Nutritional Deficiency & Impact on Health

Chapter 6

Urinary Excretion of Major Minerals: Potential Indicators of Health

Emanuella Brito[1], Camila Jaramillo[2], Shawn Kurian[2], Priya Krishnakumar[3], Amanpreet Cheema[1,2,3,4*]

[1]Halmos College of Arts and Sciences, Nova Southeastern University, Fort Lauderdale, FL, United States

[2]Dr. Kiran Patel College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL, United States

[3]Institute for Neuro Immune Medicine, Dr. Kiran C. Patel College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL, United States

[4]Department of Nutrition, Dr. Kiran C. Patel College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL, United States

*[*]**Correspondence to: Amanpreet Cheema,** Department of Nutrition, Dr. Kiran C. Patel College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL, United States.*

Email: acheema@nova.edu

Abstract

Major minerals are important for various biochemical functions in the body beyond maintaining fluid and acid-base balance. Urinary excretion of these critical minerals is generally an index of their intake. While it is normal to see urinary losses of minerals in healthy free-living individuals, the levels could indicate metabolic disturbances. Therefore, due to mineral's involvement in several biological processes, their urinary levels could be exploited as indicators of well-being, and overall health status.

Keywords: Urinary; Trace elements; Major minerals; Normal urinary values; Mineral metabolism; Mineral excretion.

1. Introduction

Minerals are micronutrients essential for optimal metabolic function and body homeostasis by their involvement in a variety of biochemical reactions crucial for cellular functioning [1,2]. Disruption in any of these pathways can dramatically affect the metabolism and processing of the nutrients resulting in many metabolic imbalances which may lead to a variety of health conditions [3]. Minerals are classified as either major minerals or trace elements

based on their utilization [3]. Required in more than 100mg/day, major minerals are sodium, potassium, calcium, magnesium, phosphorus, sulfur, and chloride whereas trace elements are iron, zinc, iodine, selenium, copper, cobalt, chromium, manganese and molybdenum which are required less than 100 mg/day [2,4]. Minerals travel through the body in different ways owing to their inorganic structure. Some are excreted by kidneys in urine, some in bile but almost all are excreted via urine, if present in excess [5]. These urinary inorganic salts levels may serve as indicators of aberrations in the metabolic pathways where minerals are crucial or the processes related to mineral utilization themselves, and hence serve as an indicator of human disease state [6]. The major minerals which are used and stored in large quantities in the body, their diet sources, recommended daily intakes, handling and use as health status indicator are discussed below.

2. Major Minerals and their Metabolites

2.1. Sodium

Sodium is an electrolyte and major determinant of extracellular fluid volume (ECFV) deemed essential for nerve impulse transmission and muscle contraction [4]. Sodium is easily absorbed by the intestinal tract and travels freely through the blood stream regulating the volume and pH of bodily fluids until it reaches the kidneys, where excess is filtered out of the blood and excreted via urine [7].

2.1.1. Recommended daily intake

Recommended dietary allowances of sodium are 110mg/d for newborns up to 6 months and 370mg/d for infants 7-12 months of age [8].

Children are recommended 800mg/d of sodium from 1-3 years of age, 1000mg/d of sodium from 4 to 8 years of age, 1200mg/d from 9 to 13 years of age and 1,500 mg/d from 14 years [8].

2.1.2. Sodium handling and human health

Sodium modulation in the body is regulated by the renin-angiotensin-aldosterone system (RAAS) [9]. In healthy individuals, this system releases a series of hormonal stimuli which can promote either sodium excretion or reabsorption based on intratubular sodium levels [9]. A chronic activation of this system has been related to pathologies ranging from hypertension and chronic kidney failure to mental disturbances and inflammatory damage [10].

Normal urinary levels of sodium free cation range around 12477(1863.49-37249.07) umol/mmol creatinine [11]. These levels can vary rapidly based on the amount of salt and fluids ingested from food sources including table salt, processed food, meats, eggs, milk and

