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BETA-2- MICROGLOBULIN PROFILE AMONG PATIENTS ON MAINTENANCE HAEMODIALYSIS IN SOUTH-WEST NIGERIA

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ABSTRACT

Introduction: Beta-2-microglobulin is a predictor of mortality and a marker of cardiovascular disease in patients with chronic kidney disease. It is a marker of clearance of middle molecules and has been suggested to be a measure of adequacy of haemodialysis.

Methods: The study was an observational, single arm, paired survey. A total of 66 patients on maintenance haemodialysis who fulfilled the admission criteria were placed on a defined haemodialysis prescription for a month and their urea reduction ratio, Kt/V and percentage reduction in beta-2-microglobulin were calculated.

Results: The mean age of study participants was 42.9 (± 11.5) years. The mean percentage reduction of β_2M, urea reduction ratio and Kt/V, were 48.2±24.4; 54.2±18.3; and 0.9±0.5 respectively. The mean pre dialysis β_2M and post dialysis β_2M were 27.3±12.8 and 16.9±11.3 respectively. The sensitivities and specificities of URR (100% and 88.1%) respectively and % reduction in β_2 microglobulin were (46.7% and 60.9%) respectively. A positive correlation was found between Kt/V and % reduction of β_2M ($r = 0.4$; $p<0.001$) as well as URR and % reduction in β_2M ($r = 0.3$; $p<0.05$). Also, a line graph showed that a Kt/V of 1.2 corresponded to a 56% reduction of beta-2- microglobulin.

Conclusion: Percentage reduction of beta-2-microglobulin is a less sensitive and specific marker of assessing adequacy of dialysis compared to URR and Kt/V and is therefore a less reliable marker of adequacy of haemodialysis at least in our setting.

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INTRODUCTION

Beta-2-microglobulin (β2M) is a low molecular weight peptide encoded by a gene in chromosome 15 in humans, consisting of 100 amino acids and a molecular weight of 11800 Da1. It interacts with the alpha chain of the human leucocyte antigen (present on all nucleated cells) and this interaction is essential for antigen presentation2. It is a marker of clearance of middle molecules and has been suggested to be a measure of adequacy of haemodialysis3. Patients with pre-dialysis serum β2M levels of 42.5-50 mg/l had relative risk of death approximately 60% greater than those with levels <27.5mg/l3. Predictors of serum β2M levels include dialyzer clearance of β2M, duration of haemodialysis and residual kidney function3. Independent determinants of serum β2M levels in chronic haemodialysis patients include: duration of ESKD, residual kidney function, dialyzer clearance, body composition3.

Beta-2-microglobulin is an amyloid precursor molecule with very low serum concentrations in normal healthy people, usual range is between (1-3) mg/l4. Due to its renal elimination, it tends to accumulate in patients with end stage kidney disease and this serves as a precondition for its deposition in amyloid fibrils in such patients4,5.

The aim of this study is to determine the β2 microglobulin profile of patients on maintenance haemodialysis.

MATERIALS AND METHODS

Consecutively presenting ESKD patients for haemodialysis at the Owena Dialysis Centre, University College Hospital (UCH), Ibadan were enrolled in the study between May 2018 to January 2019. Written informed consent was obtained from all participants. Ethical approval for this study was obtained from the joint University College Hospital and University of Ibadan Ethical Review Committee.

Data Collection

Patients were dialyzed as follows for one month following enrolment: Blood flow rate was 200-300ml/min, and dialysate flow rate at 500ml/min; Ultrafiltration goal was calculated as weight gain in the interdialytic period, duration of dialysis was 4 hours. Bicarbonate-based dialysate was used, dialyzer was polysulfone hollow fiber dialyzer with a surface area of 1.8m2. A maximum tolerable ultrafiltration rate of 6 litres was applied to patients whose interdialytic weight gain exceeded 6 litres. Each patient had haemodialysis by this regimen for one month. There was no reuse of dialyzer. Ultrafiltration was adjusted for fluids infused or consumed by patient intradialysis to maintain the dry weight of the patient.

Ten (10) ml of venous blood was collected at enrolment under aseptic conditions immediately before the first session of haemodialysis for albumin, calcium, urea and creatinine. Pre dialysis samples for urea and beta-2-microglobulin were collected immediately before haemodialysis prior to infusion of saline or other diluents6 while post dialysis samples were collected from the dialyzer inflow port (arterial circuit) using a slow-flow method in which the blood flow rate is reduced to 100ml/min for 15 seconds before sample collection is done6. Serum β-2-Microglobulin was measured using the Latex enhanced Immunoturbidimetric method on, serum urea was measured using the enzymatic colorimetric UV method, while serum

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creatinine assay was done using enzymatic colorimetric method on the same automated chemistry analyzer. Serum Albumin was measured using Bromocresol Green method and serum Calcium was measured using Arsenazo III. All biochemical analysis was done using an automated chemistry analyzer (LandWind C 100 Plus) manufactured by Accurex Biomedical, India. Samples were stored at -20 OC in a LG chest freezer with solar and inverter power back up and centrifuged using a uniscope laboratory centrifuge (Surgifriend Medicals, England).

