Impact of Intensive Dietary Counseling on Serum Albumin in Haemodialysis Patients with Chronic Liver Disease

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People on maintenance haemodialysis (MHD) are at risk of developing malnutrition, which is defined as the consequence of insufficient food intake or a suboptimal quality diet. The kidney and the liver play a central role in protein metabolism. The major aim of the study was to evaluate, for the first time in Romania, the impact of intensive dietary counseling and personalised diets on serum albumin (SA) and others nutritional parameters, but also the relationship between albumin level, inflammation and nutritional status in a cohort of haemodialysis patients which associate or not chronic liver disease (CLD). We prospectively analysed the inflammatory status and malnutrition in 162 HD patients, mean age 56±13 years, from a single dialysis centre. At baseline we evaluated: a. calorie-protein intake using patient's diet history with the help of 72 hrs recall method;b. nutritional status by anthropometric measures- post dialysis body weight (BW), body mass index (BMI), TSF (tricipital skinfold), MAC (mid-arm circumference), MAMC (mid-arm muscle circumference);c. modified subjective global assessment score (mSGA);d. biochemical tests: pre-dialysis serum albumin, serum creatinine, alkaline reserve, Kt/V and Protein C Reactive (CRP). The patients were followed-up for 6 months.

Keywords: haemodialysis, inflammation, albumin, nutritional intervention, malnutrition.

Albumin is a negatively charged, water-soluble protein (molecular weight 65 kD) that is synthesized in the liver. Serum albumin (SA) levels are determined by rates of hepatic synthesis and secretion and the two most influential factors regulating hepatic albumin synthesis are nutritional intake - specifically *protein consumption - and illness* [1]. It is a widely used biomarker of nutritional status in patients with chronic kidney disease [2], but its usefulness is still debated.

Routine monitoring of nutritional status is important in end stage renal disease (ESRD) patients. Protein energy wasting syndrome (PEW) is a common complication and an important predictive factor for morbidity and mortality in chronic dialysis patients [3]. Patients in MHD require proper, intensive and sufûcient instruction, as well as repeated reinforcement to deal with the complex renal diet [4]. The main goals of nutritional counseling should be helping patients manage their own diet in the correct way and help them feel in control [5]. There are some retrospective studies which indicate that improving protein energy status by nutritional interventions, dietary counselling and oral nutrition are the first steps in the management of these patients and can improve their outcomes, although this has not been tested in large scale, prospective and clinical trials [6,7]. In Romania, the nutritional status in MHD patients has been a subject rarely approached.

The aim of the present project was to analyse for the first time in Romania the impact of intensive dietary counselling and personalised diets on nutritional biochemical markers (serum albumin and creatinine level), protein-calorie intake, anthropometry measurements and mSGA score in ESRD patients with/ without CLD. Secondly we wanted to study the relationship between serum albumin, inflammatory (serum CRP) and other nutritional markers (protein intake, anthropometry measurements and mSGA score).

Experimental part

Material and methods

Study design and patients characteristics

This was a unicenter longitudinal intervention study with 6 months of follow-up, that comprised 162 hemodynamic stable patients on hemodialysis treatment for at least 3 months recruited from B BRAUN Avitum Hemodilysis Unit, Botosani, Romania, between september 2015-march 2016. Study group were selected from 270 MHD patients according to the following exclusion criteria: age below 18 years, hospitalization or acute illness in the preceding 3 months, psychiatric disorders (like mental retard or dementia). Participants gave informed consent before enrolling in the study. The study was approved by the ethical committee. All patients received a four hours/session, three times/ week. Patients were divided into 4 groups depending on the level of SA and the presence or absence of CLD (the characteristics of the study sample are summarized in table 1).

