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Serum Transthyretin Profile in Patients with Chronic Renal Failure on Hemodialysis at Souro Sanou University Hospital in Bobo-Dioulasso

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Abstract: *Introduction*: Transthyretin (prealbumin) is a protein secreted by the liver that is involved in the assessment of undernutrition and nutritional intake. Undernutrition in hemodialysis patients is associated with a worsening of vital prognosis. The main objective of this study was to investigate the transthyretin profile in hemodialysis patients with chronic kidney disease (CKD) in the absence of inflammation in Bobo-Dioulasso, Burkina Faso. *Material and methods*: This was a prospective study of CKD hemodialysis patients recruited at the CHU-SS from 1er January 2022 to 28 February 2022. Socio-demographic data were obtained after examination of the medical records of hemodialysis CKD patients. All biochemical parameters were measured on the COBAS® 6000 automated system. Colorimetric methods were used to measure urea (urease/Glutamate dehydrogenase), creatinine (modified Jaffé) and albumin (bromocresol green). CRP, alpha-1-glucoprotein acid and transthyretin were determined by the immunoturbidimetric method. *Results and discussion*: A total of 41 hemodialysis patients were included in the study. The mean age was 42.93±12.21 years with extremes ranging from 22 to 72 years. There was a male predominance with a sex ratio (M/F) of 1.56. The mean BMI of the patients was 20.70±2.87 kg/m^2 with extremes from 14.45 to 28.28 kg/m^2. Mean transthyretin was 0.47±0.13 g/L. Significant positive correlations were observed with albumin (r=0.77; p=0.0000) and alpha 1 glycoprotein acid (r=0.43; p= 0.004). In the absence of inflammation in the patient group, only one patient (2.44%) presented with hypotranthyretinemia. *Conclusion:* Transthyretin provides quantitative and clinically useful data for better management of undernutrition and, above all, for predicting the morbidity and mortality associated with protein-energy undernutrition.

Keywords: Assessment of Undernutrition, Prealbumin, Albumin, Chronic Renal Failure, Dialysis

1. Introduction

Chronic kidney failure constitutes a major public health problem worldwide [1] whose mortality rate is currently increasing sharply [2]. Hemodialysis patients are subject to high morbidity and mortality. This may be due to chronic kidney disease (CKD), hemodialysis, comorbidities or malnutrition, which can affect the immune system [3, 4].

Undernutrition impairs the quality of life and management of hemodialysis patients with CKD. Several studies have

evaluated malnutrition in hemodialysis patients with prevalence's ranging from 20 to 61%, particularly when the estimated glomerular filtration rate was less than 35 ml/min/1.73 m^2 [5-10].

Transthyretin is a biochemical marker proposed by several authors for the assessment of malnutrition and nutritional support [11-14]. This is a marker whose interpretation often requires prior knowledge of the inflammatory state of patients. Indeed, the literature describes a collapse of transthyretin in the face of inflammatory conditions [8, 15, 16].

In Burkina Faso, there are few studies on this marker. This is how we conducted the present study, which aimed to evaluate the serum transthyretin profile in patients with CKD on dialysis in the absence of an inflammatory state. We hypothesized that in the absence of inflammatory conditions (CRP < 5 mg/L), transthyretin could be used to identify undernourished hemodialysis patients with CKD or requiring nutritional support.

2. Material and Methods

2.1. Framework and Period of Study

This was a cross-sectional analytical study, with data collection taking place over a two-month period from 1er January 2022 to 28 February 2022.

2.2. Patients

The study population consisted of CKD patients undergoing dialysis in the nephrology-dialysis department who had undergone their biological work-up in the laboratory department of the Souro Sanou University Hospital (SS-UH) in Bobo-Dioulasso, Burkina Faso. The study included hemodialysis patients with CKD aged over 18 years and a CRP < 5 mg/L.

