# **Research Article**

# Acid Base Imbalance in Dialysis: Risk Factors and Impact on Intradialysis Blood Pressure Changes. Findings from a Single Center Prospective Study in Nigeria

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**Abstract:** Introduction: Despite improvements in hemodialysis delivery, acid base imbalance is still common in the dialysis population and it is associated with intradialysis blood pressure changes, dialysis termination, inadequacy and poor treatment outcome. We studied acid base imbalance in maintenance hemodialysis, its determinants and relationship with intradialysis blood pressure changes.

Materials & Methods: A prospective study carried out at Babcock University Teaching Hospital, Ilishan-Remo between May 2019 and April 2021 that involved 298 participants who had 1642 hemodialysis sessions.

**Results:** The mean age was 51.44 + 7.31 years, with the females been older than males, P=0.04. The mean predialysis and post dialysis serum bicarbonate were  $18.41 \pm 3.63$  mmol/l and  $20.61 \pm 6.26$  mmol/l (P<0.001). The prevalence of pre and post dialysis metabolic acidosis were 79.0% and 38.3% (P<0.001) and of intradialysis hypotension and hypertension were 19.1% and 25.0% (P=0.02). The risk of intradialysis hypotension was negatively correlated with predialysis bicarbonate while intradialysis hypertension was positively correlated with predialysis bicarbonate while intradialysis was commoner in elderly and females, and was associated with intradialysis hypotension, dialysis termination and inadequacy. Aging and infrequent dialysis, predicted metabolic acidosis.

**Conclusion:** Metabolic acidosis is common in maintenance hemodialysis, particularly in females, aged and infrequent dialysis, and leads to intradialysis hypotension, dialysis termination, inadequacy and poor treatment outcome.

**Keywords:** Metabolic acidosis, Maintenance hemodialysis, Dialysis dose, Intradialysis hypotension, Intradialysis hypertension, Predialysis bicarbonate, Poor treatment outcome.

## **INTRODUCTION**

Acid base imbalance (ABI) still, common in maintenance hemodialysis (MHD) results from low bicarbonate generation, inadequate dialysis and drugs (phosphate binders) [1]. Metabolic acidosis, the commonest ABI in MHD could be associated with both intradialysis hypotension (IDH) and intradialysis hypertension (IDHT) [2, 3]. Serum bicarbonate concentration (SBC) could be affected by time between sample collection and analysis, and transporting medium [4].

More studies on ABI and intradialysis blood pressure (BP) are needed in view of its implication on treatment outcome. We therefore studied acid base imbalance in maintenance hemodialysis, its determinants and, relationship with intradialysis BP changes.

## MATERIALS AND METHODS

#### **Study Design**

A prospective study conducted at Babcock University Teaching Hospital, Ilishan-Remo, Nigeria, between May 2019 and April 2021.

## **Study Population**

Two hundred and ninety eight consented participants, 16 years or older, who had ESRD, according to KDOQI 2012 criteria, on MHD, were consecutively recruited after receiving MHD for at least a month [5].

Patients with renal graft, tumors, infections and sessions less than once weekly were excluded. Between 4 and 6 sessions were studied per participant. Variable retrieved included age, gender, pharyngitis/skin sepsis in childhood, and CKD etiology.

#### **Predialysis Assessment**

The height (in meters) and weight (in kilogram) were measured without shoes, cap or head gear and on light clothing and body mass index (BMI) was calculated by dividing the weight in kilogram by the square of the height in meters (kg/m<sup>2</sup>). The predialysis oxygen saturation (SPO<sub>2</sub>), pulse rate (PR) and BP, were taken and repeated half hourly. All BP readings were taken manually.

One milliliter of blood was withdrawn from the internal jugular catheter (to confirm patency) and discarded, predialysis samples were taken and arterial and venous ends were

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flushed with heparinized saline. Samples were taken from newly sited femoral catheters, and for arterovenous fistula (AVF), from a vein in contralateral arm.

