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SALT RESTRICTION INDUCED HYPONATREMIA IN HYPERTENSIVE PATIENTS: CASE CONTROL STUDY

A dissertation submitted in partial fulfillment of the requirements for the award of the Master of Medicine in Internal medicine

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Kigali, July 2020

DECLARATION

I hereby declare that the work presented in this dissertation entitled *"Salt restriction induced hyponatremia in hypertensive patients: case control study"* is my original work. I have not copied from any other colleagues' work or from any other sources except where due reference or acknowledgement is made explicitly in the text, nor has another person written any part of this work on my behalf, and it has been passed through anti-plagiarism system and found to be compliant.

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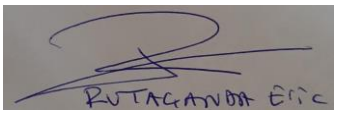

Dr RUTAGANDA Eric, Supervisor

DEDICATION

To my beloved wife

To my beloved sons Bruno and Brice

To my parents, brothers and sisters

I dedicate this dissertation

ACKNOWLEDGEMENT

It is with heartfelt gratitude that I first thank God: The Father, The Son and The Holy Spirit. I believe that He has always been with me, led my path and helped me to achieve my goals; I highly acknowledge the intercession of The Virgin Mary, Our Lady of KIBEHO.

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ABSTRACT

BACKGROUND: Salt intake is essential to life. Despite the physiological need of salt, when taken in excess, it is linked to raised blood pressure; hence many guidelines for treatment of hypertension recommend salt restriction to control blood pressure. WHO recommends a sodium intake of 2 g per day. Rwanda, as any other east Africa country, has a low sodium diet intake with an average of 1.6 g per day per person. Despite this low salt intake, national protocol for treatment of hypertension still recommends a salt restriction. As any other developing country, Rwanda population protein intake is low too. When combined, low salt intake and low protein intake, they lead to low solute intake, a condition known to cause hyponatremia by decreasing free water excretion capacity. Hyponatremia, especially in elderly has many adverse outcomes including poor cognitive function, and some studies suggested that low salt intake might be linked with increased mortality as do high salt intake.

METHODOLOGY: Main objective of the study was to determine association between salt restriction and hyponatremia in hypertensive patients. Secondary objectives were to determine prevalence of salt restriction and to determine other possible risk factors of hyponatremia in hypertensive patients on treatments. A case control study was conducted on adult hypertensive patients in two main tertiary hospitals in Kigali. Cases were defined as hypertensive patients with hyponatremia and Controls were defined as hypertensive patients without hyponatremia. Outcome was hyponatremia. Exposure was salt restriction. Cases and Controls were matched on age, gender, use of diuretics and duration of hypertension treatment.

Results: 245 participants were selected; out of them, 110 (44.9%) were cases and controls were 135 (55.1%). 159 (64.8%) participants were salt restricted and out of them, 74 (46.5%) were taking salt free diet. Among cases 98 (89.1%) were exposed and in controls 61 (45.1%) were exposed. Odd ratio of having hyponatremia if exposed was 9.90 (95%CI, P-value<0.001). Evaluation of other risk factors of hyponatremia in hypertensive patients revealed an odd ratio of 3.00 and 2.33 with p-value: 0.060 and 0.090 of getting hyponatremia for heart disease and renal disease patients respectively. Odds of having hyponatremia when using diuretics were 1.652 with a p-value: 0.208 in thiazide diuretics and 1.66 with a p-value: 0.197 in loop diuretics. Odd ratio of getting hyponatremia for patients aged above 35 years was 1.930 with a p-value: 0.925 compared to patients aged of 25-35 years. Odds of hyponatremia in patients who have been hypertensive for more than 5 years is 1.510 with a p-value: 0.110 compared to odds of 0.287 with a p-value of 0.063 observed in first year of hypertension.

Conclusion: Our study revealed a strong association between salt restriction and hyponatremia in hypertensive patients on treatment. Heart disease, renal disease, use of diuretics, advanced age and long duration on treatment of hypertension showed an association with hyponatremia in hypertensive patients but this association is not significant.

KEY WORDS: Hypertension, Salt restriction, Hyponatremia, Association.

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LIST OF ABBREVIATIONS

ACEI: Angiotensin-Converting Enzyme Inhibitors

ADH: Antidiuretic Hormone

AHA/ACC: American Heart association/American College of Cardiology

ANP: Atrial Natriuretic Peptide

ARB: Angiotensin Receptor Blocker

BNP: Brain natriuretic peptide

BP: Blood Pressure

BUN: Blood Urea Nitrogen

CCB: Calcium Channel Blocker

CHUK: Centre Hospitalier Universitaire de Kigali

CMHS: College of Medicine and Health Sciences

DM: Diabetes mellitus

ESH/ESC: European Society of Hypertension/European Society of Cardiology

ID: Identification number

IRB: Institutional Review Board

JNC 8: Eighth Joint National Committee

K: Potassium

MOH: Ministry of Health

Na: Sodium

NaCl: Sodium chloride

OR: Odd ratio

RAAS: Renin Angiotensin Aldosterone system

RMH: Rwanda Military Hospital

SIADH: Syndrome of Inappropriate Antidiuretic Hormone secretion

sNa: Serum sodium concentration

TBW: Total Body Water

UR: University of Rwanda

WHO: World Health Organization

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Chapter I: INTRODUCTION

I.1 BACKGROUND

Arterial hypertension is one of main causes of global burden of disease and has many devastating complications if not well managed; it is highly linked with cardiovascular complications and the latter is ranked as number one cause of death globally; Thus, an appropriate management of hypertension to normotensive state is crucial and essential(1–3).

Despite the fact that salt is essential to life and humans have some physiological mechanisms to drive salt intake(4,5), studies have shown that high salt intake is associated with a raised blood pressure. Strong evidences of salt restriction effect on blood pressure control are well documented(4,6,7).

Global salt intake exceed the world health organization recommendations, nevertheless regional salt intake is close to the WHO recommendations with national salt intake in Rwanda being in norms with WHO salt intake recommendations(8,9).

This has an impact on management of hypertension in Rwanda as a country of low salt intake compared to western countries where salt intake exceeds WHO recommendations. Despite that, Rwanda Ministry of health still recommends to reduce salt intake(10). We aim to analyze the effect of salt restriction on serum sodium concentration in our country which is already known to be a low salt intake community.

It is worth noting that low serum sodium concentration known as hyponatremia also has some bad outcomes especially in elderly people(11,12).

Our aim is to determine the association between salt restriction and hyponatremia in patients who are affected by arterial hypertension on treatment; and to find out other possible risk factors for hyponatremia in those patients. We hypothesize that salt restriction is highly associated with hyponatremia in hypertensive patients on treatment.

Since there is no study done in Rwanda on the effect of salt restriction on serum sodium concentration, we carried out this case control study at two teaching hospitals in Kigali: Centre Hospitalier Universitaire de Kigali and Rwanda Military hospital.

I.2: LITTERITURE REVIEW

I.2.1 Terms definitions

I.2.1.1 Arterial hypertension

According to 2017 American college of cardiology/American Heart Association, arterial hypertension is defined as any blood pressure above or equal to 130/80mmHg taken as 24-hour ambulatory BP monitoring which is equal to 140/90mmHg taken as office-BP measurement as well as 135/85mmHg taken as Home BP monitoring(13).

