RESEARCH ARTICLE

Serum sodium: Pattern, determinants and correlates in nigerians with hypertension and chronic kidney disease: A comparative study

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ABSTRACT

Introduction: Sodium is the major determinant of extracellular volume and tonicity of plasma. Derangements in its serum concentration are common and could be dependent on factors like intake, age, hydration status and kidney function. Due to its contribution to the extracellular volume, derangement could produce widespread clinical manifestations.

Methods: A single centre, observational study in which variables of hypertensive and non-dialyzed Chronic Kidney Disease (CKD) patients were compared. Serum electrolytes, urea, creatinine, hematocrit, albumin and urine dip strip protein were assessed. Predictors of hyponatremia were determined.

Results: One hundred and forty one hypertensives and 67 CKD cohorts were studied. The mean age of the hypertensive and CKD cohorts were 52.91 ± 15.73 years and 58.14 ± 16.13 years respectively. Overweight/Obesity, systolic, and diastolic hypertension were more likely to be found in CKD than hypertension, P=0.05, P=0.05 and P=0.07 respectively. The mean serum sodium of hypertensives and CKD cohorts were 136.94 ± 5.23mmol/L and 132.81 ± 8.45mmol/L, P<0.001. Normonatremia and, hyponatremia was commoner among the hypertensives and CKD cohorts (88.14% versus 11.91%) and (78.13% versus 21.87%) respectively. The mean serum sodium was positively related to blood pressure (P=0.02), eGFR (P<0.001), hematocrit (P=0.002) and serum albumin, P<0.001, but was inversely related to the age (P=0.003), potassium (P=0.01) and anion gap (P=0.003). The mean eGFR was statistically lower in CKD than hypertension, P=0.001. Advancing age (OR-1.95, 95% CI-0.94-2.16), CKD (OR-4.13, 95% CI-3.47-8.36), comorbidities (OR-3.16, 95% CI-2.89-6.46), independently predicted hyponatremia.

Conclusion: The serum sodium concentration was lower in CKD than in hypertension, and was positively related to blood pressure, hematocrit and serum albumin while it was negatively related to age, kidney function and anion gap. Sodium, being the major determinant of the extracellular fluid volume and plasma tonicity, It is imperative to keep its concentration within normal to avert the many adverse consequences of its derangement.

Key words: *Serum sodium concentration; Extracellular volume; Plasma volume; Hypertension; Chronic kidney disease; Hyponatremia; Anemia; Hypoalbuminemia*

INTRODUCTION

Sodium as the major electrolyte in the Extra Cellular Space (ECS), contributes the most to the tonicity of the ECS and its balance is maintained primarily through thirst-mediated water intake, and excretion, under regulation of the Anti-Diuretic Hormone (ADH) [1]. The ADH mediates its activity *via* aquaporin 2 water channels in the apical membranes of the principal cells of the Collecting Duct (CD) [2]. The World Health Organization (WHO) recommended a daily salt (sodium chloride) intake of <4 g and defined >5 g as excessive salt intake [3]. A sodium load in health results in a hypertonic plasma causing fluid movement from intracellular to the ECS, this cause vasodilators (bradykinins, nitric oxide and Prostaglandin E2 (PGE2)) under the influence of the natriuretic peptides to be mobilized to excrete the sodium load [4].

Recent findings have given deeper insight into the interdependence of the ECS, Blood Pressure (BP), the Renin Angiotensin Aldosterone System (RAAS) and the Sympathetic Nervous System (SNS), regarding the concentration, actions and effects Serum Sodium Concentration (SSC) and its variations [4,5]. Disease states can affect water homeostasis leading to imbalances in the intake and/or loss, abnormal fluid distribution between body compartments and, plasma dilution or hypertonicity (surrogate makers of hyponatremia or hypernatremia respectively) [6]. Altered water homeostasis will also lead to defective urine concentration, and imbalances between the Intra Cellular (IC) and the ECS manifesting as edema, alterations in the various transport and metabolic pathways of which sodium plays principal roles [5-7]. The maintenance of sodium homeostasis depends on tubular function and derangement could manifest as acid base imbalance, majorly Metabolic Acidosis (MA), and Metabolic Alkalosis (Malk) [8]. The activities of the sodium hydrogen exchanger isoform 3 (NH3), sodium phosphate co-transporter ($NaPi^2$) along the apical membrane, and the sodium-potassium (Na^+K^+) exchanger at the basolateral membrane mediate sodium transport in the proximal tubules [8,9]. Sodium transport is driven by the Na^+K^+2Cl co-transporter in the Thick Ascending Limb (TAL), the sodium-chloride co-transporter (NCC) in the distal tubule, and in the collect duct, by the Epithelial Sodium Channels (ENaC) mediated by aldosterone, outer medullary K^+ channels and the Aquaporin 2 (AQP2) water channels under the influence of arginine vasopressin of the principal cells [10-12]. Inhibitors of the natriferic effects of aldosterone and the water retaining actions of vasopressin induce vasodilatation, diuresis (natriuress), which if excessive, can lead to hyponatremia [4].