Participants were connected through arterial, then venous portal. When the blood flow rate (BFR) was altered, the mean was calculated. When IDH or IDHT occurred, vital signs were taken quarter hourly. The dialysate flow rate (DFR) was 500ml/min and unfractionated heparin, 5000IU, was the standard anticoagulation dose for most of the sessions. With increased risk of bleeding, heparin dose was reduced or withheld depending on the clotting profile. The dialysate fluid composition was: bicarbonate-34mmol/l, sodium-140mmol/l, potassium-2mmol/l, chloride-100mmol/l, and calcium-1.25mmol/l.

Using the stop dialysate flow method, at the end of dialysis time, dialysate flow was stopped and blood flow reduced to 100 ml/min. Five minutes after stopping dialysate flow, blood was taken from the arterial portal, for serum electrolytes (minimizes access recirculation), then hematocrit [6]. Urea reduction ratio (URR) was calculated using pre and post dialysis urea while Kt/V was calculated with Daugirdas second generation logarithmic estimation of single pool, using pre and post dialysis urea, ultrafiltration volume, post dialysis weight and dialysis duration [7].

Relating the two formula: Kt/V = In (1-URR), where In is natural log [8].

Electrolytes were analyzed using Ion Selective Electrode method and, serum albumin, by bromocresol green method which overestimates it by about 3.5g/dL in renal diseases. Therefore, cut-off values for normal albumin were raised by about 3-3.5 or 5.5-7 g/dl compared to the bromocresol purple or the immunophelometric assay respectively [9]. Hematocrit was determined with hematocrit centrifuge.

Participants stopped major meals 2 hours before and through out dialysis to reduce risk of IDH. Monthly means of variables were used for each participant.

## DEFINITIONS

Metabolic Acidosis: SBC <22mmol/l [10].

Interdialytic Weight Gain (IDWG): Predialysis weight minus preceding sessions' post dialysis weight.

Targeted Post Dialysis Weight: Predialysis weight plus administered fluid minus UFV.

Hypertension:  $\geq 140/90$  mmHg [11].

IDH: >20 mmHg fall in systolic BP with symptoms, without nursing intervention according to the European Best Practices Guidelines (EBPG) [2].

IDHT: >10 mmHg rise in systolic BP [3].

Anaemia: Hematocrit <33% [12]. Hypoalbuminaemia: Albumin <35g/dL [13]. Very Low Predialysis SBC: <20.0 mmol/l. Low Predialysis SBC: 20.0-21.9 mmol/l. Suboptimal Predialysis SBC: <22.0 mmol. Normal Predialysis SBC: >22.0 mmol/l. Inadequate Dialysis Dose: (Kt/V <1.2; URR <65.0%) [14]. Adequate Dose: (Kt/V  $\ge$ 1.2; URR  $\ge$ 65.0%) [14]. Hypertension Associated CKD (HACKD): Long standing hypertension complicated by kidney disease, common from middle age upwards. Chronic Glomerulonephritis (CGN): Kidney disease leading to hypertension in the young and early middle age with or without pharyngitis or skin sepsis in childhood.

Participants with subnormal SBC routinely receive sodium bicarbonate tablets.

## STATISTICAL ANALYSIS

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 22.0 (IBM, CA, USA). Continuous variables were presented as means with standard deviation, compared using paired t-test. Categorical variables were presented as proportions and percentages, compared using Chi square test or Fisher's exact test. Two or more variables were compared using an analysis of variance (ANOVA). A univariate analysis was used to determine the relationship between subnormal predialysis SBC (<22.0 mmol/l) and participants' variables. Variables with P<0.025 were entered into a multiple regression model to determine independent predictors of subnormal predialysis SBC (<22.0 mmol/l) using backward elimination to adjust for confounders. Associations between variables were considered to be significant for P-values <0.05.

## ETHICAL APPROVAL

This study was approved by the Human Research Ethics Committees of Babcock University, Ilishan-Remo (BUHREC/723/19), and this study followed the tenets of the Helsinki 1975 declaration as revised in 2000 [15].

