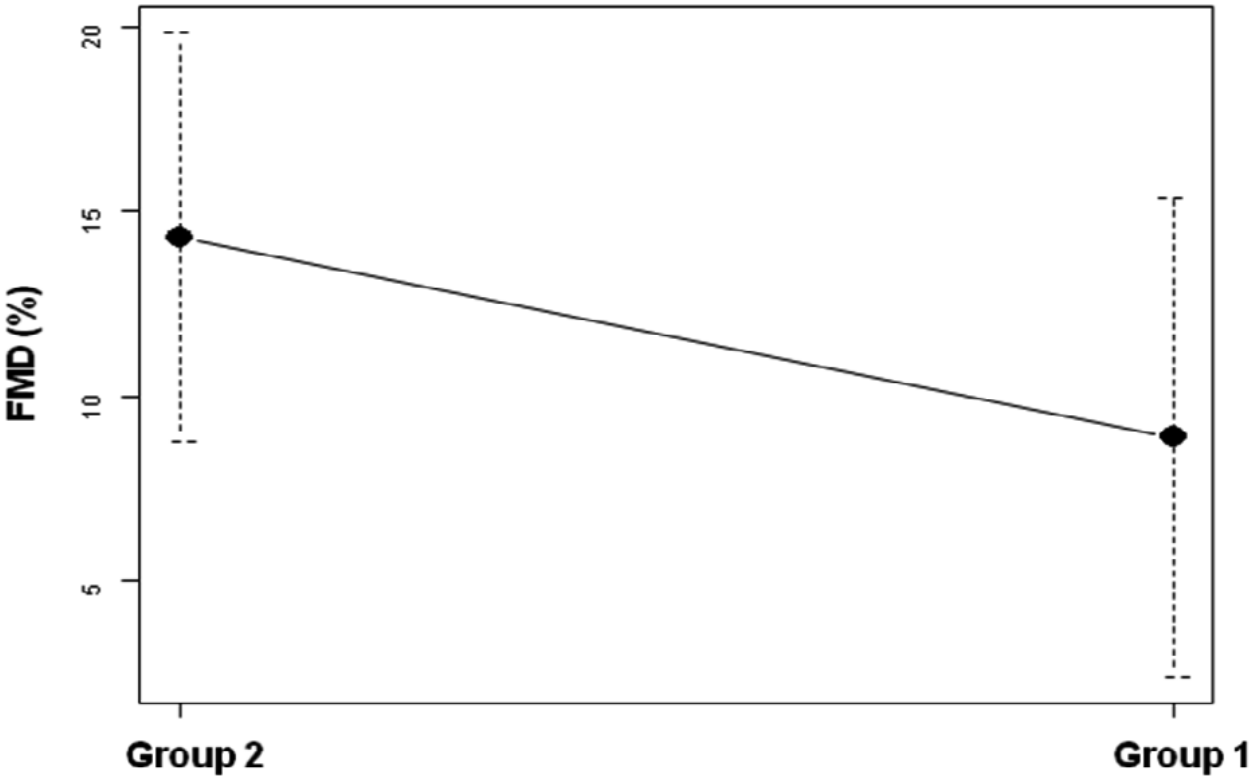
***Table I. The laboratory and vascular assessments in group 1,subgroups A and B***

*FMD=flow mediated dilatation, NMD=nitroglycerine mediated dilatation, BMI=body mass index, CRP=C-reactive protein, Hb=hemoglobin, PTH=parathomone, Ca=calcium, P=phosphorus*

