Original Research Article

24 hour urinary sodium excretion in essential hypertension

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Abstract

Hypertension is a common medical condition; its prevalence increases with age. It is one of the most important risk factors for cardiovascular disease, which is the leading cause of mortality. High salt intake is associated with high blood pressure. The incidence of hypertension is higher in salt-sensitive individuals. Evidence shows that reduced sodium intake lowers blood pressure and can prevent hypertension. Urinary sodium excretion was used as measure of sodium intake, which equals urinary excretion under normal circumstances. The relationship between salt intake and renal ability to excrete sodium has suggested being a major importance for the long-term blood pressure treatment especially in essential hypertension. In the present study there was increased 24 hour sodium excretion in essential hypertensives indicating a high intake of sodium, which may be the cause for hypertension. Patients with high sodium excretion, who are salt sensitive hypertensives will respond to diuretics, when compared to others. The long term reduction in salt intake may significantly reduce the prevalence of hypertension and thereby decrease the associated morbidity and mortality.

Key words

Urinary Sodium Excretion, Essential Hypertension.

Introduction

High blood pressure (BP) is one of the most important risk factors for cardiovascular disease (CVD), which is the leading cause of mortality [1]. Approximately 54% of strokes and 47% of coronary heart diseases, worldwide, are attributable to high BP [2]. Hypertension is a common medical condition; its prevalence

increases with age [3], and is estimated to affect 65% of those ≥60-years-old [4]. The global population is aging. By 2030, an estimated 20% of the global population will be ≥65-years-old [5]. Hypertension doubles the risk of cardiovascular diseases, including coronary heart disease (CHD), congestive heart failure (CHF), ischemic and hemorrhagic stroke, renal failure, and peripheral arterial disease (PAD) [6]. Furthermore, this risk increases with progressive elevations in blood pressure, beginning at even normal levels of blood pressure [6].

Hypertension is largely a modifiable risk factor, with dietary salt being one of the main contributors. The link between dietary salt intake and hypertension is well established, and a reduction in salt intake has been shown to lower blood pressure (BP) [7]. High salt intake is associated with high blood pressure, which, in turn, increases the risk of stroke and cardiac vascular disease. Nevertheless, individuals respond differently to dietary salt intake, with some exhibiting an increase in BP with increasing dietary salt, while others show no significant change in BP. This phenomenon is called salt sensitivity [8]. Weinberger, et al. [9] have estimated salt sensitivity to be present in 51% of hypertensive and 26% of normotensive individuals, with the incidence of hypertension being higher in salt-sensitive individuals than in salt-resistant individuals [10]. Moreover, salt sensitivity is considered an independent risk factor for cardiovascular disease and mortality. Normotensive salt sensitive adults have a cumulative mortality rate similar to that of hypertensive adults, whereas salt-resistant normotensive adults have an increased survival rate [11].

Evidence shows that reduced sodium intake lowers blood pressure and can prevent hypertension. Observational data indicate a strong positive association between sodium intake and blood pressure within and between populations [6, 12]. Randomized trials of sodium reduction in people with and without hypertension have supported these observational findings [13, 14]. The dietary approaches to stop hypertension (DASH-sodium) study offers strong evidence of short term effects on blood pressure in a dose-response fashion [15], and five large randomized trials that lasted at least one year have confirmed a modest effect of sodium reduction on blood pressure in those with high normal blood pressure ("Pre hypertension") [16, 17]. Urinary sodium excretion was used as measure of sodium intake, which equals urinary excretion under normal circumstances [13]. The relationship between salt intake and renal ability to excrete sodium has suggested being a major importance for the long-term blood pressure treatment especially in essential hypertension. The present study is aimed at studying the relationship of 24 hour sodium excretion in essential hypertension.

High sodium intake

The PURE study estimated that in 2010, global sodium intake was 3,950mg per day, which is considerably higher than the recommended amount of ≤2,300 mg per day in all published guidelines [18]. In addition, sodium consumption varied considerably by world region from >4,200mg per day in East Asia, Central Asia and Eastern Europe to <3,300 mg per day in Latin America and sub-Saharan Africa [18].

Animal experiments, observational epidemiological studies and randomized clinical trials have demonstrated a causal relationship between sodium intake and elevated BP [19]. The majority of the observational studies was cross-sectional studies and reported a positive, linear and significant association of either dietary intake or 24-h urinary excretion of sodium with BP or hypertension [20, 21].

For example, the Intersalt study investigated the association between 24-h urinary sodium excretion and BP among 10,074 men and women aged 20–59 from 52 general population cohorts in 32 countries [20]. In analyses of within-population, a 100-mmol higher individual 24-h urinary sodium excretion was associated with a 6.0-mmHg higher average SBP and a 2.5-mmHg

higher average DBP. In analyses of across-population, a "100-mmol" higher median 24-h sodium excretion was associated with a median "4.5-mmHg" higher SBP and "2.3-mmHg" higher DBP [20, 21]. When four remote populations which are observed with extremely low urinary sodium excretion, were excluded from the across-population analyses, a 100-mmol increase in median 24-h sodium excretion which was associated with a 2.5-mmHg increase in systolic BP [20]. In the PURE study [22], there is a positive and significant association between spot urinary sodium excretion and blood pressure was also observed.

In the DASH-Sodium trial, 412 people with an average systolic BP of 120–159 mmHg and diastolic BP of 80–95 mmHg were randomly assigned to high sodium (mean urinary excretion of 142 mmol per day), intermediate sodium (mean urinary excretion of 107 mmol per day) and lower sodium diets (mean urinary excretion of 65 mmol per day) for 30 days in a crossover design [23]. The results showed that reducing sodium intake from a high to an intermediate level lowered systolic BP by 2.1 mmHg ($P<0.01$) [23].

Several meta-analyses of clinical trials have shown that sodium reduction significantly lowers BP in hypertensive and normotensive individuals [24]. An Agency for Healthcare Research and Quality (AHRQ) meta-analysis that included 48 randomized control trials found a significant BP-lowering effect of dietary sodium reduction in adults both with and without hypertension [25]. In this study, a 42-mmol decrease in the weighted mean sodium intake was associated with a 3.23-mmHg (95% CI 2.41–4.06) reduction in systolic BP and a 2.24-mmHg (95% CI 1.61–2.96) reduction in diastolic BP [25].