# RESULTS

A total of 332 patients who had 1812 dialysis sessions during study duration (potentially eligible), were examined. Twenty seven patients were excluded due to presence of any one of: renal graft, tumors, infections or sessions less than once a week. Data for 7 participants (5 males, 2 females) with 38 sessions were missing hence data for 298 participants who had 1642 sessions were analyzed. The mean age of all participants, males and females were 51.44 + 7.31 years, 51.2 + 4.6 years, and 52.1 + 2.9 years respectively, P=0.04. A greater proportion, 121 (40.6%) had hypertension associated chronic

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kidney disease (HACKD) (Table 1). The mean predialysis SBP and DBP were 162.5 mmHg and 99.8 mmHg and were significantly higher than the postdialysis, SBP and DBP, P<0.001 and P=0.002 respectively. Predialysis systolic and diastolic hypertension was found in 84.2% and 86.9%

sessions. There were significant differences between the mean pre and post dialysis potassium (P<0.001), bicarbonate (P<0.001), urea (P<0.001), creatinine (P<0.001), eGFR (P<0.001) and anion gap, P<0.001 (Table **2**).

Table 1. Socio-Demographic Characteristics of the Study Population.

Variables	Frequency (%) N=298 (%)	Dialysis sessions (%) N=1642 (%)
Sex		1
Males	192 (64.4)	1064 (64.8)
Females	106 (35.6)	578 (35.2)
Ages, Years		
16-44	109 (36.5)	527 (32.1)
45-74	173 (58.1)	1064 (64.8)
≥75	16 (5.4)	51 (3.1)
CKD Etiology		
Hypertension	121 (40.6)	734 (44.7)
Chronic Glomerulonephritis	109 (36.5)	673 (41.0)
Diabetes	36 (12.1)	127 (7.7)
Others	32 (10.8)	08 (6.6)
Dialysis Sessions		
1	103 (34.6)	550 (35.5)
≥2	195 (65.4)	1092 (64.5)
Erythropoietin/Week		
1	89 (29.9)	524 (31.9)
≥2	209 (70.1)	1118 (68.1)
Body Mass Index, kg/m <sup>2</sup>		1
<25.0	170 (57.0)	933 (56.8)
≥25.0	128 (43.0)	709 (43.2)
Oxygen Saturation, %		
<95	280 (94.0)	1447 (88.1)
≥95	18 (6.0)	195 (11.9)
Predialysis Systolic BP, mmHg		
<140	54 (18.1)	260 (15.8)
≥140	244 (81.9)	1382 (84.2)
Predialysis Diastolic Blood Pressure, mmHg		
<90	36 (12.1)	215 (13.1)
≥90	262 (87.9)	1427 (86.9)

BP: Blood Pressure.

Variables	Predialysis Mean (SD)	Post dialysis Mean (SD)	Paired t-test	P-value
Sodium, mmol/l	129.3 (4.2)	133.8 (2.3)	0.8	0.06
Potassium, mmol/l	5.5 (1.3)	4.1 (1.1)	5.8	< 0.001
SBC, mmol/l	18.4 (3.6)	20.6(6.3)	5.6	< 0.001
Chloride, mmol/l	99.1 (2.7)	100.6 (7.4)	1.0	0.05
Calcium, mmol/l	2.1 (1.2)	2.3 (1.4)	5.0	0.001
Phosphate, mmol/l	2.1 (1.8)	1.8 (0.4)	5.4	< 0.001
Urea, mmol/l	19.7 (3.9)	8.9 (3.1)	10.8	< 0.001
Creatinine, umol/l	842.7 (18.4)	417.7 (18.3)	9.7	< 0.001
GFR, ml/min	6.9 (2.1)	11.8 (3.5)	8.8	< 0.001
Hematocrit, %	24.3 (4.3)	25.7 (7.3)	0.9	0.08
Anion gap, mEq/l	27.5 (6.7)	16.9 (7.2)	7.2	< 0.001

Table 2.	Comparison	between	Pre and	Post	Dialysis	Laboratory	Results
	1				2	2	

GFR: Glomerular Filtration Rate.