Nutritional assessment

Nutritional status was evaluated by using standard methods like dietary calorie and protein intake (patient's diet history with the help of 72 h recall method), biochemical markers and anthropometric measurements

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Table 1
CHARACTERISTICS OF THE STUDY SAMPLE

Group I	62 MHD patients with serum albumin < 4 g/dl without CLD
Group II (control group for the first one)	39 MHD patients with serum albumin > 4 g/dl without CLD
Group III	43 MHD patients patients with serum albumin < 4 g/dl with CLD
Group IV (control group for the third one)	18 MHD patients with serum albumin >4 g/dl with CLD

(AM). Biochemical parameters included serum albumin and creatinine, CRP, Kt/v and alkaline reserve. AM included dry weight (DW), body mass index (BMI), subcutaneous fat-tricipital skinfold (TSF- a skinfold caliper measurement, result is correlated with total body fat), mid-arm circumference (MAC), mid-arm muscle circumference (MAMC, an indicator of skeletal muscle mass and it is calculated by a specific formula MAMC= MAC- $(3.14 \times TSF)^2$) and mSGA. All were measured at initial stage, followed by their reevaluation after six months.

mSGA relied on seven components—weight change, dietary intake, gastrointestinal symptoms, functional capacity, comorbidity, subcutaneous fat, and signs of muscle wasting. Each component was given a score from 1 (normal) to 5 (severe). Thus, the MS (malnutrition score), sum of all components, ranged from 7 (normal) to 35 (severely malnourished). Patients were categorized into three groups: mild malnutrition (score of $>7<21$), moderate malnutrition (score of $\geq 21<35$), and severe malnutrition (35) [8].

Groups of patients I and III had received intensive nutritional counselling and personalised diets, groups II and IV were the control groups.

Statistical analysis

The analysis was made with SPSS 18.0. *P*-values <0.05 are considered statistically significant. Continuous variables are expressed as mean ± standard deviation and the statistical significance of mean differences is compared using ANOVA and *t student*-test across cohorts as appropriate. Pearson's correlation is used to assess the magnitude and direction of association between SA and protein-energy intake, anthropometric measurements, inflammation, and MS.

Results and discussions

Baseline characteristics

From 162 patients 53.7% were men, the mean age was 56.32 ± 13.45 years and mean BMI was 24.64±4.85 kg/m^2. 5.5% were underweight (BMI < 18.5 kg/m^2), 50.7% had a BMI between 18.5 and 24.9 kg/m^2, the prevalence of overweighed patients was 25.9% (BMI 25.0–29.9 kg/m^2) and 17.9% were obese (BMI > 30.0 kg/m^2). Patients had received renal replacement treatment (HD) for a mean duration of 5.6 ± 5.1 years.

85.2% from all study patients recorded signs of mild PWS and 14, 8% of moderate PWS. 22.6% from group I and 20.9% from group III showed signs of moderate malnutrition. No patient experienced any signs of severe malnutrition. mSGA recorded better scores in men ($p=0.025$), in patients aged below 60 years ($p=0.001$) and it was significantly and inversely correlated with the educational level ($p=0.012$)(table 2). On the other hand a study by Yang et al. (2007) reveled that there were no statistically significant differences in age, height, weight, gender distribution, causes of hemodialysis, duration of hemodialysis, between the well-nourished group and the malnourished group [9].

Statistically significant differences between the hypoalbuminemic patients (I and III) and control groups (II and IV) regarding calorie-protein intake, AM, MS, inflammation, acidosis and biochemical nutritional markers were summarized in table 3. Table 4 shows statistically significant correlation for the whole study sample between SA, inflammation and various biochemical nutritional markers.

