24-hour urine sodium and potassium excretion in six-year-old children and their parents

- Association to diet quality and blood pressure -

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Supervisors: Professor Ingibjörg Gunnarsdóttir and
Þórhallur Ingi Halldórsson assistant professor

Thesis for the degree of Master of Science in Human Nutrition
Faculty of Food Science and Nutrition, School of Health Sciences
University of Iceland 2012

HÁSKÓLI ÍSLANDS

Natríum- og kalíumútskilnaður sex ára barna og foreldra þeirra

- Tengsl við gæði mataræðis og blóðþrýsting -

Oddný Kristín Kristbjörnsdóttir

Leiðbeinendur: Ingibjörg Gunnarsdóttir prófessor og
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ÁGRIP

Bakgrunnur og markmið: Natríum (Na) og kalíum (K) útskilnaður í þvagi (sólarhringsþvagsöfnun) er talinn vera nákvæmasti mælikvarðinn á neyslu þessara efna. Helstu uppsprettur K í fæði eru matvæli sem talin eru holl og eru hluti af opinberum ráðleggingum um fæðuval. Mælt er með takmörkun á Na í fæði. Na og K útskilnaður í þvagi hefur verið tengdur blóðþrýstingi meðal fullorðinna, en minna er vitað um tengslin meðal barna. Verkefnið er hluti af stærri rannsókn á mataræði sex ára barna á Íslandi (2002-2003). Markmið þess hluta rannsóknarinnar sem meistaraverkefnið byggir á var að afla upplýsinga um Na og K neyslu sex ára barna með mælingu á styrk Na og K í þvagi. Markmið var einnig að kanna hugsanleg tengsl milli Na og K útskilnaðar, gæði mataræðisins og blóðþrýstings. Ennfremur eru teknar saman niðurstöður um Na og K útskilnað foreldra barnanna.

Aðferðir: Þátttakendur voru sex ára börn (n=61) og foreldrar þeirra (n=43 mæður og n=26 feður) af Stór-Reykjavíkursvæðinu. Þvagi var safnað í einn sólarhring og styrkur Na og K mældur. Gildi þvagsöfnunarinnar var metið með para-amínóbenzoic acid prófi (PABA). Þriggja daga vigtuð fæðuskráning var notuð til að meta neyslu fæðutegunda. Gæði heildarmataræðis (1-6 stig) var áætlað út frá því hversu vel börnin fylgdu fæðutengdum ráðleggingum um fæðuval. Við útreikninga voru þátttakendur flokkaðir eftir því hvort þeir fylgdu einni eða minna, tveimur, þremur eða a.m.k. fjórum fæðutengdum ráðleggingum. Tengsl Na og K útskilnaðar við gæði heildarmataræðis annars vegar og blóðþrýstings hins vegar voru metin með línulegri aðhvarfsgreiningu, leiðrétt fyrir orkuneyslu og kyni.

Niðurstöður: Na útskilnaður barna var að meðaltali 1,66 g Na/24klst sem samsvarar 4,15 g af salti/24klst. Samsvarandi gildi voru 3,19 g Na/24klst og 7,98 g salt/24klst fyrir mæður og 4,28 g Na/24klst og 10,7 g salt/24klst fyrir feður. K útskilnaður var að meðaltali 1,21 g K/24 klst fyrir börn, 2,20 g K/24klst fyrir mæður og 2,54 g K/24klst fyrir feður. Áætluð lækkun Na útskilnaðar barna fyrir hverja aukna einingu á gæði mataræðis, leiðrétt fyrir kyni og orkuinntöku var 0,16 g Na/24 klst (95% CI: -0,31; -0,06). Fyrir K, var samsvarandi aukning 0,18 g K/24 klst (95% CI: 0,06; 0,29) Hvorki systólískur né díastólískur blóðþrýstingur var tengdur útskilnaði á Na eða K eða gæðum heildarmataræðis

Ályktanir: Niðurstöðurnar benda til að neysla á salti meðal sex ára barna á Íslandi sé hærri en æskilegt megi teljast, ≤3,2 g salt/24klst miðað við meðalorkuneyslu þátttakenda. Meðalneysla K var lág miðað við ráðlagðan dagsskammt og er hugsanlega hægt að skýra það með lágri neyslu grænmetis og ávaxta. Aukin gæði mataræðis sex ára barna endurspeglast í hærri útskilnaði á K og lægri útskilnaði Na. Mikil saltneysla foreldra í rannsókninni er áhyggjuefni og aðgerða er þörf

ABSTRACT

Background and aims: Twenty-four hour (24h) excretion of sodium (Na) and potassium (K) in urine are considered to be the golden standard for dietary intake of these substances. The main dietary sources of K are components of many food based dietary guidelines (FBDG) but the main sources of Na are considered less healthy. Studies in adults have shown increased Na and decreased K excretion in urine to be associated with higher blood pressure but less is known about the association in children. The project is part of a bigger study on nutrition and health when studied at the age of 6 years (2002-2003). The aim of the thesis was to gather information on Na and K intake of six-year-old children using 24h urine excretion. The aim was also to assess the association between Na and K excretion, diet quality and blood pressure (BP). Furthermore, the aim was to gather information on Na and K intake of the parents using 24h urine excretion.

Methods: The participants were six-year-old children (n=61) and their parents (n=43 mothers and n=26 fathers) living in the greater Reykjavik area. Na and K excretion were analyzed from 24h urine collections. Para-aminobenzoic acid (PABA) check was used to validate completeness of urine collections. Three-day weighed food records were used to assess dietary intake of children and adherence to FBDG. Diet quality score (1-6 points) was divided into four groups based on adherence to FBDG, those following one or less, two, three or at least four of the dietary guidelines. The associations between Na and K excretion and diet quality score, as well as blood pressure were estimated by linear regression, adjusting for energy intake and gender.

Results: The urinary excretion of Na for six-year-old children was 1.66 g Na/24h, corresponding to 4.15 g salt/24h. Corresponding values for mothers were 3.19 g Na/24h and 7.98 g salt/24h, respectively and for fathers 4.28 g Na/24h and 10.7 g salt/24h, respectively. The urinary excretion of K was on average 1.21 g K/24h for children, 2.20 g K/24h for mothers and 2.25 g K/24h for fathers. Estimated decrease in Na excretion by 1-unit increased diet quality score, adjusted for sex and energy intake, was 0.16 g Na/24 klst (95% CI: -0.31; -0.06). For K, the corresponding increase was 0.18 g K/24h (95% CI: 0.06; 0.29) with 1-unit increased diet quality score. Neither systolic nor diastolic blood pressure was related to excretion of Na or K or adherence to FBDG.

Conclusions: The results show that the consumption of salt is higher than recommended (≤3.2 g salt/24klst) according to the average energy consumption of the participants among six-year-old children in Iceland. The average consumption of K was rather low, according to recommended value. Possible explanation is low consumption of vegetable and fruits. Increased diet quality of six-year-old children are reflected in higher excretion of K and lower Na excretion. High salt intake of the parents in this study is of concern, and it is important to respond to it.

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ABBREVIATIONS

24h	24-hour
3dwfr	Three day weighed food record
ACTH	Adrenocorticotropic Hormone
ADH	Antidiuretic Hormone
BMI	Body Mass Index (kg/m^2)
CD	Collecting Duct
DASH	Dietary Approaches to Stop Hypertension
ECF	Extracellular Fluid
EPIC	the European Prospective Investigation into Cancer and Nutrition
FAO	Food and Agriculture Organization
FBDG	Food Based Dietary Guidelines
FFQ	Food Frequency Questionnaire
HEI	Healthy Eating Index
K	Potassium
NA	Not Available
Na	Sodium
NaCl	Sodium Chloride or Salt
NNR	Nordic Nutrition Recommendation
PABA	para-Aminobenzoic Acid
PT	Proximal Tubule
RAAS	Renin-angiotensin-aldosterone system
RDA	Recommended Daily Allowance
RFS	Recommended Foods Score
TAHL	Thick Ascending Limb of Henle's loop
TAL	Thick Ascending Limb
WHO	World Health Organization

1 INTRODUCTION

Sodium (Na) and potassium (K) intake can be estimated from dietary surveys, food composition tables and by urine collections. Most studies rely on dietary surveys and food composition databases to estimate intake of Na and K but these methods might either over- or underestimate actual intake. Collections of 24h urine have been shown to provide the most accurate estimate of Na and K intake [1, 2]. In adults, increased Na and decreased K excretion in urine has been shown to be associated with higher blood pressure [3, 4]. There are relatively few studies which have estimated Na and K intake using 24h urine excretion in children and its association with both diet quality and blood pressure is less well established than in adults.

The main dietary sources of K are components of many food based dietary guidelines (FBDG) (milk and milk products, cereals, fruits and vegetables), that have been established as a result of studies showing the importance of the overall diet rather than specific nutrients in the fight against chronic diseases [5-7]. On the other hand, the main dietary sources of Na are considered to be less healthy, including processed meat and fast food dishes [8, 9]. The association between total diet quality and Na or K excretion has not been reported previously in children.

This thesis is based on data from a larger, longitudinal study on infant diet and diet of Icelandic 2-year-olds with a follow-up at the age of six years. Several scientific papers have been published presenting results both from the original studies on infant diet [10] and diet of Icelandic 2-year olds [11], and from the follow-up study [11-16].

The aim of the thesis was to:

1. Estimate Na and K intake in six-year-old children and their parents by 24h urine excretion.
2. Assess the relationship between urine Na and K excretion and diet quality in six-year-old children.
3. Assess the relationship between urine Na and K excretion and blood pressure in children.

Na and K excretion had never been assessed in Icelandic children prior to the present study or in a healthy adult population since 1988 when Iceland was part of an international study of electrolyte excretion and blood pressure, INTERSALT [17].

The thesis is mainly based on a review of the literature, and the manuscript “Association between 24-hour urine sodium and potassium excretion, diet quality and blood pressure in six-year-old children: a cross sectional study”. A brief result section is also included describing results on Na and K excretion of the parents.

2 REVIEW OF LITERATURE

2.1 Physiology

Water makes up 50-75% of the body mass. The intracellular compartment contains about two-third of the total water and the remaining is held in the extracellular compartment. K largely determines the intracellular and Na the extracellular compartment [18]. Na and K are electrolytes in the body. Electrolytes are substances that become ions in solution and acquire the capacity to conduct electricity. Electrolytes are present in the human body and the balance of the electrolytes in our bodies is essential for normal function of our cells and organs [19].

