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Hypoproteinemia as a factor in assessing malnutrition and predicting survival on hemodialysis

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Running Head: Proteins in association with malnutrition on hemodialysis

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Abstract:

Series of studies have described malnutriotion as one of the main non-traditional risk factors associated with poor prognosis and treatment outcome in patients on hemodialysis (HD). The aims of this study were to evaluate the link between HD tretment quality and the nutritional status and to additionally investigate the association of malnutrion and overall survival. A total of 134 adult out-patients (56.4% male, mean age 60.8±16.15 years) were enrolled in the study. Clinical and laboratory data were obtained from the medical records. Anthropometric measurements were performed prior to HD. Malnutrition-Inflammation Score (MIS) was used as a scoring system representing the severity of protein energy wasting (PEW). Malnourished patients were significantly older when compared to non-malnourished patients. They had significantly longer dialysis vintage and lower residual diuresis, BMI, serum proteins and albumins and lean tissue indeks (LTI). Malnourished patients survived significantly shorter than non-malnourished patients. Hypoproteinemic patients had significantly lower values of serum albumins and LTI and survived shorter than normoproteinemic patients. Only malnourishment and age were associated with higher overall mortality in all group of patients. By focusing on MIS and serum protein status rather than dialysis-related factors and different treatment techniques we could accomplish better nutrition status and improved overall outcomes. While anticipating new and more effective measures for preventing malnutrion, our results clearly demonstrate that striving for highest possible nutrition status should be one of the key strategies in improving the outcomes in this specific group of patients.

Key words: protein-energy wasting; hemodialysis; hypoproteinemia; survival

Introduction

Malnutrition is highly prevalent yet oftenly neglected in chronic kidney disease (CKD) patients[1-3]. Protein-energy wasting (PEW) is a dynamic state of decreased protein and fat body stores which arises from inadequate nutrient intake and increased catabolism [4]. Series of studies have described it as one of the main non-traditional risk factors associated with poor prognosis and treatment outcome in this specific population [3,5-7]. Mechanisms responsible for muscle loss are complex an cannot be exclusively linked to reduced protein intake, although it has been shown that anorexia had one of the key roles in the development and maintenece of PEW [4,8].

CKD is a state of chronic inflammation characterized by the constant presence of increased acute phase reactants. This is assocciated with numerous factors such as older age, uremia, acid-base and hormonal disorders, long-term hemodialysis (HD), and other co-morbidities. By acting jointly they create a vicious cycle leading to enhanced amino acid catabolism, reduced regenerative potential of skeletal muscles, protein breakdown, valuable micronutrient loss and eventually malnutrition [9-12]. Malnutrition and inflammation are strong contributors for increased mortality in HD patients [10]. Although the long-term exposure to dialyser membrane promotes inflammatory response, there is a growing body of evidence suggesting the usage of high-flux techniques, biocompatible membranes, ultrapure dialysate and higher dialysis dosage could decrease acute phase reactants' levels thus favorably affecting the nutritional status [13-15].

The aims of this study were to evaluate the link between HD tretment quality and the nutritional status and to additionally investigate the association of malnutrion and overall survival.

Material and Methods:

A total of 134 adult out-patients treated reguIary with HD for at least 12 weeks were included in this cross-sectional observational study which lasted from February 2016 to February 2017. Informed consent was obtained from all participants and the study has been approved by the local Research Ethics Committee. Clinical data were obtained from the medical records and charts. This included demographic data, underlying kidney disease, HD vintage and treatment characteristics (duration, ultrafiltration (UF) rate, vascular access, blood flow, Kt/V representing dialysis dose), as well as residual kidney function (daily diuresis > 300 ml). Bicarbonate HD and ultrapure dialysate with flow rate of 500 ml/min was used for all patients, as well as high-flux polysulphone dialysers. Patients treated with hemodiafiltration were excluded from investigation while only several patients from our centre were treated with this method of dialysis. Blood samples for routine analysis were obtained before the beginning of HD treatment on a mid-week day and measured using standard techniques. Anthropometric measurements were performed prior to HD treatment. This included „dry" body weigt and hight, body mass index, triceps and scapula skinfold, neck, forearm, waist and hip circumference, hip/waist ratio and body composition analysis, lean and fat tissue indeks (LTI and FTI), using bioimpedance spectroscopy (The Fresenius Medical Care Body Composition Monitor – BCM). Malnutrition-Inflammation Score (MIS) created by Kalantar-Zadeh K. and colleagues was used as a scoring system representing the severity of PEW, inflammation and anemia in CKD patients [3]. Patient follow-up continued until the last enrolled patient reached the 365-day time point or till time of death.