vegetables [4,12]. Sodium restricted diets have shown to lower sodium levels in the urine to 10mEq/L within 3-5 day [13]. Lower levels of sodium in urine relates to decreased blood volume as it promotes sodium reabsorption by the release of aldosterone [14]. Inversely, high blood pressure caused by the expansion of extracellular fluids increases sodium excretion due to elevated renal perfusion press ion [14]. Sodium excretion is also enhanced in response to hypertension and hypervolemia due to the release of atrial natriuretic peptide from atrial myocytes which acts against sodium-conserving pathway [14]. In short, alterations in sodium control mechanisms, may contribute to pathologies that are attributed to the ingestion of this mineral [14]. Abnormally high urinary levels of sodium are seen in conditions such as Addison's disease, Hypopituitarism, and Hypothyroidism due to increased anti-diuretic hormone secretion (ADH), which promotes water reabsorption by the kidneys [14-17]. Cirrhosis, Nephrotic Syndrome, and Diabetes Insipidus are conditions associated with low urinary levels of sodium caused by the inappropriate activation of the RAAS system which favors sodium conserving pathways and can be a risk factor for hypertension [14,18,19].

The underlying causes of hyponatremia, blood sodium levels less than 130mmol/L, can be determined by assessing a patient's hydration status through the measurement of urine osmolality [20]. A test of urine sodium is recommended in the cases of euvolemia where hypotonic hyponatremia is confirmed with urine osmolality greater than 100 msOsm/kg. The urine Na greater than 20 mmol/L then indicates the presence of syndrome of inappropriate antidiuretic hormone secretion (SIAD) in which case, First equation ratio ascertains the degree of fluid restriction needed to correct the hyponatraemia [20]. On the other hand, urine Na lower than 20mmol/L indicates the possibility of hypo/hypervolemia. Low urine sodium levels in the case of hypervolemia are often secondary to an underlying condition such as cardiac failure, renal failure, and liver cirrhosis.20 Urinary sodium is hence a reflection of renal integrity and its measurement if combined with fractional excretion of sodium can potentially distinguish acute azotemia from acute tubular necrosis (ATN) [21].

2.2. Potassium

Potassium is the major intracellular cation and aids in maintenance of normal cellular fluid levels [22]. Sodium-potassium pumps regulate homeostasis and potassium is crucial for nerve transmission, muscle contraction, cell integrity, and blood pH balance [4,22]. It enters the body through food ingestion and excess is filtered out of the blood and excreted via urine by the kidneys [22]. Fruits and vegetables are the main dietary sources of potassium [4].

2.2.1. Daily recommended intake

Recommended dietary allowances of potassium differ for different age groups.

The requirement is 400mg/d for infants up to 6 months after birth and 860mg/d from 7-12 months [8]. Children are recommended 2,000mg/d of potassium from 1 to 3 years of age and 2,300mg/day from 4 to 8 years of age [8].

From 9 years and above, the recommendations vary based on gender.

Men require 2,500mg/d from 9-13 of age, 3,000mg/d for 14-18 years, and 3,400 mg/d for 19 years and above.8 Women are recommended 2,300mg/d of potassium from 9-18 years of age and 2,600mg/d for 19 years and above [8].

Lactation and pregnancy condition affect potassium RDAs.

For the ages 14-18 and 19-50, pregnant women require 2,600mg/d and 2,900mg/d of potassium respectively and lactating women require 2,500mg/d and 2,800mg/d [8].

2.2.2. Potassium handling and human health

Potassium handling by the kidneys happens mainly in the glomerulus where free potassium ions are filtered and can either be excreted through urine or reabsorbed by the proximal tubule and loop of Henle, and a small portion by the distal nephron [22]. Reabsorption mainly happens via passive transport, and it is proportional to sodium and water [22]. The glomerular potassium filtration, reabsorption and excretion in the nephron dictates the daily levels of urinary excretion of potassium, with normal levels noted to be 3593.14 (553.33-8078.58) umol/mmol creatinine [11]. Glucose ingestion and insulin release temporarily force potassium to move from the extracellular fluid (ETF) into the intracellular fluid (ITF) [23]. The kidneys then excrete ingested or excess potassium, increasing K+ ions in the urine in the following hours after a meal. Adrenaline release and metabolic alkalosis cause the movement of potassium ions from the ETF to the ITF, leading to a lower excretion of potassium ions by the kidneys [23]. Metabolic acidosis, noradrenaline and aldosterone release, dehydration, trauma, burns, rhabdomyolysis, a sodium rich diet, and bleeding in the upper GI tract from ulcers or esophageal varices, have the opposite effect and cause potassium to move to the extracellular fluid, increasing the amount of potassium filtered out of the blood [23]. Test for urine potassium concentration can help determine if the dyskalemia is kidney related [21]. Urine potassium levels of 5-15 mEq/L indicate non kidney originated dyskalemia, while values higher than 40 mEq/L indicate that the disorder is kidney responsible [21]. The values of urine potassium lower than 2.5 mEq K+/mmol creatinine can either indicate cell shift due to hypokalemic periodic paralysis, insulin administration, beta 2-adrenergic stimulation, or gastrointestinal loss due to diarrhea [21]. Urine potassium greater than 2.5 mEq K+/mmol creatinine, requires blood pressure and arterial blood volume assessment in order to make a diagnosis [21]. Urinary potassium measure reflects fluid and electrolyte imbalances and renal integrity. The levels help establish the pathophysiologic mechanism behind conditions like