Despite the strong positive association between dietary sodium intake, BP and risk of hypertension, the associations of sodium intake with risk of CVD, CKD and mortality are inconsistent [25]. Some studies have found a positive association between dietary sodium intake and these clinical outcomes, whereas others have found inverse, J-shaped or U-shaped associations [26, 27]. These conflicting findings can likely be partly explained by methodological limitations, such as systematic and random error in sodium measurements, reverse causality, insufficient statistical power, residual confounding, and inadequate follow-up duration [25, 28].

In summary, dietary sodium reduction should be recommended to lower population BP levels and risk of hypertension. More research is needed, however, to determine optimal dietary sodium intake for the prevention of CVD, CKD and mortality.

Mechanism of essential hypertension:

No single specific cause is referred to as primary in preference to essential. Blood pressure is product of cardiac output and peripheral vascular resistance (B.P=C.O*PVR). Since persistent hypertension can develop only in response to an increase in cardiac output or a rise in peripheral resistance, defects may be present in one or more of the multiple factors that affect these two forces. This can be described under the following headings

1. Non renal factors 2. Renal factors.

1) Non renal factors

Essential hypertension is a complex multi-factorial and polygenic disorder that results from an interaction between an individual's genetic background and various environmental factors.

Genetic predisposition:

In studies of twins and family members in which degree of familial aggregation of blood pressure level is compared with the closeness of genetic sharing, the genetic contributions have been estimated to range from 30% to 60%. Harrap [29] suggested that the average population blood pressure is determined by the environment but the blood pressure rank within the distribution is decided largely by genes. Epidemiological data suggest that for population variability in blood pressure, 30-35% is contributed genetic factors,

common household environment is contributed about 10-15% and the contribution of the remaining 50-55% is non-familial factors. If genetic markers of a predisposition for the development of hypertension are found, then specific environmental manipulations could then be directed toward the susceptible subject [30]. Pratt [31], from his observations of bimodal distributions of blood pressure in some families with hypertensive subjects, proposed autosomal dominant mode of inheritance. Pickering [32] proposed that blood pressure is a quantitative trait with genetic contribution which is polygenic. Polymorphism of genes involving RAS system, aldosterone synthesis and adrenergic receptors has been noted to be more common in the hypertensive than normotensive patients [33]. Genetic abnormalities may be monogenic in some rare forms of hypertension like glucocorticoid remediable aldosteronism, Liddle syndrome, and apparent mineralocorticoid excess [34].

Vascular remodelling

Hypertension elicits two different kinds of diffuse structural changes in the systemic microcirculation. One, (1) termed rarefaction, consists in an abnormally low spatial density of arterioles, capillaries, and possibly venules. The other (2) concerns structural modifications of resistance small arteries and arterioles, which lead to a reduction in lumen diameter and are grouped under the generic name of "remodelling" [35]. Vascular wall remodeling is the result of changes in cellular and non-cellular components, depending on the disease process causing the changes. Changes in the growth and migration of VSMC, endothelial dysfunction, inflammatory processes, and the synthesis or degradation of extracellular matrix components may be present during the disease process [35]. The term remodeling was first applied to resistance vessels by Baumbach and Heistad, based on observations made in pial arterioles from stroke-prone spontaneously hypertensive rats (SPSHRs), to indicate a structural rearrangement of existing wall material around a smaller lumen [36]. Hypertension in these resistance vessels is associated with structural changes such as reduction in lumen diameter and increase in Media/Lumen ratio. This mode of structural change has been called "remodeling" [36]. Remodeling of these vessels leads to increase in Peripheral vascular resistance and contributes to high blood pressure and its associated target organ damage [37].

Neuro humoral causes of Essential hypertension

A large number of circulatory hormones and locally acting substances may be involved in the development of hypertension which causes hypertension by vascular hypertrophy, capillary rarefaction and unpaired microvascular dilation [38].

A. Sympathetic nervous system:

Increased sympathetic nervous system activity increases blood pressure and contributes to the development and maintenance of hypertension through stimulation of the heart, peripheral vasculature, and kidneys, causing increased cardiac output, increased vascular resistance, and fluid retention [39]. In addition, autonomic imbalance (increased sympathetic tone accompanied by reduced parasympathetic tone) has been associated with many metabolic, hemodynamic and trophic abnormalities that result in increased cardiovascular morbidity and mortality [40].

Clinical studies have shown positive correlations between circulating norepinephrine levels, left ventricular mass, and reduced radial artery compliance (an index of vascular hypertrophy) [41]. Thus, sympathetic mechanisms contribute to the development of target organ damage, as well as to the pathogenesis of hypertension.

B. Renin angiotensin system:

Both as a direct pressor and as a growth promoter renin angiotensin system may be also involved in pathogenesis of hypertension. All functions of renin are mediated through the angiotensin II. This system is the primary stimulus for the

secretion of aldosterone and hence mediates mineralocorticoid responses to varying sodium intake and volume overload when sodium intake is reduced or effective plasma volume shrinks, the increase in renin- angiotensin II stimulates aldosterone secretion which in turn is responsible for a portion of the enhanced renal retention of sodium and water.

When large proportions of hypertensives are surveyed, only about 30 percent have low plasma renin activity levels, whereas 50 percent have normal levels and the remaining 20 percent have high levels [42].

Normal and high renin hypertension:
Some persons with essential hypertension have normal or high renin activity. The concept of "nephron heterogencity" [43] described by Sealy & colleagues, assumes a mixture of normal and ischemic nephrons caused by afferent arteriolar narrowing. Excess renin from the ischemic nephrons could raise the total blood renin levels to varying degrees and cause high renin levels in patients with essential hypertension.

C. Hyperinsulinemia / Insulin resistance
An association between hypertension and hyperinsulinemia has been recognized for many years, particularly with accompanying obesity but also in about 20% of non-obese hypertensive patients [44]. The hyperinsulinemia of hypertension arises as a consequence of resistance to effects of insulin on peripheral glucose utilisation. This association does not apply to pima Indians but it has been found in blacks, Asians and as well as whites.

The impairment of the peripheral actions of the insulin results from a defect in the usual vasodilatory effect of insulin mediated through increased synthesis of nitric oxide, which normally counters the multiple pressors effects of insulin [45]. These pressor effects include activation of sympathetic activity, a trophic action on vascular hypertrophy, and increased renal sodium reabsorption resulting in a rise in blood pressure that may be either a primary cause of hypertension or, at least, a secondary potentiator.