I.2.1.2 Sodium, salt and Hyponatremia

Sodium is the principal cation electrolyte of the extracellular fluid in the human body and as an osmotic determinant, it regulates volume of extracellular fluid hence, it controls plasma volume. Extracellular fluid contains 95% of total body sodium content of the body. Sodium intervenes in cell membrane action potential and active molecular transport across cell membranes. It regulates proper nerve and muscle functions(1,14).

Salt is an ionic compound made up of sodium at 40% and chloride at 60%; it is the principal source of sodium. It serves globally in food preparation, seasoning and food preservation(14).

Hyponatremia is a plasma sodium concentration level below 135mmol/l(15).

I.2.2 Physiology of sodium

The human cells dwell in water that contains solutes, and the main solute of that water is sodium making it saline water. The wellbeing of those cells depends on the ability of maintaining this salinity of that fluid(15). Through different physiological mechanisms, water and sodium are maintained in equilibrium and the physiology of sodium is linked to the physiology of water.

The total body water accounts for 50% of total body weight for females and 60% of total body weight for males, it is distributed in 2 major compartments: intracellular space occupying 55-75% and extracellular space 25-45%(1,16).
The extracellular fluid is also divided into 2 main spaces: intravascular space (plasma) and extravascular space (interstitial) in a ratio of 1:3(1).

The fluid flow between intracellular and extracellular space is driven by osmotic gradient. This osmotic gradient is made by solutes dwelling in water.
The solutes are divided into 2 major categories: electrolytes and nonelectrolytes; the nonelectrolyte solutes have bonds that do not allow them to dissociate in solutions and most of those solutes are organic molecules like glucose, lipids, creatinine, and urea. On the other hand, electrolyte solutes dissociate in solutions and give ions that are electrically charged. The latter include salt, acids and bases as well as some proteins. Electrolytes have much greater osmotic power than nonelectrolytes because when dissociated they give at least two molecules(1,15,16).

The main solutes in extracellular fluid are sodium accompanied by its anions chloride and bicarbonate which determine the osmolality of extracellular fluid; whereas the main solutes in intracellular fluid are potassium and its major anions hydrogen phosphate and anion proteins and they determine the osmolality of intracellular fluid.

Both intracellular and extracellular fluid should have the same osmolality to prevent swelling or shrinkage of cells; sodium and potassium are the main contributors to extracellular and intracellular osmolalities respectively. Both osmolalities are maintained in constant state by “sodium pump” (Na+/K+–ATPase) that expels sodium out of cells and drives potassium inside the cells. Sodium is the single most abundant cation in the extracellular fluid and the only one significantly exerting osmotic pressure; hence water follows sodium(15,16).

The plasma sodium depends on total exchangeable sodium, total exchangeable potassium and total body water as it is proven by Edelman equation simplified as:

$[Na^+]$ = (Na + K)/TBW(15,17)**.** This demonstrates the relationship between sodium, potassium and water. It shows how the Sodium homeostasis is linked to water homeostasis.

The Na-water homeostasis is inseparably linked to blood pressure and plasma volume and is regulated by neuro-hormonal mechanisms(16):
When plasma sodium concentrations decreases, the renin-angiotensin system is activates, end product is reabsorption of sodium in distal convoluted tubules and collecting ducts followed by water when possible.
The second mechanism that regulates sodium is reduction in circulating volume which stimulates the renin-angiotensin system and baroreceptors; the net outcome is sodium and water reabsorption. The Antidiuretic hormone (ADH) also known as Vasopressin once stimulated by decreased circulating volume or thirst secondary to raised plasma osmolality, enhances free water reabsorption in collecting ducts, decreasing plasma sodium concentration. On the other hand, when ADH is switched off due to declining plasma osmolality or raised circulating volume, free water is lost in collecting ducts raising plasma sodium osmolality.

Other mechanism that intervenes in sodium-water regulation is stimulation or inhibition of Atrial natriuretic peptide (ANP); Its stimulation by stretched heart atrial wall, inhibits RAAS and ADH release, owing to decreased salt and water reabsorption resulting in decreased circulating plasma volume(15,16,18). The end product of all those mechanisms is to maintain plasma osmolality, which means plasma sodium concentration, in stable state.

When water becomes too much resulting in low osmolality, which means low plasma sodium (hyponatremia), the cells swell; and inversely, when water declines,

resulting in raised osmolality which means high sodium (hypernatremia), the cells shrink(15).

I.2.3 Causes and clinical manifestations of hyponatremia

The causes of hyponatremia vary widely due to the fact that sodium physiology is linked to many other mechanisms; the following categorization helps to have an appropriate approach to hyponatremia:

3.1 Hyperglycemia induced hyponatremia: Being an active osmole, glucose attracts water from intracellular to extracellular space causing dilutional hyponatremia; this directional movement of water is different from what is normally happening in most cases of hyponatremia. The correction factor is 1.6 to every 100mdg/dl of glycaemia above 100mg/dl of blood glucose(19–21).

3.2 Diuretic-induced hyponatremia: It accounts for many cases of hyponatremia in clinical practice. The mechanism relies of the inhibition of sodium-chloride cotransporter. The main diuretic agent known to cause hyponatremia is Thiazide diuretic(19)(22–25).

3.3 Syndrome of inappropriate antidiuresis: The causes of SIAD are many; a simplified way to know them is to classify them into 4 categories: Pulmonary causes, Malignancies, nervous system disorders and drug induced-SIAD. Those pathologies cause SIAD by 4 main mechanisms: uncontrolled secretion of vasopressin, increased basal secretion of vasopressin despite normal regulation by osmolality, reset osmostat (case of pregnancy, malignancy, malnourished, tuberculosis) as well as undetected vasopressin level(in case of nephrogenic SIAD)(19,25–27).

3.4 Cerebral salt wasting: defined as renal loss of sodium in patient with intracranial disease resulting in hyponatremia. Though the mechanism is not known, it is postulated that Brain Natriuretic Peptide (BNP) leads to natriuresis which causes hypovolemia and sodium depletion(19,28).

3.5 Hypopituitarism and primary adrenal insufficiency: hypopituitarism causes hyponatremia by lack of cortisol secondary to deficiency of adrenocortical hormone, triggering inappropriate vasopressin secretion; while in primary adrenal insufficiency, both cortisol and aldosterone deficiency contribute to hyponatremia(19).

3.6 Hyponatremia in heart and liver failure: both conditions lead to ineffective volume circulation which triggers a cascade of neurohormonal response made of renin angiotensin system and vasopressin secretion resulting in expansion of extracellular fluid(19).

3.7 Low solute intake and polydipsia: This category of causes of hyponatremia doesn't dependent on ADH; the low solute intake decrease the free water excretion capacity leading to hyponatremia(1,19,29,30).

3.8 Exercise-induced hyponatremia: three biologically independent mechanisms are postulated; excessive water intake, inappropriate activation of vasopressin and interaction of osmotically active sodium and inactive sodium stores(19).

The Clinical manifestations of hyponatremia are primarily neurologic; they depend on severity of plasma sodium depletion but especially depend on the rapidity of plasma sodium change(15).

In acute settings, the symptoms of hyponatremia reflect the severity of brain edema and adaptive responses of brain cells to osmotic swellings due to rapid decline in concentration of plasma sodium. Those symptoms comprise nausea and malaise when plasma sodium drops between 125 to 130 mEq/L. When plasma sodium concentration falls below 120 to 115 mEq/L, symptoms like headaches, lethargy, obtundation seizures, coma, and eventually respiratory arrest can occur. Though acute hyponatremic encephalopathy is reversible, permanent neurologic lesions and death may occur(15,31,32).

