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RELATIONSHIP BETWEEN VISFATIN AND SOME BIOMARKERS OF BONE TURNOVER IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Abstract: Chronic kidney disease (CKD) is a progressive disease that might result in an end stage renal disease (ESRD), raising cardiovascular morbidity and mortality. Life expectancy among patients with CKD could significantly be reduced as a result of an advanced atherosclerosis and followed by a premature death from cardiovascular disease (CVD). CVD is a condition of a subclinical systematic inflammation that involves cytokines produced by adipose tissue. Visfatin is an adipocytokine with potentially important effects on glucose metabolism and atherosclerosis. Therefore, it could be treated like a new marker of endothelial dysfunction (ED) in CKD patients. It has been suggested that visfatin levels could increase as CKD progresses, which could be due to either the chronic inflammation associated with CKD and/or the hypoxia resulting from tubular necrosis, anemia and reduced capillary blood flow. As CKD progresses, visfatin levels among these patients most often spell increased mortality caused by cardiovascular events.

The current research has been conducted among a total of 80 subjects with CKD who were divided into two groups - pre-dialysis (30) and hemodialysis treatment (50) patients from the Nephrology and Dialysis Clinic at the UMHAT "Sveta Marina" Varna. Demographics indicators and levels of visfatin, iFGF-23 and iPTH were inevstigated.

Keywords: *chronic kidney disease, visfatin, endothelial dysfunction, inflammation, FGF-23.*
Field of the paper: 3) Medical sciences and Health

INTRODUCTION

Chronic kidney disease (CKD) is part of the modern pandemic of chronic, non-infectious diseases, which occupies one of the leading places in terms of frequency and cause of mortality among the world population. According to recent data, nearly 8.7% of the world's population suffers from CKD of various etiologies. Life expectancy among those patients is significantly shortened due to premature death from cardiovascular disease (CVD). Advanced atherosclerosis is among the main causes of morbidity and mortality in this group of patients - about 80-90% die from cardiovascular diseases before reaching dialysis treatment. CVD is a condition of a subclinical systematic inflammation that involves cytokines produced by adipose tissue. Endothelial dysfunction (ED), atherosclerosis, and cardiovascular disease are associated with CKD. It has been suggested that the affected kidney function may trigger an accumulation of adipokines, which in turn casts a new light on the distict dysmetabolism in CKD.

The molecular weight of visfatin, which is an adipocytokine, is 52 kDa and it is produced and secreted primarily by visceral fat. It plays the part of an inflammatory cytokine and its levels increase in a variety of acute and chronic inflammatory diseases. The hypothesis is that visfatin may be involved in uremic-associated atherosclerosis, and it has been proven there is a connection between it and ED. It is believed that Visfatin levels increase with the progression of CKD, which results from either the persistent inflammation associated with kidney disease and/or the hypoxia resulting from tubular necrosis, anemia, and reduced capillary blood flow. Deterioration of renal function leads to an increase in general inflammatory responses due to a decrease in renal clearance of factors directly or indirectly involved in the inflammatory process. With the progression of CKD, visfatin levels among these patients most often spell increased mortality caused by cardiovascular events.

Hyperphosphatemia, increased PTH levels, and vitamin D deficiency are associated with increased mortality in chronic kidney disease. FGF-23 is a hormone regulator of these factors, and it could be argued that it may be the biomarker of impaired metabolism of minerals associated with survival, which could raise the cardiovascular risk, and is also regarded as a main reason of morbidity and mortality in CKD. There are investigations that have also found that FGF-23 is associated with untimely changes in vascular function which raises the cardiovascular risk.

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MATERIALS AND METHODS

The current research has been conducted among a total of 80 subjects with CKD from the Nephrology and Dialysis Clinic at the UMHAT "Sveta Marina", Varna. They were divided into two groups - predialysis (30) and hemodialysis treatment (50), which was followed up clinically and the patients were examined by routine methods. All participants signed an informed consent prior to the study.

Visfatin levels were determined in blood serum by a ready-made Human VF (Visfatin) ELISA kit, with a sensitivity (detection threshold) of 0.188 with range of 0.313 – 20 ng/ml. The sample was serum collected with a closed Vacutainer SST II Advance gel serum separation system of the company Beckton Dickinson. The levels of FGF23 (intact) were found in serum by a ready-made FGF23 (Intact) ELISA test kit for the quantitative determination of Human Intact FGF 23, with a sensitivity of 5.4 pg/ml and range of 0-1600 pg/ml. The sample, namely serum, was collected in Vacutainer SST II Advance gel serum separation system of the company Beckton Dickinson.

