Importance of the monthly biochemical evaluation to identify patients on hemodialysis with malnutrition

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We declare no conflict of interest.

Abstract

Introduction: Malnutrition is a frequent complication in patients on hemodialysis and early diagnosis is important to reduce the morbidity and mortality of treatment. **Objective:** To investigate the usefulness of biochemical tests performed monthly in order to identify hemodialysis patients with malnutrition. **Methods:** The nutritional status of 252 patients was evaluated by objective and subjective global assessment, and the patients classified as malnourished and not malnourished. Then, during 4 consecutive months, serum creatinine, phosphorus, urea pre-and post-dialysis and Kt/V were recorded for calculation of averages. After analysis of these variables by the ROC curve we calculated the sensitivity and specificity of these parameters to identify patients with malnutrition. **Results:** In ROC curve, the area under the curve for urea was 0.683, 0.71 for phosphorus, 0.724 for Kt/V and 0.765 for creatinine. For values of urea ≤ 90 mg/dL, phosphorus ≤ 4.2 mg/dL, Kt/V ≥ 1.6 and creatinine ≤ 6.5 mg/dL, the specificity ranged between 80 and 88% and sensitivity between 26 and 51%. The negative predictive value ranged between 90 and 92% and positive predictive value between 23 and 32%. The association of two or more of these indices did not change significantly these values. **Conclusions:** Our results suggest that serum urea ≤ 90 mg/dL, creatinine ≤ 6.5 mg/dL, phosphorus ≤ 4.2 mg/dL, and Kt/V ≥ 1.6 can be used for screening patients with malnutrition. However, using these cutoffs the parameters tend to overestimate the number of patients with malnutrition.

Keywords: malnutrition, renal dialysis, diagnosis.

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Introduction

Malnutrition is a frequent clinical complication in patients on dialysis programs.[1-4] Its prevalence, however, varies in different dialysis centers. This is partially due to differences in the characteristics of the patients. However, the criteria used to establish the diagnosis of malnutrition seem to be the major responsible for such differences.[5-7]

Consensus about the best way to diagnose malnutrition in dialysis patients still lacks. Some methods rely on subjective criteria, making the diagnosis extremely dependent on the observer's experience. Consequently, patients meeting the criteria of malnutrition by use of an assessment scale can be considered only at nutritional risk or even eutrophic, when other assessment parameters are used.

In clinical practice some simple and rapid tests have been used to identify patients who might have malnutrition.[8-10] The usefulness of such tests is associated with their easy application, which speeds screening and referral of patients for assessment by a nutritionist trained in caring for chronic kidney disease patients. However, some of those instruments are influenced by the observer.[10]

This study aimed at assessing the usefulness of applying monthly laboratory tests to patients on hemodialysis (HD) programs to identify those with malnutrition.

Material and Methods

Case series

This is a cross-sectional, prospective, observational study from the medical viewpoint and interventional from the

nutritional viewpoint, involving 252 patients on chronic HD programs. The inclusion criteria were as follows: be alive on the occasion of study sampling; be on a HD program for at least four months; and have a nutritional assessment performed by a nutritionist according to the protocol of our dialysis clinic. Residual kidney function was not individually assessed, but the patients' urinary volume was lower than 300 mL in 24 hours. All participants provided written informed consent, and the protocol was approved by the Committee on Ethics of the institution.

For four consecutive months, the pre- and post-dialysis serum levels of urea, phosphorus, creatinine, potassium, calcium, and hemoglobin were recorded for calculation of the means. In parallel, patients underwent a complete nutritional study involving several assessment indices.