In chronic hyponatremia, different adaptive responses make the patient asymptomatic even when plasma sodium concentration drops below 120 mEq/L. In symptomatic chronic hyponatremia, patient may report fatigue, nausea, and vomiting, dizziness, gait imbalance, forgetfulness, confusion, lethargy and muscle pain(15,33–35).

I.2.4 Hypertension and salt

I.2.4.1 Effect of salt on blood pressure

Despite being essential to life, high salt consumption has been linked to raised blood pressure(4,6). Many studies showed a strong association between both high salt consumption and raised arterial blood pressure. One of them is INTERSALT: an international study of electrolyte excretion and blood pressure which found that salt intake was significantly related to blood pressure;

They found that when sodium consumption was increased by 50 mmol per day((~ 1.1 g of sodium which is 2.75 g of salt per day), there was increase of a mean systolic blood pressure of 5 mmHg and a mean diastolic pressure of 3 mmHg(36).

It was also found that sodium intake of 50 to 100 mmol per day is necessary but not sufficient for development of primary hypertension(6,14,36).

I.2.4.2 Salt intake

John Powles et al conducted a systematic analysis of 24 hours urinary sodium excretion and dietary surveys worldwide in 1990 and 2010; and these are the main findings for global, regional and national sodium intake in 2010: globally, sodium intake is 3.95 g/day (95% uncertainty interval: 3.89 to 4.1); which is almost 2 times than World Heart Organization recommendation limit of 2 g/day. However, the east Africa sodium intake is estimated at 2.1 g/ day, a region with low sodium intake worldwide. On national level in Rwanda, the estimated sodium intake in 2010 is 1.60 g/ day (1.31-1.95); which shows a minimal increase in sodium intake over 20 years; that is from 1.52 g/ day in 1990 to 1.60 g/ day in 2010(9).

I.2.4.3 General Principles of management of hypertension

Different international guidelines have been made for the management of hypertension; below are general principles of treating high blood pressure(13,37,38):

1. Lifestyles change: It includes salt restriction, potassium supplementation, moderate alcohol consumption, increase vegetables and fruits consumption, low-fat diet, reduce and maintain weight in acceptable BMI range as well as regular physical exercise.
2. Pharmacologic agents: These agents include calcium channel blockers, thiazide type or thiazide like diuretics, Angiotensin converting enzyme inhibitors and Angiotensin receptor blockers, potassium sparing diuretics,

beta blockers, alpha blockers, direct vasodilators, central acting antihypertensive agents and in some conditions loop diuretics.

I.2.4.4 Salt restriction in management of hypertension

Salt restriction is considered by many international guidelines as a cornerstone in management of hypertension based on proven effect of salt restriction on BP; below are some of those studies:

INTERSALT study estimated a mean systolic pressure of 5 mm Hg higher and diastolic pressure of 3 mm Hg higher if sodium intake increases by 50 mmol; this indirectly shows that when sodium intake is decreased, both systolic and diastolic pressure are decreased(36).

Nakano M et al in their study on Effect of Intensive Salt-Restriction Education on Clinic, Home, and Ambulatory Blood Pressure Levels in Treated Hypertensive Patients During a 3-Month Education Period, found that both morning home systolic BP and ambulatory 24-hour systolic BP tended to be lowered in the interventional group (with salt intake at 6 g/day) compared to control group (liberal salt intake)(39).

A Meta-Analysis of Effect of Dietary Salt Restriction on Blood Pressure in Chinese Adults done by Miao Wang et al, prove that each 1.00 g dietary salt reduction in hypertensive patient was associated with a reduction of 0.94 mm Hg in systolic BP (95% CI: 0.69 to 1.03 mm Hg); and these systolic BP reductions were 1.71 times greater in hypertensive individuals compared to normotensive(40).

WHO and international guidelines for management of hypertension have recommended salt restriction as part of hypertension management; below are different recommendations with overall WHO recommendation:

2013 ESH/ESC Guidelines for the management of arterial hypertension recommends a daily intake of 5-6 g of salt for the general population(37).

2017 AHA/ACC guidelines for management of arterial hypertension recommend a daily intake of 1.5 g of sodium any hypertensive patients(13).

WHO recommends a reduction of intake < 2 g/day of sodium (5 g of salt). This recommendation is applied to all people being hypertensive or not; however, individuals with illnesses or taking drug therapy that may lead to hyponatremia are excluded(41).

The Rwanda ministry of health recommendation on salt reduction does not precise the quantity to take based on estimated national salt intake; it states to take low salt diet(10).

I.2.4.5 Effect of extreme low salt intake

Some studies have been conducted to evaluate the possible risks associated with low salt intake, and below are some of them with their impressions:

Graudal N et al, in their meta-analysis entitled “Compared with Usual Sodium Intake, Low- and Excessive-Sodium Diets Are Associated With Increased Mortality” found a U-shaped association between sodium intake and health outcomes. Mortality risk increases with both low sodium and high sodium intake.

Low sodium was defined as mean daily sodium intake <115 mmol which is 2,645 mg sodium (equal to 6,613 mg NaCl); Usual sodium was defined as a mean daily sodium intake of 115–215 mmol; and high sodium was a mean daily sodium intake >215 mmol(11).

Rush T.M. et al in their cross sectional study done in Southern California community to assess association between dietary sodium intake and cognitive function in older adults (aged 50-96 years) found that lower sodium intake was associated with worse cognitive function in older community-dwelling adults; and this association was highly significant when adjustment to other conditions like diuretic drugs, smoking, cardiovascular disease and diet. This cognitive impairment was linked to the age: there more the age, the worst the cognition(12).

Angela J. D and Mark I. M. in their systematic review entitled: The Hyponatremia epidemic: A Frontier Too Far? reviewing the current evidence of low salt diet and prevalence of hyponatremia; postulated that the increase in the prevalence of hyponatremia is linked to the widespread adoption of low salt diet policy(42).

Drake-Holland AJ and Noble MIM in their article entitled: “should we now abandon low salt diet?” Published in 2011, showed evidences of side effects linked to low salt intake; these side effects include hyponatremia especially when associated with increased water intake, brain edema and subsequent brain injury, increased body mass index, elevated renin, angiotensin, aldosterone and the sympatho-adrenergic system(41)

I.2.4.6 Low solute intake induced hyponatremia in literature

One of the causes of hyponatremia is low solute intake: this category of causes of hyponatremia doesn't dependent to ADH; the low solute intake decreases the free water excretion capacity leading to hyponatremia(1,19,29,30).

This category of hyponatremia occurs in people who are restricted in consumption of dietary solutes; which are salt and proteins.

Classically, this category of hyponatremia occurs in individuals who excessively consume alcohol with beer as their sole nutrient; whereas the beer is very poor in protein and salt content, those individuals develop hyponatremia in hypo-osmolality state labeled as beer potomania. However, it has been also seen in nonalcoholic patients with highly restricted solute intake due to nutrient-restricted diets, for instance, extreme vegetarian diets and extreme salt restriction.