| | Group 1 | Subgroup A | Subgroup B | p * |
|---|---|---|---|---|
| FMD (%) | 8.87±6.48 | 7.93±5.99 | 9.94±7.04 | NS |
| NMD (%) | 11.27±6.84 | 8.88±4.22 | 14.17±8.34 | 0.04 |
| Visfatin (pg/ml) | 1.13 (0.00-9.65) | 1.19 (0-7.04) | 1.08 (0-9.65) | NS |
| Malondialdehyde (nmol/ml) | 2.80±0.79 | 2.54±0.71 | 2.86 (1.55-3.99) | NS |
| BMI (kg/m$^2$) | 29.53±5.15 | 31.67±4.70 | 27.10±4.66 | 0.009 |
| CRP (mg/dl) | 0.57 (0.03-8.63) | 3.61±2.85 | 0.31 (0.03-4.27) | 0.001 |
| Albumin (g/dl) | 3.89±0.35 | 3.71±0.33 | 4.07±0.27 | 0.003 |
| Ferritin mg/dl) | 517.43±175.67 | 481.91±117.42 | 550.58±197.56 | NS |
| Transferrin saturation (%) | 35.00±13.51 | 30.22±7.80 | 36.48 (17.37-87.06) | NS |
| Cholesterol (mg/dl) | 189.31±47.10 | 197.28±46.73 | 181.86±47.81 | NS |
| Triglycerides (mg/dl) | 150.00 (34.90-415.00) | 191.56±120.74 | 131.00 (47.00-326.00) | NS |
| LDL cholesterol(mg/dl) | 117.18±38.23 | 112.66±42.62 | 120.30±36.35 | NS |
| HDL cholesterol (mg/dl) | 34.90 (20.30-85.10) | 45.65±19.49 | 29.55±7.30 | 0.01 |
| Kt/V | 1.44±0.19 | 1.41±0.24 | 1.47±0.13 | NS |
| Hb (g/dl) | 12.00 (5.80-15.60) | 12.00 (5.80-13.90) | 12.05±1.57 | NS |
| PTH (pg/ml) | 210.60 (17.50-1008.00) | 217.17(18.04-1008.00) | 301.09±231.34 | NS |
| Ca (mg/dl) | 8.67±0.65 | 8.41±0.73 | 8.91 (8.43-10.26) | 0.04 |
| P (mg/dl) | 5.53±1.32 | 5.74±1.35 | 5.33±1.31 | NS |

** Independent samples Student 's t-test or independent samples Wilcoxon's test, statistically significant (p<0.05), subgroup A compared to subgroup B*

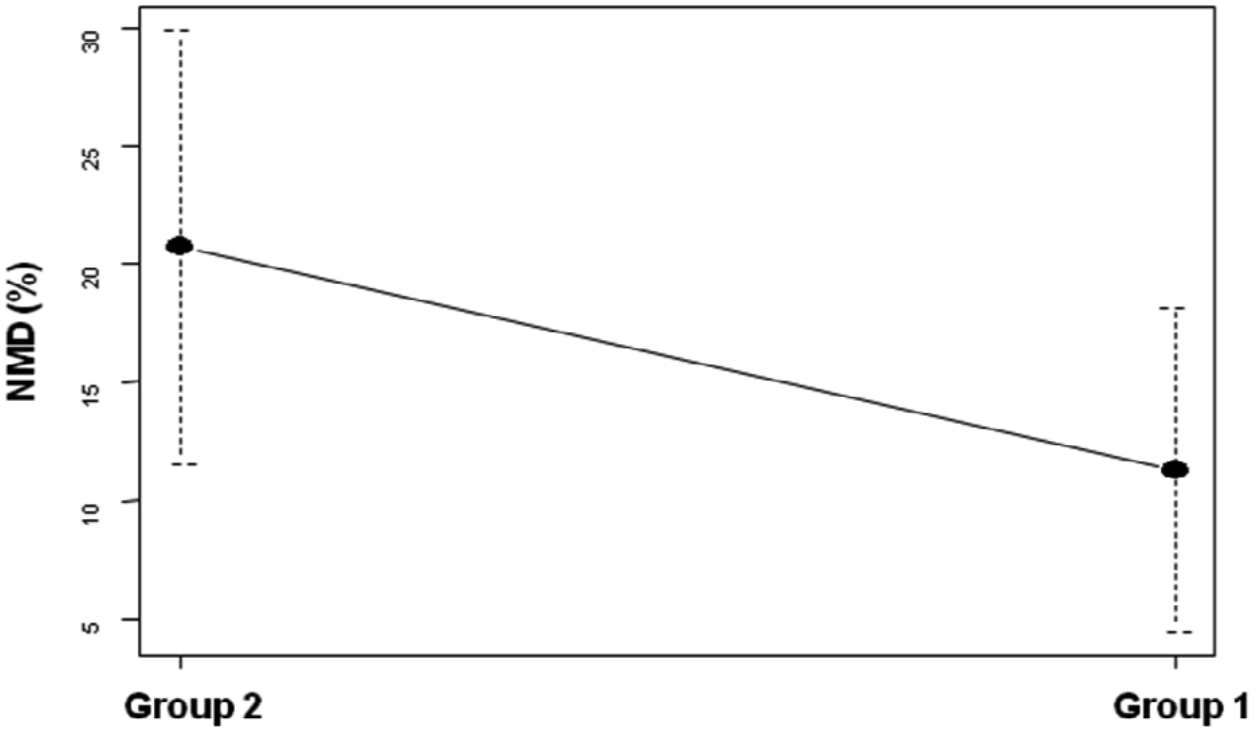
***Fig. 1. Plot of means showing the increased FMD in controls compared to hemodialysis patients***