The results are reported by measuring the optical density, dynamic range and sensitivity of the obtained solutions, based on which standard curves showing the corresponding serum concentrations are prepared using mathematical formulas. PTH levels were calculated by chemiluminescent immunoassay with Immulite 2000 XP.

The following statistical methods were used - variance analysis (ANOVA), variation analysis, correlation analysis, regression analysis, comparative analysis (hypothesis evaluation), risk assessment analysis (OR – Odd ratio), ROC curve analysis to determine the threshold value of Visfatin. Data was statistically processed using SPSS v.20.

RESULTS

No significant difference was found in the distribution of patients according to age and sex, and allowed comparability of results in subsequent analyses.

When comparing the average values of Visfatin no significant variation was discovered between the groups - dialysis group (21.7 ng/ml) versus pre-dialysis group (26.7 ng/ml) (Fig. 1, Fig. 2).

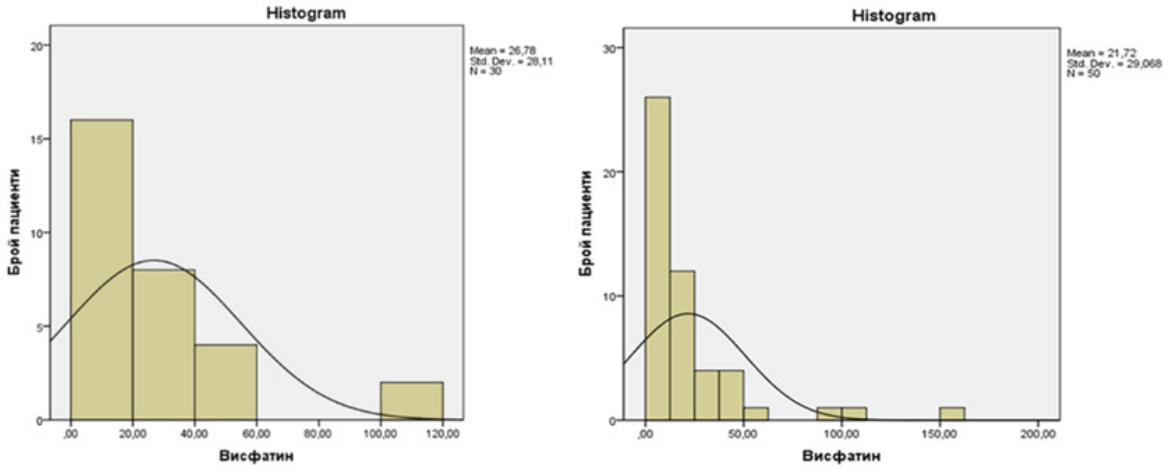

Fig. 1, Fig. 2. Visfatin mean values and distribution of patients from both groups.

Due to the lack of unified reference limits of Visfatin, the threshold value was determined to be 16.92 ng/ml (AUC=0.612 (0.485-0.739); p<0.05), at which there is a distinction between patients in the two groups with a sensitivity of 55.2% and a specificity of 57.1% (Fig. 3).

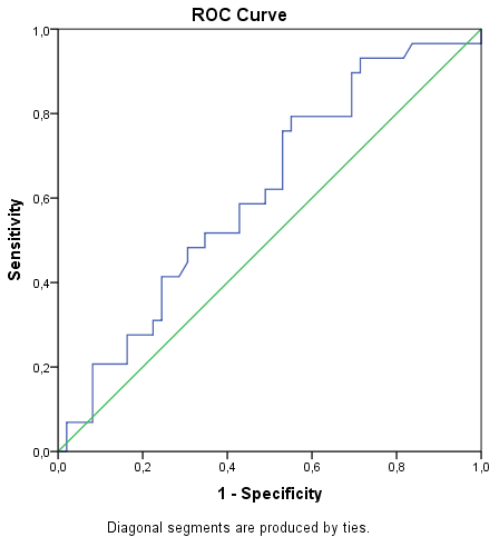

Fig. 3. ROC curve analysis to determine the threshold value of Visfatin.

When determining the Visfatin threshold value, it was found that values above 16.92 ng/ml moderately correlated with earlier stages of CKD, while lower values were associated with dialysis stage (r=0.299; p<0.05).

The basic rate of iPTH was 518.98 ± 620.09 (10.9 – 2500 pg/ml) (Fig. 4), with the average of the 25th percentile being 136.5 pg/ml, the 50th being 280.0 pg/ml and the 75th percentile is 621.5 pg/ml.