2.3. Methods

Blood samples were taken at the time of their dialysis session. The blood sample was immediately transported to the laboratory and centrifuged at 3500 rpm for 5 minutes for analysis. Biochemical marker assays were performed after calibration and internal quality control according to the biochemistry laboratory's internal procedures. All biochemical parameters were assayed on the Roche systems Cobas® 6000 (Roche/Hitachi) multiparameter automated system. Colorimetric methods were used to measure urea (urease/Glutamate dehydrogenase), creatinine (modified Jaffé) and albumin (bromocresol blue). CRP, alpha-1-glycoprotein acid and transthyretin were measured by immunoturbidimetric methods.

The study variables concerned socio-demographic aspects such as age, sex, area of residence, occupation, body mass index (BMI), date of start of dialysis and pathological history. The biological variables we investigated were uremia, creatinine, glomerular filtration rate (GFR) using the Modified Diet Renal Diseases (MDRD) formula (ml/min/1.73m^2), CRP, albumin, transthyretin (prealbumin) and alpha 1 glycoprotein.

Before the start of the study, a request for authorization to collect data was obtained from the management of the CHU-SS. Data confidentiality was maintained throughout the study.

Data were collected using Excel 2016 and statistical analyses were performed using R software version 3.6.1. Means (m) and standard deviations (SD) were calculated for quantitative variables such as age and concentrations of biochemical parameters. Student's t-test was used to compare means. Pearson's correlation coefficient was used to investigate the association of transthyretinemia with other biochemical markers. A probability of less than 0.05 was considered significant for all variables.

3. Results

3.1. Socio-Demographic Characteristics

A total of 41 CKD patients undergoing hemodialysis at the CHU-SS with dialysis durations ranging from 3 months to 49 months were included in the study.

The socio-demographic characteristics of the study population are presented in Table 1. The mean age of the study population was 42.93±12.21 years, with extremes ranging from 22 to 72 years. Males predominated, with a sex ratio (M/F) of 1.56. Patients had an average of 2 dialysis sessions per week. The duration of dialysis varied from 3 months to 49 months, with 12.2% of patients having no more than 1 year of dialysis, 82.93% of patients having between 2-3 years of dialysis and 4.88% having 4 years or more of dialysis.

The mean BMI of patients was 20.70±2.87 kg/m^2 with extremes of 14.45 to 28.28 kg/m^2. A breakdown of hemodialysis patients by BMI bracket revealed that 21.95% were malnourished.

Clinically, 80.49% of patients had hypertension, 48.78% had vascular nephropathy and 12.2% had heart disease.

3.2. Mean Values of Biochemical Markers in Hemodialysis Patients with CKD

Table 2 shows the mean values of the various biochemical parameters assessed during the study.

3.3. Correlation Between Transthyretin and the Other Biochemical Markers Studied

The correlation between transthyretin and the other biochemical markers studied is shown in Table 3.

3.4. Serum Transthyretin Profile of Hemodialysis CKD Patients at CHU-SS

The patients' serum transthyretin profile and associated factors are shown in Tables 4 and 5, respectively.

Table 1. *Socio-demographic characteristics of patients.*

Features	Parameters	Patients (N=41)
	Average age (m ± SD), (years)	**42,93±12,21**
Ages	[20-25]	3 (7,32)
	[25-30]	4 (9.76)
	[30-35]	4 (9.76)
	[35-40]	4 (9.76)
	≥40	26 (63.40)
Gender	Male, n (%)	25 (60,98)
	Female, n (%)	16 (39,02)
Area of residence	Urban, n (%)	36 (87,8)
	Rural, n (%)	5 (12,2)
Profession	Employees, n (%)	15 (36,59)
	Informal sector, n (%)	13 (31,71)
	Retailers, n (%)	8 (19,51)
	Farmers, n (%)	4 (9,76)
	Gold panners, n (%)	1 (2,44)
Pathological history	HTA, n (%)	34 (80,49)
	Vascular nephropathy, n (%)	20 (48.78)
	Cardiac pathology, n (%)	5 (12,2)
Dialysis time	Average duration (m ±ET), (years)	2,48±1,03
	Duration ≤ 2 years, n (%)	15 (36,58)
	Duration >2 years, n (%)	26 (63,41)
BMI	Average BMI (m ± SD), $(kg/m)^2$	20,7±2,87
	BMI≤ 23 (kg/m^2), n (%)	35 (85,37)
	BMI>23 (kg/m^2), n (%)	6 (14,63)