Statistical analysis was performed using SPSS version 23.0 (IBM Corp., USA). Normality of data distribution was tested using Kolmogorov-Smirnov test. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and homoscedasticity. Descriptive characteristics were expressed as numbers and frequencies. Correlations were obtained using Pearson's test for normally distributed variables and Spearman rank correlation for non-normally distributed variables. Normally distributed variables were presented as means + standard deviations and Student’s t test for independent samples was used for comparisons between two groups. Non-normally distributed data was presented as median and interquartile range and Mann-Whitney U-test was used in comparison between two groups. Baseline-to-Follow-up comparisons were done using Student's t-test for paired samples and Wilcoxon test. Categorical variables were compared using χ^2- test. Survival analysis was done with Kaplan-Meier curves which were tested with log-rank test while hazard ratios were estimated with Cox proportional hazards regression. Multiple linear regression was used to explore the influence of different variables on survival, while logistic regression was used for categorical dependent variables. A p value <0.05 (two-sided tests) was considered significant.

Ethical Approval: All subjects enrolled in this research have given their informed consent, which has been approved by my institutional comitee on human and/or animal research, and this protocol has been found acceptable by them.

Results

There were 78 male (58.2%) and 56 female (41.8%) patients, mean age 60.8±16.15 years. The leading cause of CKD was chronic glomerulonephritis (27.72%), followed by diabetic nephropathy (21.78%) and nephroangiosclerosis (14.85%). We have not found significant differences between different leading causes of CKD when patients were divided by MIS or serum protein levels. The mean HD vintage was 96.03±102.521 months, with a minimum treatment time of 3 hours for 2 to 4 times a week, and average Kt/V 1.3. Vascular access used for the treatment was an arteriovenous fistula (AVF) in 68.7% and a tunneled catheter in 31.3% of patients. When dividing the patients by MIS, 60 (44.7%) patients were well nourished (MIS 0-2) or slightly malnourished (MIS 3-7), and 74 (55.3%) patients were malnourished (MIS ≥ 8). Demographic, laboratory and clinical characteristics of patients divided by MIS 0-7 and ≥ 8 are demonstrated in Table 1. Malnourished patients were significantly older when compared to non-malnourished patients ($p<0.05$). They had significantly longer dialysis vintage while there were no differences in number of dialysis sessions per week, KtV, duration of dialysis, ultrafiltration rates, FTI, C-reactive protein or blood flow rates (all $p>0.05$). There were no differences in triceps and scapula skinfold, neck, forearm, waist and hip circumference and hip/waist ratio. Malnourished patients had significantly lower residual diuresis, BMI, serum proteins and albumins and LTI when compared to non-malnourished patients (all $p<0.05$). As shown in Table 1. malnourished patients survived significantly shorter than non-malnourished patients.

When patients were divided by normal and low (≤ 65 g/l) serum proteins we have found that hypoproteinemic patients were significantly older (Table 2.). We have not found differences regarding dialysis parameters like dialysis vintage, number of dialysis sessions per week, KtV, duration of dialysis, ultrafiltration rates, blood flow rates, and residual diuresis (all $p>0.05$). Although we have not found differences in C-reactive protein, BMI and FTI between these two subgroups, hypoproteinemic patients had significantly lower values of serum albumins and LTI and survived shorter (all $p<0.05$). There were no differences in triceps and scapula skinfold, neck, forearm, waist and hip circumference and hip/waist ratio.