*FMD=flow mediated dilation*
** Independent samples Student's t-test, statistically significant (p<0.05)*

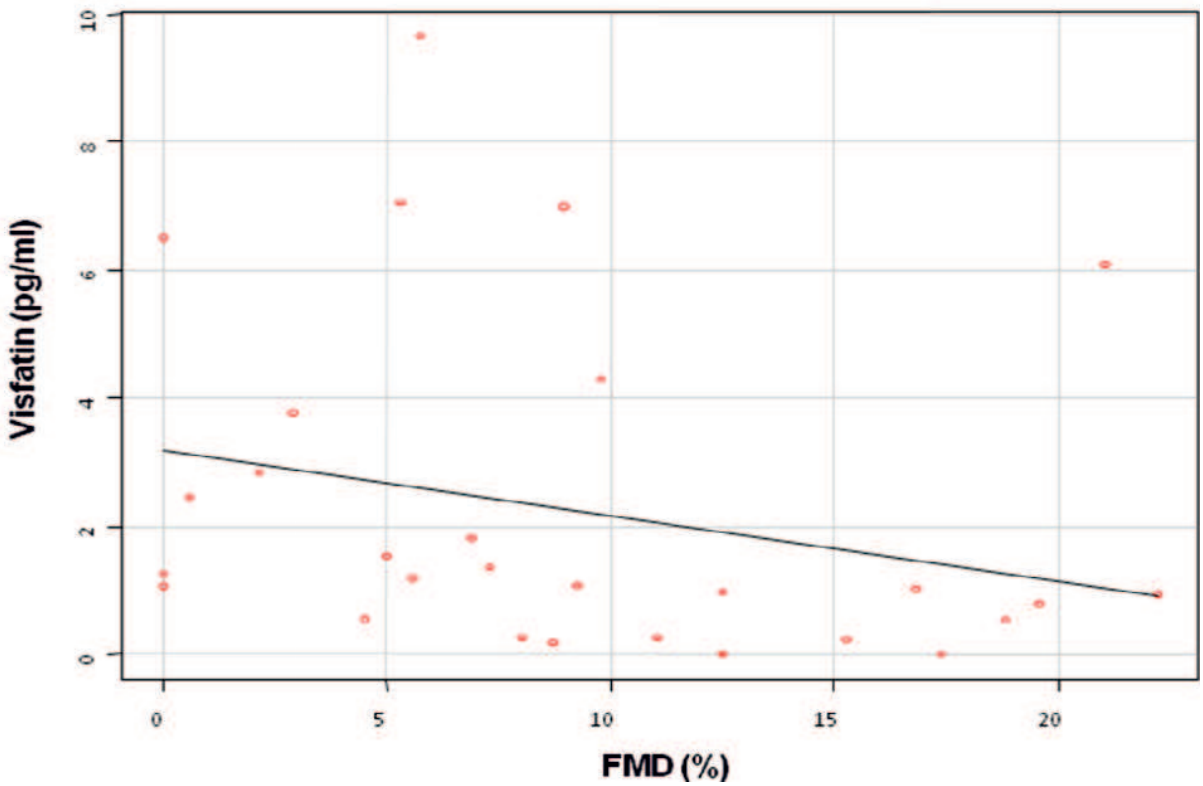

*Studia Universitatis „Vasile Goldiş", Seria Ştiinţele Vieţii*
*Vol. 22, issue 2, 2012, pp. 301-310*