Na is the major positive ion (cation) in fluid outside of cells [20] and is essential for nerve transmission and muscle function, and also helps control the acidity in the body and aids the absorption of some nutrients, such as glucose [21]. The body pool of Na is approximately 100 g. Half is found in the extracellular fluid and 10% in the cells. The rest is mainly bound in the skeleton [19]. Na is an essential nutrient because it is a major constituent of the blood plasma of humans. Variations in this concentration of plasma Na may have effects on osmotic pressure of the plasma, on plasma and interstitial fluid volumes, on acid-base balance, on the maintenance of the electrical activity of body cells and on the responsiveness of the cardiovascular system [22]. Regulation of the Na concentration and the Na content is maintained mainly by the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system, and the concentrations of catecholamine, Na and K in the blood, glomerular filtration rate and blood pressure. These control mechanisms regulate the elimination of substrates from the body in excess of need and to retain when deficit occurs [22]. See Appendix 1 (chapter 9.1) for Na absorption and urinary excretion. Salt (NaCl) is used as a food ingredient and 0.4 g Na corresponds to 1 g NaCl and 1 mmol Na corresponds to 23 mg Na [19]. NaCl occurs naturally in most foods, it is also added to processed foods, used as a flavor intensifier, a curing agent, a formulating and processing aid and a conditioner of dough (nondiscretionary). NaCl is also often added to food during cooking and at the table (discretionary) [22].

K is the major positive ion (cation) found inside of cells, important for regulating the membrane potential of the cells [23], for nerve and muscle function, blood pressure regulation and for acid-base balance [24]. One mmol K corresponds to 39 mg [19]. Approximately 175 g of K is in the human body; only 3 g are found outside the cells [22]. A gradient exists for the diffusion from intracellular to extracellular fluid, reverse of that for Na. Diffusion occurs along these gradients and is reestablished by pumps in the cell membrane that move Na out and K in. K is completely absorbed from the gut and then distributed through the intracellular fluid. The urinary plus stool excretion of K should be equal to the intake if balance is to be achieved. Defense against abnormalities of K balance occurs through two mechanisms. The long-term defense is by the kidney. Acutely, defense is achieved by extrarenal mechanisms that distribute K between the inside and the outside of cells. The maintenance of distribution between the inside and outside of cells depends on the integrity of the cell membrane and

its pumps, osmolality, pH, and the hormones insulin, aldosterone, beta$_2$-catecholamines, alpha-catecholamines, and prostaglandins [25]. See appendix 2 (chapter 9.2) for K absorption and urinary excretion.

2.2 Methods to examine Na and K intake

For water-soluble substances, like Na and K, which are readily transported into the renal glomerular filtrates, the analysis of a well defined urine collection is informative, particularly about recent dietary intake. A complete 24h urine sample is usually used and has been used as a golden standard for these substances. There is tight homeostatic control of the blood levels of Na and K, and therefore blood levels do not reflect dietary intake except at the extremes of deficiency [1].

The validity of measurements of dietary intake in free-living individuals is not easy to assess because most methods rely on information given by the subjects themselves, which may not be correct [26]. The dietary record for three days is the most accurate method because it does not rely on the memory of the subjects. This method on the other hand has a high participation burden and habitual eating patterns may be influenced or changed by the recording process [27]. Food frequency questionnaires (FFQ) are widely used for large population surveys like the Nurses' Health study [28] and the EPIC study [29]. It has, though, limitations like other dietary assessment methods, like imprecise recall period and inaccurate quantification of food intake [27].

Dietary records and FFQ can provide good information about the consumption of food items and food groups. If, on the other hand, substances like Na and K are analyzed, the reliability is upon the food composition database to ensure that the content of these substances is similar between various types of food items. For example breads, which are a large and variable group and a great contributor of salt, over or underestimation of salt intake is inevitable. Mostly because the values in the database are based on estimated means and only a small part of all breads are included in the database and home baked breads are not included in the database. Therefore, it is difficult to be sure whether the product consumed is exactly the same as the product recorded.

Biological specimens have been used that closely reflect dietary intake, especially of Na and K, but which do not rely on reports of food consumption [26]. Urine collection is a method that works properly to detect dietary Na and K intake. Urine collections have several implementations, morning urine or spot samples, overnight and 24h urine samples, which is believed to be the best way to assess the intake. Urinary Na excretion is a good way to detect dietary Na intake particularly since fecal and skin losses of Na are minimal. K is also measured in urine with good success. However, fecal excretion of K is greater and more variable than Na [2]. Three principal issues must be addressed when using one 24h urine collection to quantify nutrient intake: timing, the beginning and end of the collection,

obtaining a complete collection, and dealing with the large day-to-day variation in excretion of electrolytes [30].

2.2.1 Complete collection

Although the urine collection is considered the best way, the unreliability of 24h samples is well-known. Creatinine has been used to check the completeness of urine collections for a long time, reputedly because constant excretion varies from day to day in an individual. However, it appeared that the range of normal outputs is large, 9-22 mmol/24h [2], which suggest inconsistency. The meat content of the diet may affect the creatinine pool size and day-to-day variability in creatinine excretion. The completeness of urine collection is consequently not guaranteed.

The para-aminobenzoic acid (PABA) check test was developed to verify the completeness of 24h urine collections [31], which is safe, accurate, and easily administered and analyzed. PABA is normally present in some foods and vitamin capsules. In humans, the maximum between-person range in PABA excretion is only 15%, compared with an 80% range in creatinine excretion per kg fat free mass per 24h. Average urinary recovery is 93% of the administered dose in single 24h collections and the collection are complete when PABA excretion is over 85% [2]. Possible explanations, for low PABA recovery values, besides the under collection of urine samples are failure to take all three tablets, taking tables late in the evening with a large meal that reduces gastric emptying time and uptake in the intestine, impaired renal function, errors in preparation of urine aliquots and analytical errors [32]. In the present study, PABA check [33] was used to validate completeness of urine collections.

2.2.2 Day-to-day variation

A diurnal and day-to-day fluctuation of individual's urine Na and K excretion exists. Intra-individual variation is about 30% for Na and 24% for K and inter-individual variation for Na 12% and 22% for K [33] for adults. Liu et al [34] showed that fourteen 24h urine collections of Na were needed to limit the correlation between lifestyle factors and traits to less than 10% and seven samples to rank individuals into two groups. Simpson et al [35] found similar results. For K, the corresponding collections were 16 to limit the error to 5% and eight collections to limit the error to 10%.

Children are more stable than adults; estimated ratio of intra-to-inter individual variance is 1.98 for children compared with 3.20 for adult men [34]. Five 24h urine specimens would be needed to reduce the diminution of the correlation coefficient between 24h urine and blood pressure to less than 15% and eight to reduce it to 10%. If we compare this result to overnight Na, number of overnight urinary Na measurements needed to limit diminution to <10% is 11 [36].

2.2.3 Timing

Twenty-four hour urine samples can be challenging to collect in non-institutionalized population groups. Instead, first-voided fasting morning urine specimens are often used as they are less affected by recent dietary intake. When first-voided fasting or casual urine specimens are collected, urinary excretion is sometimes expressed as a ratio of the nutrient to urinary creatinine to correct for both diurnal variation and fluctuations in urine volume [32].

In the present study, on the first morning of the urine collections, instructions were given to discard the first specimen, and from then on to collect all specimens for up to 24 hours, up to and including the first specimen the following day.

2.3 Na and K intake estimated by 24h urine excretion

Table 1 and 2 shows an overview of studies in children and adolescents where 24h urine excretion of Na and K are examined; table 1 show cross sectional studies and table 2 intervention studies. Most studies are from the USA (n=12) and focus on children aged 10-15 years. A few studies are in the group of six-year-old children, one in Germany on children 4-8 year old, one in Spain 6-7 year old and in Japan 5-6 year old. Studies conducted in Austria and Netherlands included 8-9 year old children.

No studies were retrieved from the Nordic countries other than those relying on estimates from dietary surveys only.

2.4 Requirement and recommended intake

2.4.1 Sodium (Na)

Minimal daily requirement of Na is often estimated as 0.23 g (10 mmol) per day corresponding to about 0.58 g of salt [19]. Deficiency is not common, although it can occur during heavy sweating, with large fluid intakes devoid of Na and in vomiting and diarrhea without salt supply [20]. Most people are asymptomatic or have symptoms like headaches, lethargy and nausea. More severe deficiency can cause muscle seizures, loss of appetite and circulation disturbance and can lead to coma and death [37].

On the other hand, increased intake of dietary salt is a great concern as it is more common to consume excess portions [38]. Increased dietary intake of salt can cause increases in body weight, extracellular fluid volume and plasma volume and blood volume. It can also cause decreases in plasma renin, angiotensin and norepinephrine levels and increase the urinary excretion of Na, K and calcium [39]. The ingestion of Na beyond physiologic need over a short term generally is not harmful

Table 1. Cross sectional studies in children containing Na and K excretion

Study & country	Participants: age in years (n)	Number of 24h urine collections	Na excretion (g/24h)	Na excretion (g/kg/24h)	K excretion (g/24h)	K excretion (g/kg/24h)	Urine volume (ml/24h)
Alexy, Cheng, Libuda, Hilbig, & Kersting, 2011 Germany [40]	4-8 (115)	1	1.60	NA	1.40	NA	657
Haga & Sakata, 2010 Japan [41]	5≤6< (17)	1	2.16	0.12	NA	NA	575
Maldonado-Martin, et al., 2002 Spain [42]	6-14 (613)	1	3.14	0.08	1.53	0.04	NA
Zwiauer, Eberlein, & Widhalm, 1991 Austria [43]	8-9 (72)	1	3.74	0.12	2.05	0.07	NA
Moriyama & Saito, 1988 Japan [44]	8 (12)	1	2.58	0.10	1.46	0.06	NA
Knuiman, et al., 1988 Netherlands [45]	8-9 (28)	7	2.32	NA	1.83	NA	NA
Cooper, Liu, Trevisan, Miller, & Stamler, 1983 USA [46]	11-13 (A: 72, B: 97, C: 72)	7	A: 3.05 B: 2.92 C: 2.47	A: 0.06 B: 0.06 C: 0.05	A: 1.62 B: 1.39 C: 1.28	A: 0.03 B: 0.03 C: 0.02	NA
Voors, Dalferes, Frank, Aristimuno, & Berenson, 1983 USA [47]	5-14 (249, half black) 8-18 (106, half black)	1	White: 3.46 Black: 3.02	NA	White: 2.74 Black: 2.08	NA	NA
Cooper, et al., 1980 USA [48]	11-14 (73)	7	3.05	0.11	1.62	0.06	NA