Nutritional guidelines suggest daily energy intake higher than 30–35 Kcal/Kg ideal b.w. (body weight) and daily protein intake higher than 1.1–1.2 g/Kg ideal b.w [10]. At baseline in our study sample the lowest mean value of calorie intake was noted in group I, significantly lower than that recorded in group II ($p = 0.003$). The highest mean value has been found in group IV but without significant differences comparatively to group III ($p = 0.152$). Protein intake recorded better mean values in control groups II and IV (1.16 g/kg/d; respectively 1.22 g/kg/d) than groups I and III (0.79 g/kg/d; respectively 0.88 g/kg/d). It is possible that hypoalbuminemic patients registrated lower calorie-protein intake than the control groups probably in

Demographic	factors	n	mSGA (mean value±SD)	Test F$_{ANOVA}$ p
Sex	Masculin	87	14.69±5.99	**0.025**
	Feminin	75	16.75±5.55	
Age (years)	< 60	96	13.88±4.94	**0.001**
	≥ 60	66	18.21±6.17	
Educational level	Elementary school	17	17.88±6.73	**0.012**
	Middle school	43	17.30±6.33	
	High school	91	14.80±5.44	
	University	11	12.64±3.07	
Enviroment	Urban	55	16.38±5.26	0.251
	Rural	107	15.26±6.14	

n-number of patients, SD-standard deviation; p<0.05 value statistically significant.

Table 2
ASSOCIATION BETWEEN DEMOGRAPHIC FACTORS AND mSGA

the context of poor financial resources, low educational level, absence of family support, physical activity, geographical, cultural or traditional factors.

Regarding the anthropometric measurements BMI, TSF, MAC and MAMC revealed no significant statistical differences between hypoalbuminemic groups (-/+CLD) versus control groups.

SA (g/dL) recorded a mean value of 3.92±0.33, with significant statistical differences between groups I and II (p=0.001), respectively groups III and IV (p=0,001). This biological nutritional marker seems to be in a strong indirect correlation to mSGA in all four groups (group I r = -0.614, p=0.001; group II r = -0.531, p=0.001; group III r = -0.424, p=0.005; respectively group IV r =-0.679, p=0.002), which indicates the lower the albumin, the more severe the malnutrition score. There are studies in HD patients that have demonstrated a potential relationship between malnutrition and hypoalbuminemia, both depending on poor nutrition but also on micro-inflammatory state [11, 12]. Indeed it was reported that a majority of uremic patients undergoing hemodialysis suffer from nutritional disorders [13]. Our ûndings suggest positively correlation between SA and protein intake in all the samples (group I r= +0.39, p=0.002; group II r= +0.307, p=0.05; group III r= +0.669, p=0.001; group IV r= +0.319, p=0.042). In only 21.4% from study patients was found a similar trend between SA and MAC (r= +0.214; p=0.006) and in 23.3% with MAMC (r= +0.233; p=0.003). Relationship between MAC and SA was statistically significant only in groupI I (r = +0.280; p=0.028).

Serum CRP registrated a significant statistically difference between groups I and II (7.37 *vs* 5.84 mg/dL; p=0.05). Surprisingly despite to literature data, the forth group which is one of the control group with a SA corresponding to nutritional guideline, registrated a CRP level higher than the third group (6.58 *vs* 2.74 mg/dl; p=0033). It is thought that serum CRP may be a powerful determinant for anorexia, hypoalbuminemia and the diagnosis of malnutrition in renal failure patients since increased serum CRP inhibits the SA generation in hemodialysis patients[10]. Compatible with some studies and in contrast to other studies, the association serum CRP levels with serum albumin and other nutritional factors (mSGA) in this study was insignificant, suggesting that CRP is a poor predictor of malnutrition in dialysis patients. There also is evidence that acidosis contributes to the low level of SA in dialysis patients [14]. Being common in kidney failure it's stimulating and accelerating the degradation of protein, especially muscle protein. Mean value of alkaline reserve (mmol/L) was 23.18±2.68 with no statistical differences between the hypoalbuminemic and control groups. Our present study showed no correlation between SA and alkaline reserve.

Creatinine kinetics have also been advocated as a method to assess nutritional status. Our findings showed the lowest mean value in group I and the highest in group II (p=0.002), without significant differrences between the last two groups (p=0.187). On the one hand a higher serum creatinine it is thought to estimate the muscular mass, but on the other hand it seems to be corellated with an inadequate hemodialysis session. Kt/V as a marker of dialysis adequacy registrated in our study a mean value of 1.48±0.22 which means that it has been reached a good level of the eficiency of hemodialysis session (cut-off Kt/V >1.2). No statistical differences was recorded between the samples and only in group III was found a direct correlation between SA and Kt/V.