***Fig. 2. Plot of means showing the increased NMD in controls compared to hemodialysis patients***




*NMD=nitroglycerine mediated dilation*
** Independent samples Student's t-test, statistically significant (p<0.05)*

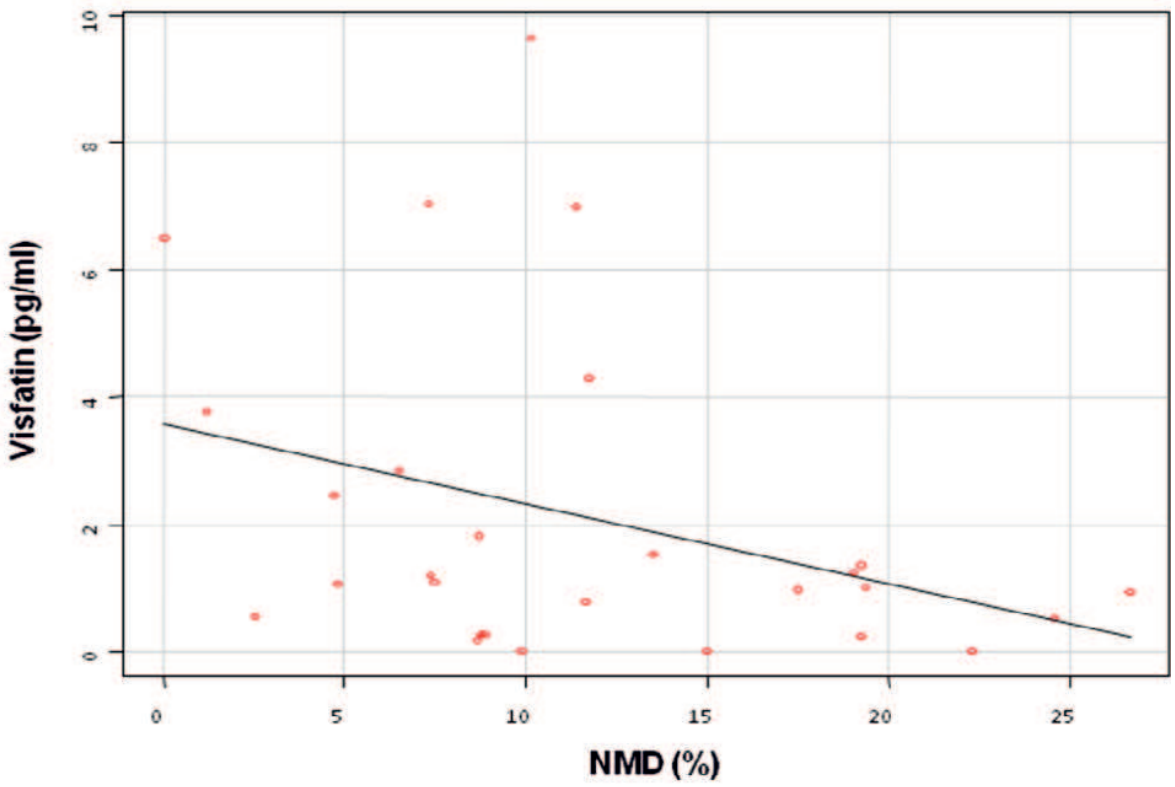
***Fig. 3. Scatter plot showing the significant negative relatioship between plasma visfatin concentration and FMD in hemodialyis patients***




FMD=flow mediated dilation
* Spearman rank-order, statistically significant (p<0.05)


