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Research Article

Serum Prealbumin and Calprotectin Levels in Chronic Hemodialysis Patients

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Abstract

Background: Inflammation, as well as poor nutritional status and protein loss, are common in chronic hemodialysis patients. Serum calprotectin and prealbumin levels are factors which can predict or indicate the inflammation and the malnutrition respectively. We aimed to assess the relationship between serum calprotectin and prealbumin levels in hemodialysis patients and to correlate them with parameters such as the presence of diabetic condition in the patients, their BMI, the dialysis vintage, the gender, smoking and their serum biochemical profile.

Methods: Serum lipid, glucose levels, hepatic enzymes, creatinine, urea and uric acid levels were determined before HD session. Serum calprotectin and prealbumin levels were also measured.

Results: The average mean levels of serum calprotectin in the patients studied was 2.98±2.12 (mg/l) while mean prealbumin levels were 270.51±361.65 (mg/l). No significant correlation was found between serum calprotectin and prealbumin levels (Spearman, rs = -0.063, p = 0.621). Neither calprotectin nor prealbumin values were correlated with the kidney failure time period, the years of hemodialysis, the BMI, and serum uric acid levels. In addition neither calprotectin nor prealbumin levels significantly differ between males and females or diabetic and non-diabetic individuals. In contrast to prealbumin levels, serum calprotectin levels significantly differ among smoker and non-smoker patients.

Conclusion: This study revealed there is no significant association between serum calprotectin and prealbumin levels in chronic diabetic or non-diabetic hemodialysis patients. However, smoking seems to affect serum calprotectin concentration in these patients. More detailed studies are needed to validate these outcomes and to elucidate the mechanistic pathways involved.

Keywords: Calprotectin; Prealbumin; Diabetic Nephropathy; Inflammation; Nutritional Status

Introduction

Chronic Kidney Disease (CKD) is a complicated kidney disorder which can induce permanent renal failure in progressive stages. Diabetic nephropathy is considered as the main cause of chronic renal failure and of the last stage of CKD, known as End Stage Renal Disease (ESRD) [1].

Hemodialysis (HD) constitutes the most important procedure for the management of ESRD [2]. During 2014, the Hellenic Society of Nephrology recorded 9718 patients in Greece being under the process of hemodialysis. The European Renal, Dialysis and Transplant Association (ERA-EDTA), registered 22449 prevalent counts in hemodialysis in 2012 [3].

The calprotectin is a complex of two calcium-binding proteins and zinc, known as MRP8 and MRP14 [4]. This protein is found at low levels on monocytes and in oral keratinocytes. It is also abundant in the cytoplasm of neutrophils [5]. Recent studies have shown the involvement of calprotectin in inflammatory conditions [6]. Calprotectin concentration is increased in many cases of chronic hemodialysis without an acute infectious cause and is not affected by the presence of diabetes [7].

Prealbumin is a protein present in all classes of vertebrates and the liver represents its main source [8,9]. Prealbumin constitutes a biomarker for malnutrition [10]. This biomarker appears to be at low rates in cases of an acute phase in the early stages of liver cirrhosis, allergic conditions and in cases of chronic active infection, especially in cases of people using hemo-solvents as in the case of hemodialysis patients. It is considered as a biomarker reflecting poor nutritional status or metabolic disturbances [11].

The purpose of this study is to investigate the relationship between serum calprotectin and prealbumin levels in hemodialysis patients and to correlate these with parameters such as the diabetic status of the patients, their BMI, the years of hemodialysis, the gender, smoking and the serum biochemical profile.

Materials and Methods

88 hemodialysis patients of the Artificial Kidney Unit in the General Hospital of Agrinio (Aetolia and Acarnania Regional Unit, Greece) were included in the present study. Of these, 62 were males and 26 were females. The study was approved by the Ethics Committee of National and Kapodistrian University of Athens and by the local ethical committee of the General Hospital of Agrinio and an oral informed consent was obtained from each patient. The portion of the artificial kidney was equipped with GAMBRO equipment, in which patients underwent hemodialysis.

The filters of the machines used were Kuf > 20 ml / mmHg /h/1.0 m^2, synthetic high flux membranes and surface membranes ≥ 1,5 m^2.

The study group consisted of 15 diabetic type 2 patients (5 females 10 males) and of 73 non-diabetic patients. 53 of them were males (72.60%) and 20 females (27.39%). Diabetes wasn't signified as an exclusion criterion considering that this disease is common among hemodialysis patients. Exclusion criteria for the study were cardiovascular disease and cancer.

