

Albumin as a Prognostic Factor for Malnutrition and Inflammation in Chronic Kidney Disease

GABRIEL VEISA¹, MIHAELA-DORA DONCIU¹, LIVIU SEGALL¹, LOREDANA HURJUF², IONUT NISTOR², IRINA GEORGETA URSARESCU³, SILVIA MARTU³, STEFAN LUCIAN BURLEA³, SORINA MIHAELA SOLOMON³

¹ Gr. T. Popa University of Medicine and Pharmacy, Faculty of Medicine, Department of Nephrology, 16 Universitatii Str., 700115, Iasi, Romania

² Gr. T. Popa University of Medicine and Pharmacy, Faculty of Medicine, Department of Physiology, 16 Universitatii Str., 700115, Iasi, Romania

³ Gr. T. Popa University of Medicine and Pharmacy, Faculty of Dental Medicine, Department of Periodontology, 16 Universitatii Str., 700115, Iasi, Romania

Malnutrition is a major, but under-diagnosed, risk factor for negative outcomes in patients with chronic kidney disease (CKD). The main goal of this study was to evaluate, for the first time, the relationship between albumin level, periodontal disease and inflammation in a cohort of haemodialysis patients. We prospectively analysed the inflammatory status and malnutrition in 200 haemodialysis patients, mean age 54 ± 14 years, from two Romanian dialysis centres. At baseline we evaluated: a. nutritional status by anthropometric measures- post dialysis body weight (BW), body mass index (BMI); b. subjective global assessment score (SGA); c. biochemical tests: Protein c reactive (CRP), TNF- α , pre-dialysis serum albumin, IL-6 and assessment of periodontal disease status. The patients were followed-up for 2 years.

Keywords: inflammation, albumin, end-stage renal disease, haemodialysis, periodontitis

Protein-energy wasting (PEW) is common in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) on maintenance dialysis - haemodialysis (HD) and peritoneal dialysis (PD). PEW is associated with increased morbidity and mortality. According to the definition of ISRN, PEW is diagnosed if three characteristics are present: low serum levels (of albumin, transthyretin, or cholesterol), reduced body mass (low or reduced body or fat mass or weight loss with reduced intake of protein and energy), and reduced muscle mass (muscle wasting or sarcopenia, reduced mid-arm muscle circumference).

Chronic and systemic inflammation seems to be a principal component of the pathophysiology of PEW, by causing both anorexia and increased muscle catabolism. Serum levels of pro-inflammatory cytokines (particularly, IL-6 and TNF- α) have been shown to have significant effects on wasting in dialysis patients. On the other hand, inflammation is a predictive factor for general and cardiovascular mortality in these patients.

Moderate/severe periodontal disease was found to be associated with an increased risk of cardiovascular disease and mortality, both in the general population and in ESRD patients, and it is believed that inflammation may be the key factor that explains this relationship.

In Romania, the nutritional status in chronic dialysis patients has seldom been a subject of research. In a very recently published study, we assessed the nutritional status, the risk factors for PEW, and the influence of PEW on survival in HD patients. However, in this study we have deliberately excluded patients with acute signs of infections or acute reasons for inflammation. Our present project aims to expand the area of research of our previous study[1]. Secondly, we wanted to study the relationship between inflammatory (i.e. the serum levels of CRP, IL-1 and TNF- α) and nutritional markers (anthropometry, SGA, protein intake, serum proteins and body composition,

assessed by bioelectrical impedance analysis). Thirdly we planned to study the relationship between periodontal disease and the markers of PEW and inflammation. Finally, we prospectively looked at the influence of PEW, inflammation and periodontal disease on patients' morbidity and mortality. These issues have never been addressed before in this comprehensive manner in Romania.

Experimental part

Material and methods

Study design and patients characteristics

Our objective was to evaluate for the first time, the relationship between albumin level, malnutrition and periodontal status in a Romanian cohort of hemodialysis patients.