Table 2. *Mean values of biochemical parameters in hemodialysis patients with CKD.*

Features	Parameters	Values (m±S4D)
Markers of renal function	Urea (mmol/L)	13.59 ±5.36
	Creatinine (µmol/L)	851.80±390.24
	GFR-MDRD $(mL/min/1.73m)^2$	9.05±5.56
Inflammation markers	CRP (mg/L)	1.92±1.27
	Alpha-1 glycoprotein (g/L)	1.10± 0.29
Markers of undernutrition	Albumin (g/L)	43.24±5.19
	Prealbumin (g/L)	0.47± 0.13

GFR by MDRD: Glomerular filtration rate by Modified Diet Renal Diseases $(ml/min/1.73m)^2$

Table 3. *Correlation between transthyretin and the other biochemical markers studied.*

Parameters	r	t	95% confidence interval		*p-value*
			Min	Max	
Urea	-0.07	-0.44	-0.370	0.24	0.658
Creatinine	-0.05	-0.36	-0.35	0.25	0.719
DFG-MDRD	-0.04	-0.29	-0.35	0.27	0.769
Albumin	0.77	7.74	0.61	0.87	0.000*
CRP	-0.28	-1.82	-0.54	0.03	0.076
Alpha 1 glycoprotein acid	0.433	3.00	0.14	0.65	0.004*

*p<0.05

Table 4. *Transthyretin profile of hemodialysis CKD patients at CHU-SS.*

Features	Parameters	Transthyretin (m±SD), (g/L)	p-value
Ages (years)	[20-25]	0.44±0.07	0.754
	[25-30]	0.57±0.20	
	[30-35]	0.37±0.04	
	[35-40]	0.47±0.22	
	≥40	0.46±0.10	
Gender	Male	0.495±0.15	0.041*
	Female	0.425±0.06	
Area of residence	Urban	0.477±0.12	0.102
	Rural	0.398±0.08	
Profession	Employees	0.486±0.12	0.257
	Informal sector	0.428±0.08	
	Retailers	0.462±0.14	
	Cultivators	0.497±0.21	

Features	Parameters	Transthyretin (m±SD), (g/L)	p-value
	Goldpanners	0.630	
	HTA	0.45±0.12	
Pathological history	Nephropathy	0.46±0.10	0.785
	Cardiac pathology	0.45±0.08	
Dialysis time	Duration ≤ 2 years	0.488±0.14	0.452
	Duration >2 years	0.456±0.12	
BMI	BMI≤ 23(kg/m)2	0.46±0.12	0.436
	BMI>23 (kg/m)2	0.51±0.14	

Table 5. *Factors associated with hypotransthyretinaemia in CKD patients.*

Features	Parameters	Hypoperalbuminemia (<0.3g/L)
Ages (years)	[35-40], n (%)	1 (2,44)
Gender	Male, n (%)	1 (2,44)
Area of residence	Urban, n (%)	1 (2,44)
Profession	Employees, n (%)	1 (2,44)
Pathological history	HTA, n (%)	1 (2.44)
Dialysis time	Duration ≤ 2 years, n (%)	1 (2,44)
BMI	BMI≤ 23 (kg/m2), n (%)	1 (2,44)

4. Discussion

Transthyretin, also known as prealbumin, (a 55kD homotetrameric protein) is the carrier protein for thyroid hormones. [17]. It is synthesised by the liver and normal serum concentrations vary between 0.25-0.35 g/L. Studies show that it is one of the first plasma proteins whose concentrations fall in response to marginal protein restriction, acting as an early warning signal that the adaptive mechanisms maintaining homeostasis are undergoing decompensation [17].

Because of its short half-life (2 days), high tryptophan content and good sensitivity to dietary protein intake, transthyretin is a marker of choice for diagnosing undernutrition and monitoring the effectiveness of nutritional support. [16].