Table 2. Intervention studies in children containing baseline Na and K excretion

Study & country	Participants: age in years (n)	Number of 24h urine collections	Na excretion (g/24h)	Na excretion (g/kg/24h)	K excretion (g/24h)	K excretion (g/kg/24h)	Urine volume (ml/24h)
Palacios, et al., 2010 USA [49]	11-15 (40 black, 28 white)	20	Black: 2.82 White: 2.54	Black: 0.05 White 0.05	Black: 1.83 White: 1.83	Black: 0.03 White: 0.03	Black: 1.283 White: 1300
Palacios, et al., 2004 USA [50]	11-15 (36)	20	2.60	0.05	NA	NA	1250
Sinaiko, Gomez-Marin, & Prineas, 1993 USA [51]	10-13 (210)	1	3.57	0.06	2.15	0.05	NA
Miller, et al., 1988 USA [52]	10 (149)	1	2.35	0.07	NA	NA	NA
Miller, Weinberger, & Christian, 1987 USA [53]	11 (38)	5	2.55	0.07	1.52	0.04	NA
Allison & Walker, 1986 UK [54]	3-5 (35)	1	1.43	0.07	0.98	0.05	581
Clark & Mossholder, 1986 USA [55]	13-15 (8)	1	2.39	NA	1.12	NA	NA
Connor, Connor, Henry, Sexton, & Keenan, 1984 USA [56]	10 (115)	3	2.35	0.07	1.68	0.05	NA
Liu, et al., 1979 USA [36]	12-15 (73)	7	3.05	NA	NA	NA	NA

in healthy humans. The effect of chronic ingestion of excess Na is on the other hand controversial [22].

According to the Public Health Institute of Iceland [57] the salt intake in Iceland for women should not exceed 6 g/d and 7 g/d for men. No special recommendations are set for children. The same values as in Iceland are found in the Nordic Nutrition Recommendation (NNR) 2004 [19], they also set intake below 0.5 g salt/1000 kJ (0.5 g salt/239 kcal) for children 2-18 years old, corresponding to about 3.4 g salt daily. The American Heart Association (AHA) recommends salt intake to be below 4.8 g/d for children 4-8 years old [58] and Australian guidelines recommend salt intake below 5.8 g/d for children 4-7 year old and adults, which is relatively high [59].

In the UK, 1.20 g/d Na (3 g/d salt) is the highest intake recommended for children and 1.60 g/d (4 g/d salt) for adults [60], which is much lower than in Iceland [57]. The World Health Organization (WHO) recommends an average consumption of <5 g/d salt for adults [61] and in a review by Karppanen, et al. [62] the American guidelines were set as low as 2.5 g/d of salt for adults.

2.4.2 Potassium (K)

Humans can excrete large amounts of K when given orally with only a small increase in plasma K. Hyperkalemia may occur when the renal function is impaired or in patients with diabetes and can cause cardiac arrhythmias [63].

Deficiency of K occurs mainly because of increasing losses from the gastrointestinal tract and kidneys, during diarrhea or vomiting, laxative abuse and use of diuretics. Symptoms include muscle weakness, loss of appetite and confusion. Severe deficiency can disrupt heart rhythms [23]. The amount needed to avoid low plasma levels and loss of total body K in adults is ≥1.6 g/d (40 mmol) [19].

The recommended intake of K in Iceland [57] is ≥3.1 g/d for women, ≥3.5 g/d for men and ≥2.0 g/d for children 6-9 years old. The same is recommended in the Nordic Nutrition Recommendations (NNR) [19]. The WHO have a similar referent of about ≥3.0 g/d for adults [61]. Finnish review [62]; set the guidelines of K for adolescent and adults ≥4.7 g/d and for children 4-8 years ≥3.8 g/d. Finally, the AHA recommends ≥3.8 g/d K for children of the same age [58].

2.5 Na (as NaCl) and K and health

Cardiovascular disease is the single largest risk for mortality both in developed and developing countries [64], accounting for about 30% of total reported deaths in the world [65]. The composition of

diet in childhood and physical activity in adulthood is the most important lifestyle determinants of cardiovascular diet quality [66].

2.5.1 Blood pressure

High blood pressure is one of the key cardiovascular disease risk factors accounting for nearly two-thirds of all strokes and one-half of all ischemic heart disease. Approximately 13% of deaths worldwide were estimated to be due to non-optimal blood pressure [67, 68]. Hypertension affects approximately 25% of the global adult population. By 2025, it is estimated that hypertension will affect about 30% of adults worldwide [69].

Both environmental and genetic factors are involved in hypertension and in many patients with hypertension; the exact mechanisms are poorly understood [70]. Kidneys evolved to conserve Na and excrete K. The ancient diet suited this very well. The modern Western diet, on the other hand, consists of excess Na and deficit of K and these changes increase peripheral vascular resistance and can cause hypertension as shown in figure 1 in appendix (chapter 9.3). The kidneys account for the biggest part of K loss and a small portion is excreted through the feces. This does not fit the Na-rich and K-poor modern diet [71]. Mechanisms between Na, K and blood pressure are discussed in Appendix 3 (chapter 9.3).

In a review by He and MacGregor [63], epidemiological and clinical studies show that a high K diet lowers blood pressure in individuals with raised blood pressure and as well as the average population blood pressure. Prospective cohort studies and outcome trials show that increasing K intake reduces cardiovascular disease mortality, slows the progression of renal diseases and lowers urinary calcium excretion and risk of kidney stones. Low serum K is then strongly related to glucose intolerance. Conversely, salt has opposing effects on these factors.

2.5.2 Children

Dietary tracking between childhood and adulthood has been recorded [72, 73]. According to Lauer et al [74] adult blood pressure correlates with childhood blood pressure.

According to the National Heart, Lung, and Blood Institute [75] children's blood pressure is presented in tables, including the 50^{th}, 90^{th}, 95^{th} and 99^{th} percentiles by gender, age, and height. The definition of hypertension in children and adolescents is based on the normative distribution of blood pressure in healthy children. Normal blood pressure is defined as systolic and diastolic blood pressure that are < 90^{th} percentile for gender, age, and height. Hypertension in children and adolescents is defined as systolic blood pressure and/or diastolic blood pressure, on repeated measurement, ≥95^{th} percentile. Blood pressure between the 90^{th} and 95^{th} percentile have been set as prehypertensive, also as with adults, adolescents with blood pressure levels ≥120/80 mm Hg should be considered prehypertensive.

According to this definition [75], average systolic/diastolic blood pressure for normotensive six year old boys and girls is below 113/72 and 110/71, respectively. Hypertension, according to 95th percentile is above 117/76 and 114/75 for boys and girls, respectively.

Meta analysis by He et al [76] of controlled trials (mostly urine collections) with children ≤18 years old with average of 42% salt reduction showed that modest salt intake causes immediate falls in blood pressure. On average, systolic blood pressure lowered by 1.18 mmHg (95% CI: -1.78 to -0.56 mmHg) and diastolic by 1.29 mmHg (95% CI: -1.94 to -0.65 mmHg). Studies in children where 24h urine excretion in children was used have shown some positive effects of dietary K [43, 77] and negative effects of Na on blood pressure [42]. One cohort study applied six overnight urine collections. The systolic blood pressure was 0.045 mmHg lower per year per mmol (0.04 g) K intake (95% CI: -0.069 to -0.020) and the change in systolic pressure was 0.356 mmHg greater per year for one unit greater Na/K ratio (95% CI: 0.069 to 0.642) [78]. A two year double blinded placebo controlled trial with salt sensitive school children (n=261) showed lower blood pressure by 4.3/4.8 mmHg in the supplementary group (10 mmol (0.39 g) K and 10 mmol Ca) than in the placebo group ($p<0.05$) [79].

Studies in children are inconsistent and some show no interaction between Na and K and blood pressure [50, 53]. One cross sectional study, including 8 year old children (n=330), measured total body composition by dual-energy X-ray absorptiometry and collected overnight urine. Urinary K correlated significantly with bone mineral density ($r=0.24$, $p<0.01$) [80].

2.5.3 Adults

INTERSALT, an international study of the relations between electrolyte excretion (24h urine) and other factors to blood pressure in adults involve more than 10,000 persons from 52 centers in 32 countries. The estimated mean change in systolic blood pressure associated with a 100 mmol (2.30 g) decrease in Na intake was -3.1 mmHg and 15 mmol (0.59 g) increase in K intake was associated with 1.0 mmol lower systolic blood pressure, adjusted for age, sex, body mass index and alcohol intake [81]. Metaregression analysis of randomized trials showed Na reduction of 77 mmol/24 h (1.77 g) was associated with a change of -2.54 mmHg (95% CI: -3.16 to -1.92) in systolic blood pressure and 1.96 mmHg (95% CI: -2.41 to -1.51) in diastolic blood pressure. Increased K intake of 44 mmol/24h (1.72 g) yielded 2.42 mmHg decrease in systolic blood pressure (95% CI: -3.75 to -1.08) and 1.57 mmHg decrease in diastolic blood pressure (95% CI: -2.65 to -0.50) [82]. Another study with 3681 participants without cardiovascular disease and collection of 24h urine showed decrease in cardiovascular deaths across increasing tertile of 24h Na excretion, from 4.1% deaths in the low, 1.9% in the medium and 0.8% in the high excretion group ($p<0.01$). A 100 mmol (2.30 g) increase in Na excretion was associated with 1.71 mmHg increase in systolic blood pressure ($p<0.01$) but no change in diastolic blood pressure [83]. Studies have also shown significant positive outcomes in bone health [84, 85] and in diabetes [86,87] in connection with low Na and high K.

2.6 Food sources

In the Icelandic National Surveys in 2002 [88] and 2010-2011 [89], Na and K were assessed by dietary survey. In those surveys, spices, cereals, meat and meat products, cheese and sauces contributed the most to Na. Drinks, milk and milk products, meat and meat products, cereals, fruits and vegetables and potatoes were the most common sources of K in the diet.

When we look to other countries where food groups are linked to 24h urine collections we get the same results, cereals are big sources of Na in food [90] and fruits and vegetables are high in K [77]. Studies including food records show that meat products and commercially prepared foods are large contributors of Na [9] and milk and milk products are high in K [91].