D. Endothelial cell dysfunction:
Nitric oxide is a potent vasodilator, inhibitor of platelet adhesion and aggregation, and suppressor of migration and proliferation of vascular smooth-muscle cells. Nitric oxide is released by normal endothelial cells in response to various stimuli, including changes in blood pressure, shear stress, and pulsatile stretch, and plays an important role in blood pressure regulation, thrombosis, and atherosclerosis [40]. In normal conductance arteries, platelets and monocytes circulate freely, and oxidation of low-density lipoprotein is prevented by a preponderance of nitric oxide (NO) formation. At the level of the small arterioles, reduced vascular tone is maintained by constant release of nitric oxide. Endothelin-1 normally induces no vasoconstriction or only minimal vasoconstriction through stimulation of type A endothelin receptors (ETA) located on smooth-muscle cells and contributes to basal nitric oxide release by stimulating type B endothelin receptors (ETB) on endothelial cells. In the hypertensive microvasculature, decreased activity of nitric oxide and enhanced ETA-mediated vasoconstrictor activity of endothelin-1 result in increased vascular tone and medial hypertrophy, with a consequent increase in systemic vascular resistance. At the level of conductance arteries, a similar imbalance in the activity of endothelial factors leads to a pro-atherosclerotic milieu that is conducive to the oxidation of low-density lipoprotein, the adhesion and migration of monocytes, and the formation of foam cells. These activities ultimately lead to the development of atherosclerotic plaques, the rupture of which, in conjunction with enhanced platelet aggregation and impaired fibrinolysis, results in acute intravascular thrombosis, thus explaining the increased risk for cardiovascular events in patients with hypertension. These mechanisms may be operative in patients with high normal blood pressure and may contribute to their increased cardiovascular risk [46].

2) Renal retention of excess dietary sodium

Sodium is predominantly an extracellular ion and is a primary determinant of the extracellular fluid volume. When NaCl intake exceeds the capacity of the kidney to excrete sodium, vascular volume may initially expand and cardiac output may increase. However, many vascular beds have the capacity to autoregulate blood flow, and if constant blood flow is to be maintained in the face of increased arterial pressure, resistance within that bed must increase, as arterial pressure increases in response to a high NaCl intake, urinary sodium excretion increases and sodium balance is maintained at the expense of an increase in arterial pressure. The mechanism for this "pressure-natriuresis" phenomenon may involve a subtle increase in the glomerular filtration rate, decreased absorbing capacity of the renal tubules, and possibly hormonal factors such as atrial natriuretic factor. In individuals with an impaired capacity to excrete sodium, greater increases in arterial pressure are required to achieve natriuresis and sodium balance. NaCl-dependent hypertension may be a consequence of a decreased capacity of the kidney to excrete sodium, due either to intrinsic renal disease or to increased production of a salt-retaining hormone (mineralocorticoid) resulting in increased renal tubular reabsorption of sodium. Renal tubular sodium reabsorption also may be augmented by increased neural activity to the kidney. In each of these situations, a higher arterial pressure may be required to achieve sodium balance. Conversely, salt-wasting disorders are associated with low blood pressure levels. ESRD is an extreme example of volume-dependent hypertension. In ~80% of these patients, vascular volume and hypertension can be controlled with adequate dialysis; in the other 20%, the mechanism of hypertension is related to increased activity of the renin-angiotensin system and is likely to be responsive to pharmacologic blockade of renin-angiotensin [6].

A considerable amount of circumstantial evidence supports a role for sodium in the genesis of hypertension. To induce hypertension some of the excess sodium must be retained by the kidneys such retention could arise in a number of ways.

1. Nephron heterogeneity, described as the presence of a sub population of nephrons that is ischemic either from afferent arteriolar vasoconstriction or from an intrinsic narrowing of lumen. Renin secretion from this subgroup of nephrons is tonically elevated. This increased renin secretion then interferes with capacity of normal nephrons to excrete sodium.
2. A resetting of the normal pressure natriuresis relationship- Guyton hypothesis [47].
3. An acquired inhibitor of the sodium pump or other abnormalities in sodium pump or other abnormalities in sodium transport in the nephron [48].
4. Defensive responsiveness to atrial natriuretic peptide hormone [49].

The concept of salt sensitivity and blood pressure

There is substantial evidence that blood pressure responses to dietary salt intake vary among individuals with hypertension and even with normotensive individuals. Some people can effectively excrete high dietary salt intake without an increase in arterial BP and others cannot excrete effectively without an increase in arterial BP. Former individuals who can excrete salt intake effectively are called "salt sensitive" and latter individuals who cannot are called "salt insensitive".

Strauss, et al. [50] in 1958 showed that the daily relation between dietary sodium intake and renal sodium excretion was determined in humans subjected to a step increase of salt intake from 10 to 150mmol/day. Salt sensitivity is characterized by an alteration of kidney function that necessitates higher arterial pressure to excrete a given amount of sodium and is expressed as a reduction in the slope of the pressure-natriuresis relationship. It was shown that the amount of sodium and water retained with such an increase of sodium intake leads to a body weight increase. In most studies, salt sensitivity is defined as the acute blood pressure change in mean blood

pressure corresponding to a decrease or increase of sodium intake. Usually, salt sensitivity is arbitrarily defined as an increase in blood pressure of 10% or greater during a high salt diet than that during a low salt diet.

In 1962, Dahl [51] demonstrated variability in blood pressure response to salt loading in normal rats. Dahl developed two strains of rats: a salt-sensitive (SS) strain and a salt-resistant (SR) strain. The former strain becomes hypertensive with time after receiving an 8% sodium chloride diet; the latter strain does not develop hypertension in response to a high-sodium diet [104]. Similar animal study has been performed on chimpanzees, our closest relatives on a genetic basis.

In humans, Kawasaki, et al. in 1978 [52], were among the first to recognize a great variability in blood pressure response to sodium loading in a group of patients with essential hypertension. They studied 19 hypertensive subjects who were observed after a "normal" (109mmol/d), "low" (9 mmol/d), and then "high" (249mmol/d) sodium intake. Blood pressure fell significantly ($p<0.05$) in the entire population with a dietary salt restriction and increased significantly ($p<0.05$) back to baseline levels after the high salt phase. The investigators then arbitrarily separated the population into two groups, identifying one as salt sensitive (n=9), those who demonstrated at least a 10% increase in mean arterial pressure when the low and high salt intake periods were compared, and the other as non-salt sensitive (n=10), those having smaller increases in blood pressure with salt loading. On the basis of this response, patients with hypertension were classified as either salt sensitive or not salt sensitive.