*Studia Universitatis „Vasile Goldiş", Seria Ştiinţele Vieţii*
*Vol. 22, issue 2, 2012, pp. 301-310*

***Fig.4. Scatter plot showing the significant negative relatioship between plasma visfatin concentration and NMD in hemodialyis patients***




NMD=nitroglycerin mediated dilation
* Spearman rank-order, statistically significant ($p<0.05$)

In chronic renal failure endothelial dysfunction and atherosclerosis are almost universal, generating cardiovascular complications. Hypertension and shear stress, inflammation, diabetes-associated factors such as advanced glycated end products and uremic toxins are among the risk factors of ED in CKD (Malyszko et al., 2010). Traditional cardiovascular risk factors do not explain the high cardiovascular morbidity and mortality in CKD, therefore non-traditional cardiovascular risk factors have been suggested to play an important role. In HD patients, such non-traditional cardiovascular risk factors are ED, oxidative stress, anemia, inflammation, uremic toxins and abnormalities in bone and mineral metabolism (Kendrick et al., 2008).

In the present study we investigated the presence of endothelial dysfunction in CKD patients on maintenance HD and we assessed the relationship between FMD and markers of oxidative stress, inflammation, anemia, lipid profile and calcium-phosphorus metabolism. We found that FMD and NMD are significantly decreased in HD patients compared to healthy subjects. This confirms earlier reports suggesting that endothelial dysfunction is increased in these patients (Yilmaz et al., 2008). FMD negatively correlated with plasma MDA levels in HD patients, showing the positive association between ED and oxidative stress. This association was found also by other authors (Costa-Hong et al., 2009), suggesting that oxidative stress and ED might be involved in the increased susceptibility of CKD patients to cardiovascular diseases. FMD and NMD were positively correlated with LDL-cholesterol, a rather surprisingly association which could be explained by the fact that oxidized LDL, but not native LDL-cholesterol, was shown to downregulate endothelial NO synthase activity (Fleming et al., 2005).

Chronic renal failure has been associated with impaired immunity and subclinical inflammation involving cytokines derived from adipose tissue, adipocytokines (Malyszko et al., 2010). Visfatin is an adipocytokine with critical impact on energy availability, function and survival of cells (Yang et al., 2007). In CKD patients, a major source of visfatin may be the infiltration of inflammatory cells (a component of white adipose tissue) or adipose cells (Malyszko et al., 2010). In HD patients there are some specific major sources of inflammation, such as usage of dialysis membranes with different degrees of biocompatibility, uremic toxins, infection related to vascular access and (accidental) presence of bacteria or endotoxins in the dialysis liquid.

In our study, visfatin did not differ significantly between the HD patients group and the control group, although it tended to have more reduced levels in healthy volunteers. This result does not support entirely the observation that plasma visfatin levels increase along with renal function reduction (Yilmaz et al., 2008). Visfatin was negatively correlated with FMD and NMD in HD patients, confirming the association with ED in CKD and suggesting that high levels of visfatin could be related to increased mortality in end-stage renal disease. Although visfatin is considered to be associated with inflammation, we did not find a significant relationship with CRP and albumin, but it tended to positively correlate with MDA in HD patients.

In this study we analyzed if the presence of diabetes mellitus could influence the levels of the studied parameters. FMD and visfatin did not variate significantly, but NMD was statistically significant decreased in diabetes patients, suggesting an enhanced arterial stiffness. Literature reports have contradictory results regarding the FMD values in diabetes and non-diabetes HD patients. On one hand, Rus and Buturovic-Ponikvar (Rus et al., 2009) observed a significant reduction in FMD of diabetic HD patients compared to non-diabetic HD patients, while Prasad et al., (2007) found similar FMD levels in both diabetic and non-diabetic HD patients. No association with visfatin was shown for adiposity, or for parameters of glucose metabolism in end-stage renal disease patients (Axelsson et al., 2007; Yilmaz et al., 2008). Visfatin was shown to be elevated in both diabetic and non-diabetic patients on maintenance dialysis (Ziegelmeier, 2008).