The urine sodium, which is often used to determine the sodium intake, reduces with aging, and in blacks, justifying the classification of blacks as volume dependent hypertensive who responds better to diuretic therapy particularly thiazides [13]. This fact also explains the elderly being known to respond with higher BP rise after sodium intake [14]. Males have been reported to respond more to adrenergic stimulation and less to adrenergic inhibition and this partly explains the reported faster progression of hypertension and other BP related conditions to chronic kidney disease and even, the reported faster CKD progression through the stages, to End Stage Kidney Disease (ESKD) [15].

Despite the vast literature in the developed world on serum sodium regarding its transport, actions, metabolism, and its contribution to the ECS and blood pressure, much is still needed to be known, most especially when the scares

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literature in Low Income Nations (LINs), particularly Sub Sahara Africa (SSA) is taken into consideration. We studied serum sodium and compared its determinants and correlates in hypertensive and those with CKD.

MATERIALS AND METHODS

This was a comparative, observational study carried out at the hypertension and nephrology clinic of Babcock University Teaching Hospital, Ilishan-Remo, Nigeria from August 2019 to January 2021. One hundred and forty one participants with Hypertension without CKD (HWCKD) and 67 newly diagnosed CKD (according to the KDOQI 2012 criteria) [16]. cohorts receiving treatment at the Division of nephrology and hypertension, were consecutively recruited after obtaining informed consent. All participants were at least 16 years old and had Renal Ultrasound Scan (RUS), findings of which were of used in classifying each participant into the HWCKD or CKD group as participants with kidney length <9cm on RUS but eGFR >60 mL/min were classified as having CKD [17].

DATA COLLECTION AND ANALYSIS

Data was taken from socio-demographics, history, examination findings and from participants hospital case notes. The height and weight were measured according to standard protocols and the Body Mass Index (BMI) was calculated. The temperature was taken with a hand-held thermometer. The blood pressure was taken after 5 minutes of rest, with a mercury sphygmomanometer (ACCOSON, England) with participants in the sitting position, back and arm rested on a support. A mid-stream urine sample was collected for an-on-the spot urinalysis. Three blood samples were collected from a peripheral vein for analysis of the White Cell Counts (WBC) and hematocrit, serum electrolytes, creatinine, urea and fasting lipids.

Determination of serum biochemical parameters was with an auto-analyzer (Roche Diagnostics GmbH, Mannheim Germany). The estimated Glomerular Filtration Rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [18].

Data was analyzed using SSPS [21-23], with continuous variables presented as mean with standard deviation and compared using student's t-test. Categorical variables are presented as proportions and frequencies and compared using Chi-square or fisher's exact test. The P-value <0.05 was considered statistically significant. Variables with p<0.025 from univariate analysis, were included as adjustment variables in multivariate analyses to determine variables that predicted hyponatremia. This study was approved by the Babcock University Human Research Ethics Committee (NHREC/24/01/2018 and BUHREC501/19).

Exclusion Criteria: Patients less than 16 years, with infections, cancers, diabetes, diabetic nephropathy, Chronic Liver Disease (CLD), stage IV heart failure, were excluded from the study.