Nutritional assessment

In our dialysis unit, patients are periodically assessed for classification of their nutritional status by use of objective and subjective methods, such as those described by Martins & Riella.[11] In this study, for subjective assessment, the following were used: 24-hour recall; general physical examination; and global subjective assessment based on questions about weight loss, physical appearance, appetite, energy level, and disease burden. According to the responses, the patient was classified as follows: normal nutritional status; mildly to moderately malnourished; or severely malnourished.[12]

The objective assessment comprised biochemical tests and anthropometric measures. The biochemical tests were as follows: serum concentration of albumin and transferrin; total count of lymphocytes; and protein catabolic rate normalized to body weight (PCRn). The anthropometric measures were as follows: body mass index (BMI) calculated with post-dialysis dry weight; triceps skinfold (TSF); arm muscle circumference (AMC); arm muscle area (AMA); arm fat area (AFA); waist-to-hip ratio; and knee height to estimate body height in patients with amputations or who could not stand up. In the classification of the nutritional status by use of BMI, the WHO criteria were used.[13] After assessment with all those indices, the patient was classified as follows: first, second or third degree malnourished; at nutritional risk; eutrophic; overweight; or first, second, or third degree obese.

When, by use of different indices, the patient was classified into different categories of nutritional status, the one in which the patient had the greatest number of indices was chosen, respecting the following scale of importance: BMI; biochemical assessment; AMC and TSF; 24-hour recall; and global subjective assessment.

The nutritional assessment was performed by one single nutritionist, properly trained to care for patients on renal replacement therapy. In this study, for the purpose of presenting the results, first, second, or third degree malnourished patients were classified as malnourished, while the others were classified as non-malnourished.

Characteristics of hemodialysis

All patients underwent three HD sessions per week, with a session length of 3.5 to 4.0 hours. Duration of treatment was individualized according to the urea kinetics model. During the HD sessions, blood flow was 350 mL/min and the dialysate flow was 500 mL/min. The sodium, potassium, and calcium concentrations in the dialysate were 137, 2.0, and 3.0 mEq/L, respectively. Bicarbonate, at the concentration of 36 mEq/L, was the buffer used. Glucose concentration in the dialysate was 100 mg/dL. The dialysis filters used were Fresenius Polysulfone, Hemoflow series, F8 or 10 (Fresenius Medical Care - Germany), selected according to the patient's weight and the results of the urea kinetics model. The HD machines were of the proportion type with controlled ultrafiltration module and water treatment was performed with reverse osmosis.

Urea kinetics model

The urea kinetics model used in this study was the one recommended by the National Kidney Foundation.[14] Single-pool Kt/V was calculated by use of the Daugirdas second generation formula[15], and PCRn was estimated based on Kt/V by use of the formula proposed by Depner and Daugirdas.[16]

Statistical analysis

Data are shown as mean ± standard deviation for continuous variables and as percentages for categorical variables. Means were compared by use of analysis of variance. Correlations were performed with the Pearson *r* correlation coefficient. The significance level of 5% was adopted. The programs used for statistical analysis were GraphPad Prism, version 3.00 for Windows (GraphPad Software, San Diego, California, USA), and SPSS, version 13.0 for Windows.

Results

Of the 252 patients assessed in this study, 148 (58.7%) were males and 104 (41.3%) females. Their mean age was 55.9 ± 14.6 years, and the dialysis time was 39.7 ± 21.1 months. Nutritional assessment classified 31 (12.3%) patients as malnourished, 68 (27%) as at nutritional risk, 72 (28.6%) as eutrophic, 53 (21%) as overweight, and 28 (11.1%) as obese.

Table 1 shows age, dialysis time, the laboratory test results, and the parameters of urea kinetics for each group of the nutritional assessment. Age, dialysis time, serum calcium, hemoglobin, and PCRn did not differ between groups. However, pre-dialysis serum concentration of urea, phosphorus, and creatinine were significantly lower in malnourished individuals. On the other hand, Kt/V was significantly higher in malnourished individuals as compared with that in the other nutritional categories. Potassium serum concentration was significantly higher in eutrophic and obese as compared with that in the malnourished patients, but the magnitude of the difference was small (Table 1). The ROC curve for the statistically different variables between malnourished and non-malnourished individuals is shown in Figure 1. The areas under the curve for the following variables were as follows: serum urea, 0.683; phosphorus, 0.71; Kt/V, 0.724; and serum creatinine, 0.765. Based on the ROC curves and on the mean and standard deviation values of those variables, values were arbitrarily chosen for the sensitivity and specificity analyses of the malnutrition diagnosis. After those analyses, the values selected were as follows: serum urea ≤ 90 mg/dL; phosphorus ≤ 4.2 mg/dL; Kt/V ≥ 1.6; and serum creatinine ≤ 6.5mg/dL.