In a study by Pietinen [92], food intake was recorded for four days and three 24h urine samples were collected in adults. Naturally occurring Na constituted about 13% of the total Na intake and Na from table salt used in food preparation about 43%, bread 20% and meat products 12% [92].

2.7 Diet quality

In recent years, more frequent studies have been published about the effects of diet quality on health outcomes. In earlier times, the focus was more on single dietary factors [93]. However, people consume different combinations of food, not single foods or nutrients.

The Public Health Institute of Iceland [57] developed food based dietary guidelines (FBDG) recommended for adults and children from two years of age. The Icelandic food based dietary guidelines are listed in table 3. Recommendations encourage intake of a wide variety of food and balancing energy intake. Also, the importance of regular physical activity is emphasized. The Icelandic FBDGs take into account the recommended daily allowance (RDA) of vitamins and minerals and reference values of energy need. RDA is the average daily intake level that is sufficient to meet the nutrient requirements of nearly all (approximately 98%) healthy individuals. The FBDGs are developed with the newest research on nutrition and health, national surveys, NNR and other recommendations.

The FBDG reflects a healthy diet rather well and may indicate a high K and low Na intake.

Given the main sources of Na and K, the excretion should be associated with the FBDG. Very few studies have linked this together; one study in adult patients reported a single 24h urinary K to detect a poor quality diet [94]. FFQs were used to derive the recommended food score (RFS) which contained vegetables, fruit, whole grains, low-fat dairy products, fish and poultry and wine. Urinary K correlated negatively with diets that did not follow current dietary guidelines, i.e. red meat, fast food, and high-energy drinks. Urinary K on the other hand correlated positively with the RFS ($r=0.23$; $p<0.01$). A study including children aged 6-12 years showed a linear trend for lower Na ($p=0.05$) and K

intake (p=0.05) when more servings of whole grains (≥3 servings per day) were consumed. Dietary data was assessed by single 24h dietary recall and no urinary excretion was collected. The healthy eating index (HEI) score was significantly higher when more servings of whole grains were consumed (p<0.01) [95]. The HEI index correlates positively and significantly with most recommended nutrients [96]. Research studies that have been done on eating patterns according to food based dietary guidelines for example the DASH trial [97] and Mediterranean-style diet [7].

Table 3. The Icelandic food based dietary guidelines [57]

Fruits, vegetables and juices daily, ≥5 portions per day (500 g)
Fish at least 2 times per week (300 g)
Whole-wheat bread and high fiber foods (≥25 g/d)
≥2 portions low fat dairy daily (500 g) or 1 portion low fat dairy (250g) and 1 portion cheese (25g)
Unsaturated fat instead of saturated and trans fat
Moderate sodium consumption (≤6 g women/≤7 g men)
Fish liver oil or other vitamin-D source
Water to drink

Kristjansdottir et al [98] explored the diet of seven year old children in Iceland using three-day dietary records by comparing food based dietary guidelines and reference values for nutrient intake. The FBDG on fruits and vegetables was reached by less than 20% of the children. A total of 52% reached the recommended fish intake two times a week and 41% took vitamin D supplements as recommended. The FBDG for dairy was reached by 66% of the children. Fiber intake was 2.1 g/1000 kJ (2.1 g/239 kcal) or about 15 g/d, based on an average energy intake of 1734 kcal.

The American FBDG recommends about 5 dl of fruits and vegetables daily, 14 g per 1,000 kilocalories fiber (about 25 g/d women and 38 g/d men) and about 7 dl of fat free or low fat dairy products for adults and about 5 dl for children aged 4 to 8 years. Also more than 8 ounces per week (227 g/week) of protein foods like seafood, lean meat, poultry and more [99]. Australian guidelines for children and adolescents recommend 150 g/d fruits and 150 g/d vegetables for children 4-7 years old. Fiber intake should be a minimum of the child's age + 5 g/d up to a maximum of the child's age+10 g/d. Include lean meat, fish, and poultry three to four times a week. Dairy products should be enough to meet the 800 mg/d for calcium [59]. Fiber intake based on the 2004 NNR [19] is recommended to be at least 25-35 g/d or 3 g/1000 kJ (3 g/239 kcal). School children should therefore consume at least 10 g dietary fiber/d.

3 METHODS

Methods related to the analysis of the association between Na and K excretion and diet quality as well as blood pressure is described in detail in the manuscript (see chapter 4).

In chapter 4, other results are presented, including Na and K intake and 24h excretion of parents and the association between parents' and children's excretion (assessed by Pearson correlation).

At the beginning of the study, 112 mothers and 75 fathers agreed to participate, of 180 who were invited to paricipate. Subjects invited to take part in the study on nutrition and health of Icelandic six-year-olds where from two former studies, on infant nutrition [10] and nutrition and health of two year olds [100]. Parents´ food intake was assessed using a validated semi-quantitative FFQ developed by the Icelandic Nutrition Council, including 130 different food items, reflecting food intake during the past 3 months. Quantities were estimated from photographs of four portion sizes of seven basic foods and from household measures. Results were scanned into a computer using a Hewlett Packard DeskScanII. The procedure of the 24h urine collections for adults is same as for children, described in the manuscript (see chapter 4).

According to the Icelandic Public Health Institute [57], salt intake for adults is recommended to stay below 6 g for women and 7 g for men, which corresponds to 2.40 and 2.80 g Na, respectively. The K intake for adults is set above 3.10 g for women and above 3.50 g for men.

3.1 Authors' contribution:

In June 2010 I received the data file from the follow up study and started data management and preparation of the files in order to organize the data set for the present analysis. I searched the literature for papers related to the procedure of urinary collections, studies on the Na and K excretion in children and studies on Na and K intake/excretion and health outcomes. The main search terms used were children, Na, K, diet quality, excretion and urine. Data on dietary intake in terms of grams per day were recoded into categories according to the FBDG and the association to Na and K excretion was assessed. I made the statistical analysis presented in this thesis under the supervision of Þórhallur Ingi Halldorsson and wrote the first draft of a manuscript "24-hour urine sodium and potassium excretion, diet quality and blood pressure in six-year-old children: a cross sectional study". The collection of data used in the present thesis was conducted before I started my MS studies. In order to get insight into the data collection, I participated in the data collection in another study on the same age group during summer and autumn 2011, where similar methodology was used as in the previous study.

4 MANUSCRIPT

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Association between 24-hour urine sodium and potassium excretion, diet quality and blood pressure in six-year-old children: a cross sectional study

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Abstract

Background

Limited data is available on sodium (Na) and potassium (K) intake in young children, estimated by 24 hour (24h) excretion in urine. The aim was to assess 24h Na and K excretion in six-year-old children and its relationship with diet quality and blood pressure.

Methods

The study population was a subsample of a national dietary survey, including six-year-old children living in the greater Reykjavik area (n=79). Three day weighed food records were used to estimate diet quality. Diet quality was defined as adherence to the Icelandic food based dietary guidelines. Na and K excretion was analyzed from 24h urine collections. PABA check was used to validate completeness of urine collections. The associations between Na and K excretion, diet quality and blood pressure were estimated by linear regression, adjusting for energy intake and gender.

Results

Valid urine collections were provided by 61 children. Na and K excretion was on average 1.66±0.54 g Na/24h (approx. 4.15 g salt/24h) and 1.21±0.42 g K/24h), respectively. The estimated adjusted decrease in Na excretion per 1-unit increase in diet quality score (score range: 1-4), was 0.16 g Na/24h (95% CI: -0.31; -0.06). For K the corresponding increased excretion was 0.18 g K/24h (95% CI: 0.06; 0.29). Neither Na nor K excretion were associated with blood pressure.

Conclusions

Na intake, estimated by 24h urine excretion was on average higher than recommended. Increased diet quality was association with lower Na excretion and higher K excretion in six-year-old children.

Keywords

Sodium, potassium, children, 24h urine excretion, diet quality, blood pressure.

Background

The best means of estimating sodium (Na) and potassium (K) intake is by analyzing 24-hour (24h) Na and K excretion in urine [1, 2], as the use of dietary surveys and food composition databases for estimating Na and K intake might introduce either an over- or underestimation of the actual intake. Studies including 24h urine collections for estimation of Na and K intake in children are relatively few.

Food based dietary guidelines have been established as a result of studies showing the importance of the overall diet rather than specific nutrients against chronic diseases based on studies in adults [3-5]. The main dietary sources of K are part of overall healthy diet in line with food based dietary guidelines [6-8]. On the other hand, the main dietary sources of Na in children are considered to be less healthy, including processed meat and fast food dishes [8, 9]. Tracking of dietary habits from early childhood into adulthood have been recorded [10, 11], where children with extremely high levels of for example Na intake tend to maintain those levels over time [12]. Diet in childhood can be a significant determinant of adult diet even after 21 year [13].

Studies in adults have repeatedly shown increased Na and decreased K excretion in urine to be associated with higher blood pressure [14]. Few studies have been conducted on children indicating small effects of Na and K intake on blood pressure [15-17].

The aim of the present study was to gather information about Na and K intake in six-year-old children by 24h urine excretion. The aim was also to assess the relationship of Na and K excretion to diet quality as well as systolic and diastolic blood pressure.

Methods

Subjects

The source populations were subjects invited to participate in the study on nutrition and health of Icelandic six-year-olds which was a longitudinal study including subjects from two former studies, on infant nutrition [18] and nutrition and health of two year olds [19]. Originally, families of 180 infants from four maternity wards around Iceland were invited to participate in the infant study and 130 two-year-old children were randomly selected by the Icelandic National Registry. In the infant study 138 agreed to participate, 27 were lost in follow up until 12 months of age leaving 111 eligible subjects for the follow up at six years. From the study on two year olds 69 were eligible for the follow up study at the age of six years, altogether 180 subjects. The participation rate in the follow up study was 73% where 131 completed valid three day food recording [20]. Only children who were living in the greater Reykjavík area were invited to provide 24h urine collections (n=111) due to practical reasons (closeness to the study centre), of which 79 agreed. Each family was contacted by telephone and invited to take part in the study. If consent was obtained, an introductory letter explaining the details of the study was sent by mail. The study was approved by the Local Ethical Committee at Landspitali-University Hospital in Iceland, The National Bioethics Committee and by Icelandic Data Protection Commission.