Hypobicarbonatemia (<22.0 mmol/l) was found in 79.00% and 38.3% of the pre and postdialysis sessions (Table 3). The mean albumin for all, males and females were 33.60 ± 4.32 g/dl, 34.92 ± 3.54 g/dl and  $30.9 \pm 3.1$ g/dl (P=0.01). The predialysis SBC was positively related to the BFR, dialysis duration and dialyzer surface area (P<0.001), (P<0.03), (P<0.04) and negatively related to UFV (P<0.001). The mean interdialytic weight gain (IDWG) was  $3.9 \pm 0.9$ L in sessions with predialysis SBC <20.0 mmol/l, was  $3.8 \pm 1.0$ L and  $3.8 \pm 1.7$ L in sessions with predialysis SBC 20.0-21.9 mmol/L and  $\geq$ 22.0 mmol/l respectively, P=0.03. The mean interdialytic

weight gain (IDWG) was  $3.9 \pm 1.3L$ ,  $4.9 \pm 0.9L$  in sessions with IDH,  $3.7 \pm 1.1L$  in IDHT, and  $3.9 \pm 1.5L$  in sessions with insignificant BP change, P=0.03. The mean ultrafiltration volume (UFV) for the study, sessions with IDH, sessions with insignificant BP changes and sessions with IDHT were  $3.0 \pm 1.1L$ ,  $3.9 \pm 0.7L$ ,  $2.9 \pm 0.8L$  and  $2.5 \pm 0.7L$  respectively.

About 19.1% of the sessions had IDH while 25.0% had IDHT and, 61.01% of IDH occurred in females and 67.52% of IDHT in males (Table 4). Majority (56.40%) of the terminated sessions had predialysis SBC <22mmol/l. The mean dialysis

Variables	All Sessions Mean (SD)	Pre dialysis <20.0 mmol/l N=493 Mean (SD)	Pre dialysis 20.0-21.9 mmol/l N=804 Mean (SD)	Pre dialysis ≥22.0 mmol/l N=345 Mean (SD)	ANOVA
Blood flow rate ml/min	356.5 (6.8)	316.3 (8.7)	366.3 (12.8)	392.5 (18.6)	< 0.001
Dialysis duration (hrs)	3.9 (1.7)	3.8 (1.2)	3.9 (0.3)	3.9 (0.2)	0.03
Surface area, m <sup>2</sup>	1.7 (1.1)	1.7 (1.4)	1.7 (1.0)	1.8 (0.2)	0.04
Ultrafiltration vol. liter	3.0 (1.1)	3.7 (1.4)	3.2 (0.6)	1.9 (0.8)	< 0.001

Table 3. Relationship between Predialysis Serum Bicarbonate and Prescribed Dialysis.

PDSBC: Predialysis Serum Bicarbonate Concentration.

Table 4. Relationship between Predialysis Serum Bicarbonate and Intradialysis Events and Outcome.

Variables	Frequency N=1642 Mean (SD	Intradialysis Hypotension N=314 Mean (SD)	Insignificant BP Change N=917 Mean (SD)	Intradialysis Hypertension N=411 Mean (SD)	ANOVA
Mean Pre dialysis, mmol/l	18.4 (3.6)	16.7 (2.4)	18.3 (3.1)	19.9 (4.8)	0.003
Mean Kt/V	1.16 (0.5)	1.10 (0.2)	1.2 (0.4)	1.12 (0.5)	0.03
Mean URR%	59.6 (12.0)	56.9 (9.3)	61.1 (4.8)	58.3 (11.6)	0.04

URR: Urea Reduction Ratio.