Definitions:

Anion gap (AN): Na^+ K -Cl -HCO319

Hypertension: BP >140/90 mmHg.20

Proteinuria: dip strip protein >1+21

Hyponatremia: <135 mmol/L.22

Normonatremia: 135-145 mmol/L.22

Hypernatremia: sodium >145 mmol/L.22

Hypokalemia: <3.5 mmol/L.23

Hyperkalemia: K^+>5.5 mmol/L.23

Metabolic acidosis: Bicarbonate <22 mmol/L.24

Hypoalbuminemia: serum albumin <35 mg/dL25

Anemia: Hematocrit <33%26

eGFR (CKD-EPI)-ml/min/1.73m^2 18

Dyslipidaemia: Cholesterol (total) ≥ 6.21 mmol/L.27

Elevated LDL >4.14 mmol/L 27

Low HDL Cholesterol <1.03 mmol/L 27

Hypertriglyceridemia ≥ 1.69 mmol/L27.IR24

RESULTS

Two hundred and eight participants were studied (141 HWCKD and 67 CKD).The mean age of all participants, those with HWCKD and those with CKD were was 54.3 ± 11.72 years, 52.91 ± 15.73years and 58.14 ± 16.13 years respectively. The proportion of males amongst the HWCKD was less than in CKD (64.54% versus 65.67%), P=0.8 (Table 1). Cohorts with BMI >25.0 kg/m^2, SBP >140 mmHg and DBP >90 mmHg were more likely to have CKD than HWCKD, P=0.05, P=0.05 and P=0.07 respectively. Three (4.3%) of the CKD cohort had stage 2 disease, 5 (7.2%) in stage 3a, 7 (10.1%) in stage 3b, 13 (18.8%) in stage 4 and 41 (59.4%) in stage 5 (non-dialytic).

The mean sodium of cohorts with HWCKD and CKD were 136.94 ± 5.23 mmol/L and 132.81 ± 8.45mmol/L, P<0.001. Twenty eight (19.86%) of cohorts with HWCKD as against 36 (53.73%) of the CKD cohorts had hyponatremia, P<0.001 (Table 2). The mean serum bicarbonate concentration (SBC) for cohorts with HWCKD and CKD were 28.16 ± 7.37 mmol/L and 21.45 ± 5.70 mmol/L, P=0.001. The mean eGFR for cohorts with HWCKD and CKD were 71.85 ± 10.59 mL/min and 22.55 ± 6.22 mL/min, P=0.001. The mean serum sodium for males with HWCKD and CKD were statistically higher than that of females with HWCKD and CKD, P=0.043 (Table 3). The mean serum sodium was positively related to SBP (P=0.02), DBP (P=0.001), eGFR (P<0.001), chloride (P=0.04), hematocrit (0.002) and serum albumin, P<0.001 but was inversely related to the age (P=0.003), BMI (0.802), serum creatinine (P<0.001), potassium (P=0.01) and anion gap (0.003).

The mean SBC, eGFR, hematocrit and albumin were higher in males than females, P=0.02, P=0.03, P<0.001 and P=0.01 respectively, while the AG was higher in females than males, P=0.04 (Table 4). Hyponatremia was commoner in females (P=0.04), in CKD (P<0.001), and with comorbidities (P<0.001), it was positively related to the age (P=0.02), but was negatively correlated with the hematocrit (P<0.001) and the serum albumin, P<0.001 (Table 5). Variables of participants with hyponatremia with P<0.025, were entered into a multivariate model to determine independent predictors of hyponatremia using backward elimination to adjust for confounders28 (Tables 6). Multivariate analysis showed increasing age (OR-1.95, 95% CI-0,94-2.16), CKD (OR-4.13, 95% CI-3.47-8.36), comorbidities (OR-3.16, 95% CI-2.89-6.46), anemia (OR-3.99, 95% CI-2.43-6.05), hypoalbuminemia (OR-4.11, 95% CI-1.66-576), high anion gap (1.46, 95% CI-0.78-1.91), hypobicarbonemia (OR-3.77, 95% CI-152-5.24) and hypochloremia (OR-4.59, 95% CI-1.74-7.05) independently predicted hyponatremia.