Figure 1. ROC curve for the diagnosis of malnutrition in patients undergoing a HD program.

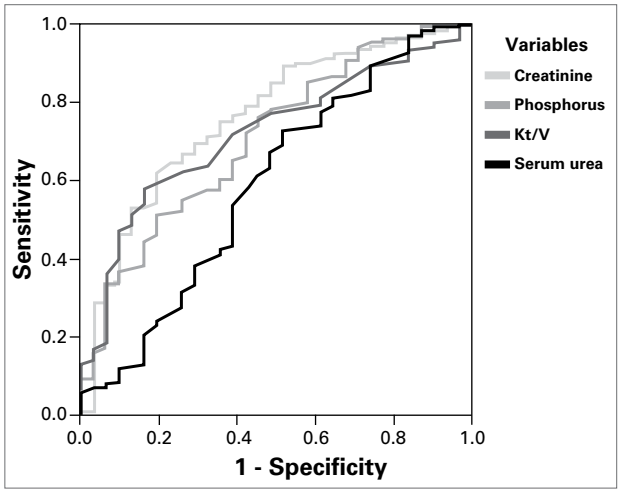


Table 2 shows the sensitivity, specificity, positive and negative predictive values for each variable regarding their capacity to screen malnourished patients. Although specificity ranged from 80% to 88%, sensitivity was low, between 26% and 51%. Unlike the high negative predictive value, between 90% and 92%, the positive predictive value was low, between 23% and 32%.

Table 3 shows the same type of analysis to assess the associations between the different variables studied. Once again, although specificity increased to the 94%-99% range, sensitivity remained low, between 6.5% and 26%.

Table 1 Demographic and laboratory data according to the classification of the nutritional status of patients undergoing a HD program

NC	n	Age (years)	HT time (m)	Pré HD U (mg/dL)	Pi (mg/dL)	Cr (mg/dL)	K (mEq/L)	Ca (mg/dL)	Hb (g/dL)	Kt/V	PCRn (g/kg/day)
MN	31	60.4 ± 18.8	35 ± 22.7	94.9 ± 23.7	4.5 ± 1.2	6.7 ± 3	4.4 ± 0.6	8.8 ± 0.7	11.3 ± 1.8	1.51 ± 0.22	0.68 ± 0.19
NR	68	59.2 ± 16.4	40.7 ± 20.2	108.3 ± 25.9*	5.3 ± 1.3†	8.1 ± 2.5*	4.5 ± 0.4	9 ± 0.8	12 ± 1.6	1.36 ± 0.25†	0.72 ± 0.17
E	72	53.5 ± 13.5	41.8 ± 23.4	113.3 ± 22#	5.5 ± 1.4#	9.8 ± 2.9#	4.7 ± 0.5*	9.2 ± 0.7	11.9 ± 1.5	1.35 ± 0.22†	0.76 ± 0.16
OW	53	54.6 ± 12.5	41.2 ± 19.2	110.2 ± 28.7*	5.7 ± 1.5#	10.2 ± 3.1#	4.5 ± 0.5	9.2 ± 0.7	11.5 ± 1.5	1.29 ± 0.21#	0.71 ± 0.17
O	28	55.6 ± 9.7	34.1 ± 18.2	114.6 ± 26.7†	6.2 ± 1.7#	10.2 ± 3.2#	4.7 ± 0.5*	9 ± 0.6	11.8 ± 1.7	1.28 ± 0.25#	0.74 ± 0.19

* p < 0.05; † p < 0.01; # p < 0.001 vs malnutrition NC: nutritional classification; MN: malnutrition; NR: at nutritional risk; E: eutrophy; OW: overweight; O: obesity; Pi: serum phosphorus; Cr: serum creatinine; HD: hemodialysis; U: serum urea.