The six months follow-up of our study showed after intensive dietary counseling a statistically significant improvement of SA reaching the level recommended by nutritional guidelines in both groups (I and III). Albumin syntesis increases in response to protein-calorie intake and decreases in response to inflammation, whereas the albumin fraction catabolic rate increases in the presence of inflammation but is suppressed in the presence of malnutrition [15]. This trend of serum albumin followed the increased in energy and protein intake in the same groups (group I- 27.81 *vs* 29.45 Kcal/kg/d; p=0.001, respectively 0.79 *vs* 1.17 g/kg/d; p=0.001; group III-30.16 *vs* 31.46 Kcal/kg/d; p=0.004, respectively 0.89 *vs* 1.16 g/kg/d; p=0.001). Accompanying these changes were the increases in anthropometric measurements (BMI, MAC, MAMC). mSGA also recorded better scores in the hypoalbuminemic groups after six months of intensive dietary counseling (group

Table 3

BASELINE GENERAL CHARACTERISTICS OF THE STUDY SAMPLE AND LABORATORY COMPARATIVE DATA (MEAN ± SD)

Parameters	Lot I (mean value±SD)	Lot II(control group) (mean value±SD)	P	Lot III (mean value±SD)	Lot IV (control group) (mean value±SD)	P
N	62	39		43	18	
CI (Kcal/kg/d)	27.81±4.48	30.73±5.09	**0.003**	30.00±3.81	31.61±4.23	0.152
PI (g/kg/d)	0.79±0.17	1.16±0.19	**0.001**	0.88±0.22	1.22±0.19	**0.001**
BMI (kg/m^2)	24.20±5.60	25.33±4.16	0.279	24.83±4.52	24.25±4.32	0.648
mSGA	18.40±5.95	11.44±2.87	**0.001**	17.02±5.67	11.94±3.61	**0.001**
TSF(cm)	1.55±0.84	1.59±0.76	0.815	1.50±0.70	1.38±0.47	0.492
MAC(cm)	26.91±4.54	28.26±2.91	0.229	27.24±3.50	27.42±2.87	0.846
MAMC(cm)	22.04±3.38	23.27±2.73	0.058	22.53±3.58	23.08±2.40	0.549
Serum albumin (g/dl)	3.72±0.23	4.24±0.20	**0.001**	3.79±0.29	4.24±0.11	**0.001**
Serum creatinine (mg/dl)	8.41±2.29	9.85±2.15	**0.002**	8.76±2.35	9.60±1.91	0.187
CRP (mg/dl)	7.37±7.93	5.84±4.47	**0.050**	6.58±7.29	2.74±1.97	**0.033**
Kt/V	1.49±0.23	1.53±0.22	0.378	1.41±0.23	1.47±0.14	0.309
AR (mmol/l)	23.26±2.60	23.29±2.77	0.954	22.69±2.42	23.83±3.31	0.141

n-number of patients, PI- protein intake,CI-energy intake, BMI-Body mass index mSGA-modified subjective global assessement, VAS-visual analog scale, TSF-tricipital skinfold, MAC- mid-arm circumference, MAMC mid-arm muscle circumference, CRP-C reactive protein, AR-alkaline reserve; p<0.05 value statistically significant.