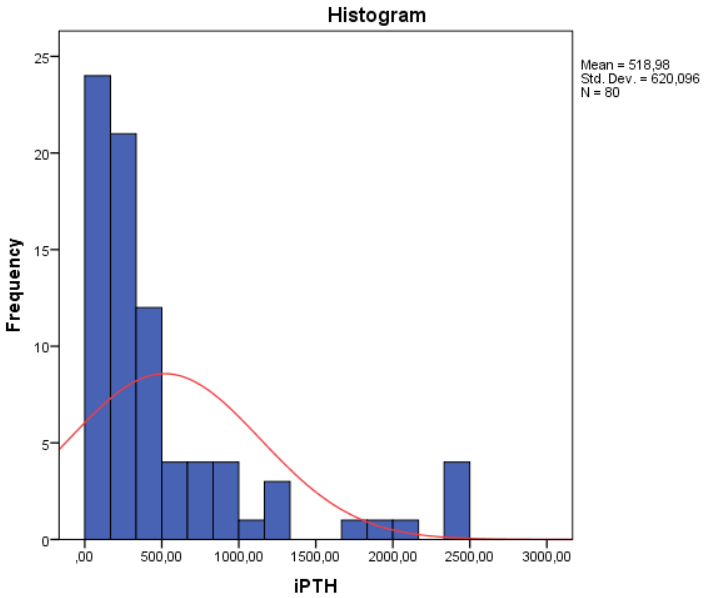

Fig. 4. Distribution of iPTH.

A marked difference (p=0.05), as well as a weak correlation between the groups and iPTH (r=0.218; p=0.05), was found, with iPTH values in the dialysis treatment patients being significantly higher (Fig. 5).

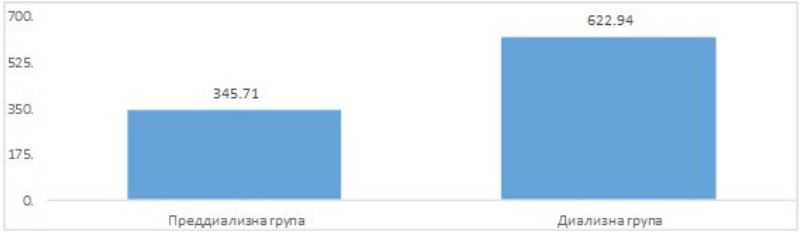

Fig. 5. Comparative analysis of iPTH values found in the studied groups

Of all the dialysis patients followed, only one had low levels of iPTH (10.90 pg/ml), and he was also characterized by an extremely low level of Visfatin (2.54 ng/ml), while individuals with iPTH values above the upper reference limit (90 %) have significantly higher visfatin concentrations (23.96 ng/ml).

No correlation was found between iPTH values and Visfatin values in either the predialysis or dialysis group, but it can be speculated that there is a significant difference in iPTH values compared to Visfatin threshold values (p=0.045) These values show the same trend in the studied groups, but in the dialysis one iPTH levels were markedly higher (Fig. 6).

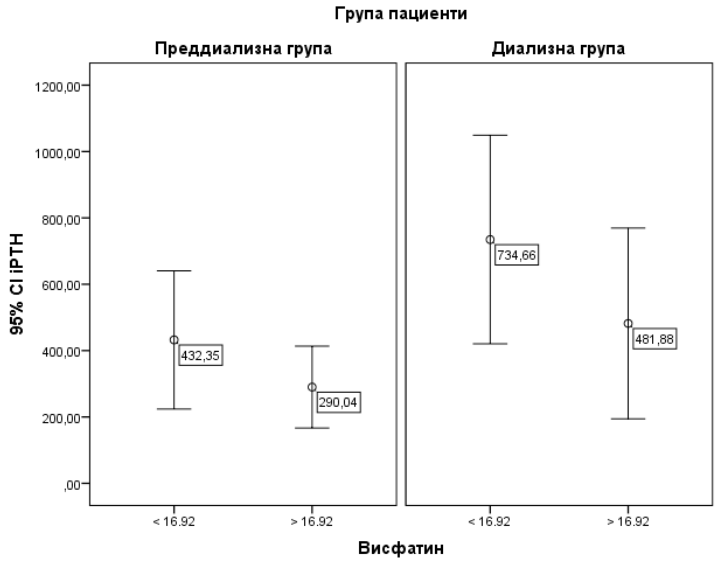

Fig. 6. Mean values of iPTH according to Visfatin threshold levels in the studied groups.