TABLE 1

Sociodemographic and clinical characteristic of participants

Variables	All participants Mean ± SD	Hypertension, no CKD Mean ± SD N=141 (%)	CKD Mean ± SD N=67 (%)	P-value
Gender Males Females	135 (64.90) 73 (35.10)	91 (64.54) 50 (35.46)	44 (65.67) 23 (34.33)	0.812
Age, yrs Mean 16.00-59.9 >60.0	54.36 ± 11.72 113 (54.33) 95 (45.67)	52.91 ± 15.73 72 (51.06) 69 (48.94)	58.14 ± 16.13 41 (61.19) 26 (38.81)	0.04 0.04

BMI, kg/m^2 <25.0 >25.0	101 (48.56) 107 (51.44)	72 (51.06) 69 (48.94)	29 (43.28) 38 (56.72)	0.05
Systolic BP, mmHg Mean <140 >140	139.84 ± 28.14 101 (48.56) 107 (51.44)	137.92 ± 28.47 71 (50.35) 70 (49.65)	144.16 ± 24.90 30 (44.78) 37 (55.22)	0.05 0.05
Diastolic BP, mmHg Mean <90 >90	84.66 ± 11.94 94 (45.19) 114 (54.81)	84.66 ± 11.94 62 (43.97) 79 (56.03)	82.4 ± 13.1 32 (47.76) 35 (52. 24)	0.17 0.09

Note: CKD:chronic kidney disease, BMI:body mass index, BP:blood pressure.

TABLE 2

Laboratory characteristics of participants

Variables	All participants Mean ± SD N=208 (%)	HTN without CKD Mean ± SD N=141 (%)	CKD Mean ± SD N=67 (%)	P-value
Serum Sodium, mmol/L Mean <135 135-145	135.58 ± 11.4 64 (30.77) 144 (69.23)	136.94 ± 5.23 28 (19.86) 113 (80.14)	132.81 ± 8.45 36 (53.73) 31 (46.27)	0.03 <0.001
Mean potassium, mmol/L	4.26 ± 1.19	3.91 ± 0.81	4.63 ± 1.01	0.003
Mean chloride, mmol/L	100.43 ± 3.74	101.03 ± 4.97	95.52 ± 6.64	0.004
Mean Bicarbonate, mmol/L	25.99 ±10.95	28.16 ± 7.37	21.45 ± 5.70	0.001
Mean calcium, mmol/L	2.44 ± 1.37		2.0 ± 0.44	0.001
Mean Phosphates, mmol/L	1.90 ± 0.62	1.58 ± 1.13	2.43 ± 1.38	<0.001
Mean anion gap, mEq	11.52 ± 6.03	9.43 ± 4.56	15.73 ± 8.44	<0.001
Mean urea, mmol/L	12.65 ± 5.87	7.94 ± 3.76	24.45 ± 11.28	<0.001
Mean creatinine, umol/L	165.78 ± 21.15	119.44 ±.32.51	248.84 ±.42;85	<0.001
Mean eGFR, mL/min/1.732	48.73 ± 3.63	71.85 ± 10.59	22.55 ± 6.22	<0.001
Low HDLC, mg/dL, (n, %)	105 (50.48)	68 (48.23)	37 (52.24)	0.05
Elevated LDLC, mg/dL, (n, %)	101 (48.57)	64 (45.39)	37 (52.24)	0.01
Elevated TG, mg/dL, (n, %)	110 (52.88)	74 (52.48)	36 (53.73)	0.6
Mean Hematocrit, %	105 (50.48)	68 (48.23)	37 (52.24)	0.05
Mean albumin, mg/dL	35.96 ± 8.26	40.11 ± 7.05	27.3 ± 5.62	0.002

Note: CKD:chronic kidney disease, eGFR:glomerular iltration rate.

TABLE 3

Serum sodium and its correlates in hypertension and in chronic kidney disease

Variables	Total Sodium, mmol/L N=208 Mean ± SD	HTN without CKD Sodium, mmol/L N=141 Mean ± SD	CKD Sodium, mmol/L N=67 Mean ± SD	P-value
Mean Sex Males Females	135.58 ± 11.44 136.04 ± 5.87 134.84 ± 3.96	136.94 ± 5.23 137.11 ± 4.74 136.77 ± 6.13	132.81 ± 8.45 133.92 ± 7.90 130.74 ± 9.12	0.035 0.043
Age, yrs <60 >60	137.18 ± 7.37 132.90 ± 6.46	138.38 ± 10.23 134.32 ± 7.15	134.65 ± 11.15 130.03 ± 8.13	0.003
BMI, kg/m^2 <25.0 >25.0	135.98 ± 6.58 135.10 ± 8.73	137.47 ± 9.48 136.26 ± 12.46	132.96 ± 13.59 132.61 ± 4.68	0.802
Systolic BP, mmHg <140 >140	134.37 ± 8.41 136.05 ± 8.96	136.85 ± 4.52 137.3 ± 6.2	129.08 ± 12.15 135.91 ± 3.57	0.025
Diastolic BP, mmHg <90 >90	133.93 ± 9.52 136.77 ± 11.27	135.22 ± 18.34 138.13 ± 13.28	130.45 ± 8.74 134.96 ± 10.29	0.001