In those people, the very low solute intake reduces urinary solute (Na and BUN) excretion leading to limited water excretion capacity and causes hyponatremia despite a normal or modest increased fluid intake. They present with a very low urine osmolality, usually <100–200 mosmol/kg, with urine Na^+ concentration that is <10–20 mmol.

The management of such hyponatremia consists of increasing solute intake leading to normalization of plasma sodium.

Rwanda, as any other sub-Saharan country, has low protein intake(43).This shows how far low solute intake could be high in Rwandans who are salt restricted.

I.2.4.7 Salt sensitive and salt resistant hypertension theory

The theory of salt sensitive and salt resistant hypertension has been controversial over decades. Though arbitrary defined level, salt sensitive individuals are persons whose blood pressure changes of more than 10% on low or high sodium loading; whereas salt resistant individuals are those whose blood pressure does not increase or decrease above 5% on sodium loading(53,54). It is said that salt sensitivity is common in black and elderly individuals.

Most of studies done on salt sensitivity and resistant used short time protocols with loading of intravenous salt for 7 days and another 7 days of low salt administration(54) and there is no enough evidence to suggest that such changes in blood pressure on this short time high salt loading could be seen in long term daily dietary salt intake(53).

According to Galletti. F and Strazullo. P, in their systematic review, concluded that even though salt sensitivity sounds well physiologically but has no practical value: it cannot be used by treating physician on daily basis for caring hypertensive patients nor be used to generate public based policies for salt reduction in population(53).

Same conclusion was made in scientific statement by the American heart association: applicability of salt sensitive blood pressure approaches to general population for salt reduction policies is limited(54).

I.3 PROBLEM STATEMENT

Our country, Rwanda, is known to be among the countries with low dietary salt intake with an average 1.6 g/day of sodium consumption per person (9); this daily sodium consumption is below the recommended sodium intake of 2 g/day by WHO(8); despite that, many hypertensive patients who are on treatment kept being restricted more on salt intake and some patients take free salt diet; In addition to that, as developing country, the protein intake is low(43): both low sodium intake and low protein intake contribute to low solute intake leading to hyponatremia(19,29,30).

No data available in Rwanda on effect of this recommendation of salt restriction to serum sodium concentration. We hypothesize that salt restriction in Rwanda is highly associated with hyponatremia; we aim to determine this association and we want to determine other possible factors that might be associated with hyponatremia in our population.

I.4 RESEARCH QUESTION

Is salt restriction associated with hyponatremia in hypertensive patients on treatment?

I.5 OBJECTIVES OF THE STUDY

I.5.1 General Objective

To assess the effect of salt restriction on serum sodium concentration in hypertensive patients.

I.5.2 Specific objectives

To determine prevalence of salt restriction in hypertensive patients.

To determine the association between salt restriction and hyponatremia in hypertensive patients.

To determine the other possible risk factors associated with hyponatremia in hypertensive patients.

Chapter II: METHODOLOGY

II.1 Study design

It is a case control study done over a period of 6 months.

II.2 Study site

The study was conducted at two tertiary hospitals in Rwanda: University teaching hospital of Kigali (CHUK) and the Rwanda Military Hospital (RMH)

II.3 Study population

The study was carried out among adult patients with arterial hypertension on treatment for at least three months.

II.4 Selection of study population

II.4.1 Inclusion criteria

- Male and female hypertensive patients aged from 18 years and above;
- Presented in outpatient and inpatient departments of the above mentioned hospitals.
- Agreed to participate by signing a written informed consent;
- On treatment of hypertension for at least 3 months.

II.4.2 Exclusion criteria

The following groups of patients were excluded from participation in the study:

1. Hypertensive patients who do not consent

2. Hypertensive patients with less than 3 months of treatment duration
3. Hypertensive patients with fluid overload status

II.5 Study procedure

II.5.1 Case definition

The Case group was made by hypertensive patients on treatment who have hyponatremia;
The control group was made by hypertensive patients on treatment who did not have hyponatremia.
The exposure was salt restriction.
In order to minimize the confounders, we matched cases and controls on age, gender, use of diuretics and duration of hypertension treatment.

II.5.2 Enrollment and procedure

All participants who met the inclusion criteria were taken blood sample for serum sodium concentration analysis and then grouped into case or control group with respect to matching criteria. Participants were interviewed using a questionnaire about their dietary salt intake, past medical history and drugs history. Cases and controls were matched by gender, age, use of diuretics and duration of hypertension treatment.

II.5.3 Sample size

Sample size consisted of hypertensive patients who presented at CHUK and RMH during the study period as follow:
Admitted patients: data was collected over 6 months

Patients in ambulatory consultations: data was collected over 3 months. Since these patients may come in outpatient clinic every one to two months, we avoided to record a single patient at different occasion of consultations.

II.6 Data management and analysis

Data collected was entered, and analyzed using Epi-info version7.2 and stata13 softwares. Logistic regression was used to calculate odds ratio at 95%CI for different variables for their association with hyponatremia in our study population and chi-square test used for p-value. Test results were considered statistically significant if the chi-square test p-value was < 0.05.

II.7 Ethical considerations

Participants' data were retained confidentially and stored anonymously. The names of the participants were coded and their personal information were protected.

Written informed consent was signed by participants or their care takers. Those who did not consent were not included and the participants had the freedom to withdraw from the study at any point without any negative consequence.

Ethical approval letter was obtained from university IRB committee as well as IRB committees from concerned hospitals (RMH and CHUK) before data collection.

Chapter III: RESULTS

III.1 General Characteristics of study population

A sample of 245 participants meeting the inclusion criteria was taken. Cases (hypertensive patients with hyponatremia) were 110 (44.9%) and controls were 135 (55.1%). All participants were followed back in time for exposure to salt restriction versus no salt restriction. The cases and controls were matched by age, gender, use of diuretics and duration on treatment of hypertension; males were 39 in cases and 45 in controls while females were 71 in cases and 90 in controls. The mean age was 63.25 ± 13.5 in case and 61.4 ±13.9 in controls.

Table 1: Matching criteria

		CASES		CONTROLS		p-value
		N	%	N	%	
Gender	Male	39	(46.6)	45	(54.4)	0.728
	Female	71	(44.1)	90	(55.9)	
Age	25-35	6	(46.1)	7	(53.9)	0.925
	>35	104	(44.8)	128	(55.2)	
	Mean	63.25 ± 13.5		61.4± 13.9		
Duration on treat-ment of hyprtension	3-6 mos	5	(21.7)	18	(78.3)	0.074
	7-12 mo	3	(20.0)	12	(80.0)	0.063
	1-3 yrs	29	(48.3)	31	(51.7)	0.538
	4-5 yrs	12	(48.0)	13	(52.0)	0.742
	>5 yrs	61	(50.0)	61	(50.0)	0.110
Diuretics use	Loops	16	(55.2)	13	(44.8)	0.197
	Thiazide	16	(35.6)	29	(64.4)	0.208

The mean serum sodium concentration in the study population was 135.29 meq/L with SD 5.16 meq/L with a minimum sodium level of 115 meq/L and maximum sodium level of 145 meq/L; the mean serum sodium concentration in cases was 130.57 meq/L with SD 3.87 meq/L and 138.98 with SD 2.14 meq/L in control.

Table 2: Serum sodium concentration in study population

	N (%)	Minimum	Maximum	Mean	Std. Deviation
sNa conc.	245 (100)	115	145	135.29	5.162
Cases	110 (44.1)	115	134	130.57	3.871
Controls	135 (55.9)	136	145	138.98	2.142

76 (69%) participants in case group had mild hyponatremia whereas severe hyponatremia was found in 6 (5%) participants.