Weinberger, et al. [53] evaluated in 378 normotensive and 198 hypertensive humans by two approaches. Blood pressure was measured after an intravenous infusion of 2 L of normal saline (0.9%) and after sodium and volume depletion induced by a low sodium diet and furosemide administration. They arbitrarily separated the population into two groups, those in whom mean arterial blood pressure decreased by at least 10mmHg after sodium and volume depletion were considered sodium-sensitive, and those with a decrease of 5mmHg or less (including an increase in pressure) were considered sodium resistant. The second study utilized the blood pressure response to modest dietary sodium restriction in 74 normotensive subjects to identify sodium sensitivity and resistance. In both studies the responses were heterogeneous. 51% of hypertensives and 26% of normotensives were found to be sodium sensitive in this study. The blood pressure response was reproducible in 28 subjects studied twice.

In the GenSalt study [54], participants received a low-sodium diet (3 g of salt or 51.3mmol of sodium per day) for 7 days followed by a high-sodium diet (18 g of salt or 307.8mmol of sodium per day) for 7 days, with BP measured three times during the last 3 days of each intervention phase. BP responses to chronic low- and high-sodium dietary interventions, usually lasting 5-14 days, were also measured. Previous prospective cohort studies have also indicated that salt sensitivity is a strong predictor for CVD and total mortality in hypertensive and normotensive participants. The GenSalt study group examined BP responses to dietary sodium and potassium interventions by sex, age, and baseline BP subgroups among 1906 Chinese men and women aged 16 years or older who participated in the Genetic Epidemiology Network of Salt Sensitivity (GenSalt) [55]. This study showed that female gender, older age, and elevated baseline BP levels increase BP responses to dietary sodium intervention. In addition, elevated baseline BP levels increase BP responses to dietary potassium intervention. Therefore, a diet low in sodium and high in potassium should be especially effective in reducing BP among persons with hypertension or prehypertension, whereas a diet low in sodium may be more effective in reducing BP among women and the elderly.

Development of Salt-Sensitive Hypertension [40]

The development of salt-sensitive hypertension is proposed to occur in 3 phases.

In the first phase, the kidney is structurally normal and sodium is excreted normally. However, the kidney may be exposed to various stimuli that result in renal vasoconstriction, such as hyperactivity of the sympathetic nervous system or intermittent stimulation of the renin–angiotensin system. During this phase, the patient may have either normal blood pressure or borderline hypertension, which (if present) is salt-resistant.

In the second phase, subtle renal injury develops, impairing sodium excretion and increasing blood pressure. This phase is initiated by ischemia of the tubules, which results in interstitial inflammation (involving mononuclear-leukocyte infiltration and oxidant generation), which in turn leads to the local generation of vasoconstrictors, such as angiotensin II, and a reduction in the local expression of vasodilators, especially nitric oxide. In addition, renal vasoconstriction leads to the development of preglomerular arteriolopathy, in which the arterioles are both thickened (because of smooth-muscle cell proliferation) and constricted. The resulting increase in renal vascular resistance and decrease in renal blood flow perpetuate the tubular ischemia, and the glomerular vasoconstriction lowers the single-nephron glomerular filtration rate (GFR) and the glomerular ultrafiltration coefficient (Ki). These changes result in decreased sodium filtration by the glomerulus. The imbalance in the expression of vasoconstrictors and vasodilators favoring vasoconstriction also leads to increased sodium reabsorption by the tubules; together, these changes lead to sodium retention and an increase in systemic blood pressure.

In the third phase, the kidneys equilibrate at a higher blood pressure, allowing them to resume normal sodium handling. Specifically, as the blood pressure increases, there is an increase in renal perfusion pressure across the fixed arterial lesions. This increase helps to restore filtration and relieve the tubular ischemia, thereby correcting the local imbalance in vasoconstrictors and vasodilators and allowing sodium excretion to return toward normal levels. However, this process occurs at the expense of an increase in systemic blood pressure and hence a rightward shift in the pressure–natriuresis curves. In addition, this condition is not stable, since the increase in blood pressure may lead to a progression in the arteriolopathy, thereby initiating a vicious circle. During this phase, sodium sensitivity may be observed as a decrease in blood pressure when sodium intake is restricted, whereas increased sodium intake will have a lesser effect on blood pressure because of the intact but shifted balance between blood pressure and natriuresis. The early phase of this pathway may be bypassed in the presence of other mechanisms, such as primary tubulointerstitial disease, genetic alterations in sodium regulation and excretion, or a congenital reduction in nephron number that limits the sodium filtration.

Aim and objectives

- To study 24 hours urinary sodium excretion in patients with essential hypertension attending Malla Reddy Institute of Medical Sciences.
- To correlate 24 hour urine sodium excretion with respect to their stages of hypertension as in Joint National Committee VII, age, sex, duration of hypertension.
- To correlate 24 hour urine sodium excretion with proteinuria, albuminuria.

Materials and methods

Inclusion criteria

- Patients with Essential hypertension aged between 40-60 years of either gender
- Patients who gave consent

Exclusion criteria

- Pregnant women
- Patients with renal diseases
- Patients with thyroid disorder
- Patients who are on steroids and OCPs
- Patients who are smokers and alcoholics
- Patients with secondary hypertension
- Hypertensive urgency and emergency
- Acute coronary syndrome
- Severe arrhythmias
- Diabetes mellitus
- Cerebrovascular accidents
- Chronic kidney disease
- Adrenal tumors

Methodology

The study was done in Department of General Medicine in Malla Reddy Institute of Medical Sciences.

Study Design: Prospective Observational Study
Study period: January 2020 to July 2021
Sample size: 50 patients.

Institutional ethics committee approval was taken and informed consent was taken from the patient. 24 hrs Urinary sodium was assessed using Roche Hitachi—an indirect ion-selective electrode to determine ion concentration [6].

Microalbuminuria was assessed by one step MAU Rapid Quantitative test.

24 hrs Proteinuria was assessed by Pyrogallol Red Method.

Results

The total number of subjects included in this study was 50. Among cases 25 were in stage I hypertension and 25 were stage II hypertension, according to JNC VII guidelines.

The age of the subjects in the study group ranged from 40 to 60 years. The mean and standard deviation for cases was 52.44±7.04 (**Table – 1**).