Serum creatinine, umol/L <110 >110	133.75 ± 6.39 138.45 ± 8.8	134.14 ± 7.49 139.94 ± 4.63	132.72 ± 9.86 133.82 ± 12.53	<0.001
eGFR, mL/min/1.732 <60 >60	135.56 ± 7.42 132.66 ± 4.38	136.94 ± 5.23	134.96 ± 6.78 132.66 ± 4.38	<0.001
Potassium, mmol/L <5.5 >5.5	135.79 ± 6.7 134.12 ± 8.6	136.97 ± 5.47 135.95 ± 7.54	133.72 ± 5.8 131.65 ± 3.2	0.01
Chloride, mmol/L <97 >97	134.05 ± 4.91 136.26 ± 6.43	133.95 ± 9.93 137.98 ± 11.39	131.23 ± 3.82 133.95 ± 4.76	0.04
Anion gap, mEq <16 >16	136.04 ± 9.84 135.60 ± 8.93	137.42 ± 9.20 136.98 ± 7.95	133.01 ± 7.4 132.73 ± 3.9	0.003
Hematocrit, % <33 >33	132.55 ± 10.37 136. 02 ± 8.62	133.59 ± 6.79 136.97 ± 12.23	131.53 ± 5.71 132.88 ± 8.69	0.002
Albumin, mg/dL <35 >35	134.18 ± 10.7 135.65 ± 8.74	132.77 ± 6.23 137.01 ± 8.94	131.14 ± 5.83 135.94 ± 9.74	<0.001

Note: HTN: hypertension, CKD: chronic kidney disease, BMI: body mass index, BP: blood pressure, eGFR: estimated glomerular iltration rate.

TABLE 4

Prevalence of factors associated with gender differences in serum sodium

Variables	All participants N=208 (%)	Males N=135 (%)	Females N=73 (%)	P-value
Age >60 years	95 (45.67)	66 (48.89)	29 (39.73)	0.04
BMI >25.0, (n, %)	107 (51.44)	74 (54.81)	33 (45.21)	0.03
Systolic BP, mmHg, (mean ± SD)	139.84 ± 28.14	143.28 ± 6.34	133.03 ± 6.11	0.001
Diastolic BP, mmHg, (mean ± SD)	84.66 ± 11.94	84.98 ± 11.64	79.97 ± 9.45	0.04
Comorbidity >1, (n, %)	118 (56.73)	81 (60.00)	36 (49.32)	0.03
Proteinuria >+1, (n, %)	53 (25.48)	35 (25.93)	18 (24.66)	0.87
Serum creatinine, umol/L, median (range)	119 (43-434)	187 (43-434)	167 (45-392)	0.04
eGFR, mL/min, median (range)	65.5 (11-104)	67.4 (11-104)	56.5 (13.4-91.6)	0.03
Potassium, mmol/L, (mean ± SD)	4.26 ± 1.19	4.25 ± 2.04	4.28 ± 1.23	0.63
Bicarbonate, mmol/L, (mean ± SD)	25.99 ± 10.95	27.02 ± 4.25	24.72 ± 3.62	0.02
Chloride, mmol/L, (mean ± SD)	100.43 ± 3.74	101.63 ± 5.69	97.05 ± 4.24	0.04
Anion gap, mEq, (mean ± SD)	11.52 ± 6.03	11.16 ± 3.02	12.60 ± 4.22	0.04
Calcium, mmol/L, (mean ± SD)	2.44 ± 1.37	2.45 ± 0.94	2.41 ± 0.88	0.06
Phosphate, mmol/L, (mean ± SD)	1.90 ± 0.62	2.06 ± 4.29	1.78 ± 3.95	0.03
Low HDL cholesterol, mg/dL, (n, %)	105 (50.48)	81 (60.00)	24 (32.88)	0.003
Elevated LDL cholesterol, mg/dL, (n, %)	101 (48.57)	70 (51.85)	31 (42.47)	0.04
Triglyceride, mg/dL, (n, %)	110 (52.88)	78 (57.78)	32 (43.84)	0.05
Hematocrit, %, (mean ± SD)	35.96 ± 8.26	38.15 ± 8.53	31.96 ± 4.26	<0.001
Albumin, mg/dL, (mean ± SD)	39.93 ± 12.74	41.06 ± 8.85	38.02 ± 6.22	0.01