We conducted a prospective study, that comprised hemodynamic stable patients on hemodialysis treatment for at least six months, recruited from two dialysis units auxiliary to "Dr. C. I. Parhon" University Hospital, Iasi, Romania. The patients' observation period was between March 2013 to October 2015. Participants gave informed consent before enrolling in the study. The study was approved by the Hospital's Ethical Committee and was performed in agreement with Helsinki's declaration of human rights.

The exclusion criteria were age under 18 years, ongoing acute illnesses, and who declined to participate in the study.

Demographic characteristics, chronic medical associated conditions, biochemical and dialysis parameters were obtained from the patients' medical records and from their primary nephrologist. All patients received HD a four hours/session, three times/week. Laboratory measurements for biochemical data were taken under fasting predialysis conditions, but not necessarily on a midweek dialysis day.

* email: gabriel_veisa@yahoo.com

Statistical analysis

The analysis was made with SPSS 20.0 statistical standard package for Mac OS X and a p value < 0.05 was considered statistically significant. Descriptive statistics of the demographic data of the study population and Pearson's correlation were calculated. Baseline characteristics of the study sample, assessed by descriptive statistics, are presented as means \pm standard deviation (SD) or as percent, as appropriate.

Inflammation and malnutrition

Nutritional markers

Body weight (BW) was measured at the end of a HD session (i.e., the "dry weight"). The body mass index (BMI) was calculated by the BW (kg) over height (H) 2 (m²) ratio. Subjective global assessment was based on history and physical examination, according to the method described by Detsky et al., and the results were recorded on a special sheet. In the end, patients were classified into three categories ("the SGA mark"), as follows: A (well nourished), B (mild PEW), and C (severe PEW). Also, serum albumin level was measured.

Inflammatory markers

Regarding the serum markers of inflammation in hemodialysis patients, these included C-reactive protein, interleukin 6 and TNF α .

Periodontal disease

The patients were submitted to an oral clinical examination which included periodontal probing and the assessment of periodontal disease index (PDI), associated with the bacterial plaque index (PI) and the calculus index (CI) components. The type of edentulous ridge was recorded; for the determination of the edentulous type we used the Kennedy classification system. Each patient filled a questionnaire which offered data regarding the oral hygiene habits, diet, vicious habits and the presence/absence of xerostomia. The data were recorded in individual observation charts and statistically analyzed.

Results and discussions

This prospective study included a total of 200 patients (101 males) (the general characteristics of the study sample are summarized in table 1). The mean age was

Table 1
BASELINE GENERAL CHARACTERISTICS OF THE STUDY SAMPLE
(MEAN \pm SD AND N, % AS APPROPRIATE)

General baseline characteristics	Total (N=200)
Males (n, %)	101 (50.5)
Age (years)	54.11 \pm 14.37
Living environment (urban, n, %)	91 (45.5)
Vascular access (arterio-venous fistula, n, %)	187 (93.5)
Smoking status (n, %)	36 (18)
Dialysis vintage (years)	5.6 \pm 5.2
Kt/v	1.38 \pm 0.24
Serum Hb (g/dl)	11.65 \pm 1.65
Serum Ferritin (ng/ml)	36.43 \pm 8.26
TSAT (%)	28.68 \pm 15.53
Serum total cholesterol (mg/dl)	182.54 \pm 45.08
Predialysis HCO ₃ (mmol/l)	22.63 \pm 2.9
Serum Phosphate (mg/dl)	5.25 \pm 1.48
Serum iPTH (pg/ml)	828.81 \pm 712.36

Table 2

CHARACTERISTICS AND SCORES OF INFLAMMATORY MARKERS, NUTRITIONAL MARKERS AND PERIODONTAL EVALUATION IN THE STUDY SAMPLE (MEAN \pm SD)

Inflammatory markers	Total (N=200)
CRP (mg/l)	9.55 \pm 14.80
IL-6 (pg/ml)	285.76 \pm 433.98
TNF α (pg/ml)	481.127 \pm 839.70
Nutritional markers	Total (N=200)
Albumin (g/dl)	4.24 \pm 0.43
SGA ("7 points scale" - total score)	2.5 \pm 1.63
Periodontal evaluation	Total (N=200)

54.11 \pm 14.37 years, mean Kt/v 1.38 \pm 0.24 and mean Hb g/dL was 11.65 \pm 1.65. Patients had received renal replacement treatment (HD) for a mean duration of 5.6 \pm 5.2 years.