Weighed food records

Parents kept weighed food records for their children for three consecutive days including one weekend day and 2 week days using a kitchen scale (PHILIPS HR 2385, Austria) around the time of the 6th birthday. Each family received a booklet with which to record all food eaten during this time period. Parents were instructed to record date and time of the meals, how to use the scales, to specifically record brand or type of food, to include recipes of homemade dishes, record all drinks and vitamin intakes. All data were entered into an interview-based nutrient calculating program, ICEFOOD, designed for the national dietary survey of The Icelandic Nutrition Council [21]. Nutrient losses due to food preparation were included in the calculations. This program included 452 food codes or recipes from the Icelandic Nutrition Council, based on 394 food items from the National Nutrition Database, ISGEM.

Diet quality

Adherence to the Icelandic food based dietary guidelines was used to assess diet quality score. The food based dietary guidelines (FBDG) are based on six recommendations. Portion sizes used to determine diet quality score were adjusted according Kristjansdottir et al [27], based on 20% lower energy need of six-year-old children than of an adult. It included on a daily basis on average: ≥400 g fruits and vegetables, ≥34 g fish, ≥5 g fish liver oil and ≥400 g milk and milk products (or 200 g milk and milk products and 20 g cheese). The Public Health Institute of Iceland [6] recommends K intake ≥2 g/d for children 6-9 year old and NNR [28] ≤0.5 g salt/1000 kJ (0.5 g salt/239 kcal) for children 2-18 years old, corresponding to about 3.2 g salt daily (according to energy intake of 1530 kcal/d in the present study). Fiber consumption (of at least 11 g/day), was used in the evaluation of diet quality score as an indicator of whole grain cereals [29, 30]. It was summarized from the weighed food record data how many of those FBDG were followed. One point was obtained by following each guideline, maximum of six points. Diet quality score was divided into four groups based on adherence to FBDG, those following one, two, three or at least four of the dietary guidelines.

Na and K excretion

Parents and caretakers were given both verbal and written instructions in assisting children to collect a 24h urine sample on one of the three days of food recording. Each child was provided with a urine collection bottle, a backpack in which to carry the jug and three 80 mg PABA tablets (PABA check, The royal veterinary and agricultural pharmacy, Cophenhagen). On the first morning of the urine collections, instructions were given to discard the first specimen, and from then on to collect all specimens for up to 24h, up to and including the first specimen the following day. Instructions were given to take three 80 mg PABA tablets, one tablet during each main meal at the same day as the urine collections. On return to the laboratory, urine volume was recorded. PABA check [22] was used to validate completeness of urine collections. Collections that contained 85% or more of the PABA ingested were considered complete [23]. Recovery between 50% and 85% was adjusted according to a formula developed by Johansson and Bingham 1999 [24]: Na excretion = excretion [mg/day] + (0.82 x (93-PABA recov) and K excretion = excretion [mg/day] + (0,60 x (93-PABA recov)).

Na and K concentration was measured immediately by flame emission photometry [25] at Landspitali University Hospital, but spare samples were stored at -20°C for later analysis of PABA which was measured colorimetrically at Forskningsinstitut for Human Ernæring, in Cophenhagen Denmark [26].

Blood pressure and anthropometrics

Blood pressure, height and weight of study participants were measured at Landspitali – Children's Hospital. Blood pressure was measured three times, and the average was used, by a trained nurse using an electronic Propaq$_{cs}$encore® (WelchAllyn, 8500 SW Creekside Place, Beaverton, OR 97008, USA) networks security® modem, in a sitting position, after a 5 min rest. Subjects wore light weight clothing and no shoes. Height was measured to the nearest 0.1 cm, using ulmer stadiometer, Busse design (Nersinger Straβe 18, 89275 Elchingen, Germany), and weight was measured to the nearest 0.05 kg using a Taniter BWB-620 electronic scale (2625 South Clearbrook Drive, Arlington Height, Illinois 60005, USA).

Statistical analysis

Statistical analyses were conducted using SPSS for Windows, version 17 (SPSS Inc, Chicago). Descriptive analyses (mean and standard deviation) were used for describing the characteristics of study participants. As visual inspection of histograms suggested that Na and K urinary excretion instrument was normally distributed. Independent samples t-test was used to test the difference between boys and girls. It was also used to see whether Na and K excretion was significantly different between those who follow each food based dietary guideline and who do not follow the guideline.

For examining the association between diet quality score and Na and K excretion and blood pressure we used multivariate linear regression analyses were energy intake and gender were included as covariates. We included gender as a covariate to account for potential gender dependent differences in behavioral and physiological factors. Total energy intake was included as those with high intake were more likely to meet the food based dietary recommendation (as cutoffs in grams/day were used), while at the same time they have higher intake of Na and K.

Results

Of 79 children completing the 24h urine collection, twenty eight children had PABA recovery greater than 85% and 51 less than 85%. Children below 50% and above 110% were excluded (n=18) and we used a formula [24] to use the urine where PABA recovery was between 50% and 85% (n=35). Characteristics of the subjects included after taking PABA excretion into account (n=61), and information on Na and K excretion is shown in Table 1. No significant gender difference was observed. Children's blood pressure was on average 110/64 and according to the National heart, lung and blood institute [31] this is within the normal range for six year old children. Nine children (15%), four boys and five girls, were above normal blood pressure range (113/72 for boys and 110/71 for girls).

After correction of urine collections with PABA recovery between 50%-85% the average Na excretion was 1.66 g/24h, corresponding to 4.16 g NaCl (table salt) per 24h. The average K excretion was 1.21 g/24h.

Table 2 shows the proportion of children meeting each of the guidelines that where part of the diet quality index in the present study. Greatest adherence was found for dairy products and fish where consumption of 61% and 41% of the children was in line with the recommendations. Those children who consumed dairy products and dietary fiber in line with the recommendations had significantly greater K excretion than those who did not meet the recommendations (p=0.01) and (p=0.02), respectively, and K excretion was of borderline significance greater among children who consumed fish at least twice a week (p=0.05).

The association between total diet quality and Na or K excretion was assessed by linear regression. The average Na and K excretion according to diet quality score is shown in table 3. Linear trend was observed, where the estimated decrease in Na excretion by 1-unit increased diet quality score was 0.16 g/24h adjusted for energy intake and gender (95% CI: -0.31; -0.06). For K the corresponding adjusted increased excretion by 1-unit increased diet quality score was 0.18 g K/24h (95% CI: 0.06; 0.29). Systolic or diastolic blood pressure was neither significantly related to excretion of Na or K nor adherence to diet quality. Excluding the salt recommendation from the definition of diet quality did not change the findings.

Discussions

In the present study Na and K excretion were associated with diet quality among six-year-old children but not with blood pressure.

Na excretion in this study of six-year-old children was 1.66 g/24h (0.07 g/kg/24h), that corresponds to about 4.2 grams table salt. The average consumption of salt is generally high in the world, mostly in industrialized countries. In the Nordic nutrition recommendations from 2004 [28] ≤0.5 g salt is recommended per 1000 kJ (0.5 g salt/239 kcal) for children 2-18 years old. The average energy intake in the present study was 1530 kcal/day, so that the average salt intake should have been close to or under 3.2 g salt daily. Less than one third (29%) of the children in the present study met the recommendation for salt intake, 3.20 g/d [28]. Na is part of various additives and hence added to most foods, either by the industry or in cooking. It coordinates with the fact that about 75% of Na consumed comes from processed foods and food eaten away from home [32]. Other studies in children have shown similar results for Na excretion [33-35]. However, Japanese study [36] and Austrian study [37] show a much higher excretion or 3.00-4.00 g/24h or 1.20-2.00 g Na/kg/24h, respectively.

K excretion in the present study was 1.21 g/24h or 0.05 g/kg/24h. A few studies exist on K excretion but two studies examined 8-9 year old children and received excretion of about 1.80 g/24h [35] and 2.00 g/24h (0.07 g/kg/24h) [37]. Another study on 3-5 year old children showed K excretion of 1.00 g/24h or 0.05 g/kg/24h [34]. It is often challenging to compare values from studies of children, mainly because of the various ages of the children and various weights. To ease the comparison, it might be convenient to use the per kilogram approach. K excretion was associated with many of the components of the diet quality index used in the present study, such as dairy and whole grain (fiber). K excretion seeded also higher among those children following the recommendations on fruit and vegetable intake. However, difference did not reach statistical significance, most likely due to lack of power as very few children consumed these products in line with recommendations. This is consistent with previous studies of low fruits and vegetable consumption of Icelandic children [27], which is lower than in many other European countries [27].

Linear trend was observed between decreased Na and increased K excretion and increased adherence to diet quality in the current study. Only few studies have assessed the association between diet quality and excretion of Na or K and none of them included children. K excretion was found to be associated with diet quality in a study of adults with kidney stones ($r=0.23$, $p<0.01$) [38]. Recommended food score (RFS) was used as an index of healthy diet, which contained food groups like vegetables, fruits, whole grains, low fat dairy, fish and poultry, similar to the present study. Adult nephrolithiasis patients from the Health Professionals Follow-up Study and the Nurses' Health Studies (NHS) I and II collected 24h urine sample and fill out semiquantitative FFQ. Dietary DASH score were given based on seven components: high intake of fruits, vegetables, nuts and legumes, dairy products, and whole grains and low intake of sweetened beverages and red and processed meats. It was found that higher DASH scores were associated with higher K in all the three cohorts (*P* for trend all ≤0.01) [39]. In 12 healthy adults, two weeks elimination of fruits and vegetables from the diet resulted in a decrease in urinary K of 62% ($p<0.05$), assessed from 24h urine [39].

Systolic or diastolic blood pressure was neither related to excretion of Na or K nor adherence to diet quality score, perhaps because of lack of statistical power. Effects of hypertension on child health are poorly understood, unlike in adults were this association is well studied [40-42]. A few studies including 24h urine collection have been done in children related to health. One Meta analysis included ten trials of children with mean age 13 years old with 42% (IQR: 7%-58%) reduce in salt intake and the blood pressure decreased significantly by 1.17 mmHg systolic (95% CI: -1.78 to -0.56; $p<0.01$) and 1.29 mmHg diastolic (95% CI -1.94 to -0.65, $p<0.01$). From a population viewpoint, a reduction in BP of 1/1 mmHg in this age group would have major effects of preventing cardiovascular disease in the future [43].