Regarding patient survival, HD treatment quality and nutritional status, statistical analysis showed significant negative correlation of survival with age ($r=-0.258$, $p<0.01$) and MIS ($r=-0.341$, $p<0.001$) and significant positive correlation of survival with C-reactive protein, serum albumins, serum proteins and LTI ($r=0.233$, $p<0.05$; $r=0.237$, $p<0.001$; $r=0.248$, $p<0.001$; $r=0.233$, $p<0.001$). Malnutrition, higher MIS, was significantly correlated, except with variables from which is calculated, with serum protein levels ($r=-0.501$, $p<0.001$). Serum protein levels showed significant negative correlation with age and C-reactive protein ($r=-0.298$, $p<0.001$; $r=-0.245$, $p<0.05$) and significant positive correlation with LTI ($r=0.277$, $p<0.05$).

In the linear regression model better MIS was the only predictor of longer survival ($\beta=-0.249$, $p=0.04$) while other variables like age, residual diuresis and LTI have not shown this association. The patients were followed for 12 months, 15 hypoproteinemic and 8 normoproteinemic patients died. Three patients have died from multi-organ failure caused by sepsis, four from cancer and eight have died from myocardial infarction or stroke in the hypoproteinemic group while two patients have died from multi-organ failure caused by sepsis, one from cancer and 5 patients have died from myocardial infarction or stroke in the normoproteinemic group of patients. Mean survival time was shorter in hypoproteinemic group of patients than in normoproteinemic group (341.4 (95% CI 329.0, 353.8) vs. 358.5 (95% CI 353.9, 363.1) days, log-rank $p=0.016$) (Figure

1). We have found similar difference when we analyzed patients with MIS, malnourished patients survived shorter than non-malnourished patients (342.1 (95% CI 331.8, 352.3) vs. 362.3 (95% CI 358.6, 366.0) days, log-rank $p<0.001$) (Figure 2). Patients with serum albumin levels ≤ 38 g/l survived significantly shorter when compared to patients with serum albumin levels >38 g/l (342.7 (95% CI 332.7, 352.7) vs. 362.2 (95% CI 358.4, 366.0) days, log-rank $p<0.001$) (Figure 3). We have not find differences in survival when residual diuresis and LTI were analyzed (both $p>0.05$). Only malnourishment (HR 1.12 [1.00, 1.28]) and age (HR 1.05 [1.00, 1.10]) were associated with higher overall mortality in all group of patients.

Discussion

The prevalence of CKD is slowly increasing year by year, almost reaching epidemic proportions [16]. Despite great efforts put into treating well-known and highly prevalent traditional risk factors, and continuous improvements in dialysis techinques, mortality rates of this population remained inexplicably high [17].

PEW is a condition defined by the continuous decline in protein and fat reserves arising from poor appetite and chronic inflammation, its onset gradual and associated with the progressive loss of kidney function [4,18-22]. Chronic inflammation, a state of increased pro-inflammatory cytokines and CRP levels, is one of the key features of CKD. Whether this is a consequence of the uremic milleau, comorbidities or long-term renal replacement therapy is still not entirely known, although all these factors intertwine in a complex mesh of events leading eventually to enhanced oxidative stress, accelerated atherosclerosis and poor clinical outcome [3,5-7,9-12].