5 ml of venous blood was collected from the patients -after a 12-hour fasting period- for biochemical analysis (serum lipid and glucose levels, serum alkaline phosphatase (ALP), serum creatinine, urea and uric acid levels) and for the determination of calprotectin and prealbumin levels.

In briefly collected blood were placed in plastic Wasserman tubes without anticoagulants and were kept at room temperature for approximately 30 minutes. The samples were then centrifuged at 3000 rpm for 10 minutes for serum preparation. Biochemical analysis was performed in the biochemical lab of the hospital whereas remaining. Serum was stored at -80 degrees Celsius for further analysis.

Serums were transferred into liquid nitrogen to the "Laboratory for Experimental Surgery and Surgical Research N. S. Christeas" in the Medical School of Athens. Serum calprotectin and prealbumin were measured using commercially available kits. For prealbumin levels determination, the assay was carried out using an Elisa kit, Immunodiagnostik AG, Stubenwald-Allee 8a, D-64625 Bensheim, Germany. Calprotectin was measured using calprotectin enzyme linked immunosorbent assay [ELISA] kit (Calprotectin ELISA kit, Eurospital, Trieste, Italy).

The final numbers of serum samples analyzed for prealbumin and calprotectin levels determination were 64 and 81 respectively due to technical issues.

The medical history of each patient was recorded and further evaluated. Medical history included information regarding previous treatments or hospitalization, the use of specific pharmaceutical substances, such as corticosteroids, antimalarial medications, or anti-inflammatory drugs. 84 chronic hemodialysis patients were under statin treatment, while 4 patients which were under hemodialysis less than a year were not.

In order to obtain comprehensive information on patients characteristics and lifestyle, a questionnaire was filled. The questions were in the form of an interview during the hemodialysis procedure. The questions concerned age, gender, height, weight, smoking, number of cigarettes per day, years undergoing hemodialysis and nutritional habits

Statistical Analysis

Statistical data analysis was implemented with SPSS software (IBM, ver. 19). All tests are presented together with the resulted statistical function (s.f.), and its associated p-value (the maximum significant level we might not reject the null hypothesis). Ad hoc, a 5% probability of error type I: a null hypothesis is rejected although is valid, was selected for the outcome of the statistical analysis. Either parametric or non-parametric tests were applied with respect to the sample's data normality or not respectively. Data normality was initially tested with the Kolmogorov-Smirnov non-parametric test (s.f. Z). Where data normality is rejected, the skewness index s (positive or negative for asymmetry to the right or left respectively, otherwise symmetry) is presented too. For continuous data samples such as renal failure duration, Body Mass Index (BMI) and serum uric acid, serum lipid and glucose levels, ALP levels, creatinine and urea levels, calculations of arithmetic mean ± standard deviation (μ ± σ) and median (δ) were extracted. Pearson's and Spearman's correlation coefficient between two samples was calculated for normal and not normal data respectively. Levene's parametric test examined the equality of variances (s.f. F) between independent samples. Student's test was examined the equality of arithmetic means between two independent samples (s.f. t) of normal data. In the case of non-normal data of independent samples, non-parametric Mann-Whitney test was used to examine the equality of medians (s.f. U). Further statistical analysis was applied to either CP or PA serum levels or the duration of renal failure, BMI and serum uric acid levels (all using Spearman's correlation), either smokers or non-smokers, gender, and diabetes.

Results

Patients characteristics and biochemical measurements

The patients' average age was 64.7 ± 14.45 years and ranged from 29 to 87 (Z = 1.310, p = 0.065). Mean BMI was 25.24 ± 4.77 (kg/cm2), ranging from 17.48 to 36.91 (Z = 0.94, p = 0.34) and the vast majority of participants (78.4%) were smokers. The mean duration of the renal failure of the patients was 5.9 ± 6.74 years and ranged from 7 days to 33 years, (s = 2.066, Z = 2.422, p < 0.001) with no significant different means (F = 0.194, p = 0.660; t = 0.424, p = 0.67) between smokers (6.07 ± 7.07 years) and non-smokers (5.32 ± 5.48 years). The biochemical profile of the patients is presented in Table 1.

Serum glucose levels significantly differed among diabetic type 2 and non-diabetic individuals (p = 0.013). Serum lipid levels, ALP levels, and serum concentrations of urea and creatinine did not differ between diabetic and non-diabetic patients (p > 0.05 in all cases). Mean serum uric acid levels determined in 86 participants was 156.48 ± 46.05 (mg/dl) and the values ranged from 58 to 249 (Z = 0.701, p = 0.71).