Low Na and high K in children's´ diet is a diet quality of importance because tracking of nutrient intake begins about 3-4 years of age and children with extreme levels of intake tend to maintain those levels over time [12]. The diet can be significant determinant of adult diet even after two decades [13].

Strength and limitations

Strength of the study is an accurate food record for three days, 24h urine excretion with validation. More days are needed on individual basis but here are groups used.

Limitations of the study are possible uncertainty in blood pressure and limited statistical power. This is a cross sectional study and follow up is then recommended.

Conclusions

Na intake, estimated by 24h urine excretion was on average higher than recommended. Increased diet quality was associated with lower Na excretion and higher K excretion in six-year-old children.

Table 1. Characteristics of study participants

	N=61 (52% boys)
Age, months (sd)	72 (1.0)
Height, cm (sd)	120 (4.6)
Weight, kg (sd)	23 (3.3)
Systolic blood pressure, mmHg (sd)	110 (10.8)
Diastolic blood pressure, mmHg (sd)	64 (11)
Urine volume, mL/24h (sd)	659 (290)
Na excretion	
mmol/24h (sd)	72 (24)
mmol/L (sd)	120 (44)
g/24h[1] (sd)	1.66 (0.54)
g/kg/24h (sd)	0.07 (0.02)
K excretion	
mmol/24h (sd)	31 (11)
mmol/L (sd)	52 (20)
g/24h[2] (sd)	1.21 (0.42)
g/kg/24h	0.05 (0.02)
Na/K excretion	1.6 (1.3)

[1]Na excretion corrected for PABA = excretion in mg/day + (0,82 x (93-PABA recov)) [24]

[2]K excretion corrected for PABA = excretion in mg/day + (0,60 x (93-PABA recov)) [24]

Table 2. Na and K excretion (g/24h) according to adherence to food based dietary guidelines [6]

	Recommendation	Children follow (n=59) [n (%)]	Na excretion (Mean (sd))		K excretion (Mean (sd))	
			Following FBDG	Not following FBDG	Following FBDG	Not following FBDG
Fruits, vegetables and pure juices	≥400 g/d[1]	5 (8.5)	1.89 (0.99)	1.62 (0.48)	1.44 (0.33)	1.19 (0.43)
Fish ingestion	≥34 g/d[1]	24 (40.7)	1.60 (0.51)	1.68 (0.56)	1.34 (0.52)	1.12 (0.34)
Fish liver oil	≥5 g/d[1]	9 (15.3)	1.84 (0.62)	1.61 (0.52)	1.12 (0.38)	1.23 (0.44)
Dairy products	≥two servings/d[1]	36 (61.0)	1.65 (0.62)	1.65 (0.39)	1.32 (0.46)	1.04 (0.32)[4]
Fiber	≥11 g/d[2]	22 (37.3)	1.59 (0.49)	1.67 (0.56)	1.38 (0.48)	1.12 (0.36)[4]
Salt	≤3.2 g/d[3]	17 (28.8)	1.11 (0.18)	1.88 (0.48)[5]	1.33 (0.48)	1.16 (0.40)

sd: standard deviation

[1] [6] adjusted according to [27]

[2] [30]

[3] [28]

[4] $p<0.05$ between following FBDG and not following FBDG

[5] $p<0.01$ between following and not following FBDG

Table 3. Excretion of Na and K (g/24h) in urine and BP (mmHg) according to diet quality

	Diet quality score[1]				B (95% CI)	
	1 (n=13)	2 (n=24)	3 (n=10)	4 n=11)	Unadjusted	Adjusted[2]
Sodium	1.70 ± 0.35	1.75 ± 0.73	1.45 ± 0.27	1.45 ± 0.87	-0.10 (-0.25; 0.04)	-0.16 (-0.31; -0.06)
Potassium	1.09 ± 0.29	1.08 ± 0.39	1.51 ± 0.55	1.59 ± 0.29	0.19 (0.08; 0.29)	0.18 (0.06; 0.29)
Na/K ratio	1.7 ± 0.6	2.1 ± 2.1	1.1 ± 0.4	1.0 ± 0.7	-0.25 (-0.60; 0.10)	-0.28 (-0.66; 0.11)
Systolic BP	111 ± 12.5	108 ± 9.07	110 ± 11.6	117 ± 9.94	1.05 (-2.12; 4.23)	0.68 (-2.76; 4.11)
Diastolic BP	66 ± 12	63 ± 10	64 ± 13	63 ± 6.1	-0.81 (-3.90; 2.28)	-1.10 (-4.37; 2.17)

[1]1: Follows one of the FBDG; 2: Follows two of the FBDG; 3: Follow three of the FBDG; 4: Follows at least four of the FBDG [6, 27, 28, 30].

[2]Adjusted for gender and energy intake.

List of abbreviations

24h: 24-hour

K: Potassium

Na: Sodium

Competing interests

The authors declare that they have no competing interests.

Authors´ contributions

IT and IG contributed to design, data collection, interpretation and final writing of the paper. TIH contributed statistical analysis, interpretation and final writing. OKK contributed handling/management, statistical analysis, interpretation and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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5 RESULTS

The main results for children are found in the manuscript (see chapter 4). In this chapter additional results are provided for the parents, including distribution of Na and K excretion that have not been published previously. Na and K intake of parents were estimated from the urine excretion and compared with reference values. Additional information regarding children includes comparison of estimated Na and K intake by 3dwfr and 24h urine excretion. A similar result have been reported previously for these adults where K intake estimated by the FFQ used in the present study correlated with K excretion, but was not found to be a suitable tool to estimate Na intake [101,102].Correlation of N and K excretion between parents as well as parent-child relationship is also presented in this chapter.

5.1 Na and K excretion; parents

Of 112 mothers who answered the FFQ, 57 provided a 24h urine collection and of 75 fathers 32 provided 24h urine collection. Forty-four mothers had PABA recovery greater than 85% and 13 less than 85%. Twenty-three fathers had PABA recovery greater than 85% and 9 less than 85%. PABA recovery below 50% and above 110% were excluded and we used a formula [103] to analyze the urine where PABA recovery was between 50% and 85% (mothers=8, fathers=6). In the end 43 mothers and 26 fathers were included in the analysis. The characteristics of children, mothers and fathers are described in table 4.

Based on the 24h Na excretion the average intake of salt was 8 g/day among the mothers and nearly 11 g/d among the fathers in the present study. Twenty six percent of mothers had an intake of salt that was in line with the recommendations for salt intake of not more than 6 g/day [57]. Nineteen percent of the fathers consumed 7 g/day or less salt, which is the limit set for adult men [57].

The estimated average K intake for mothers was 2.20 g/day and 2.54 g/day for fathers. Na/K ratio was 1.5 for mothers and 1.9 for fathers.

5.2 Intake vs. excretion; children

Na intake assessed by 3dwfr was 1.94 g/24h (4.86 g salt/24h) (see table 4). Corresponding value for K intake was 1.91 g/24h. According to these values, it appears that the Na intake from the dietary records was 14% higher and K intake was 36% higher compared to urinary excretion measures.

5.3 Correlation between children, mothers and fathers

Although it is not entirely appropriate to treat the data on an individual basis due to day-to-day variation in urinary output, it was decided to use Pearson correlation to examine relationships between

children and parents with regard to Na and K in 24h urine. K excretion of the fathers correlated with K excretion (r=0.45, p=0.02) of the mothers. No relationship was found between parent and children, neither for Na or K.

Table 4. Characteristics (mean ± sd) of children, mothers and fathers

	Children (n=61)	Mothers (n=43)	Fathers (n=26)
Age (months/years)[1]	72 ± 1.0	36 ± 5.3	37 ± 6.0
Height (cm)	120 ± 4.58	169 ± 6.03	180 ± 5.65
Weight (kg)	23.4 ± 3.31	71.2 ± 12.8	85.0 ± 14.2
Systolic BP (mmHg)	110 ± 10.8	NA	NA
Diastolic BP (mmHg)	64 ± 11	NA	NA
Energy intake (kcal)	1529 ± 340.2	1929 ± 2619	2361 ± 929.7
Excretion			
Na (mmol/24h)	71.8 ± 23.7	139 ± 55.6	186 ± 53.1
K (mmol/24h)	30.8 ± 10.9	56.4 ± 19.2	65.0 ± 20.9
Urine volume (ml)	659 ± 290	1712 ± 720.8	1477 ± 488.9
Na corrected[2] (g/24h)	1.66 ± 0.54	3.19 ± 1.28	4.28 ± 1.22
K corrected[3] (g/24h)	1.21 ± 0.42	2.20 ± 0.75	2.54 ± 0.82
Na/K	1.6 ± 1.3	1.5 ± 0.6	1.9 ± 1.0
Intake[4]			
Na (g/24h)	1.94 ± 0.60	2.14 ± 0.63	2.70 ± 0.93
K (g/24h)	1.91 ± 0.60	3.01 ± 0.87	3.56 ± 1.17
Na/K	1.1 ± 0.3	0.7 ± 0.1	0.8 ± 0.2

[1] In months for children

In years for parents

[2] Sodium excretion corrected for PABA = excretion in mg/day + (0,82*(93-PABA recov)) [103]

[3] Potassium excretion corrected for PABA = excretion in mg/day + (0,60*(93-PABA recov)) [103]

[4] Intake estimated by 3dwfr for children and FFQ for mothers and fathers

6 DISCUSSIONS

The main results for children are discussed in the manuscript (see chapter 4).

6.1 Na and K intake of Icelandic children

Based on the information from the 3dwfr Na intake of six-year-olds in the present study was 1.94 g/24h (4.86 g salt/24h). Other dietary studies of children in Iceland show slightly higher intake. However, the difference might be related to different methodology used in the different studies. One study of five year olds in 2007 reported an average intake of 2.38 g/d, assessed by three day estimated dietary record [104]. Another study of nine year olds in 2003-2004 showed intake of 2.86 g/d, assessed by two 24h dietary recalls [105]. Similar numbers have been reported in studies performed abroad. In a large review in Europe 2004 [106] where variety of data methods were used (dietary record, FFQ, 24-h recall), the Na intake was around 2.00 g/d, 2.28 g/d in UK, 2.23 g/d in Poland and 1.69 g/d in Greece. According to these findings, it is often suggested that most people are consuming more Na than they need.