Table 3: Degree of hyponatremia in Case group

sNa conc	N	Minimum	Maximum	Mean	SD
<125	6	115	122	119.17	2.927
125-129	28	125	129	127.39	1.166
130-134	76	130	134	132.64	1.476

Calcium channel blockers (CCB) are the most prescribed antihypertensive drugs, followed by angiotensin receptor blockers (ARB), and thiazide diuretics

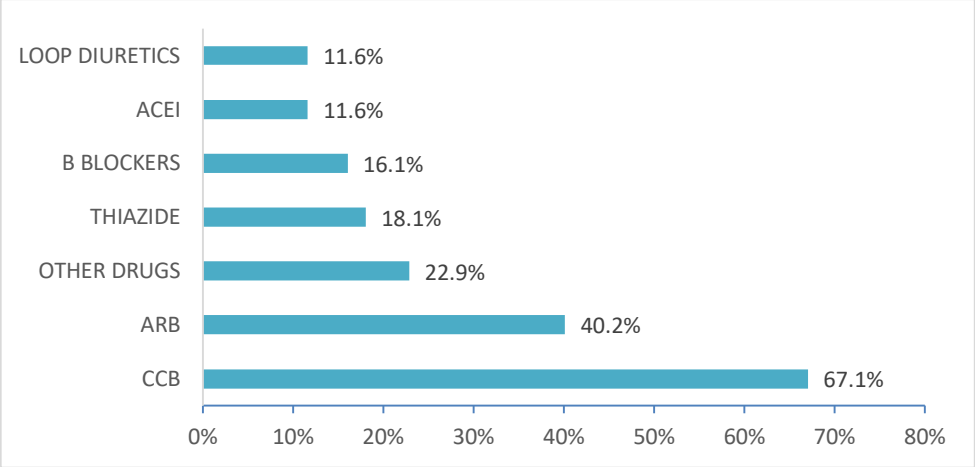

Figure 1: Antihypertensive drugs of participants

III.2 Prevalence of salt restriction in study population

The prevalence of salt restriction (decreased salt intake compare to family salt diet) among hypertensive patients on treatment was 159 (64.8%);

Out of them, 74 (46.5%) were taking salt free diet (no salt at all) and 85 (53.5%) were taking a low salt diet (decreased salt) compared to the family salt diet.

III.3 Association between salt restriction and hyponatremia in study population

Among cases, 98 (89.1%) were exposed (salt restricted) and in controls, 61 (45.1%) were exposed. OR of having hyponatremia if being exposed (salt restricted) is 9.907 (95%CI, P-value<0.001).

Table 4: Association of hyponatremia with salt restriction in hypertensive patients

			sNa conc.(outcome)					
			CASES		**CONTROLS**			
			N	(%)	N	(%)	p-value	OR
EXPOSURE	*Salt*	**YES**	98	(89.1)	61	(45.1)	0.000	**9.907**
	restricted	**NO**	12	(10.9)	74	(54.9)		

Adjusted to the gender, OR of having hyponatremia if exposed (salt restricted) is 19.83 with a p-value <0.001 and 7.37 with a p-value <0.001 in males and females respectively. Adjusted to the age, OR of having hyponatremia once exposed (salt restricted) is 5.00 with a p-value: 0.170 and 10.99 with a p-value<0.001 in age groups of 25-35 years and above 35 years respectively.

Table 5: Association between salt restriction and hyponatremia adjusted to gender and age

				sNa conc.					
				CASES		CONTROLS			
				N	(%)	N	(%)	p-value	OR
Gender	Male	salt	Yes	35	(89.7)	14	(31.1)	0.000	19.375
		restricted	No	4	(10.3)	31	(68.9)		
	Female	salt	Yes	63	(88.7)	47	(52.2)	0.000	7.205
		restricted	no	8	(11.3)	43	(47.8)		
Age group	25-35	salt	yes	4	(66.7)	2	(28.6)	0.170	5.000
		restricted	no	2	(33.3)	5	(71.4)		
	>35	salt	yes	94	(90.4)	59	(46.1)	0.000	10.993
		restricted	no	10	(9.6)	69	(53.9)		

III.4 Risk factors associated with hyponatremia in study population

The analysis of comorbidities revealed an association between heart disease and hyponatremia with OR of 3.00, but not statistically significant with a p-value of 0.060; the same for renal disease with OR of 2.33 and a p-value of 0.090.

Table 6: Factors associated with hyponatremia in hypertensive patients on treatment

		CASES	CONTROLS		
	N	**%**	**%**	**P-value**	**OR**
Drug used					
Thiazide	45	35.6%	64.4%	0.208	1.652
CCB	167	41.9%	58.1%	0.346	0.776
ACEI	29	48.3%	51.7%	0.622	1.015
ARB	100	48.0%	52.0%	0.298	1.110
B Blockers	40	52.5%	47.5%	0.237	1.003
Loop Diuretics	29	55.2%	44.8%	0.197	1.663
Diet behavior					
Processed food	3	33.3%	66.7%	0.708	0.633
Alcohol intake	37	51.4%	48.6%	0.329	1.023
Comorbidities					
Heart Disease	13	69.2%	30.8%	0.060	3.030
Renal Disease	42	50.0%	50.0%	0.090	2.337
Diabetes mellitus	89	44.9%	55.1%	0.823	1.061
Brain Disease	8	50.0%	50.0%	0.728	1.283
Lung Disease	3	33.3%	66.7%	0.708	0.633
GI Disease	8	50.0%	50.0%	0.728	1.283

Furthermore, analysis of duration by which the patients have been with hypertension revealed association of hyponatremia with long standing hypertension compared to short duration of hypertension, however, this association is not statistically significant. The analysis of age revealed an association between increased age and hyponatremia with OR: 1.930 but not statistically significant with p-value: 0.925.

Table 7: Age, gender and duration of hypertension treatment as independent risk factors of hyponatremia

		CASES		CONTROLS			
		N	(%)	N	(%)	p-value	OR
Gender	Male	39	(44.3)	49	(55.7)	0.940	1.02
	Female	71	(43.8)	91	(56.2)		
Age	25 – 35 years	6	(46.1)	7	(53.9)	0.925	1.930
	>35 years	104	(44.6)	128	(55.4)		
Duration with HTN	3-6 months	5	(21.7)	18	(78.3)	0.074	0.310
	7-12 months	3	(20.0)	12	(80.0)	0.063	0.287
	1-3 years	29	(48.3)	31	(51.7)	0.538	1.201
	4-5 years	12	(48.0)	13	(52.0)	0.742	1.149
	>5 years	61	(50.0)	61	(50.0)	0.110	1.510

Chapter IV: DISCUSSION

IV.1 Prevalence of salt restriction in study population

Salt restriction to 5 g/day (2g/day of sodium is recommended by WHO as one way of treating hypertension(8), and national sodium intake average is 1.6g/day(9). In our study, serum sodium concentration of 245 patients who are on antihypertensive drugs has been analyzed with 110 (44.9%) of Cases (participants with hypertension on treatment who developed hyponatremia) and 135 (55.1%) of Controls (participants with hypertension on treatment who do not have hyponatremia). Exposure to salt restriction has been analyzed on both groups to determine any possible association between salt restriction and hyponatremia in our study population.