According to inflammatory markers the means values were: CRP (mg/L) 9.55 \pm 14.80, IL-6 (pg/mL) 285.76 \pm 433.98, TNF α (pg/mL) 481.127 \pm 839.70. In terms of nutritional markers, mean Albumin (g/dL) was 4.24 \pm 0.43 and mean of total score of SGA "7 point scale" was 2.5 \pm 1.63.

Following the odontal-periodontal examination, we observed a high percentage of terminal edentations, of 49.27% of the cases. From the questionnaire analysis, an important number of patients with frequent xerostomia (62.31%) was recorded.

Statistically significant correlation for the whole study sample between the different inflammation and nutritional markers, and various biochemical and medical parameters were summarized in table 3 and table 4. Table 3 shows the correlation coefficients between inflammation markers (protein C-reactive (mg/L), IL-6 (pg/L), TNF- α (pg/mL) and relevant variable (TSAT %, SGA, dialysis vintage). First inflammation marker, **CRP**, was positively correlated with IL-6 (r= 0.53, p<0.01), SGA (r=0.02, p<0.01), TNF- α (r=0.57, p<0.01); second, **IL-6**, positively correlated with dialysis vintage (r=0.22, p<0.01), TNF- α (r=0.49, p<0.01), SGA (r=0.21, p<0.01); and the last one, **TNF- α** , positively correlated with SGA (r=0.17, p<0.05).

Table 4 shows the correlation coefficients between nutritional markers (Albumin g/dL), SGA (total score), BMI (kg/m²) and relevant variable (age, CRP, dialysis vintage, TSAT, GPC, BPC). The nutritional marker, **SGA**, was positively correlated with age (r=0.14, p<0.01) and with dialysis vintage (r=0.19, p<0.01). Another nutritional marker, **BMI**, was positively correlated with age (r=0.28, p<0.01), with GPC (r=0.16, p<0.05) and with BPC (r=0.14, p<0.05).

During the study follow-up (two years) we registered 14 deaths in total, most of them (ten out of 14) due to cardiovascular diseases. Only for two patients the cause of death was infection.

This pilot study prospectively examined in a cohort of 200 HD patients, for the first time, the relationship between baseline nutrition and inflammatory markers in a population with chronic kidney disease. We found that inflammation (CRP, IL-6, TNF α) is linked with anemia (decreased of TSAT) or malnutrition (SGA increase). When looking at nutritional status, we found that malnutrition is linked with age (albumin, SGA, BMI) and CRP (SGA, albumin).

Previous studies found that CKD patients have high level of inflammation and this might be linked with mortality [2]. In our analysis, SGA increase with one unit is associated

Table 3
ASSOCIATION OF EACH INFLAMMATION MARKERS WITH NUTRITIONAL MARKERS

Total (N = 200)	Age (years)	Dialysis vintage (years)	TSAT (%)	Albumin (g/dl)	CRP (mg/dl)	IL-6 (pg/ml)	TNF- α (pg/ml)	SGA (total score)	Hospitalizations for respiratory infections	Hospitalizations for urinary infections	Hospitalizations for CV impairment									
Pearson's r coefficient, p value																				
CRP (mg/dl)	0.04	0.5	-0.15*	<0.05	-0.23**	<0.05	-	-	0.53**	<0.01	0.57**	<0.01	0.20**	<0.01	0.35**	<0.01	0.08	0.2	0.28**	<0.01
IL-6 (pg/ml)	0.22**	<0.01	-0.22**	<0.01	-0.94	0.18	0.53**	<0.01	-	-	0.49*	<0.01	0.21**	<0.01	0.12	0.09	0.12	0.08	0.33	0.05
TNF- α (pg/ml)	0.04	0.53	-0.18*	<0.05	-0.06	0.3	-0.57**	<0.01	0.49**	<0.01	-	-	0.17*	<0.05	0.17	<0.05	0.14*	<0.05	0.18**	<0.01