Biochemical measurements	Mean	SD
Serum urea levels (mg/dl)	154.40	46.53
Serum creatinine levels (mg/dl)	8.71	3.05
Serum glucose levels (mg/dl)	104.75	43.46
Alkaline phosphatase levels (U/l)	89.43	48.55
Serum cholesterol levels (mg/dl)	167.77	37.28
HDL/LDL Cholesterol levels ratio	0.52	0.27

Table 1. Average Mean ± Standard Deviation (SD) of Serum Urea, Creatinine, Glucose, Alkaline Phosphate, Cholesterol And HDL/LDL Cholesterol Ratio Levels In The Enrolled Patients.

No significant correlation was found between the duration of renal failure and either BMI (Spearman, r_s = -0.19, p = 0.076) or uric acid levels (Spearman, r_s = 0.095, p = 0.382) (Table 2).

Variable	CP	PA
Duration of kidney failure	r_s = -0.127, p = 0.260, N=81	r_s = -0.213, p = 0.092, N=64
BMI	r_s = -0.158, p = 0.159, N=81	r_s = 0.043, p = 0.736, N=64
Uric Acid	r_s = -0.071, p = 0.529, N=80	r_s = 0.063, p = 0.623, N=63
Smoke-Non Smokers	U = 372.0, p = 0.027, N = 81	U = 235.0, p = 0.107, N = 64
Gender	U = 599.5, p = 0.382, N = 81	U = 378.0, p = 0.373, N = 64
Diabetes	U = 366.0, p = 0.198, N = 81	U = 135.0, p = 0.071, N = 64

Table 2. Correlation Of Serum Prealbumin (PA) And Calprotectin (CP) Levels With Parameters Of The Hemodialysis Patients. Correlation Coefficient Between Samples (Spearman's Association).

Calprotectin (CP) and Prealbumin (PA) levels

The mean levels of serum CP (mg/l) among the 81 patients studied were 2.98 ± 2.12 (mg/l) and ranged from 1.42 to 16.07 (Z = 1.74, p =0.005, s = 2.26). In 64 participants the mean serum PA levels were 270.51 ± 361.65 (mg/l), ranging from 7.08 to 1764.7 (Z = 1.74, p = 0.006, s = 2.26). No significant correlation was found between CP and PA serum levels (Spearman, r_s = -0.063, p = 0.621). In summary, neither serum CP nor PA measurements were correlated with the kidney failure time period, BMI and uric acid measurements. In addition neither CP nor PA measurements significantly differ between males and females and persons that suffer from diabetes or not. Contrariwise CP levels differ among smoker (Mean levels: 12.89 ± 6.31) and nonsmoker patients (Mean levels: 10.69 ± 8.86). In contrast, serum PA concentration did not differ among smokers or nonsmokers (Table 2).

Regarding smokers, values of CP (18 patients) and PA (13 patients) were found 12.88 ± 6.31 (mg/l) and 12.97 ± 25.37 (mg/l) respectively. Comparing CP with PA, analysis showed either not any significant difference (Wilcoxon, Z = -1.433, p=0.152) or significant correlation between both variables (Spearman's rho = 0.462, p=0.112).

Conclusion

Prealbumin is a plasma protein, synthesized in the liver. Its expression occurs also at endocrine cells in the islets of Langerhans. The expression of prealbumin has been shown in alpha (glucagon) cells. Islets derived from type 2 diabetic patients have proportionally more prealbumin reactive islets cells in accordance with the known loss of beta cells in the disease. The function of prealbumin in these cells is not known. There is a possibility that prealbumin may be bound to the glucagon precursor and effects its processing [12]. Prealbumin constitutes a biomarker of malnutrition in diabetic patients. Indeed, diabetic patients following chronic hemodialysis are considered to be at increased risk of malnutrition [13]. In a number of clinical investigations, diabetic patients showed decreased prealbumin levels, caused by the accumulation of metabolic conditions that lead to poor protein status, during hemodialysis [14].

Mean serum prealbumin levels were relatively low, a finding that was in accordance with the conclusions of other studies on renal and hemodialysis patients. Specifically, Fellah et al (2008), observed that the risk of serum prealbumin levels <300 mg/l, was higher in malnourished renal patients [15]. However, no significant differences in prealbumin levels were recorded between diabetic and nondiabetic patients in our study. This could be partially explained due to the relatively small number of the diabetic patients included in the study or because the low prealbumin levels in all patients are a result of the malnutrition situation during the years of the chronic hemodialysis [16].