Both pre and post samples were collected at the last session of haemodialysis (after a month) during the study. Mathematical formulae were used to calculate the percentage reduction of serum β2M, urea reduction ratio and Kt/V (Daugirdas formulae)7. The percentage reduction of beta-2-microglobulin was calculated as follows:

(Pre dialysis β2M - Post dialysis β2M) / Pre dialysis β2M was used to calculate % reduction in beta-2- microglobulin.

Urea reduction ratio was calculated as follows: (pre dialysis urea- post dialysis urea)/(pre dialysis urea. The quotient was multiplied by 100%.

Data Management

Data analysis was done using Statistical Package For Social Sciences Software (SPSS), version 20. A 95% confidence interval was used and a P value < 0.05 was regarded as statistically significant

RESULTS

Table 1.1: Mean URR, Kt/V and % reduction of β_2M among study participants

Marker of dialysis	Mean ± SD	Min	Max
URR	54.2 ±18.3	4.95	89.20
Kt/V	0.9± 0.5	0.03	2.20
% β_2M	48.2 ± 24.4	0.60	96.40

Key: URR is urea reduction ratio, Kt/V is an index of urea clearance, % β_2M is % reduction of beta-2 microglobulin (mg/l).

Table 1.2 shows the beta-2- microglobulin (β_2M) in mg/l profile among study participants

β_2M	Mean ± SD	Min	Max
Pre Dialysis	27.3 ± 12.8	3.2	50.0
Post Dialysis	16.9 ± 11.3	0.8	49.7
% reduction	48.2 ± 24.4	0.6	96.4

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Table 1.3: Shows the sensitivity and specificity of URR and % reduction of beta-2-microglobulin.

Haemodialysis	Variable	Kt/V	
		Positive	Negative
URR	Positive	15 (75.5%)	5 (25.5%)
	Negative	0 (0.0%)	37 (100.0%)
	Total	15 (26.3%)	42 (73.7%)
$\beta_2$microglobulin	Positive	7 (30.4%)	16 (69.6%)
	Negative	8 (24.2%)	25 (75.8%)
	Total	15 (26.8%)	41 (73.2%)

For URR

1. Sensitivity = 15/15 = 100.0%
2. Specificity = 37/42 = 88.1%

% reduction of β_2 Microglobulin

1. Sensitivity = 7/15 = 46.7%
2. Specificity = 25/41= 60.9%

Table 1.4: Relationship between Urea, Creatinine, Albumin and β_2Microglobulin

Variable	Urea	Creatinine	Albumin	β_2M
Urea	1.00			
Creatinine	0.66** <0.001	1.00		
Albumin	0.05 0.71	0.10 0.44	1.00	
β_2M	0.45** <0.001	0.59** <0.001	0.17 0.19	1.00

β_2M is pre dialysis beta-2- microglobulin

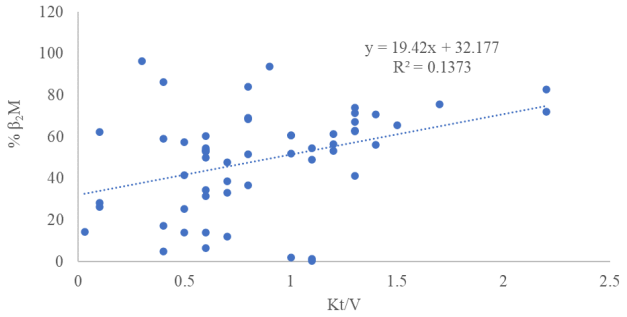

Figure 1.1 – Linear relationship between % reduction of beta-2 –microglobulin and Kt/V (r=0.4;P<0.001)

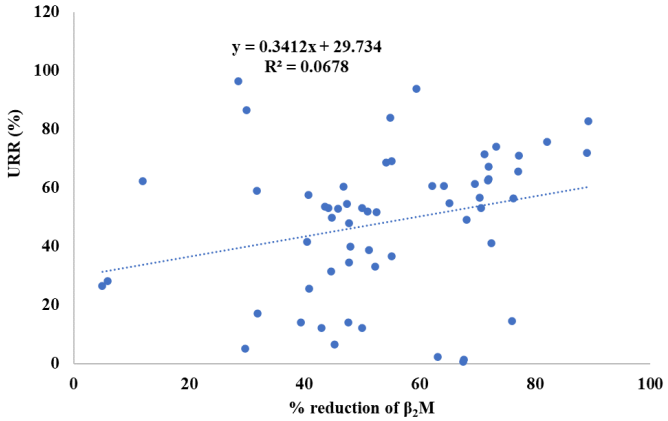

Figure 1.2: Linear relationship between URR and percentage reduction of beta-2-microblobulin (r=0.3;P<0.05)