Results of our study demonstrate that survival of HD patients is strongly associated with the parameters regarding nutritional status. When estimating nutritional status through MIS, it is evident that by improving serum albumins and proteins levels and therefore LTI and MIS we could be able to achieve better nutritional and survival outcomes. According to statistical analysis, hypoproteinemia contributed significantly to lower lean tissue mass and thus decreasing MIS. Malnutrition associated with hypoalbuminemia is in many studies related with increased mortality in HD patients [3,7]. Both cardiovascular diseases and infectious causes of death are increased with malnutrition and hypoalbuminemia. Hypoproteinemia is well known risk factor for development of sepsis but is not yet associated with fatal cardiovascular incidents like myocardial infarction and stroke. It is possible that increased interdialytic weight gain and therefore higher ultrafiltration rates and volume removal generate a higher frequency of intradialytic hypotension episodes which results with higher cardiovascular mortality. Furthermore, older age and chronic inflammation with consequently higher mortality were correlated with hypoproteinemia as expected but other well known dialysis-related factors like dialysis vintage, KtV, blood flow rates and residual diuresis were not. Interestingly, not only serum albumins but serum proteins as well were correlated with MIS and therefore could be, at least by our results, considered as an additional factor in assessing malnutrition in HD patients and predicting overall survival.

Malnutrition and inflammation are strong contributors for increased mortality in HD patients [10]. It is often associated with the development of atherosclerosis and higher cardiovascular morbidity and mortality. MIS is consisted of many variables related to dialysis and is often influenced by some of them which underestimates its importance. According to Cox survival analysis of our data, age and MIS were strong and independent predictors of mortality while other dialysis-related and chronic inflammation parameters included in the analysis were not significant at all. Interestingly, in multivariate linear regression analysis only better MIS, and not serum albumins and proteins and LTI, was associated with prolonged survival confirming our presumption that malnutrition is a direct reflection of MIS and therefore is an independent predictor of mortality in HD patients. This independent association could be observed as an additional proof that malnutrition is strongly correlated with chronic inflammation in HD patients. Persistent education in order to promote reaching specific caloric goals and moderate physical activity, in-center meals during dialysis and oral supplements intake are certainly among valuable measures against protein loss and malnutrition [23-25]. Although by implementing these interventions negative nutrient balance could be slightly reversed, they remain extensively dependent on patient complience [24-26]. While anticipating new and more effective measures for promoting anabolism and muscle growth, our results clearly show that striving for highest possible nutrition status should be one of the key strategies in improving the outcomes in this specific group of patients.

Our work has sevelar limitations. First, it would be better to compare measured variables in HD patients with a control group with normal kidney function to improve quality of our study. Further studies with larger sample sizes and healthy controls are needed to confirm these results. Second, our results are only on HD patients from a single center limiting the ability of generalizing our results.

Conclusion: Even though results are novel and should be interpreted with caution especially taking into account rather small sample size, it seems that by focusing on MIS and serum protein status rather than dialysis-related factors and different treatment techniques we could accomplish better nutrition status and improved overall outcomes. However, this is neither simple nor easy when bearing in mind that nutrition status is negatively associated with longer dialysis vintage, chronic inflammation and more advanced age.

Conflict of interest: **The authors declare that they have no conflict of interest**

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binders and may prevent a decline in nutritional status and quality of life. Nephrol Dial Transplant 2008;23(9):2902-2910.

Table 1. Demographic, laboratory and clinical characteristics of patients divided by MIS 0-7 and ≥ 8

	MIS ≥ 8 (N=74)	MIS 0-7 (N=60)	p
Demographic variables			
Mean age (yr)	67.5±1.6	54.7±2.2	<0.001
Men N (%)	42 (56.7)	36 (60.0)	0.77
Renal residual function ml	233 (88-368)	895 (710-1078)	<0.001
Mean hemodialysis variables			
Vintage (months)	102.3±11.7	64.8±10.5	0.02
Sessions per week (N)	2.96±0.03	2.88±0.05	0.19
Mean dose (Kt/V)	1.31±0.03	1.28±0.04	0.45
Duration (h)	3.7±0.04	3.7±0.05	0.88
Blood flow rate (ml/min)	324.5±37.3	305.9±33.3	0.66
Ultrafiltration (kg)	2.54±0.09	2.67±0.13	0.41
Mean laboratory values			
Hemoglobin (g/L)	105.7±12.3	110.5±12.4	0.03
Leucocytes (*10^9/L)	5.7±0.21	6.6±0.26	<0.01
Creatinine (μmol/L)	724.8±20.4	833.7±26.4	<0.001
Urea (mmol/L)	19.7±0.61	22.6±0.69	<0.001
Cholesterol (mmol/L)	4.0±0.15	4.3±0.16	0.13
Phosphate (mmol/L)	1.33±0.04	1.64±0.06	<0.001
C-reactive protein (mg/L)	16.2±0.7	8.3±0.7	0.32