Among subjects in the study group there were 29 males and 21 females (**Table – 2**).

Table – 1: Distribution of cases in relation to age.

Age in years	No. of patients	Percentage
40 to 45	12	24%
46 to 50	7	14%
51 to 55	8	16%
56 to 60	23	46%
Mean	52.44	
S.D	52.44±7.04	

Table – 2: Distribution of cases in relation to gender.

Sex	No. of patients	Percentage
Male	29	58.0%
Female	21	42.0%

Table – 3: Distribution of cases in relation to stage of hypertension.

Stage of Hypertension	No. of patients	Percentage
Stage 1	25	50.0%
stage 2	25	50.0%

Table – 4: Mean SDP and DBP with stage of hypertension.

Stage of Hypertension	Mean SBP (mm of Hg)	Mean DBP (mm of Hg)
Stage 1	151.6	94.6
Stage 2	160.0	100.0

The study group comprises both stage I and stage II hypertensives. Among stage I hypertensives total number of cases were 25 and mean SBP is 151.6 and mean DBP was 94.6 mm of Hg. Among stage II hypertensives there were 25 cases and mean SBP and mean DBP 160.0, 100.0 mm of Hg respectively (**Table – 3, 4**).

The group of cases comprises of both stage I and stage II hypertensives. Among stage I hypertensive cases there were 13 males and 12 females. Among stage II hypertensives there were 16 males and females (**Table – 5**).

Based on duration of hypertension total cases were distributed as denovo, less than 1 year, and 1 to 5 years and more than 5 years which

includes number of cases as 21,9,14,6 respectively. Most of the cases included in the study are of denovo hypertensives comprising 42% (**Table – 6**).

Table – 5: Distribution of cases with stage of Hypertension in relation to Sex.

Sex	Stage I		Stage II	
	Number	percentage	Number	percentage
Male	13	52%	16	64%
Female	12	48%	09	36%
Total	25	100%	25	100%

Table – 6: Distribution of cases with Duration of hypertension.

Duration of hypertension	No. of patients	Percentage
Denovo	21	42%
1 year and less	9	18%
1 to 5 years	14	28%
More than 5 years	6	12%

Table – 7: 24 hour urinary sodium excretion levels.

24 Hour Urinary Sodium Excretion Levels	<220	>220
No. of patients	11	39
Mean sodium excretion value	168.6±8.48	347.41±118.0

Table - 8: 24 hr urinary sodium excretion levels and systolic blood pressure.

24 Hr Urinary Sodium (mmol/24hrs)	SBP		P Value (t-test)
	Mean	Std. Deviation	
Normal	145.45	8.202	0.054
Increased	153.59	12.873	

Table - 9: 24 Hour Urinary Sodium Excretion Levels And Diastolic Blood Pressure.

24 Hr Urinary Sodium (mmol/24hrs)	DBP		P Value (t-test)
	Mean	Std. Deviation	
Normal	90.00	7.746	0.013
Increased	95.90	6.373	

Table - 10: Relation between SBP and urinary sodium excretion.

	SBP	
24 Hr Urinary Sodium (mmol/24hrs)	Pearson Correlation	.467
	Sig. (2-tailed)	.001
	N	50

The main aim of our study was to study twenty four hour Urine sodium among subjects. Among 50 number of total patients 11 patients had normal sodium excretion mean value of sodium excretion was 168.6 and S.D.8.48 and 39 patients had increased sodium excretion with mean value of sodium excretion was 347.41 and S.D.118.0 (**Table – 7**).

In a total of 50 subjects, cases with normal 24 hr urinary sodium excretion had mean SBP was 90mmHg with S.D 8.202 and patients with increased sodium excretion mean SBP was

153.59 with S.D 12.873.SBP in patients with increased 24 hr urinary sodium excretion is higher than patients with normal 24 hr urinary sodium excretion. P-value was 0.054 which was statistically not significant. This suggests that there was no significant relation between SBP with increase in 24 hour urinary sodium excretion (**Table – 8**).

Table – 11: Relation between DBP and urinary sodium excretion.

	DBP	
24 Hr Urinary Sodium (mmol/24hrs)	**Pearson Correlation**	.515
	Sig. (2-tailed)	.000
	N	50

Table – 12: Stage of hypertension and urinary sodium excretion.

Stage of hypertension	**Total no of patients**	**Increased urinary sodium excretion**
Stage 1	25	17
Stage 2	25	23

Table - 13: 24 Hr Urinary Sodium Excretion Levels And Stages Of Hypertension.

Stage of HTN	**24 Hr Urinary Sodium (mmol/24hrs)**		**P Value (t-test)**
	Mean	**Std. Deviation**	
Stage 1	251.20	67.826	<0.001
Stage 2	369.64	120.261	

Table – 14: Left ventricular Hypertrophy.

Left ventricular hypertrophy	**No. of patient**	**Percentage**
LVH present	18	32.0%
LVH absent	32	68.0%

Table – 15: Urinary sodium levels and LVH.

LVH Present			**LVH Absent**		
Total No. of subjects	**Normal sodium**	**Increased sodium**	**Total no. of patients**	**Normal sodium**	**Increased sodium**
16	1	15	34	9	25

Table - 16: Mean Sodium Excretion With Left Ventricular Hypertrophy.

LVH	**24 Hr Urinary Sodium (mmol/24hrs)**		**P Value (t-test)**
	Mean	**Std. Deviation**	
Present	401.94	126.324	<0.001
Absent	267.35	77.152	

In a total of 50 subjects, cases with normal 24 hr urinary sodium excretion had mean DBP was 90mmHg with S.D 7.746 and patients with increased sodium excretion mean DBP was 95.90 with S.D 6.736. DBP in patients with increased 24 hr urinary sodium excretion is higher than patients with normal 24 hr urinary sodium excretion. P-value was 0.013 which was statistically significant. This suggests that there was significant relation between DBP with increase in 24 hour urinary sodium excretion (**Table – 9**).

Table – 17: Relation between urinary sodium excretion and proteinuria.

24 Hr Urinary Proteinuria (mg/L)	24 Hr Urinary Sodium (mmol/24hrs)		Total
	Normal	Increased	
Normal	11	19	30
Abnormal	0	20	20
Total	11	39	50

P Value 0.002(Chi-Square Te Test)

Table – 18: Mean sodium excretion and proteinuria.