Note: BMI:body mass index, BP:blood pressure, GFR:glomerular iltration rate, HDL:high density lipoprotein, LDL:low density lipoprotein.

TABLE 5

Association between participants' variables and serum sodium

Variables	Hyponatremia	Normonatremia	OR	95% CI	P-value
Sex Males Females	38 (28.15) 26 (35.62)	97 (71.85) 47 (64.38)	1.97	1.01-4.26	0.04
Age, yrs <60 >60	23 (20.35) 41 (43.16)	90 (79.65) 54 (56.84)	2.96	1.04-4.94	0.02
BMI, kg/m^2 <25.0 >25.0	30 (29.70) 34 (31.78)	71 (70.30) 73 (68.22)	0.93	0.71-1.05	0.7

Systolic BP, mmHg <140 >140	35 (34.65) 29 (27.10)	66 (65.35) 78 (72.90)	1.53	1.14-2.89	0.05
Diastolic BP, mmHg, <90 >90	34 (36.17) 30 (26.32)	60 (63.83) 84 (73.68)	1.32	0.09-1.82	0.06
Proteinuria None/Trace >1+	33 (22.15) 31 (58.49)	116 (77.85) 22 (41.51)	2.14	1.03-3.66	0.03
Potassium, mmol/L 3.5-5.5 >5.5	42 (23.73) 22 (70.97)	135 (76.27) 9 (29.03)	2.01	1.60-3.58	0.04
Chloride, mmol/L <97 >97	34 (66.67) 30 (10.11)	17 (33.33) 127 (80.89)	5.85	4.83-12.34	<0.001
Bicarbonate, mmo/L <22.0 >22.0	48 (48.49) 16 (14.41)	49 (50.51) 95 (85.59)	3.89	2.38-7.84	<0.001
Anion gap, mEq <12 >12	27 (18.24) 37 (61.67)	121 (81.76) 23 (38.33)	3.36	1.42-5.03	0.001
Creatinine, umol/L <110 >110	31 (32.63) 33 (29.20)	64 (67.37) 80 (70.80)	2.53	3.44-5.67	0.01
GFR, mL/min <60 >60	39 (34.21) 25 (26.60)	75 (65.79) 69 (73.40)	2.97	2.56-5.98	0.02
Hematocrit, % <33.0 >33.0	34 (53.13) 30 (20.83)	30 (46.87) 114 (79.17)	5.03	2.04-11.58	<0.001
Serum Albumin, mg/dL <35.0 >35.0	36 (43.37) 28 (12.44)	47 (56.63) 197 (87.56)	5.12	4.74-15.43	<0.001
LDL Cholesterol, mg/dL <4.14 >4.14	23 (21.50) 41 (40.59)	84 (78.50) 60 (59.41)	1.16	0.88-1.86	0.07
Diagnosis Hypertension CKD	14 (9.93) 50 (74.63)	127 (90.07) 17 (25.37)	5.38	4.56-10.24	<0.001
Comorbidities None >1+	7 (7.78) 57 (48.31)	83 (92.22) 61 (51.69)	4.74	2.68-7.06	<0.001

Note: BMI:body mass index, BP:blood pressure, eGFR:estimated glomerular iltration rate, CKD:chronic kidney disease.