Table 4

ASSOCIATION OF SERUM ALBUMIN WITH INFLAMMATION AND OTHER NUTRITIONAL MARKERS AT BASELINE

	n		PI	mSGA	MAC	MAMC	CRP	Kt/V	AR	Feritina
GROUP I	62		r=-0.040	r=-0.614	r=+0.280	r=+0.277	r=-0.033	r=+0.109	r=+0.055	r=+0.195
			p=0.757	p=0.001	p=0.280	p=0.029	p=0.798	p=0.399	p=0.671	p= 0.128
GROUP II	39		r=-0.082	r=-0.531	R=+0.235	r=+0.366	r=+0.071	r=-0.076	r=-0.056	r=-0.113
		SA	p=0.632	p=0.001	P=0.150	p=0.022	p=0.201	p=0.645	p=0.737	p= 0.499
GROUP III	43	(g/dl)	r=+0.026	r=-0.424	R=+0.011	r=0.034	r=-0.052	r=+0.315	r=-0.054	r=-0.053
			p=0.871	p=0.005	P=0.945	p=0.829	p=0.742	p=0.040	p=0.732	p=0.737
GROUP IV	18		r=+0.175	r=-0.679	R=+0.230	r=+0.388	r=+0.204	r=-0.019	r=-0.044	r=-0.303
			p=0.488	p=0.002	P=0.359	p=0.041	p=0.416	p=0.939	p=0.863	p=0.202

n- number of patients, SA-serum albumin, PI-protein intake, mSGA -modified subjective global assessement, MAC- mid-arm circumference, MAMC mid-arm muscle circumference, CRP-Creactive protein, AR-alkaline reserve.

Table 5

EVOLUTION OF THE MEAN VALUES OF CLINIC AND LABORATORY NUTRITIONAL MARKERS AFTER SIX MONTHS OF INTENSIVE DIETARY COUNSELING

Indicator clinic si paraclinic	Lot I			Lot II			Lot III			Lot IV		
	T0	T6	p	T0	T6	p	T0	T6	p	T0	T6	p
EI(Kcal/kg/d)	27.81	29.45	**0.001**	30.60	31.30	0.060	30.16	31.46	**0.004**	31.61	31.50	0.805
PI(g/kg/d)	0.79	1.17	**0.001**	1.16	1.22	**0.048**	0.89	1.16	**0.001**	1.22	1.15	0.172
DW(kg)	68.54	68.94	0.250	72.99	73.77	**0.038**	70.55	71.25	**0.017**	71.59	72.31	**0.021**
BMI(kg/m^2)	24.20	24.72	**0.001**	25.21	25.58	**0.035**	24.47	24.93	**0.027**	24.25	24.57	0.138
mSGA	18.40	15.58	**0.001**	11.44	11.44	1.000	17.02	15.12	**0.001**	11.94	12.22	0.439
TSF(cm)	1.55	1.51	0.102	1.59	1.56	0.142	1.50	1.46	0.160	1.38	1.39	0.651
MAC(cm)	26.91	27.27	**0.001**	28.26	28.27	0.885	27.24	27.46	**0.002**	27.42	27.50	0.514
MAMC(cm)	22.04	22.52	**0.001**	23.27	23.39	0.104	22.53	22.87	**0.001**	23.08	23.13	0.599
Albumin(g/dl)	3.72	4.08	**0.001**	4.24	4.28	0.245	3.79	4.00	**0.001**	4.24	4.21	0.598
Creatinine(mg/dl)	8.41	7.60	**0.001**	9.85	8.90	**0.001**	8.76	7.84	**0.001**	9.60	8.79	**0.002**
CRP(mg/dl)	12.14	1.13	**0.001**	4.88	0.67	**0.001**	7.12	1.36	**0.001**	3.61	0.66	**0.001**
Kt/V uree	1.49	1.47	0.323	1.53	1.56	0.207	1.42	1.44	0.374	1.47	1.43	0.061
RA	22.26	18.86	**0.001**	23.29	19.43	**0.001**	22.69	19.47	**0.001**	23.83	19.28	**0.001**

PI- protein intake,EI-energy intake, BMI-Body mass index mSGA-modified subjective global assessement, VAS-visual analog scale, TSF-tricipital skinfold, MAC- mid-arm circumference, mid-arm muscle circumference, CRP-Creactive protein, AR-alkaline reserve; p<0.05 value statistically significant.