24 Hr Urinary Proteinuria (mg/L)	24 Hr Urinary Sodium (mmol/24hrs)		P Value (t-test)
	Mean	Std. Deviation	
Normal	249.60	67.327	<0.001
Abnormal	401.65	108.575	

Table – 19: Correlation between increased sodium excretion and proteinuria.

		24 Hr Urinary Proteinuria (mg/L)
24 Hr Urinary Sodium (mmol/24hrs)	Pearson Correlation	.807
	Sig. (2-tailed)	.000
	N	50

Table – 20: Relation between urinary sodium excretion and microalbuminuria.

Micral Test	24 Hr Urinary Sodium (mmol/24hrs)		Total
	Normal	Increased	
Normal	9	14	23
Increased	2	25	27
Total	11	39	50

Table – 21: Relation between mean urinary sodium excretion and microalbuminuria.

Micral Test	24 Hr Urinary Sodium (mmol/24hrs)	
	Mean	Std. Deviation
Normal	246.61	74.526
Increased	364.78	113.890

Table – 22: Correlation between increased sodium excretion and albuminuria.

	Micral Test	
24 Hr Urinary Sodium (mmol/24hrs)	**Pearson Correlation**	0.673
	Sig. (2-tailed)	.000
	N	50

Correlation between SBP and urinary sodium excretion was observed in the study. Statistical analyses showed a positive correlation between SBP and urinary sodium excretion (r=0.467) and it was statistically significant (P=0.001) as per **Table – 10**.

The relationship between DBP and urinary sodium excretion is observed. In 50 total number of cases 24hr urinary sodium excretion was positively correlated with DBP(r=0.515). P-value was <0.001 which was statistically significant (**Table – 11**).

Table – 12 shows the no. of patients with increased sodium excretion with each stage of hypertension.25 patients with stage 1 hypertension shows increased sodium excretion in 17 patients. 25 patients with stage 2 hypertension shows increased sodium excretion in 23 patients.

Table - 13 shows the mean and standard deviation of urinary sodium among cases with stage 1 and stage 2 hypertensives. The urinary sodium level was significantly higher among stage I hypertensives than stage II hypertensives. (P value= <0.001).

Among 50 subjects, left ventricular hypertrophy was seen in 18 cases. **Table - 14** shows the number of patients with LVH and without LVH
Table - 15 shows the subjects with presence and absence of LVH with urinary sodium excretion.16 subjects with LVH presence 1 subject had normal sodium excretion and 15 subjects had increased sodium excretion.34 subjects with absent LVH 9 subjects had normal sodium excretion and 24 had high sodium excretion.

Table - 16 shows mean and standard deviation of urinary sodium excretion with respect to LVH. The statistical analysis of urinary sodium and with respect to their LVH showed that there is significantly high urinary sodium in cases with LVH present than cases with LVH absent (P=<0.001).

In a total of 50 subjects, 11 cases have normal 24 hr urinary sodium excretion with normal proteinuria. Total of 39 patients with increased 24 hr urinary sodium excretion 19 cases have normal proteinuria and 20 cases have increased proteinuria. P-value was 0.002 which is statistically significant. This suggests that there was significant increase in proteinuria with increase in 24 hour urinary sodium excretion (**Table – 17**).

In the study, the mean sodium excretion in the patients with normal proteinuria was 249.60 with S.D.67.327 and in patients with increased sodium excretion was 401.65 with S.D.108.575. The patients with increased proteinuria was having more amount of 24 hour urinary sodium. P-value was <0.001 which is statistically significant. This suggests that there was significant increase in proteinuria with increase in 24 hour urinary sodium excretion (**Table – 18**).

In our study relationship between sodium excretion and proteinuria is positively correlated with pearson correlation coefficient 0.807 with P-value <0.001. This suggests that there was significant increase in proteinuria with increase in 24 hour urinary sodium excretion (**Table – 19**).

In a total of 50 subjects,9 cases have normal 24 hr urinary sodium excretion with normal microalbuminuria and 2 cases have normal 24 hr urinary sodium excretion with increased microalbuminuria. Total of 39 patients with increased 24 hr urinary sodium excretion 14 cases have normal microalbuminuria and 25 cases have increased microalbuminuria. P-value is 0.007 which was statistically significant. This suggests that there was significant increase in microalbuminuria with increase in 24 hour urinary sodium excretion (**Table – 20**).

In the study, the mean sodium excretion in the patients with normal microalbuminuria was 246.61 with S.D.74.526 and in patients with increased sodium excretion was 364.78 with S.D.113.890. The patients with increased microalbuminuria were having more amount of 24 hour urinary sodium. This suggests that there was significant increase in proteinuria with increase in 24 hour urinary sodium excretion (**Table – 21**).

In our study, relationship between sodium excretion and microalbuminuria is positively correlated with pearson correlation coefficient 0.807 with P-value <0.001. This suggests that there was significant increase in microalbuminuria with increase in 24 hour urinary sodium excretion (**Table – 22**).

Discussion

Hypertension is one of the world's greatest public health problems and leading cause of death [56]. Essential hypertension accounts for about 90% of all hypertensive patients [57]. Multiple factors are responsible for the development of hypertension. One of the causal factors proposed for hypertension is high sodium [58]. Present study was conducted to see increased sodium excretion in hypertensive patients which is an indirect measure of high salt intake. In the present study most of the patients belong to the age group 55-60 comprising 46% and males are more in the study i.e. 58%. According to the study done by G Radhika, et al. [56]; Mean dietary salt intake (8.5 g/d) in the population was higher than the recommended by the World Health Organization (< 5g/d).

24 hour urine sodium and hypertension

Hypertension is a major contributor to cardiovascular disease (CVD), the leading cause of death in the United States. Control of blood pressure (BP) among individuals with hypertension would avert ~46,000 deaths per year. Thus, hypertension control is a major public health priority. Yet rates of hypertension and hypertension control are not uniformly distributed throughout the population. In our study the mean and standard deviation for 24 hour urine sodium in is 290.22 and standard deviation is 141.71.

According to a study done by RA Jan, et al. [59] (2006), Srinagar, Kashmir urinary sodium excretion was more in stage 2 hypertensives than stage 1 hypertensives. In our study the mean and standard deviation for 24 hour urine sodium in stage 1 and stage 2 hypertensives were 270.76± 133.48and 317.68±140.82. So, there is more increase in sodium excretion in hypertensive patients (more in stage II than stage I hypertensives). This observation was consistent with the RA Jan, et al. study.