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dose was  $1.16 \pm 0.51$ , highest in sessions with insignificant BP change and lowest in sessions with IDH, P=0.03 Dialysis dose was adequate in 13.10% of the sessions.

From univariate analysis (Table 5), the mean predialysis SBC was significantly higher in males than females (P=0.04), was positively related to dialysis frequency, (P<0.001), and was

Table 5. Univariate Analysis of Factors A	sociated with Suboptimal Predialysis Bicarbonate.
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Variables	Predialysis SBC <22.0 mmol/l N=1297(%)	Predialysis SBC ≥22.0 mmol/l N=345(%)	OR	95% CI	P-value
Gender					
Males	833 (78.29)	231 (21.71)	1.88	0.45-1.96	0.04
Females	464 (80.28)	114 (19.72)			
Age, Years					
<75	1253 (78.8)	338 (21.2)	5.4	1.24-8.74	< 0.001
≥75	44 (86.3)	7 (13.7)			
CKD Etiology					
Diabetes	97 (85.8)	16 (14.2)	3.7	2.04-3.79	0.03
Non-diabetic	1200 (78.5)	329 (21.5)			
Dialysis Sessions/wk					
1	526 (95.6)	24 (4.4)	8.5	0.93-11.71	< 0.001
≥2	771 (70.6)	321 (29.4)			
SPO <sub>2</sub>					
<95	1294 (99.8)	153 (0.2)	9.4	2.58-13.89	< 0.001
≥95	3 (1.5)	192 (98.5)			
Systolic BP, mmHg					
<140	43 (16.5)	217 (83.5)	5.6	1.53.6.16	< 0.001
≥140	1254 (90.7)	128 (9.3)			
PD Sodium, mmol/l					
<135	1278 (83.8)	247 (16.2)	1.2	0.89-1.72	0.05
≥135	19 (16.2)	98 (83.8)			
PD Potassium, mmol/l					
≤5.5	264 (92.6)	21 (7.4)	2.6	0.11-3.41	0.02
>5.5	1033 (76.1)	324 (23.9)			
PD Creatinine, umol/l					
<500	197 (49.5)	134 (40.5)	5.0	1.09-6.33	< 0.001
≥500	1100 (83.9)	211 (16.1)			
GFR, ml/min	·				
<5	295 (68.9)	133 (31.1)	3.6	0.71-3.38	0.001
≥5.0	802 (79.1)	212 (20.9)			
Hematocrit,%					
<33.0	1185 (93.7)	79 (6.3)	6.6	5.84-10.42	< 0.001
≥33.0	112 (29.6)	266 (70.4)			
Kt/V		·		· · · · · ·	
<1.2	1271 (89.1)	156 (10.9)	5.8	3.69-8.11	<0.001
≥1.2	26 (12.1)	189 (87.9)			

PDSBC: Predialysis Serum Bicarbonate Concentration, BP: Blood Pressure.

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negatively related to the age and creatinine, P<0.001 and P<0.001. From multivariate regression analysis (Table 6)

dialysis frequency, SPO<sub>2</sub>, potassium, urea and hematocrit independently predicted metabolic acidosis.

Table 6. Multivariate	Regression	Analysis	Showing	Predictors	of Metabolic	Acidosis.
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Variables	aOR	95% CI	P-value
Age, Years	0.04	0.039-0.051	0.06
Dialysis Frequency	7.72	1.59-8.32	< 0.001
Erythropoietin	1.02	0.16-1.18	0.06
PD Percent Oxygen Saturation	5.18	2.04-9.64	< 0.001
PD Systolic Blood Pressure, mmHg	3.33	1.26-3.99	0.03
PD Diastolic Blood Pressure, mmHg	2.96	2.93-4.13	0.05
PD Potassium, mmol/l	4.68	1.57-6.22	0.001
PD Urea, mmol/l	6.35	2.14-8.43	< 0.001
PD Creatinine, umol/l	3.23	0.12-4.53	0.03
Glomerular Filtration Rate, ml/min	3.42	2.32-3.52	0.04
Hematocrit, %	6.02	0.01-6.95	< 0.001

aOR: Adjusted Odd Ratio, CI: Confidence Interval, PD: Predialysis.