TABLE 6

Multivariate analysis showing independent predictors of hyponatremia

Variables	OR	95% CI	P-value
Age >60years	1.95	0.94-2.16	0.04
Chloride <97mmo/L	4.69	1.74-7.05	<0.001
Bicarbonate <22 mmol/L	3.77	1.52-5.24	0.001
Anion gap <12 mEq	1.46	0.78-1.91	0.05
Creatinine > 110 umol/L	2.02	1.42-2.75	0.03
eGFR <60 umol	1.90	1.27-2.88	0.04
Hematocrit <33%	3.99	2.43-6.05	0.001
Albumin <35 mg/dL	4.11	1.66-5.76	<0.001
CKD	4.13	3.47-8.36	<0.001
Comorbidities >1+	3.16	2.89-6.46	0.002

Note: eGFR:estimated glomerular iltration rate, CKD:chronic kidney disease.

DISCUSSION

The serum sodium was higher in males than females, in hypertension than CKD and decreased with aging, with increasing weight and with associated comorbidities. We found normonatremia in 69.23% of all cohorts, 90.07% of the hypertensives and 25.37% of the CKD cohorts. Hyponatremia was found in 30.77% of the cohorts, 9.93% of the hypertensives and 74.63% of the CKD cohorts. The incidence of hyponatemia mirrors that of Hoorn et al. [29] who in systemic review reported prevalence between 4-30%. The higher sodium in hypertension than CKD in our study agrees with findings by Schrier et al. [30] and Tsai et al. [31] who reported, separately, that with a declining kidney function, the water excreting capacity of the kidney diminishes leading to fluid retention and consequent plasma sodium dilution. The higher salt restriction commonly place on CKD cohorts compared to hypertensives could further account for the lower sodium in them. Furthermore, pressure natriuresis, in response to a high sodium intake, (through the activation of natriferic substances like angiotensinogen and atrial natriuretic peptides) is better mediated in normotensives than in hypertensives, and least in CKD cohorts [4-32]. The higher sodium in males than females in hypertension and CKD mirrors findings by Rao et al. [33] and Han et al. [34]. who found hyponatremia commoner in females than males. Our findings however are not in agreement with Hawkins et al. [35] who found higher serum sodium in females. The negative regulatory effects of estrogens on the Epithelial Sodium Channels (ENaC) causes reduced sodium reabsorption at the distal convoluted tubules. Female animal model (wild type rat) are reported to respond more to inhibition of the thiazide sensitive Sodium Chloride Contransporter (NCC) with thiazides drugs like hydrochlorothiazide [13-36]. In humans, progesterone and prolactin are reported to up regulate plasma NCC [37]. which are more in females, who respond more to the activities of the thiazide sensitive NCC producing water diuresis when inhibitors of NCC are used. This partly explains the lesser urine sodium in the aged and in blacks associated with a volume dependent hypertension commonly found in them hence their greater response to thiazide diuretics [13]. The inverse relationship between serum sodium and aging in this study, coupled with reduced urine sodium implies higher sodium retention, increased plasma osmolality which stimulates the thirst center and the release of anti-diuretic hormone with attendant sodium-poor water retention (hyponatremia) typical of the syndrome of inappropriate antidiuretic hormone [2-12]. The lower serum sodium in the CKD cohorts is therefore partly accounted for by been older than the hypertensives.

The inverse relationship between serum sodium and the BMI mirrors findings by Bjorke-Monsen et al. [38]. who reported that weight loss in the obese was associated with increased serum sodium. The renal degradation of insulin is suppressed in kidney disease and this could lead to a relative hyperinsulinemia, commonly seen in the obese. Our finding of a positive relationship between the serum sodium and the blood pressure agrees with reports by Mckee et al. [39]. Obesity and elevated blood pressure are known to be positively related. Hyperinsulinemia associated with obesity induces a higher proximal tubule urate, and sodium absorption through enhanced NH3 exchanger leading to hypertension [9]. The resultant delivery of a lesser sodium load to the apical cells of the distal tubules' NCC coupled with the use of diuretics, particularly thiazides, can induce hyponatremia in CKD [11]. The resulting expansion involves Total Body Water (TBW), interstitial and plasma volumes and reflecting in larger end diastolic volumes and pressures. The higher renal protein wasting in CKD compared to hypertension necessitates higher hepatic production of lipoproteins, particularly the more atherogenic subunits. A consequence of this is a higher systolic BP in CKD compared to hypertension secondary to atherosclerosis and arteriolosclerosis from fatty depositions in the vascular bed [40].