24 hr urine sodium excretion and systolic blood pressure

High systolic blood pressure (SBP) is the largest single risk for death globally. High intake of sodium is an important dietary risk factor for high blood pressure (BP). High-quality epidemiological studies and systematic reviews show strong evidence that high sodium intake causes high BP and there is moderately strong evidence from clinical trials for causing cardiovascular diseases. In general, the current diets of populations across the globe contain much higher than recommended sodium [60].

In study done by Naser AM, et al. [61], a total of 9804 person-visits with 24-h urine collections, 7176 (73%) reported no missed voids, and 5524 (56%) reported 22–26 h of urine collection and no missed voids, they identified a plateaued relationship between the urine sodium and systolic blood pressure relationship above the 50th percentile distributions of urine sodium. Randomized controlled trials, in contrast, show a mostly linear relationship between dietary sodium intake and blood pressure, with potentially a steeper relationship at sodium intake below 100 mmol/day.

In a study done by Sandra L Jackson, et al. [62], with an objective was to assess the associations of blood pressure and hypertension with 24-hour urinary excretion of sodium and potassium among US adults. Cross-sectional data were obtained from 766 participants age 20 to 69 years with complete blood pressure and 24-hour urine collections in the 2014 National Health and Nutrition Examination Survey, a nationally representative survey of the US non-institutionalized population. After multivariable adjustment, each 1000-mg difference in usual 24-hour sodium excretion was directly associated with systolic (4.58 mm Hg; 95% confidence interval (CI), 2.64-6.51) and diastolic (2.25 mm Hg; 95% CI, 0.83-3.67) blood pressures. Hypertension was linearly associated with progressively higher sodium and lower potassium excretion(P=<0.001).In our study the mean SBP in patients with normal sodium excretion is 145.45 mm of Hg with S.D 8.202 and mean SBP in patients with increased urinary

sodium excretion is 153.59 mm of Hg with S.D. 12.873, which is statistically not significant (P=0.054).There is a positive correlation between SBP and 24 hour sodium excretion which indicates higher the sodium excretion is associated with increase in SBP, the findings which are consistent with the above study (r=0.467, P=0.001).

In a study done by Weizhong Han, et al. [63] with main objective of this study was to determine baseline salt intake levels in a sample of the adult population of Shandong province and to establish the relationship between urinary sodium excretion and blood pressure. A total of 512 participants were recruited, and all the participants provided complete 24-hour urine collections. Correlations between blood pressure and urinary sodium were analyzed by calculating Spearman correlation coefficients. Urinary sodium excretion showed a significant positive correlation with SBP (r = .73, P < .001) and DBP (r = .62, P < .001) in all subjects. Similar observation is seen in our study with Urinary sodium excretion showed a significant positive correlation with SBP (r = .467, P =.001) and DBP (r = .515, P < .001)

24 hour urine sodium excretion and diastolic blood pressure

B.M.Y. Cheung, et al. [64], studied 70 Hong Kong Chinese patients with untreated hypertension and 47 normotensive controls. The primary hypothesis tested was a correlation between diastolic blood pressure and 24 hour sodium excretion. In hypertensive patients, diastolic blood pressure correlated with 24-h urinary sodium excretion (r=0.41, p<0.001).This observation is consistent with our study diastolic blood pressure correlated with 24-h urinary sodium excretion (r=0.515, p<0.001).

In a study done by Li-qin Duan, et al. [65], A total of 643 participants were observed. The results revealed that 24-h urinary sodium excretion and morning urinary sodium concentration significantly positively correlated with SBP and DBP (P=<0.001). The SBP and DBP increased by 0.022 and 0.022 mmHg, respectively, with an increase in every 1 mmol of 24-h urine sodium concentration. Our study is also consistent with the observations of the above study with positive correlation between 24 hr urinary sodium excretion and DBP.

24 hour urine sodium in relation with age

Age was the first factor to be independently associated with blood pressure .Age influences the capacity of kidneys to conserve sodium [35]. Advancing age leads to both a decline in glomerular filtration rate and an increased incidence of renal disease [36] which contributes to increased urinary sodium excretion in elderly people [37]. This was proved by our study which showed a significant increase in 24 hour urinary sodium excretion with advancing age.

24 hour urine sodium in relation with duration of hypertension

In this study, the effect of duration of hypertension on 24 hour sodium excretion is observed. The patients with denovo hypertension had high levels of mean 24 hour sodium excretion (319.57 mmol/24hrs) with S.D. 119.627. Patients diagnosed as hypertension in less than 1 year had mean 24 hour sodium excretion 271.89 mmol/24 hrs with S.D. 100.77 and the patients with hypertension with a duration of 1-5 years mean 24 hour sodium excretion 341.07 mmol/24hrs with S.D. 120.647 and patients with hypertension with a duration of >5 years mean 24 hour sodium excretion mean 24 hour sodium excretion 264.67mmol/24hrs with S.D. 84.092 which is not statistically not significant compared to other studies stating that as duration of hypertension increases damage to the renal vasulature increases causing more increase in sodium excretion.

24 hour urine sodium in relation with stage of hypertension

Our study observed significant influence of 24 hour urinary sodium excretion on the severity of hypertension. The mean 24 hour urinary sodium excretion in grade 1 hypertension is 251.20 mmol/24hrs with S.D. 67.826 and mean 24 hour

urinary sodium excretion in grade 2 hypertension is 369.64 mmol/ 24hrs with S.D. 120.261.The mean 24 hour urinary sodium excretion was significantly higher in patients with severe hypertension as compared to mild to moderate hypertension which was statistically significant (p value = <0.001). Similar observations were also recorded by RA Jan, et al. in 2006 [4].

24 hrs urine sodium excretion and left ventricular hypertrophy

Results from observational studies among and within various populations have shown a positive relationship between sodium intake and arterial pressure in all age groups [66, 67]. In addition, a meta-analysis of 78 trials indicated that the change in arterial pressure associated with a reduction in sodium intake by 50 mmol for 5 weeks or longer resulted in an average decrease in systolic pressure of 5 mm Hg in normotensive subjects and 7 mm Hg in hypertensive patients.3 As previously suggested in a European study,4 investigators of the Dietary Approaches to Stop Hypertension study recently showed that reduction in daily sodium intake from 150 to 100 and 50 mmol for 30 days resulted in a decrease in systolic arterial pressure of 2.1 and 6.7 mm Hg, respectively, in patients with moderate essential hypertension maintained on their usual diet [68].