If K levels are examined in the present study of six-year-olds, the intake is 1.91 g/24h, assessed by 3dwfr. That is, like Na, slightly lower than has been observed in Iceland. K intake of five year old children in 2007, from three day dietary records was 2.37 g/d [104]. The corresponding intake for 9 year olds in 2003-2004, assessed by two 24h dietary recalls was 2.60 g/d for [105]. K intake according to Lambert et al [106] was around 2.00-3.00 g/d for 4-10 year old children, which is much higher than in our study.

Na and K excretion in urine is used as a golden standard to estimate Na and K intake [1]. In the present study the three day weighed food record (3dwfr) tended to overestimate both Na and K intake among children. It is difficult to compare these results with other studies of children where very different approaches are used to assess the intake. For example, a study of 3 to 5 year old children with 24h urine excretions and three day dietary diaries collected using the household measures method, showed Na intake 10% higher than excretion and K intake almost two times higher than excretion [54]. In another study of adolescent girls, intake was calculated from a food composition table; duplicate analysis was performed for four days and 24h urine was collected. Results from this study reported Na intake was 26% lower than excretion and K intake was 15% higher than excretion. It is clear that Na is more stable than K and reflects the intake rather well.

6.2 Parents

The average intake of mothers and fathers is in excess of recommendations. Only 26% of the mothers and 19% of the fathers followed the recommended guidelines for salt intake. The K intake of mothers and fathers from 24h urine were 2.20 and 2.54 g/24h, respectively. The results regarding the proportion of individuals following the recommended intake levels and the presented distribution of intake should be interpreted with caution, due to known day-to-day variation in Na and K excretion. However, the high mean Na excretion should be alarming.

When analyzing the Na/K ratio of 24h urine collection, it is interesting to note that mothers had a better ratio than fathers. It is quite clear that fathers are consuming a higher proportion of Na than the mothers. Also men usually eat less vegetables and fruits than women, as seen in the National Survey of diet in Iceland 2010-2011 [89], which could affect K intake and increase the Na/K ratio.

Salt intake is not only high in Iceland but also in many other parts of the world. Most adult populations have mean Na intakes >2.30 g/d, and for many mean intakes are >4.60 g/d (mainly Asian countries) [107]. INTERSALT; an international study of electrolyte excretion and blood pressure assessed both Na and K in 24h urine in many countries in 1988. It was found that Belgium, Finland, Germany, Netherlands and the UK had a similar excretion or 3.20-3.60 g/24h. However, Hungary, Italy, Poland, Portugal and Spain all had excretion above 4.00 g/24h [17]. According to this study Iceland had Na excretion 3.18 g/24h which is considerably lower than in the current study. If other studies in the Nordic countries are reviewed, it emerges that Na intake in the Danish population was 3.54 g/24h [108], in the Swedish diet about 4.60 g/24h [109], and in the Finnish diet 3.28 g/24h [110]. K, according to INTERSALT [17] is too low, as reported in this current study. The highest values are in Finland, 2.98 g/d, 2.83 in the Netherlands, 2.62 in Spain, 2.60 in Denmark, 2.60 in Germany and around 2.50 in Iceland. Other values for Belgium, Hungary, Italy, Poland and UK were around or right above 2.00 g/24h.

The current study was done in 2002-2003 at the same time as National survey in Iceland was conducted [88]. In the National survey in Iceland 2002, one 24h dietary recall was used to estimate dietary intake. Na intake at the age of 20-39 year old reflected the estimated value in the present analysis by 24h urine excretion rather well. The Na intake was 4.26 g Na/d (10.65 g salt/d) for men and 3.19 g Na/d (7.98 g salt/d) for women. On the other hand, a greater difference was observed in K intake where the intake from the National survey was higher than the excretion from our study. The National survey showed K intake for the age group 20-39 year old was 3.63 g K/d for men and 2.57 g K/d for women. The consumption has not changed much since 2002. In the National survey in Iceland in 2010 and 2011 [89] two 24h dietary recalls were used to estimate dietary intake. Na intake has declined slightly but the K intake has not changed as much. The Na intake in the National survey in 2010 and 2011 in the age group 31-60 year old were 3.78 g Na/d (9.45 g salt/d) of men and 2.63 g Na/d (6.58 g salt/d) of women. K intake was 3.49 g/d of men and 2.71 of women.

No relationship was found between urine excretion of Na and K of the children and their parents. Thorsdottir et al [14] have reported a relationship between vitamin C and β-carotene intake and serum concentration in the same study on six-year-old children and their parents. This might indicate that the correlation between salty food and K rich food is not as strong as for vitamin C and β-carotene. One possible explanation is that fruit and vegetable intake is better correlated between parents and children that dairy intake, but dairy is a good provider of K.

6.3 Strengths and limitations

The main strength is that we have 24h urine collection to assess Na and K excretion among children. To date, no comparable studies have been conducted in Iceland or in the Nordic countries. Moreover, an accurate method was used to evaluate dietary intake in the children and investigate data on diet quality and contribution of food groups to total energy intake.

Main limitation is the relatively few subjects which limit the statistical power to assess possible associations between Na and K intake to blood pressure, or the parent child association. Further this is a cross sectional study and thus the results only reflect how it is at one point and follow up is necessary.

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8 FUTURE PERSPECTIVES

Assessing the intake of Na and K is difficult, especially the Na intake because of the discretionary use in cooking and at the table. Food records, recalls and FFQ do not take this consumption into account. Thus the 24h urine collections could be used to assess this intake and it is likely a simpler method for children rather than weighing and recording all foods and beverages that they eat. In the future, 24h urine collection may be a good option to use to estimate dietary intake and to assess adherence to dietary guidelines.

More research is needed in this area with larger samples and potentially more 24h urine collections to give even more valid results.

A new study with six-year-old children is now in process. Unfortunately no urine collection is available but according to the present results, the difference between intake and excretion in children was rather small. Consequently, the new study should reflect the possible changes in the consumption well.

9 APPENDIXES TO THE LITERATURE REVIEW

9.1 Appendix 1 - Na absorption

Regulation of Na^+ content of the ECF is closely related to the systemic control of ECF volume. If the body Na^+ burden is increased, water is also retained and ECF volume increases; conversely, if the body Na^+ burden falls the ECF volume decreases. Changes in ECF volume are detected by sensors of pressure and distension which are located in the cardiac atria and right ventricle, the pulmonary vasculature, the carotid arteries and the aortic arch. From these sensors afferent nerve pathways end in the medulla and hypothalamus. When ECF or blood volume falls retention is stimulated, sympathetic nervous activity increases, stimulating the nerves supplying the afferent renal arterioles to induce vasoconstriction and thereby producing a redistribution of renal blood flow which, by reducing glomerular filtration, increased Na^+ and water retention. Additionally, sympathetic nervous stimulation of the juxtaglomerular apparatus increases production of renin. This in turn leads to an increase in circulating angiotensin II, adrenal medullary secretion of noradrenaline and adrenaline, and pituitary release of adrenocotricotrophin (ACTH) and antidiuretic hormone (ADH) [1].

ACTH and angiotensin II induce adrenal cortical secretion of aldosterone and other mineralocorticoids which stimulate Na^+ retention and K^+ loss by the kidneys and the distal bowel. Increased secretion of ADH promotes Na^+ reabsorption from the renal distal tubules and the colon may also be involved. Renal Na^+ excretion is increased by factors which include specific natriuretics hormone, and vasodilators, parathyroid hormone, prostaglandins and kinins [1].

Two important functions for Na^+ and water balance, filtration and reabsorption exist in the kidneys. Filtration is normally autoregulated but reabsorption is adjusted for variable input and output. Every minute, 125 ml of filtrate containing 17 mmol of Na^+ enters the proximal tubule (PT). There 99% is reabsorbed and 1% is excreted. The reabsorption of filtered Na^+ is 65% in the PT, 20% in the Thick Ascending Limb of Henle's loop TAHL, 10% in the distal tubule and 4% in the collecting duct (CD) [2]. In the PT, reabsorption occurs by the action of several Na^+ driven apical transporters and is then critical for amino acid, glucose, bicarbonate and inorganic phosphate reclamation. In the TAL, Na^+ reabsorption depends on the $Na^+/K^+/2Cl^-$ cotransporter in the absence of any water reabsorption and, thus, is critical for the concentrating and diluting power of the kidney. Despite the quantitative importance of PT and TAL where almost 90% of the filtered load of Na^+ is reabsorbed, these nephron segments are believed to play a minor role in the daily adaptation of Na^+ urinary excretion, because the amount of Na^+ that escapes the loop of Henle is tightly controlled [3]. Salt sensing and the regulation of salt excretion is provided mainly via tubuloglomerular feedback (TGF) in the juxtaglomerular apparatus (JGA) consisting of macula densa (MD), mesangial, granular and vascular smooth muscle cells (VSMC) and located in the cortical TAHL [4].

Plasma Na^+ is mainly determined by plasma water content (determined by water intake), “insensible” losses and urinary dilution [5].

The concentration of Na^+ in urine (urinary dilution) is then determined during the passage through the CD, which is controlled by aldosterone [6]. Aldosterone is synthesized in the hypothalamus and stored in and released from the posterior pituitary [5].

Na^+ is reabsorbed in the CD from the urinary lumen into the extracellular compartment through a tight epithelium formed by principal and intercalated cells [6]. The principal cells control the active transport of Na^+ out of the cell [7]. The concentrated urine is produced by water reabsorption across the renal CD, mediated by cellular membrane transport proteins called aquaporins [8]. The opposite occurs with decreased extracellular Na^+, the thirst center and vasopressin secretion is inhibited, resulting in diuresis [5].

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9.2 Appendix 2 - K absorption

Excretion of K^+ into urine is by both filtration and secretion. A small amount is excreted in feces [1]. Absorption is determined by dietary K^+ intake and intestinal K^+ transport processes, both diet and intestinal transport physiology are analyzed [2].

K^+ is freely filtered at the glomerulus [3]. About 90% of dietary K^+ is absorbed in the small bowel and equivalent amount is excreted in the urine through the kidneys. The rest (about 10%) is fecal excretion [4]. The CD regulates the K^+ excretion.

Along the collecting duct, K^+ is both secreted and absorbed. Secretion of K^+ occurs primarily in the initial collecting tubule and the cortical collecting duct. K^+ secretion in the CD is variable and depends on dietary K^+ intake. The cell in the CD that is mainly responsible for K^+ secretion is the principal cell which controls the active transport of K^+ into the cell. The intercalated cell in the CD is responsible for reabsorption of K^+. Five major physiologic factors stimulate K^+ secretion in the CD: aldosterone, high Na^+ delivery to the CD, high urine flow rate, high serum K^+ level and delivery of negatively charged ions to the CD. Aldosterone directly increases the activity of the basolateral membrane Na^+/K^+-ATPase, thereby stimulating secretion of K^+ into the tubular lumen. The kidney is, therefore, responsible for long term K^+ homeostasis. The major regulators of K^+ shifts into cells are insulin and stimulation of β2-adrenergic receptors [5].