Table 2 Sensitivity and specificity of different indices in the diagnosis of malnutrition in patients undergoing a HD program

Risk factor	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Urea ≤ 90mg/dL	41.9	80.5	23.2	90.8
Pi ≤ 4.2mg/dL	41.9	82.8	25.5	91
Cr ≤ 6.5mg/dL	51.6	85.1	32.6	92.6
Kt/V ≥ 1.6	25.8	88.2	23.5	89.4

PPV: positive predictive value; NPV: negative predictive value. Pi: serum phosphorus; Cr: serum creatinine.

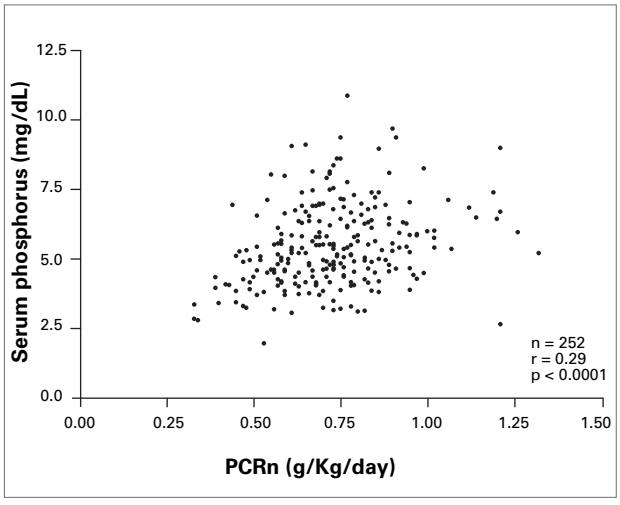
Table 3 Sensitivity and specificity of different combinations of indices in the diagnosis of malnutrition in patients undergoing a HD program

Risk factor	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
U ≤ 90 mg/dL e Cr ≤ 6.5 mg/dL	22.5	93.7	33.3	89.6
U ≤ 90 mg/dL e Pi ≤ 4.2 mg/dL	22.6	93.7	33.3	89.6
U ≤ 90 mg/dL e Kt/V ≥ 1.6	19.9	96.8	36.4	88.8
Pi ≤ 4.2mg/dL e Cr≤6.5mg/dL	25.8	93.7	36.4	90
Kt/V ≥ 1.6 e Cr ≤ 6.5 mg/dL	12.9	97.3	40	88.8
Kt/V ≥ 1.6 e Pi ≤ 4.2 mg/dL	9.7	97.3	33.3	88.5
Kt/V ≥ 1.6 e Pi ≤ 4.2 mg/dL e Cr ≤ 6.5 mg/dL	9.7	98.2	42.9	88.6
Kt/V ≥ 1.6 e Pi ≤ 4.2 mg/dL e U ≤ 90mg/dL	6.4	98.2	33.3	88.2
Kt/V ≥ 1.6 e Cr ≤ 6.5 mg/dL e U ≤ 90mg/dL	6.4	99.1	50	88.3
Pi ≤ 4.2mg/dL e Cr ≤ 6.5 mg/dL e U ≤ 90 mg/dL	12.9	96.8	36.4	88.8

PPV: positive predictive value; NPV: negative predictive value; U: serum urea; Pi: serum phosphorus; Cr: serum creatinine.

This study has not assessed the caloric intake of patients, but the estimate of protein intake, calculated by use of the urea kinetics model, which did not differ among the five nutritional categories (Table 1). In our results, the low protein intake (0.73 ± 0.17 g/kg/day) is worth noting, although the patients received an adequate dialysis dose (Kt/V = 1.35 ± 0.24). Finally, our results evidenced a positive correlation between protein intake, estimated by PCRn, and the serum concentration of phosphorus (Figure 2).

Figure 2. Correlation between protein catabolic rate (PCRn) and serum concentration of phosphorus in patients undergoing a HD program.



Discussion

Possibly one of the most difficult diagnoses in clinical nephrology is that of malnutrition in dialysis patients. In more advanced cases, diagnosis is easy, but less exuberant cases can be controversial in regard to diagnostic parameters.