Biologically, in patients with renal failure, concentrations < 0.30 g/L are associated with protein-energy malnutrition [18, 19]**.** In addition, for proper interpretation of serum transthyretin concentrations in patients with conditions other than liver disease, knowledge of the patient's inflammatory status is imperative. In fact, several studies have shown that transthyretin collapses with any inflammatory condition [8, 15, 16].

All hemodialysis CKD patients in our study had CRP<5mg/L with a mean CRP of 1.92±1.27 mg/L and a mean transthyretin of 0.47±0.13 g/L. A negative Pearson correlation was observed between CRP and transthyretin, suggesting that as serum CRP concentrations increased, transthyretin decreased (r=-0.28; p=0.076). The same finding was observed by Lee et al. who found serum CRP concentrations =7.2±16.3 mg/L and a mean transthyretinemia of 37.6±10.8 mg/L (CRP vs transthyretin, r=- 0.328, p<0.0001) [20]. In addition, several studies have shown that serum transthyretin concentrations are a sensitive and independent predictor of mortality in hemodialysis patients and also that there is a good correlation with markers of undernutrition and inflammation [11, 13, 20].

Hypotransthyretinaemia affected 2.44% of patients in our study. Duggan et al. found 33% of hemodialysis patients with transthyretinaemia <30mg/L [21]. Duang et al. noted a higher prevalence of 39.4% of hypotransthyretinaemia [22]. The low frequency observed in our study could be explained by the absence of malnutrition-inflammation syndrome in our study population (mean CRP =1.92±1.27 mg/L). The study showed positive and statistically significant Pearson correlations between transthyretinemia and albuminemia (r=0.77, p<0.000). Rajanna et al. found r=0.42, p<0.01 [14] Mittman et al. found r=0.53, *p<0.*0001 [23] and Lee et al. found r=0.417, p<0.0001 [20]. This correlation between albumin and transthyretin is well described in the literature [15, 16, 19, 24].

Transthyretin was also correlated with alpha1glucoprotein acid (r=0.433; p<0.0004), showing that these 2 markers were also moving in the same direction. Alpha1glucoprotein acid is a marker synthesised by the liver whose concentrations increase in the face of all diseases with an inflammatory component. In our study, alpha1-glucoprotein acid and mean CRP had low mean concentrations of 1.10±0.29 g/L and 1.92±1.27 mg/L respectively. These data could be evidence that, in the absence of inflammation, hemodialysis CKD patients have a low rate of undernutrition.

Transthyretin in hemodialysis CKD patients varied significantly by sex. Males had significantly higher mean concentrations of prealbumin than females. Gender dimorphism is attributed to the impact of androgenic hormones known to exert direct stimulatory effects on hepatic synthesis of prealbumin [25] and to anabolic events associated with post-pubertal alterations [17, 26].

Hypotransthyretinaemia in our study was present in only one hemodialysis CKD patient. The associated factors were male gender, age [35-40] years, clinically hypertension, dialysis duration ≤ 2 years with a BMI≤ 23(kg/m^2). Several studies found that various factors were associated with hypotransthyretinaemia. These factors favoring hypotransthyretinaemia could be categorized as iatrogenic and non-iatrogenic. The iatrogenic factors were related to the poor adequacy of dialysis results, which leads to poor correction of

uremia and metabolic acidosis. [20, 27-29]. Non-iatrogenic factors include inadequate dietary intake, poor appetite associated with an increase in inflammatory markers and poor dietary quality (non-varied and incomplete diet), and psychosocial and financial barriers to an optimised diet. [20, 27-29].

5. Conclusion

In our study, we found that, in the absence of inflammation, hemodialyzed CKD patients had a low proportion of hypotransthyretinaemia. Thus, apart from inadequate nutrition, this low frequency of hypotransthyretinaemia could be associated clinically with inadequate dialysis (number and duration of dialysis) and associated hypertension. In the light of this information, haemodialysis CKD patients without inflammatory syndrome could have a better nutritional status.

Biochemical biomarkers of undernutrition provide quantitative and clinically useful data for better management of undernutrition and, above all, for predicting the morbidity and mortality associated with protein-energy undernutrition.

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