## DISCUSSION

The prevalence of predialysis and post dialysis MA were 79.0%, and 38.3%, with IDHT commoner than IDH. Our finding mirrors findings by Raphael *et al.* [10] who found a prevalence of 80% in CKD stage 5, using a SBC <22.0 mmol/l but higher than the 68.85% found by Sajgure *et al.* [1] using a SBC cut-off of 22.0 mmol/l, and lower than the 94.7% found by Oliveira *et al.* [16] who used a SBC cut-off of 22.0 mmol/l. Considering the impact of MA on dialysis outcome and the quality of life of patients on MHD, the KDOQI recommendation of a minimum predialysis SBC of 22.0 mmol/l is justified [17].

The prevalence of IDH of 19.1% is higher than 17.2% found by Sands *et al.* [18] using a SBP fall of >30 mmHg. A SBP fall of >30 mmHg in this study, would have given a lower prevalence of IDH. Metabolic acidosis depresses myocardial contractility, reduces the effective blood volume (EBV) through cutaneous vasodilatation, thereby increasing the risk of IDH and ultimately, inadequate dialysis which impacts negatively on quality of life (QOL), morbidity and mortality, particularly with SBP dropping to a nadir <90mmHg [19, 20]. The concurrent DBP drop cause myocardial hypo perfusion and can lead to myocardial ischemia, stunning and cardiac fibrosis [21].

Our study's IDHT prevalence of 25.0% was higher than the 19.7% found by Raikou *et al.* [3]. The wide difference could be attributed to the lower dialysis dose in our study population. The higher prevalence of IDHT over IDH agree with findings in a local study that found prevalence of 45.3% and 31.3% respectively [22]. As ultrafiltration compromises cardiac output (CO), volume replacement during the initial

steep slope of the Frank Sterling Curve (FSC) augments the systolic and diastolic functions resulting in increased stroke volume (SV) and CO preventing fall in BP. However, volume replacement in plateau phase reduces SV and cardiac output [23]. Park *et al.* found a 'J' or 'U' shaped relationship between peridialytic BP variations and cardiovascular outcome [24].

Our finding of greater male predominance agrees with findings of a female bias in accessing health care in Nigeria [7]. It also partly explains the lower mean age of males at dialysis initiation [25].

We attribute the inverse relationship between MA and albumin to the low oncotic pressure causing endothelial microcirculatory dysfunction with albuminuria [26]. Loop and thiazides diuretics, calcium based phosphate binders and bicarbonate supplementation can induce transient Malk and ameliorate acidosis [27]. High dialysate bicarbonate could lead to chronic alkalemia although dialysate bicarbonate of 40-42 mmol/l is considered safe and beneficial. Having used a dialysate bicarbonate of 34 mmol/L in this study, a reasonable level of acid buffering would have been achieved [28]. Sevelamer use worsens MA through the 1:1 chloride buffering by bicarbonate [29].

We encountered some limitations in this study. We were unable to determine participants' dry weight, the residual kidney function and its contribution to the dialysis dose. Despite being a better measure in assessing ABI, blood PH was not done on account of cost In addition, the presence of some co-morbidities/confounders could not be ruled out, just as some dialysis interval were not regular. Compliance with directives to avoid heavy meals two hours prior to dialysis and adherence to drug use were difficult to ascertain. The relatively large sample size contributed to the strength of the study.

## CONCLUSION

The risk factors for MA included aging, females, infrequent dialysis, lower GFR, temporary catheters and shortened dialysis time. MA was associated with IDH, as IDHT (which was commoner than IDH) was associated with anemia. Targeting a predialysis SBC of >22.0 mmol/l will significantly improve dialysis dose and treatment outcome.

## **CONFLICT OF INTEREST**

#### Declared none.

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