Table 4
ASSOCIATION OF EACH NUTRITIONAL MARKERS WITH CLINICAL AND BIOCHEMICAL PARAMETERS, AND PERIODONTAL EVALUATION

Total (N = 200)	Age (years)	Dialysis vintage (years)	CRP (mg/dl)	IL-6 (pg/ml)	TNF- α (pg/ml)	TSAT (%)	CGP	CPB	Hospitalizations for respiratory infections	Hospitalizations for CV impairment										
Pearson's r coefficient, p value																				
Albumin (g/dl)	-0.30**	<0.01	-0.05	0.4	-0.23**	<0.01	-0.09	0.18	-0.06	0.39	-0.05	0.41	-0.05	0.44	-0.13	0.06	-0.07	0.28	0.17*	<0.05
SGA (total score)	0.14**	<0.05	0.19**	<0.01	0.20**	<0.01	0.21**	<0.01	0.17*	<0.05	-0.12	0.07	-0.02	0.68	-0.04	0.55	0.20**	<0.01	0.19**	<0.01
BMI (kg/m ²)	0.38**	<0.01	-0.09	0.19	0.11	0.11	-0.006	0.93	-0.09	0.17	0.16*	<0.05	0.16*	<0.05	0.14*	<0.05	0.00	0.98	-0.006	0.93

with 62% higher mortality. Also, albumin increase with 1g/dL is associated with 79% lower mortality.

Our results are similar with the recent work of Pereira and collaborators [3]. They showed that the prevalence of sarcopenia in CKD patients on conservative therapy varies according to the method applied. Sarcopenia defined as reduced handgrip strength and low skeletal muscle mass index estimated by BIA was an independent predictor of mortality in these patients.

Regarding the oral health status, the presence of odontal-periodontal units is essential; the absence of such units, especially in the premolar-molar area, leads to occlusal overloading of the remaining teeth and can also generate a nutritional deficit by lack of occlusal surfaces. It was particularly this type of edentation which presented a high percentage in the study group. Xerostomia has an important role, being a risk factor for periodontal impairment and also a negative factor in taste perception, swallowing and malnutrition [4]. Xerostomia was frequently encountered among the study subjects. The presented data are preliminary results obtained through the period of the study [5].

The strength of our study included the multidisciplinary approach and global evaluation of nutrition and inflammation with old and new markers (SGA, albumin, TNF- α , IL6, CRP, bioimpedance). The second strength is linked with the systematic approach and evaluation of the periodontal disease.

The limitations of our study are related with the observational study design. All our findings must be interpreted with caution since other co-factors might explain the results.

Conclusions

In our HD patients, albumin and nutritional status (evaluated by SGA score) were associated with a significantly increased death risk. Further evidence is needed in order to support inflammation markers as a long-term predictor for decline in ESRD patients.

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References

- SEGALL L., MARDARE N.G., UNGUREANU S., BUSUIOC M., NISTOR I., ENACHE R., et al., Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. 2009, **24**(8), pp.2536-40.
- ARAUJO I.C., KAMIMURA M.A., DRAIBE S.A., CANZIANI M.E., MANFREDI S.R., AVESANI C.M., et al., J Ren Nutr. 2006, **16**(1), pp.27-35.
- PEREIRA R.A., CORDEIRO A.C., AVESANI C.M., CARRERO J.J., LINDHOLM B., AMPARO F.C., et al., Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. 2015, **30**(10), pp.1718-25.
- PETROVSKI M., MINOVSKA A., IVANOVSKI K., AGOP FORNA D., FORNA N.C., Rev. Chim.(Bucharest), **66**, no. 10, 2015, p.1614
- SOLOMON S., FORNA N., URSARESCU I., SEGAL L., NISTOR I., VEISA G., Rom. J. Oral. Rehab., 2014, **6**(1), pp.9-14

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