The secretion of K^+ in these distal segments (distal convoluted tubule and the CD) is indirectly but tightly coupled to Na^+ reabsorption; increased Na^+ reabsorption increases whereas decreased Na reabsorption decreases K^+ secretion [6].

Fecal K^+ is absorbed or secreted mainly by passive mechanisms; the rectum and perhaps the sigmoid colon have the capacity to actively secrete K^+, but the quantitative and physiological significance of this active secretion is uncertain [4].

There are extrarenal mechanisms that control the distribution of K^+ between the intracellular and extracellular fluid. These mechanisms are critical, particularly in protecting against sudden changes in K^+ concentration. The integrity of the cell is an important factor, if the cell is injured, frozen, lysed or crushed, K^+ leaves the cell and acute hyperkalemia may ensue. The tonicity is also important, when water leaves the cell as the osmolality outside the cell increases, concentrating the cellular K^+; the gradient for K^+ exit is enhanced, and increased amounts of K^+ leave the cell. Acid-base status, when the hydrogen ion concentration in blood increases, hydrogen ions enter cells to be buffered and, as a results, K^+ exits. Hyperkalemia is treated with insulin and glucose. Insulin is given because it “drives” K^+ into cells; glucose is given to prevent hypoglycemia. K^+ enters the cells without glucose [3].

9.2.1 References

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9.3 Appendix 3 - Physiology of blood pressure linked to Na and K

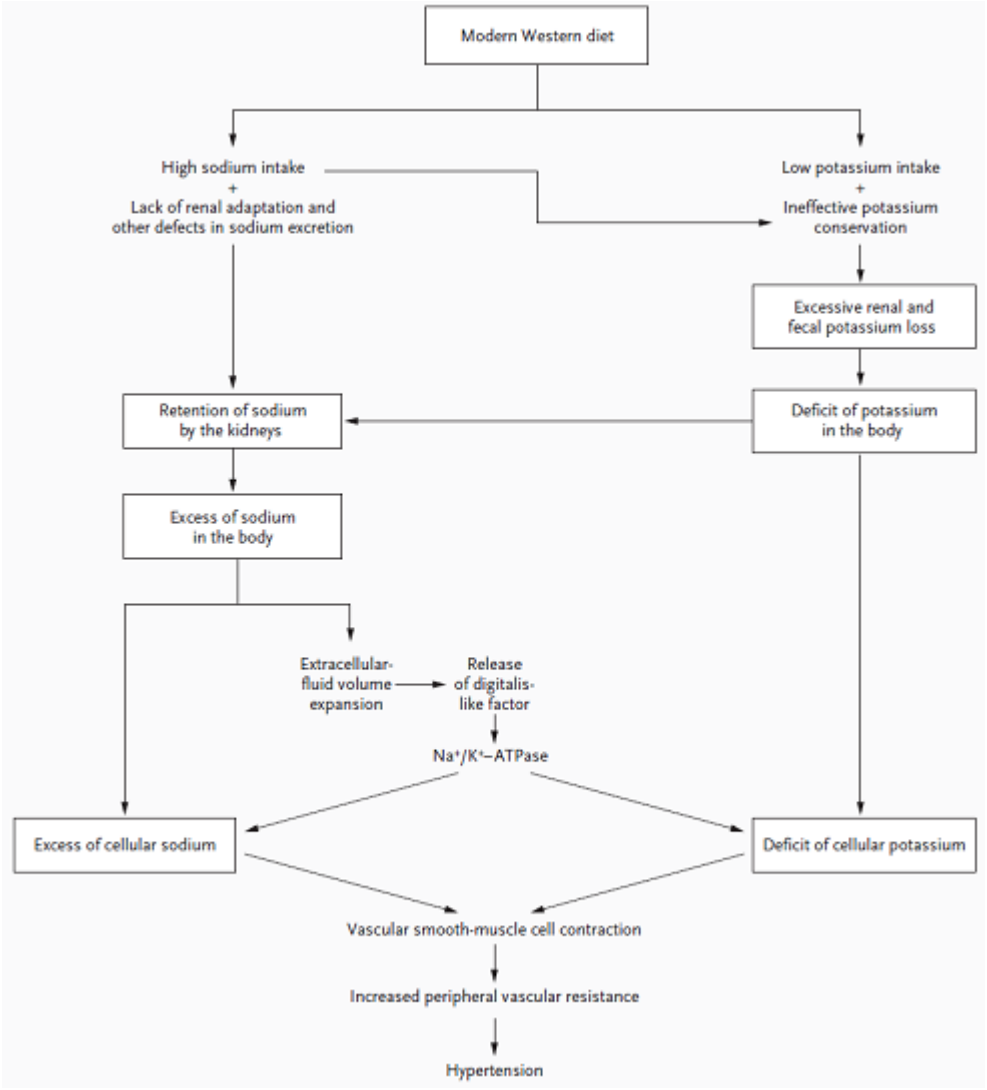

Figure 1: The Modern Western Diet and the kidneys in the pathogenesis of primary hypertension [1]

The modern diet includes excessive dietary Na^+ and chloride (Cl^-) and deficient dietary K^+ and bicarbonate (HCO_3^-), which is problematic in individuals with salt-sensitive blood pressure and hypertension (see figure 2) [2]. Salt-sensitive individuals are salt resistant and they will experience a significant rise in blood pressure when switching from a low salt to a high salt diet. Other non-salt sensitive individuals will only experience minimal change in blood pressure [3]. This may be caused by either a decreased ultrafiltration coefficient or increased tubular reabsorption. When dietary Na^+ intake is increased under such abnormalities, body fluid volume and systemic blood pressure increases [4]. Dietary deficiencies of both K^+ and bicarbonate interact with dietary NaCl overload to induce physiologic and metabolic disturbances that over time can determine the expression of hypertension [2].

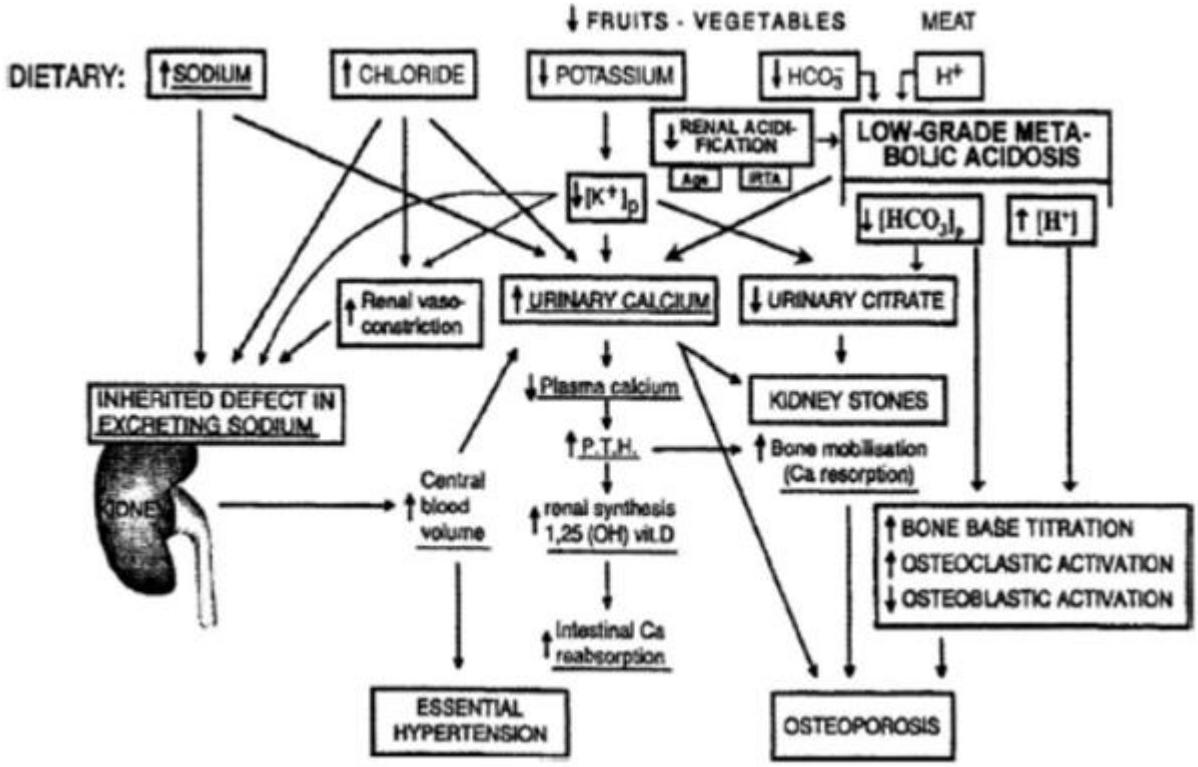

Figure 2: Hypothesized relationship between electrolytes and bicarbonate, the kidney, essential hypertension, kidney stone, and osteoporosis [2]

The key factors in the Na^+-induced mechanisms of blood pressure control include Na^+, ENaC (epithelial sodium channels), the RAAS, EDLF (endogenous digitalis-like factors), oxidative stress and the CNS sympathetic nervous system. Agents that influence these factors can either induce or decrease hypertension [5].

Any decrease in extracellular fluid volume, due to falling plasma volume lowers blood pressure and any rise in extracellular fluid volume increases blood pressure by increasing plasma volume [6]. An acute Na^+ load can lead to transient increases in blood pressure because of the sympathetic nervous system via osmotic, angiotensinergic and volume mechanisms. In healthy people, such acute ingestion does not cause sustained hypertension [7].

The membrane proteins for Na^+ transport, in the distal convoluted tubule to the CD, have been identified, though the clinical implications of Na^+ handling by those transporters have not been fully determined [8].

One theory of mechanisms linking salt to high blood pressure is connected to the discovery of endogenous ouabain, an adrenocortical hormone. Ouabain is a selective Na^+ pump inhibitor and has cardiotonic and vasotonic effects. Plasma ouabain levels are significantly elevated in about 40% of patients with essential hypertension [9].

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