Among factors susceptible to affect the relationship between arterial pressure and target organs, angiotensin II may play an important role through its effect on cellular hypertrophy. Although there was a tendency for a decrease in plasma renin activity with increase sodium intake, plasma renin activity was not affected by quintiles of urinary sodium. It is thus conceivable that interaction between angiotensin and target cells could be enhanced with increasing sodium intake with an increase in type 1 or a decrease in type 2 angiotensin receptor expression and function. It was reported that essential hypertensive patients with high circulating levels of angiotensin II in relation to sodium excretion had a greater LVM than those with “relatively low” angiotensin II levels, despite similar values of ambulatory systolic and diastolic arterial pressure.26 In addition to angiotensin II, other endogenous prohypertrophic substances may be implicated in the modulatory role of sodium intake on LVM such as endothelin,27 the circulating level of which increases during high sodium intake in salt-sensitive patients, and norepinephrine, which decreases during long-term restriction in sodium intake, the circulating level of which increases during high sodium intake in salt-sensitive patients, and norepinephrine, which decreases during long-term restriction in sodium intake [69].

Experimental data suggest four possible mechanisms by which increased dietary sodium may be a pathogenetic factor for LVH: 1) activation of the renin-angiotensin aldosterone system by sodium-mediated increase in cardiac aldosterone; 2) induction of myocardial protein synthesis through angiotensin II-dependent mechanisms 3) augmentation in sympathetic tone; and 4) increase in circulatory blood volume [70].

In several large studies a positive correlation between left ventricular geometry and sodium intake, estimated by 24-h urinary collections [7, 8] was found. In 1972, it was observed that addition of salt to food before tasting was associated with an increase (40% v 22%) in the prevalence of electrocardiographic evidence of LVH in hypertensive men.18 Interestingly, echographic LVH was present in 38% of sodium-sensitive (representing 60% of the total population) and only 16% of non sodium-sensitive hypertensive Japanese subjects.21 Long-term (12 months) dietary sodium reduction (by approximately 45%) was associated with a decrease in LVM by 8.6% and a decrease in systolic pressure by 10% (both factors being correlated) in a small group of patients with LV hypertrophy [71].

A study done by Guilhem du Cailar, et al. [72], with a study population consisted in 839 subjects positive correlation was found with patients having increased sodium excretion and left

ventricular hypertrophy with r = 0.15, P .0001.These findings were consistent with the findings of our study where out of 18 patients with increased sodium excretion 17 patients had left ventricular hypertrophy (p=<0.001) .

24 hour urine sodium and proteinuria

In our study, proteinuria was observed in 21 patients with increased sodium excretion and 7 patients with normal sodium excretion. According to study done by Guilhem du Cailar, et al. [72], secondary to pressure natriuresis there is injury to renal capillaries, there is increase in protein excretion which is a sign of end organ damage. Our study observation is consistent with the study done by Guilhem du Cailar, et al. There is a positive correlation between sodium excretion with proteinuria in the present study(r=0.807, P-value-<0.001).

24 hour urine sodium and microalbuminuria

In Feng Huang, et al. [73] study, an association between increased sodium excretion, and increase in blood pressure with increased CVD risk is explained. The potential reason may be related to vascular structural and functional changes, through alterations in endothelial function. An increased urinary albumin excretion has been reported in the patients with hypertension. Microalbuminuria could reflect the renal arteriolar damage, and is closely associated with cardiovascular events and mortality [27]. This study showed that with an increase in the urinary sodium excretion, the urinary albumin excretion were increased. Our observations are consistent with the above study.

In Sang Youb Han, et al. [74], study of KNHANES V-2 survey, done in Korean population of 5,187 individuals aged 19 years and older. In this population-based analysis, a higher salt intake as represented by the estimated 24-h urinary sodium excretion was associated with the presence of albuminuria. This association between salt intake and albuminuria was clear, even after adjusting for age and other factors. These findings suggest that salt intake is an important determinant of albuminuria in the adult Korean population. In our study 25 out of 39 patients with increased sodium excretion patients have increased microalbuminuria with prevalence of 64.1% and there is a significant correlation is seen in the study between increased sodium excretion and microalbuminuria (r=0.67, P-value-<0.001). Our study is consistent with observations seen in the Sang Youb Han, et al. study.

In a study done by J W Xu, et al. [2], among Chinese population aged between 18 years and 69 years. A total of 2400 subjects were selected from different provinces in china and were analyzed for the relationship between 24 hour sodium excretion and microalbuminria. In the study it was observed that with the increase of urinary sodium level, the level of urinary albumin increased (*P*<0.001), and the prevalence of microalbuminria also showed an upward trend (*P*<0.001) and showed an increase in 24 h urinary sodium is associated with the prevalence of microalbuminria and salt reduction can help in reduction of microalbuminria. Our study is also consistent with the observations seen in the study done by J W Xu, et al. and Arenti Triantafyllou, et al. [3] showing a positive correlation between 24 h urinary sodium and the prevalence of microalbuminria.

In a study done by Ningling Sun, et al. [75], relationship of 24 h urinary sodium excretion with arterial distensibility and urine albumin was studied in 341 hypertensive patients who were not on medication. In this study the group of subjects who are having high urinary sodium excretion (≥200mmol/24h) had higher levels of microalbuminuria compared to other groups with less sodium excretion values (P=0.027). The observations in our study is consistent with the above study, where in the patients with increased sodium excretion had high levels of microalbuminuria (P=<0.001).

Conclusion

The following conclusions were derived from our study.

1. Markedly increased 24 hours sodium excretion in hypertensives indicates a very high intake of sodium, which may be the cause for hypertension.
2. Age and sex doesn't have any influence on urinary sodium excretion and blood pressure.
3. Our results suggest that sodium excretion in the hypertensive patients were higher. The high sodium excretion was related with the renal arterial damage causing proteinuria and microalbuminuria suggestive of end organ damage.
4. High 24 hour sodium excretion is associated with high blood pressure and complications such as Left ventricular hypertrophy.
5. Patients with high sodium excretion, who are salt sensitive hypertensives will respond to diuretics, when compared to others.
6. The final conclusion from our study is that long term reduction in salt intake will significantly reduce the prevalence of hypertension and thereby decrease in the associated morbidity and mortality, due to cardiovascular disease and cerebrovascular stroke.

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