Iron (μmol/L)	11.3±0.5	12.2±1.8	0.27
Serum proteins (g/L)	64.9±0.7	66.9±0.5	0.04
Serum albumins (g/L)	36.2±0.5	39.0±0.4	<0.001
Mean anthropometric values			
Mean body mass index (kg/m²)	23.4±0.5	26.7±0.7	<0.001
Mean lean tissue index (kg/m²)	10.9±0.3	13.3±0.4	<0.001
Mean fat tissue index (kg/m²)	11.7±0.5	13.3±0.7	0.08
Survival (days)	342.1±5.2	362.3±1.9	<0.001

MIS-malnutrition-inflammation score; results are shown as mean +/- SD or median (interquartile range)

Table 2. Demographic, laboratory and clinical characteristics of patients divided by low (≤ 65 g/L) and normal serum proteins

	Low serum proteins (N=58)	Normal serum proteins (N=76)	p
Demographic variables			
Mean age (yr)	66.8±1.8	57.9±1.9	<0.01
Men N (%)	32 (55.2)	46 (60.5)	0.41
Renal residual function ml	529 (331-718)	529 (328-722)	0.99
Mean hemodialysis variables			
Vintage (months)	68.4±8.7	98.6±12.6	0.07
Sessions per week (N)	2.88±0.05	2.96±0.03	0.17
Mean dose (Kt/V)	1.31±0.04	1.29±0.03	0.68
Duration (h)	3.7±0.05	3.8±0.04	0.22
Blood flow rate (ml/min)	340.2±46.8	297.4±43.4	0.31

Ultrafiltration (kg)	2.49±0.12	2.68±0.10	0.23
Mean laboratory values			
Hemoglobin (g/L)	105.7±12.3	110.5±12.4	0.71
Leucocytes (*10^9/L)	5.7±0.21	6.6±0.26	0.25
Creatinine (µmol/L)	752.9±27.1	789.4±21.5	0.23
Urea (mmol/L)	21.1±0.81	20.8±0.56	0.76
Cholesterol (mmol/L)	4.3±0.18	4.0±0.12	0.33
Phosphate (mmol/L)	1.48±0.06	1.45±0.05	0.71
C-reactive protein (mg/L)	14.7±0.8	11.1±0.8	0.65
Iron (µmol/L)	12.5±0.6	11.1±0.5	0.11
Serum albumins (g/L)	35.7±0.5	38.7±0.4	<0.001
Mean anthropometric values			
Mean body mass index (kg/m^2)	24.8±0.5	25.0±0.6	0.77
Mean lean tissue index (kg/m^2)	11.4±0.3	12.5±0.3	0.03
Mean fat tissue index (kg/m^2)	12.8±0.6	12.1±0.6	0.43
MIS	8.8±0.5	7.3±0.4	0.02
Survival (days)	341.5±6.4	358.5±2.3	<0.01

MIS-malnutrition-inflammation score; results are shown as mean +/- SD or median (interquartile range)

Figure 1. Outcome for 1-year survival in all patients subdivided by serum protein levels at the end of follow-up

Figure 2. Outcome for 1-year survival in all patients subdivided by MIS at the end of follow-up

MIS-Malnutrition-Inflammation Score

Figure 3. Outcome for 1-year survival in all patients subdivided by serum albumin levels at the end of follow-up