Overall, the prevalence of salt restriction (decreased salt intake compared to family salt diet) among hypertensive patients on treatment was 64.8%; and 46.5% of them were taking salt free diet (no salt at all).

VI.2 Association between salt restriction and hyponatremia

The analysis revealed a strong association between hyponatremia and salt restriction in hypertensive patients with OR: 9.907 with 95% CI, P-value <0.001.

This association can explain what Angela J. D and Mark I. M. in their systematic review entitled: “The Hyponatremia epidemic: A Frontier Too Far? Reviewing the current evidence of low salt diet and prevalence of hyponatremia” postulated that the increase of prevalence of hyponatremia is linked to the widespread adoption of low salt diet policy(42).

The association between salt restriction and hyponatremia seen in this study, was postulated by Drake-Holland AJ and Noble MIM in their article published in 2011 which showed that low salt intake can lead to hyponatremia(41).

The association between salt restriction and hyponatremia has also been demonstrated by Giordano M. et al in their study on seasonal variation of serum sodium in the emergency department which showed that hyponatremia during summer is partly linked to decreased salt intake during that period(44).

The above association is explained by the mechanism of hyponatremia resulting low solute intake; in this category of hyponatremia which does not dependent on ADH, low solute intake (low salt intake and low protein intake) lead to decreased free water excretion capacity leading to hyponatremia(29,30) and this low solute intake is especially seen in our population: low sodium intake as it was observed by Powles J. et al in their study entitled "Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide"(9) and low protein intake reported in the study of Rawlins R. et al evaluating the impact of livestock donation programs in Rwanda on nutritional outcomes(43).

The odds of having hyponatremia was 19.37 with P-value <0.001 in males and 7.20 with P-value <0.001 in females; however, gender alone is not associated with hyponatremia; and this lack of association between hyponatremia and gender was also seen by Hawkins, R.C in his study of age and gender as risk factors of hyponatremia and hypernatremia where he stated that gender is not an important risk factor to disturb serum sodium concentration(45).

IV.3 other independent risk factors associated with hyponatremia in study population

Analysis of other possible factors that might have association with hyponatremia in hypertensive patients on treatment showed that the longer the patient has been hypertensive, the more the risk of getting hyponatremia though this risk is not statistically significant; the odds of having hyponatremia if the participant has been hypertensive for more than 5 years is 1.510 with a p-value of 0.110 compared to odds of 0.252 with a P-value of 0.063 within first year of hypertension treatment.

OR of getting hyponatremia is 1.930 for participants above 35 years of age compared to participants aged between 25-35 years, though not statistically significant due a p-value of 0.925. This difference of odds of getting hyponatremia among age group was also seen in the study of Hawkins, R.C on age and gender as risk factors of hyponatremia and hypernatremia and it was found that increased age is an independent risk factor for hyponatremia(45).

There is no single drug found to be an independent risk factor associated with hyponatremia in hypertensive patients on treatment; however, loop diuretics have highest odds of 1.663 but not statistically significant with a p-value of 0.197. Almas, A. et al had the same findings in their study which showed that the association of diuretics with hyponatremia in hypertensive adult patients who are treated with loop diuretics is not significant(49). OR of getting hyponatremia when using thiazide diuretics was 1.652, but not statistically significant with a p-value of 0.208. Same findings were seen in the above mentioned study of Almas, A. et al.

Heart disease and renal disease were found to be linked with raised odds for developing hyponatremia but not statistically significant. OR of having hyponatremia in heart disease was 3.030 with a p-value of 0.060 and it was 2.337 with a p-value of 0.090 in renal disease. In these two conditions, hyponatremia is caused by water retention causing dilutional hyponatremia(50–52).

IV.4 Study limitations

As any other case control study, recall bias is one of the limitations to our study; we matched cases and controls for age, gender, use of diuretics and duration of hypertension in other to minimize the confounding bias however, we cannot exclude confounders to zero percent.

We did not test urine sodium concentration which could help to confirm low sodium excretion seen in low solute intake.

We did not include rural hospitals and non-communicable disease clinics in rural area; however, the two tertiary hospitals chosen received patients from both rural and urban areas around the country.

Chapter V: CONCLUSION AND RECOMMENDATION

V.1 Conclusion

The above results confirm our hypothesis which states that salt restriction is associated with hyponatremia in context of Rwanda where the general population salt intake is by far lower compared to western countries. This association has been shown and revealed in many other studies. The particularity of our study resides in the fact that our population is known to have low salt diet and often associated with low protein intake, which put our population at risk of low solute intake causing decreased free water excretion by kidneys leading to hyponatremia. This category of hyponatremia does not dependent on ADH.

Mild hyponatremia represents the majority of hyponatremic participants, however, some participants have severe hyponatremia. Other factors seen to be associated with hyponatremia in hypertensive patients on treatment are advanced age and long duration on hypertensive treatment, but the observed association is not statistically significant. The use of diuretics, heart disease and renal disease are associated with hyponatremia in study population but not statistically significant.

This study does not determine a causal relationship between salt restriction and hyponatremia in hypertensive patients; it determines the association between salt restriction and hyponatremia in hypertensive patients who are on treatment in two tertiary hospitals of Rwanda. It also shows a prevalence of salt restriction among hypertensive patients and determines other possible factors that may be associated with hyponatremia as stated above.

V.2 Recommendations

Our recommendations to Rwanda ministry of health consists of individualizing the international guidelines regarding salt restriction to the country level, to update the current guidelines on management of hypertension in regard to the low salt diet culture in Rwandan population. This individualization of salt restriction regimen should also be titrated to personal level because the harm of low plasma sodium concentration is as dangerous as hypertension.

Our recommendations to the teaching hospitals and the university is to carry out more advanced studies in attempt to determine a causal relationship between salt restriction and hyponatremia with impact on the quality of life of patients who might be affected by hyponatremia.

Our recommendation to treating health professionals who follow hypertensive patients is to regularly check their electrolytes and act before getting severe hyponatremia which is associated with increased mortality especially in elderly.

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Chapter VII: ANNEXES

VII.1 Consent Form

Informed Consent Form for salt restriction induced hyponatremia in hypertensive patients: case control study

This Informed Consent Form is for adult men and women who we are inviting to participate in research on how salt restriction could affect your serum sodium when you are taking drugs for hypertensions combined with life style modifications. *The title of the research is salt restriction induced hyponatremia in hypertensive patients: case control study*

This Informed Consent Form has two parts:
• Information Sheet (to share information about the research with you)
• Certificate of Consent (for signatures if you agree to take part)
You will be given a copy of the full Informed Consent Form.

PART I: Information Sheet

Introduction
My name is Dr. BIZIMANA Emmanuel, Resident in Internal Medicine in the University of Rwanda College of Medicine and Health Sciences (UR/CMHS). We are performing a research on your salt intake regimen and its effect on your serum sodium. We would like to know if restricting salt intake could affect your serum sodium level
I am going to give you information and invite you to participate in this research. You do not have to decide today if you would like to participate in this research. If you do not understand some of the words or concepts, please let me know and I will take the time to explain it to you. Before you decide on whether you would like to participate in this research, you can discuss it with anyone you feel comfortable with who could help you. If you have any questions at any time, you can discuss it with me or with any staff involved in the study.