An important contrast was observed in the medium intact fibroblast growth factor (iFGF 23) rates in accordance with the visfatin threshold value in patients in predialysis group (p<0.05), while in the dialysis part iFGF 23 levels remained consistently high regardless of visfatin values (Fig. 7).

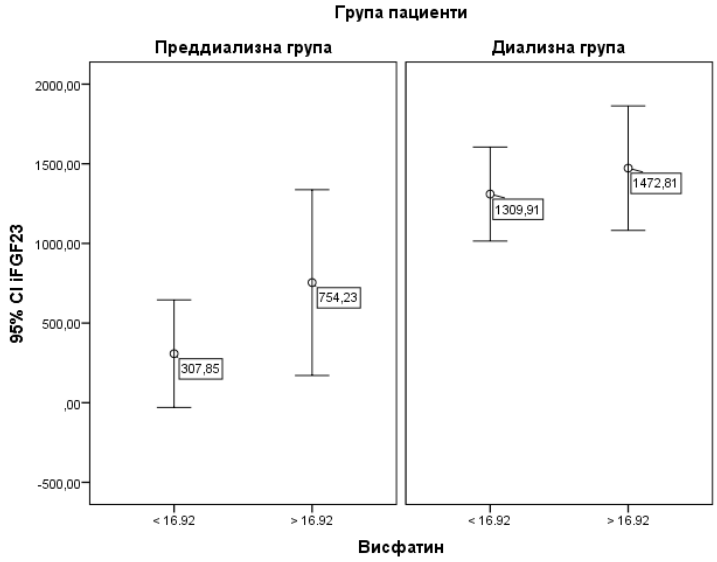

Fig. 7. Mean values of iFGF 23 in accordance with the visfatin threshold levels in the studied groups.

DISCUSSIONS

Evidence that has been accumulated indicates that adipose tissue is no longer regarded only as a triglyceride (TG) storage depo, but also as a true endocrine organ that synthesizes and secretes bioactive

factors called adipokines. Those can be secreted and can affect the adipose tissue. Visfatin is released by adipocytes and the estimated physiological plasma level of visfatin is 15 ng/ml and the concentration of plasma visfatin increases as fat accumulates. Axelsson J and Yilmaz M have demonstrated in their studies that the concentrations of visfatin increases in CKD patients compared to controls. This statement is also supported by our results - persistently elevated values of visfatin were registered in both the pre-dialysis and dialysis group of patients.

Nüsken et al. found low levels of serum visfatin among a cohort of patients with terminal kidney disease who were treated with hemodialysis, which may be due to the fact that their patients showed a decrease in body fat mass and an increase in insulin levels. Our results support this thesis - visfatin values were lower among dialysis patients compared to the pre-dialysis group.

Recently, considerable attention has been given to the role of adipokines in CKD as proinflammatory markers - visfatin, resistin and other. Adiponectin values found in subjects with ESRD appeared to be higher than in control groups. Increased levels of serum of FGF23 are closely connected with higher cardiovascular morbidity in patients with CKD. Consequently, the levels of FGF23 rise as renal function deteriorates, with the result that in subjects with ESRD, FGF23 contributes to hypertension, vascular calcification, and left ventricular hypertrophy through different mechanisms. Adiponectin and leptin have been found to directly stimulate skeletal FGF23 expression, which suggests a connection between them and FGF23. Spoto et al. discovered that adiponectin is a powerful trigger of the FGF23 answer to vitamin D receptor activation in CKD patients. VDR activation significantly increased FGF23 gene expression and significantly increased FGF23 levels in healthy vitamin D-deficient individuals and CKD patients. FGF23 also shows a relationship with epicardial adipose tissue in individuals at a different stage of CKD. Our review of the literature database found no other direct comparisons and established relationships between FGF 23, iPTH and visfatin in patients with different stages of CKD.

CONCLUSIONS

Constant inflammation plays a main part in CKD and is responsible, in part, for both cardiovascular and total mortality, the development of malnutrition and other diseases. A number of agents are blame for the chronic inflammatory status in CKD, including elevated output and reduced purification of proinflammatory cytokines, altered adipose tissue metabolism, chronic and recurrent infections, oxidative stress and acidosis. Fat tissue is a endocrine organ which secrets multiple factors that lead to kidney complications. Adipokines are involved in CKD by mediating ED, oxidative stress and variations in the immune answer. They plays a part in the fragile balance between protective and pathophysiological effects.

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