Chronic inflammation is inherent to the metabolic syndrome [17]. It has been shown that the insulin resistance and the β-cell failure are mainly implicated in the development of type 2 diabetes. However, during the recent decades, other mechanisms such as the immune system, have been involved in pathogenesis of this endocrine disease [17].

According to the outcomes of a large scale clinical study, the low grade inflammation was able to predict and precede diabetes development in middle-aged adults [18].

The adipocytes secrete proinflammatory cytokines, which inhibit the insulin signaling [19]. These adipocytes act through proinflammatory regulators having as purpose to modulate the expression of inflammatory proteins' genes and to alter insulin sensitivity [20]. Calprotectin, which is considered as an important factor of inflammation, has been linked to insulin resistance besides its presence in inflammation status [21]. Following its secretion, this protein interacts with RAGEs (Receptor for Advanced Glycation End Products) acting like a ligand. This interaction is able to intervene detrimental effects caused by the activation of NF-Kβ via the pathway of RAGE-MAPK (RAGE and Mitogen-activated protein kinase) [22]. It is well known that the activation of IK-β kinase may induce insulin resistance [23].

The increased serum calprotectin levels recorded in our study as compared with the normal range (0.15 -0.9 mg/l) [24], provide an evidence for the participation of this biomarker in the inflammation processes occurring in these patients. According to our findings, no significant differences were recorded in calprotectin concentration between diabetic and non diabetic patients. In addition the years of hemodialysis had no significant impact on calprotectin levels. A possible explanation for this could be that the hemodialysis patients had elevated calprotectin levels due to the chronic hemodialysis and for this reason they received anti-inflammation treatment (intake of statins for a period of time) that may have normalized the differences among the different patient groups [25]. No correlation was observed between calprotectin and prealbumin levels. This may be explained because of the different pathways in which these proteins are involved. In each pathway there is not any common element [26].

Moreover, no significant correlation was observed between the duration of smoking period and the years of hemodialysis. The smoking can certainly increase the plasma circulating products of lipid-peroxidation, whose amounts are already high in hemodialysis patients as compared with healthy individuals [27]. In the smoker hemodialysis patient low plasma levels of ascorbate have been recorded and this suggests that these group of patients are more sensitive to the tissue damage caused by oxidative stress during smoking.

BMI was not related with the years of hemodialysis according to our study. In addition no significant differences were recorded in BMI, between diabetic and non diabetic patients.

A survival benefit with increasing BMI in patients during the years of hemodialysis has been reported [28]. However in chronic hemodialysis patients, weight loss is not recommended for two reasons. Firstly, because malnutrition is common in these patients and secondly because high BMI is positively associated with the survival. The paradox of high BMI and the better survival is described in chronic hemodialysis patients. That means that is not common to notice a differentiation in this factor between hemodialysis patients. In the first years of hemodialysis, patients may lose weight; this decrease of BMI may be due to the exceeding onus of illness at the time of initiation of the dialysis. Afterwards, weight gain, can be noticed accompanied by better nutrition due the improved appetite when patients are steadying on dialysis therapy [29].

The results of our study show that there is a relationship between calprotectin levels and the factor of smoking. We noticed that calprotectin levels are different between the smokers and non smokers. This may be attributed to the impact of smoking-induced oxidative stress. The oxidative stress caused by the combustion derived nanoparticles during smoking, causes inflammation through pathways such as MAPK and NF-kb and a transcription of pro-inflammation genes [30,31].

A limitation of our study was the relatively small number of diabetic hemodialysis patients as compared with the non-diabetic individuals, a fact that might influence the likelihood, relations between the diabetic status with the malnutrition or the period of hemodialysis to be revealed.

In conclusion, no significant association among serum calprotectin and prealbumin levels in chronic diabetic and non diabetic hemodialysis patients was observed. However, smoking seems to affect serum calprotectin levels in these patients. Further clinical studies are required in the field in order to define the correlation of diabetes with hemodialysis, of serum calprotectin concentration with the period of hemodialysis and the level of the renal disturbances with the smoking parameter while more detailed research will elucidate the mechanistic pathways involved.

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Conflict of Interest

No conflicts of interest, financial or otherwise, are declared by the authors

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