Purpose of the research

Salt restriction is one of the life style change often imposed on patients with hypertension irrespective of their salt intake; despite being important in management of hypertension, if salt restriction goes down beyond WHO recommended salt intake, it could lead to severe condition called hyponatremia (low sodium in your blood) which can be life threatening condition; we would like to assess if restricting salt could not lead to this condition of hyponatremia.

Type of research intervention

We will take you a sample of blood of 2 ml for measuring your serum sodium and then we will give you a 2 pages survey to assess your salt intake regimen, your drugs for hypertension and other diseases that you have

Participant selection

We are inviting all adults who have hypertension and who are taking the drugs for lowering blood pressure

Voluntary Participation

Your participation in this research is entirely voluntary. You can decide whether to participate or not. If you choose not to participate you will continue to receive all the same services that you had previously received and nothing will change. You can choose to stop participating in this study any time that you like and your prior service will continue as before.

Procedures and Protocol

There are two parts of this study if you choose to participate. In the first part, you will be taken a small sample of your blood of 2 ml for measuring your sodium; and in the second part, the result of your serum sodium will be put on a small questionnaire that you will be asked to fill it and it is brief(10 minutes). Your serum sodium level as well as your answers to the confidentially under code.

Duration

This study will take place over a period of 6 months but you will be assessed only once.

Side Effects

There are no side effects associated with participating in this study.

Risks

There are no anticipated risks with participating in this study.

Reimbursements
There is no reimbursement for your participation in this study.

Confidentiality

The information that we collect from this study will be confidential. We will not be sharing the identity of those participating in the research. Information that we collect about you will be stored in a locked file on a locked computer. Any information about you in this file will have a number on it instead of your name. Only the researchers will know this number and we will keep it locked. This file will not be shared with anyone with the exception of those directly involved in the study.

Sharing the results

We plan to publish the results of the study in journals. Your confidentiality will not be breached at any time.

Right to Refuse or Withdraw

You have no obligation to take part in this research and if you choose to not participate, there will be no penalty or change in your care. You can also stop participating in this study at any time that you like and your care at this clinic will not be impacted.

Who to Contact

You can ask questions at any time during this study. You can ask them now, or if you would like to ask questions in the future, you may contact: Dr. BIZIMANA Emmanuel, emmyone00@gmail.com or Dr RUTAGANDA Eric, rutagander@gmail.com
For any query you can refer to the Chairperson of the CMHS IRB (0788 490 522) or the Deputy Chairperson (0783 340 040) or research committee (researchcenter@ac.ur.rw Tel +250 788563311).

Part II: Certificate of consent

I have read the information regarding this study as above, or this information has been read to me. I have been able to ask all questions that I have and these have been answered to my satisfaction. I consent to voluntarily be a participant in this study.

Printed Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

If illiterate

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____

AND Thumb print of participant:

Signature of witness _____

Date _____

Day/month/year

Statement by the researcher/person taking consent:

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands the above information.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this Informed Consent Form has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____

Day/month/year

VII.2 Data collection tool

DATA COLLECTION FORM FOR SALT RESTRICTION INDUCED HYPONATREMIA IN HYPERTENSIVE PATIENTS: CASE CONTROL STUDY.

Identification number: ……. Code…….

Date ……

I. Socio-demographic characteristics

Date of birth (year) ……

Gender: Male ☐ Female ☐

Provenance: Kigali city ☐ East ☐ West ☐ South ☐ North ☐

Region : Urban ☐ Rural ☐

Level of Education: None ☐ Primary ☐ Secondary ☐ University ☐

Marital status

Single: ☐ Married: ☐ Widow/ Widower: ☐

Divorced: ☐

II. LABORATORY RESULTS

Serum sodium**……..**

III. Clinical characteristics

III.1. How long have you been on antihypertensives?

3-6 months ☐ 7-12 months ☐ 1-3 years ☐

4-5 years ☐ > 5 years ☐

II.2 Antihypertensives drugs you are taking:

CCB ☐ Thiazides Diuretics ☐ ACEI ☐ ARB ☐

Loop diuretics ☐ B blockers ☐ Other agents ☐

II.3 Life styles measures

II.3.1 Have you received salt restriction advise from your doctor

Yes ☐ No ☐

II.3.2 salt intake

I do not take any kind of salt at all ☐

I decrease salt in my meal compared to my family's meal ☐

I take the same salt in my meal as my family's meal ☐

I add salt to my meal compared to my family's meal ☐

I use pharmacy salt ☐

II.3.2 Processed foods

I am used to take processed foods

Yes ☐ No ☐

II.3.3 Alcohol intake

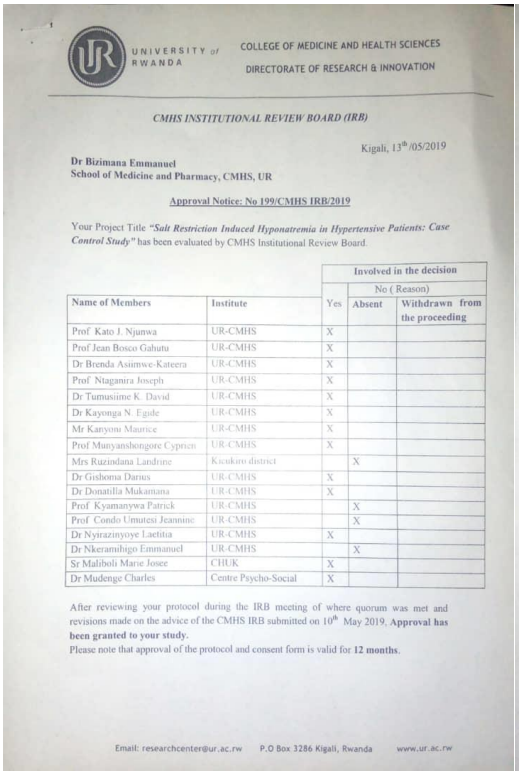
Regularly ☐ Occasionally ☐ No alcohol at all ☐

II.4 Comorbidities

Heart disease ☐ Renal disease ☐ DM ☐ Brain disease ☐

Lung disease ☐ GI disease ☐ Other disease ☐

VII.3 IRB Approval letters



UNIVERSITY of RWANDA

COLLEGE OF MEDICINE AND HEALTH SCIENCES

DIRECTORATE OF RESEARCH & INNOVATION

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 13th/05/2019

Dr Bizimana Emmanuel
School of Medicine and Pharmacy, CMHS, UR

Approval Notice: No 199/CMHS IRB/2019

Your Project Title ***"Salt Restriction Induced Hyponatremia in Hypertensive Patients: Case Control Study"*** has been evaluated by CMHS Institutional Review Board.

		Involved in the decision		
			No (Reason)	
Name of Members	**Institute**	Yes	**Absent**	**Withdrawn from the proceeding**
Prof Kato J. Njunwa	UR-CMHS	X		
Prof Jean Bosco Gahutu	UR-CMHS	X		
Dr Brenda Asiimwe-Kateera	UR-CMHS	X		
Prof Ntaganira Joseph	UR-CMHS	X		
Dr Tumusiime K. David	UR-CMHS	X		
Dr Kayonga N. Egide	UR-CMHS	X		
Mr Kanyoni Maurice	UR-CMHS	X		
Prof Munyanshongore Cyprien	UR-CMHS	X		
Mrs Ruzindana Landrine	Kicukiro district		X	
Dr Gishoma Darius	UR-CMHS	X		
Dr Donatilla Mukamana	UR-CMHS	X		
Prof Kyamanywa Patrick	UR-CMHS		X	
Prof Condo Umutesi Jeannine	UR-CMHS		X	
Dr Nyirazinyoye Laetitia	UR-CMHS	X		
Dr Nkeramihigo Emmanuel	UR-CMHS		X	
Sr Maliboli Marie Josee	CHUK	X		
Dr Mudenge Charles	Centre Psycho-Social	X		

After reviewing your protocol during the IRB meeting of where quorum was met and revisions made on the advice of the CMHS IRB submitted on 10th May 2019, **Approval has been granted to your study.**
Please note that approval of the protocol and consent form is valid for **12 months**.