In the diabetes mellitus group we found that BMI and CRP were significantly elevated compared to non-diabetic patients group, while albumin was significantly lower, showing a tendency for overweight, increased inflammation and poor nutrition. HDL-cholesterol was significantly lower in nondiabetic HD patients compared to diabetic HD patients, but the mean values were low for both groups. The difference in Ca values between subgroups should be careful interpreted since the patients were treated with calcium-containing phosphate binders.

CONCLUSIONS

In conclusion, endothelial dysfunction, measured by flow mediated dilatation, is increased in patients undergoing chronic hemodialysis compared to controls and it is associated with visfatin and oxidative stress, when measured by malondialdehyde. The presence of diabetes mellitus seems to be associated with increased arterial stiffness, when explored by nitroglycerin-mediated dilatation, but does not influence flow mediated dilatation and visfatin, in hemodialysis patients, even if inflammation is enhanced in this subgroup of patients. More and larger studies are needed to evaluate endothelial dysfunc-



Studia Universitatis „Vasile Goldiş", Seria Ştiinţele Vieţii
Vol. 22, issue 2, 2012, pp. 301-310

tion in patients on maintenance hemodialysis.

REFERENCES

Axelsson J, Stevinkel P, Role of fat mass and adipokines inchronic kideny disease. Curr Oppin Nephrol Hypertens,17, 25-31, 2008

Axelsson J, Witasp A, Carrero JJ, Qureshi AR, Suliman ME, Heimburger O, Barany P, Lindholm P, Alvestrand A, Schalling M, Nordfors L, Stevinkel P, Circulating levels of visfatin/Pre-B-cell colony-enhancing factor 1 in relation to genotype, GFR, body composition, and survival in patients with CKD. Am J Kidney Dis,49, 237-244, 2007

Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, Lloyd JK,

Deanfield JE, Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet, 340,1111-1115, 1992

Chen MP, Chung FM, Chang DM, Tsal JC, Huang HF, Shin SJ, Lee YJ, Elevated plasma level of visfatin - pre-B cell colony enhancing factor in patients with type 2 diabetes mellitus. J Clin Endocrin Metab, 91, 295-299, 2007

Costa-Hong V, Bortolotto LA, Jorgetti V, Consolim-Colombo F, Krieger EM, Lima JJ, Oxidative stress and endothelial dysfunction in chronic kidney disease. Arg Bras Cardiol, 92(5), 381-866, 398-403, 413-418, 2009

Del Vecchio L, Locatelli F, Carini M, What we know about oxidative stress in patients with chronic kidney disease on dialysis-clinical effects, potential treatment and prevention. Semin Dial, 24(1), 56-64, 2011

Fleming I, Annisuddin Mohamed, Jan Galle, Ljudmila Turchowa, Brandes RP, Fisslhaller B, Busse R, Oxidized low-density lipoprotein increases superoxide production by endothelial nitric oxide synthase by inhibiting PKCalfa. Cardiovascular Research, 65(4), 897-906, 2005

Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K, matsuki Y, Murakami M, Ichisaka T, Murakami H, Watanabe E, Takagi T, Akiyoshi M, Ohtsubo T, Kihara S, Yamashita S, Makishima M, Funahashi T, Yamanaka S, Hiramatsu R, Matsuzawa Y, Shimomura I, Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science, 307, 426-430, 2005

Haider DG, Schaller G, Kapiotis S, Maier C, Luger A, Woltz M, The release of the adipocytokine visfatin is regulated by glucose and insulin. Diabetologia, 49, 1909-1914, 2006

Kari JA, Donald AE, Vallance DT, Bruckdorfer KR, Leone A, Mullen MJ, Bunce T, Dorado B, Deanfield JE, Rees L, Physiology and biochemistry of endothelial function in children with chronic renal failure. Kidney Int, 52(2), 468-472, 1992

Kendrick J, Chonchol MB, Nontraditional risk factors for cardiovascular disease in patients with chronic kidney disease. Nature Reviews Nephrology, 4, 672-681, 2008