I 18,40 *vs* 15.58, p=0.001~ respectively group III 17.02 *vs* 15.12, p=0.001). Despite to the results obtained above creatinine as a marker of muscular mass registered a decrease in serum level although Kt/V kept a linear aspect of the dialysis adequacy. Also alkaline reserve recorded a decrease of the mean values comparatively to baseline, an event that can be somehow probably attributed to increase in protein intake. Although control groups did not benefit from an intensive dietary counseling, similar data to those recorded at baseline regarding SA, AM (TSF, MAC, MAMC) and mSGA were found after six months of folow-up.

Conclusions

There is a paucity of data on the assessment of nutritional status in patients with ESRD with CLD in Romania. Our study suggests that intensive dietary intervention contributes to the improvement of important nutritional parameters in patients receiving MHD treatment with or without CLD. CLD appears to be an independent factor without being an obstacle in the process of correcting nutritional status in the presence of rigorous dietary counseling, marking that nutritional approach in these patients should be based on a careful, adequate dietary intake and proper nutritional support. The limitations of our study included the small sample size and the recruitment of the patients from a single dialysis center.

References

1.ROTHSCHILD, M.A., ORATZ, M., SCHREIBER, S.S., Annu Rev Med, nr. 26, 1975, p. 91

2. DRAGANESCU, M., BAROIU, N., BAROIU, L., DIACONU, C., BUZIA, O.D., Rev. Chim. (Bucharest), **68**, no. 3, 2017, p. 602

3.ERDOGAN, E., TUTAL, E., UYAR, M.E., BAL, Z., DEMIRCI, B.G., SAYIN, B., SEZER, S., Transplant Proc., **45,** nr. 10, 2013,

4.GARAGARZA, C.A., VALENTE, A.T., OLIVEIRA, T.S., CAETANO, C.G., Hemodial Int, **19,** nr. 3, 2015, p. 412.

5.FORD, J.C., POPE, J.F., HUNT, A.E., GERALD, B., J Ren Nutr, **14**, nr. 1, 2004, p. 36.

6.JADEJA, Y.P., KHER, V., Indian J Endocrinol Metab, **16**, nr. 2, 2012, p. 246.
7.HAJIRA, B., MANZOOR, M., SAMIULLAH, M., CHAWLA, R.K., J Pak Med Assoc, **67**, nr. 9, 2017, p. 1327.
8.JANARDHAN, V., SOUNDARARAJAN, P., RANI, N.V., KANNAN, G., THENNARASU, P., CHACKO, R.A., REDDY, C.U., Indian J Pharm Sci, **73**, nr. 1, 2011, p. 38.
9.YANG, F.L., LEE, R.P., WANG, C.H., FANG, T.C., HSU, B.G., Renal failure, **29**, nr. 8, 2007, p. 997.
10.FOUQUE, D., VENNEGOOR, M., TER WEE, P., Nephrol Dial Transplant, **22**, suppl. 2, 2007, p. S45.
11. VEISA, G., DONCIU M.D., SEGALL, L., HURJUI, L., NISTOR, I., URSARESCU, I.G., MARTU, S., BURLEA, S.L., SOLOMON, S.M., Rev. Chim.(Bucharest), **67**, no. 1, 2016, p. 103.
12. ROACH, L.A., LAMBERT, K., HOLT, J.L., MEYER, B.J., J Ren Care, 2017 (Epub ahead of print);
13.BOSSOLA, M., MUSCARITOLI, M., VALENZA, V., PANOCCHIA, N., TAZZA, L., CASCINO, A., LAVIANO, A., LIBERATORI, M., LODOVICA MOUSSIER, M., ROSSI FANELLI, F., LUCIANI, G., Nephron Clin Pract, **97**, nr. 3, 2004, p. 76.
14. MOVILLI, E., VIOLA, B.F., CAMERINI. C., MAZZOLA, G., CANCARINI, G.C., J Ren Nutr, **19**, nr. 2, 2009, p. 172.
15. KAYSEN, G.A., DON, B.R., Kidney Int Suppl, **84**, nr.1, 2003, p. S94.

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