Although some complex methods to diagnose malnutrition, such as dual-energy X-ray absorptiometry (DXA)17,18 and electric bioimpedance,19-21 have been validated, they are not available at most dialysis centers. Consequently, in practice, some subjective tests are used, in addition to a few laboratory measurements. This makes the diagnosis of malnutrition particularly dependent on the observer's experience.

For dialysis patients, the early establishment of the malnutrition diagnosis is important, since it is associated with greater morbidity and mortality.[22, 23] On the other hand, to rescue a malnourished patient is complex, difficult, and may take long. Thus, all effort should be made to rapidly detect malnutrition, so that individualized therapeutic planning could be provided to every patient.

This study aimed at evaluating the usefulness of the monthly biochemical assessment of dialysis patients for the screening of the diagnosis of malnutrition. Our results suggest that pre-dialysis serum concentrations of urea, creatinine, and phosphorus, as well as Kt/V, can be used for that purpose. However, although specificity is high, sensitivity is low. And, although the negative predictive value is high, the positive predictive value is low.

Together, our results suggest that those indices tend to overestimate the number of malnourished patients. However, it is worth emphasizing that the indices should not be used to establish the diagnosis of malnutrition, but only to select patients to be referred for nutritional assessment with an adequately trained professional in following dialysis patients up.

In addition, our results have shown that the association of two or more of those indices, although having increased specificity and positive predictive value, had no effect on sensitivity and negative predictive value. This means that assessing patients by use of the multiple associations of those indices complicates clinical reasoning and does not improve results.

The cutoff values for each index assessed in this study have undoubtedly influenced sensitivity and specificity of the test. In our study, those values were arbitrarily defined, because the ROC curve showed no well-defined inflection point. Thus, we chose to consider, in addition to the ROC curve, the mean and standard deviation values for each variable in the group of malnourished patients as compared with those of non-malnourished individuals. By using that technique, our results suggest that concentrations of urea £ 90 mg/dL, of creatinine £ 6.5 mg/dL, of phosphorus £ 4.2 mg/dL, and Kt/V ³ 1.6 can indicate the likelihood of a patient being malnourished.

The serum concentration of creatinine is proportional to muscle mass. In malnourished individuals, muscle mass is reduced, and, thus, the creatinine concentration is lower.5 On the other hand, the concentrations of urea and phosphorus are directly related to the protein intake rate. Thus, one can infer that the reduced protein intake of malnourished patients can account for the lower concentration of urea and phosphorus.

Surprisingly, in our study, the protein intake rate, estimated by the protein catabolic rate, was markedly reduced in all categories of nutritional assessment, being much lower than the levels recommended for patients on HD programs.5 Although the explanation for that requires further studies, the socioeconomic level of our population is likely to have influenced those results.24 Still, that observation should be considered, because reduced protein intake is associated with an increase in morbidity and mortality in dialysis.

Despite the low protein intake, our results show a positive correlation between PCRn and serum concentration of phosphorus. Thus, although the serum concentration of phosphorus is influenced by variables, such as dialysis time and use of phosphorus binders, our results show that it can be used as an estimate of protein intake.

Kt/V is an inverse ratio of the urea distribution volume (V), which is directly related to the patient's weight. Malnourished patients have a low BMI. As that index was one of the criteria used to classify patients into the different nutritional categories, malnourished individuals are supposed to have a reduced volume V, which results in an increase in Kt/V. Thus, even in conditions of high efficiency dialysis, extremely high values of Kt/V can indicate the presence of malnutrition.

Our study has some limitations. As the nutritional inquiry was not performed, the actual protein-calorie intake was not assessed. On the other hand, although our patients were on dialysis for a long time, residual renal function, which is known to influence serum concentration of urea, creatinine, and phosphorus, was not assessed. This may be one of the major reasons for the low sensitivity of the indices evaluated in this study. Despite those limitations, although the indices overestimate the number of malnourished individuals, overloading the nutritional team, they reduce the number of malnourished patients not referred for nutritional assessment.

In conclusion, our results show that the monthly biochemical assessment of the serum concentration of urea, creatinine, and phosphorus, and Kt/V can be used to screen malnutrition in patients undergoing a chronic HD program.

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