A greater derangement in serum biochemistry that was observed with declining kidney function was associated with lower serum sodium. With declining kidney function, the concentrating ability of the kidneys is more affected compared to the diluting capacity hence a greater sodium load is retained, further worsening BP control [39]. The positive relationship between serum sodium and albumin is widely reported as hypoalbuminemia induces the release of ADH leading to salt (sodium) poor water retention [24-41]. The resulting Extra Cellular Fluid (ECF) dilution and plasma hypotonicity that results, can induce osmotic changes between the ECF and Intracellular (IC) spaces particularly in the Central Nervous System (CNS), where, in acute shifts, these transcellular shift can induce brain edema, or osmotic demyelination that could manifest with both sensory and motor symptoms [42]. Cellular swelling or shrinkage that are resultant effects of these osmotic shift result from hyponatremia and hypernatremia respectively [42]. Antidiuretic hormone causes equilibration between the luminal (apical) membrane and the surrounding interstitial spaces leading to urinary concentration. The greater derangement of urinary concentration than dilution in advanced kidney disease therefore reflects lesser activity of ADH and a lesser decline in serum sodium, compared to earlier stages of CKD or hypertension [41]. This partly explains the lower incidences of osmotic demyelinating injury in CKD compared to conditions with normal kidney function. It is however worth remembering that albumin, being an acute phase reactant, and CKD, being a chronic inflammatory condition, the interpretation of results of albumin assays in CKD cohorts should be with caution particularly when assays of other inflammatory markers are not carried out [25].

We found a positive association between the hematocrit and the serum sodium. A lower hematocrit entails a larger ECF and plasma volume, and when severe, could increase the TBW, associated with hyponatremia, plasma dilution and hypotonicity. This partly accounts for the poor prognostic effect of hyponatremia in patients with CKD and ESRD who developed heart failure, commonly with hypovolemic hyponatremia [43]. The higher AG in CKD cohorts than hypertensives mirrors findings by Feldman et al. [44]. who found an inverse relationship between the AG and serum sodium. The hypertensive cohorts mostly had normal AG unlike the CKD cohorts who mostly had hyperchloremic MA. Transiting from normal AG in hypertension to hyperchloremic AG in CKD therefore entails a declining bicarbonate with an increasing serum chloride but this mathematical estimation could only be justified by an increasing serum potassium as was found in the CKD cohorts compared to the hypertensives [19].

The occurrence of comorbidities like proteinuria and dyslipidemia in our cohorts increased the risk of hyponatremia and this mirrors findings from previous studies that reported the negative association between comorbidities and serum sodium, with hyponatremia implicated in extended hospital stay, increased morbidity and mortality in its sufferers [45].

We found higher phosphate with lower calcium in our CKD cohorts and this was associated with lower sodium, typical findings in CKD. Laboratory evidence of CKD bone mineral disease (CKD-BMD) is commonly seen from stage 3 disease. Although, we didn't assess CKD-BMD in our study, the findings of higher AG, lower albumin and HCT, higher phosphate, lower calcium, associated with declining sodium in the CKD cohorts is highly suggestive of hyperparathyroidism in the CKD cohorts. We infer that this to some extent, accounted for the differential sociodemographic, clinical and laboratory differences found in this study between the hypertensive and CKD cohorts.

We encountered some limitations in this study. We couldn't determine Urine Albumin Creatinine Ratio (UACR), urine osmolality and fractional sodium excretion. The effects of diuretics on cohorts serum sodium was not assessed as all CKD and most of the hypertensives received diuretics, and due to frequent changes in diuretics regimen, findings were unlikely to be reliable. The strength of this study is in its prospective design and the fact that quite a lots of variables were assessed.

CONCLUSION

Serum sodium as the major determinant of the ECF volume, its concentration is lower in CKD than hypertension, higher in males, and positively related to the blood pressure, serum chloride, bicarbonate, albumin and hematocrit. Its concentration is inversely related to age, BMI, potassium, anion gap and eGFR. Comorbidities commonly increase the risk of hyponatremia which amongst other factors is commonly associated with plasma dilution with or without ADH activation. Deranged sodium concentration could also result from altered or defective tubular transport systems that mediate its tubular absorption and secretion. Predictors of hyponatremia included advancing age, metabolic acidosis, hypoalbuminemia, anemia and CKD.

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CONFLICT OF INTEREST

None declared.

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