Lindner A, Charra B, Sherrad DJ, Scribner BH, Accelerated atherosclerosis in prolonged maintenance hemodialysis. N. Engl. J. Med, 290, 697-701, 1974

Malyszko J., Mechanism of endothelial dysfunction in chronic kidney disease. Clin Chim Acta 411(19-20), 1414-1420, 2010

Malyszko J, Malyszko JS, Mysliwiec M, Visfatin and endothelial dysfunction in dialyzed patients. Nephrology, 15, 190-196, 2010

Malyszko J, Malyszko JS, Wolczynski S, Brzosko S, Mysliwiec M, Adiponectin is related to CD146, a novel marker of endothelial cell activation/injury in chronic renal failure and peritoneally dialyzed patients. J Clin Endocrinol Metab, 89, 4620-4627, 2004

Pagano C, Pilon C, Olivieri M, Mason P, Fabris R, Serra R, Milan G, Rossato M, Federspell G, Vettor R, Reduced plasma visfatin/pre-B cell colony-enhancing factor in obesity is not related to insulin resistance in humans. J Clin Endocrinol Metab, 91(8), 3165-3170, 2006

Prasad N, Kumar S, Singh A, Sinha A, Chawla K, Gupta A, Sharma RK, Sinha N, Kapoor A, Carotid intimal thickness and flow-mediated dilatation in diabetic and nondiabetic continuous ambulatory peritoneal dialysis patients. Perit Dial Int, 29(Suppl 2), S96-S101, 2009

Recio-Mayoral A, Baneriee D, Streather C, Kaski JC, Endothelial dysfunction, inflammation and atherosclerosis in chronic kidney disease – a cross-sectional study of predialysis, dialysis and kidney-transplantation patients. Atherosclerosis Feb 18, 2011 [Epub ahead of print]

Rus R, Buturovic-Ponikvar J, Intima media thickness and endothelial function in chronic hemodialysis patients. Ther Apher Dial, 13(4), 294-299, 2009

Takami R, Takeda N, Hayashi M, Sasaki A, Kawachi S, Yoshino K, Yakami K, Nakashima K, Akai A, Yamakita K, Body fatness and fat distribution as predictors of metabolic abnormalities and early carotid atherosclerosis. Diabetes Care, 24, 1248-1252, 2001

Wang TD, Chen WJ, Cheng WC, Lin JW, Chen MF, Lee YT, Relation of improvement in endothelium-dependent flow-mediated vasodilation after rosiglitazone to changes in asymetric dimethylarginine, endothelin-1, and C-reactive protein in nondiabetic patients with the metabolic syndrome. Am J Cardiology, 98, 1057-1062, 2006

Yang H, Yang T, Baur JA, Perez E, Matsui T, Car-

mona JJ, lamming DW, Souza-Pinto NC, Bohr VA, Rosenzweig A, de Cabo R, Sauve AA, Sinclair DA, Nutrient-sensitive mitocondrial NAD+ levels dictate cell survival. Cell, 130(6), 1095-1107, 2007.

Yilmaz MI, Saglam M, Carrero JJ, Qureshi AR, Caglar K, Eyileten T, Sonmez A, Cakir E, Yenicesu M, Lindholm B, Stevinkel P, Axelsson J, Serum visfatin concentration and endothelial dysfunction in chronic kidney disease. Nephrol Dial Transplant, 23, 959-965, 2008

Yilmaz MI, Saglam M, Qureshi AR, Carrero JJ, Caglar K, Eyileten T, Sonmez A, Cakir E, Oguz Y, Vural A, Yenicesu M, Stevinkel P, Lindholm B, Axelsson J, Endothelial dysfunction in type-2 diabetics with early diabetic nephropathy is associated with low circulating adiponectin. Nephrol Dial Transplant, 23(5), 1621-1627, 2008

Ziegelmeier M, bachmann A, Seeger J, Lossner U, Kratzsch J, Bluher M, Stumvoll M, Fasshauer M, Adipokimes influencing metabolic and cardiovascular disease are differentially regulated in maintenance hemodialysis. Metabolism, 57(10), 1414-1421, 2008