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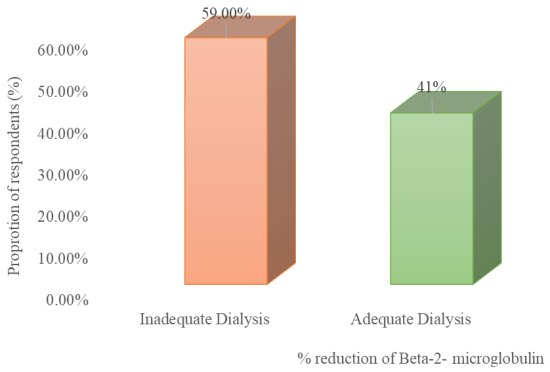

Figure 1.3 showing adequacy of haemodialysis using % reduction of beta-2- microglobulin. Inadequate dialysis (% reduction of beta-2-microglobulin < 56%) and adequate dialysis (% reduction of beta-2-microglobulin ≥ 56%).

DISCUSSION

From this study, the percentage reduction in serum β-2-microglobulin is spread over a wide range of concentration suggesting that the ability of the dialyzer (polysulfone hollow fiber dialyzer with diameter of 1.8m[2]) to remove β-2-microglobulin from the patient's blood may be unpredictable. The contribution of other factors affecting serum β-2-microglobulin levels in chronic haemodialysis patients such as duration of ESKD, residual kidney function, body composition may also play a role[3].

For the purpose of this study and for ease of interpretation, pre dialysis concentration of beta-2-microglobulin > 30 mg/l is a surrogate marker of inadequate dialysis and % reduction of beta-2- microglobulin < 56% is regarded as a measure of inadequate haemodialysis in this study. A percentage reduction of β-2-microglobulin of 56% corresponds to a Kt/V of ≥ 1.2 on a line graph of Kt/V and % reduction in β-2-microglobulin shown earlier. According to both (pre dialysis β-2-microglobulin concentration and % reduction in β-2-microglobulin) cutoff levels, 59% of study participants had inadequate dialysis, which is lower than that identified by both URR and and Kt/V in this study. This suggests that URR and Kt/V can identify more patients with inadequate dialysis than beta-2- microglobulin, Kt/V identifying the most patients in this study. Using sensitivity testing (Kt/V as a standard), % reduction in beta-2-microglobulin had lower sensitivity and specificity in detecting patients with inadequate dialysis. Residual kidney function is known to be an important determinant of serum beta-2-microglobulin levels, because the kidneys are the primary route for the elimination of this protein[6]. Baseline residual kidney urea clearance and dialyzer beta-2- microglobulin clearance were strong predictors of predialysis serum beta-2-microglobulin[3]. Beta-2- microglobulin is a surrogate marker for middle molecular weight uraemic toxins and major protein component in dialysis-related amyloidosis and is also associated with vascular calcification[6]. It is independently associated with overall mortality[7].

In this study, pre dialysis beta-2- microglobulin showed moderate positive correlation with serum urea, creatinine, uric acid and negative correlation with serum calcium which is in keeping with chronic uraemia. This relationship may be chronic uraemic state. Also, there is a direct relationship between % reduction of β-2-microglobulin (≥56%) and Kt/V≥ 1.2 as well as URR ≥ 65%. This suggests that as small molecules are cleared, there is also some clearance of middle molecules. As a caveat in this study, significant overestimation

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of % reduction in β-2-microglobulin can occur when it is calculated from predialysis and immediate post dialysis plasma concentration using a single compartment, this is due to substantial rebound of beta-2- microblobulin[8]. In that same study, the % reduction of beta-2-microglobulin was 27.1(±4.0)% using high flux dialyzers, the % rebound of the molecule post haemodialysis was also estimated as 44.8±21.4% (30 minutes post HD) and 45.9(±15.9) (60 minutes post HD)[8]. Patients with beta-2-microglobulin levels of 42.5 to 50 mg/l had a relative risk of death of about 60% > those with levels < 27.5 mg/l[3].

CONCLUSION

Percentage reduction of beta-2-microglobulin is a less sensitive and specific marker of inadequate dialysis compared to URR and Kt/V. Several factors affect the concentration of pre dialysis beta-2-microglobulin and its high % rebound post dialysis makes it less reliable as a marker of adequacy of haemodialysis at least in our setting

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