Email: researchcenter@ur.ac.rw P.O Box 3286 Kigali, Rwanda www.ur.ac.rw

You are responsible for fulfilling the following requirements:

1. Changes, amendments, and addenda to the protocol or consent form must be submitted to the committee for review and approval, prior to activation of the changes.
2. Only approved consent forms are to be used in the enrolment of participants.
3. All consent forms signed by subjects should be retained on file. The IRB may conduct audits of all study records, and consent documentation may be part of such audits.
4. A continuing review application must be submitted to the IRB in a timely fashion and before expiry of this approval.
5. Failure to submit a continuing review application will result in termination of the study.
6. Notify the IRB committee once the study is finished.

Sincerely,

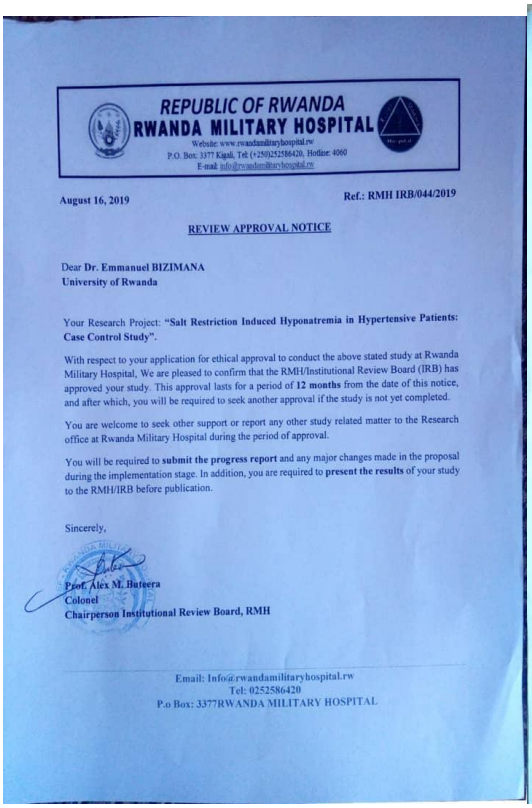
Date of Approval: The 13th May 2019

Expiration date: The 13th May 2020

Professor GAHUTU Jean Bosco
Chairperson Institutional Review Board
College of Medicine and Health Sciences, UR

Cc:
- Principal College of Medicine and Health Sciences, UR
- University Director of Research and Postgraduate Studies, UR

Email: researchcenter@ur.ac.rw P.O Box 3286 Kigali, Rwanda www.ur.ac.rw



REPUBLIC OF RWANDA
RWANDA MILITARY HOSPITAL
Website: www.rwandamilitaryhospital.rw
P.O. Box: 3377 Kigali, Tel: (+250)252586420, Hotline: 4060
E-mail: info@rwandamilitaryhospital.rw

August 16, 2019 **Ref.: RMH IRB/044/2019**

REVIEW APPROVAL NOTICE

Dear **Dr. Emmanuel BIZIMANA**
University of Rwanda

Your Research Project: **"Salt Restriction Induced Hyponatremia in Hypertensive Patients: Case Control Study".**

With respect to your application for ethical approval to conduct the above stated study at Rwanda Military Hospital, We are pleased to confirm that the RMH/Institutional Review Board (IRB) has approved your study. This approval lasts for a period of **12 months** from the date of this notice, and after which, you will be required to seek another approval if the study is not yet completed.

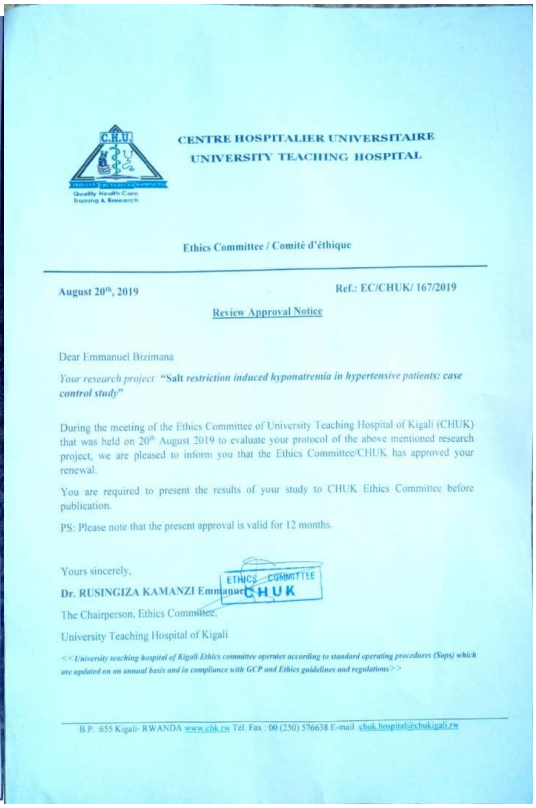
You are welcome to seek other support or report any other study related matter to the Research office at Rwanda Military Hospital during the period of approval.

You will be required to **submit the progress report** and any major changes made in the proposal during the implementation stage. In addition, you are required to **present the results** of your study to the RMH/IRB before publication.

Sincerely,

Prof. Alex M. Ruteera
Colonel
Chairperson Institutional Review Board, RMH

Email: Info@rwandamilitaryhospital.rw
Tel: 0252586420
P.o Box: 3377RWANDA MILITARY HOSPITAL



CHUK
Quality Health Care
Training & Research

CENTRE HOSPITALIER UNIVERSITAIRE
UNIVERSITY TEACHING HOSPITAL

Ethics Committee / Comité d'éthique

August 20th, 2019 **Ref.: EC/CHUK/ 167/2019**

Review Approval Notice

Dear Emmanuel Bizimana

Your research project: **"Salt *restriction induced hyponatremia in hypertensive patients: case control study*"**

During the meeting of the Ethics Committee of University Teaching Hospital of Kigali (CHUK) that was held on 20th August 2019 to evaluate your protocol of the above mentioned research project, we are pleased to inform you that the Ethics Committee/CHUK has approved your renewal.

You are required to present the results of your study to CHUK Ethics Committee before publication.

PS: Please note that the present approval is valid for 12 months.

Yours sincerely,

ETHICS COMMITTEE CHUK

Dr. RUSINGIZA KAMANZI Emmanuel

The Chairperson, Ethics Committee,

University Teaching Hospital of Kigali

<<University teaching hospital of Kigali Ethics committee operates according to standard operating procedures (Sops) which are updated on an annual basis and in compliance with GCP and Ethics guidelines and regulations>>

B.P. :655 Kigali- RWANDA www.chk.rw Tel. Fax : 00 (250) 576638 E-mail :chuk.hospital@chukigali.rw