hypokalemia and aids in formulating differential diagnosis (whether its kidney related or not) [24].

2.3. Calcium

Calcium is the most abundant mineral in the body. It is the structural and storage component of bones and teeth [22]. Calcium also acts as a protein activator, crucial for processes such as muscle contraction, neurological signaling, hormonal secretion, and blood clotting [22]. Calcium can be obtained through the ingestion of calcium-rich foods such as dairy, cereals, legumes, and vegetables [4]. Calcium absorption by the organism is based on need, excess of which is filtered out of the blood and excreted by the kidneys [25].

2.3.1. Dietary recommended intake

Recommended dietary allowances of calcium for infants up to 6 months after birth are 200 mg/d and 260mg/d for infants 7-12 months after birth [8].

Children from 1 to 3 years of age are recommended 700mg/d of calcium, while children from 4 to 8 years of age are recommended 1,000mg/d of potassium [8].

For ages 9-18, the requirement is 1300 mg/day for both males and females. For male adults aged 19-70, the recommendation is 1,000 mg/d and 1,200mg/d after 71 years of age. For adult females aged 19-51, calcium RDA is 1,000 mg/d and 1,200mg/d after 51 years of age [8].

2.3.2. Calcium handling and human health

A good half of the calcium present in the plasma is freely filtered in the kidneys and most of it is reabsorbed by passive transport in the renal tubules [26], with normal urinary levels of calcium average at 200.0 (16.9-520.0) umol/mmol creatinine in healthy individuals [11]. Absorbed calcium equals excreted urinary calcium, however, this can vary based on age and sex [27]. Urinary calcium levels balance is regulated by parathyroid hormone (PTH), which when released in excess such as in primary hyperthyroidism (pHPT) causes the calcium release from the calcium stores in the bones to the extracellular fluid, increasing urinary calcium [25]. Urinary calcium excretion is also increased by anti-diuretic hormone (ADH) and could be an indicator of kidney stones, renal insufficiency, and nephrocalcinosis [25]. Patients with familial hypocalciuric hypercalcemia (FHH), a rare genetic mutation, present low levels of urinary calcium [28]. A 24-hour urine calcium test is used to distinguish pHPT from FHH [25]. Urinary calcium is usually moderate/high in patients with pHTP with levels greater than 400 mg calcium/24 hours while in patients with FHH urine calcium levels are low, usually less than 100 mg calcium /24 hours [25,28]. Apart from the above-mentioned states, hypercalciuria can be seen in hyperparathyroidism, multiple myeloma and other osteolytic neoplasm disorders, osteoporosis, vitamin D overdose, renal tubular acidosis, hyperthyroidism,

Paget's disease, and sarcoidosis [27,29]. Drugs such as some antiacids which contain calcium and calcium supplements can also lead to direct increase of calcium in urine [29]. On the contrary, decreased urine calcium ions are seen in conditions such as hypoparathyroidism, pseudo hypoparathyroidism, rickets, hypothyroidism, steatorrhea, and nephritis [29]. Hypocalcaemia can also be caused by drugs such as thiazide and benzothiadiazide diuretics, as well as estrogen.29 Diet, especially minerals, and vitamins can influence the excreted amount of calcium by the body [27]. For example, vitamin D availability has been found to be intrinsically related to regulation of calcium absorption by the large intestine and renal calcium excretion with vitamin D mediated calcium reabsorption accounting for up to 8% of all the calcium reabsorbed by the kidneys [27]. Additionally, sulfate has shown to be a competitive inhibitor of the reabsorption of calcium in both the proximal and distal tubules of the kidneys, promoting calciuria [30]. A high intake of other dietary components such as sodium and caffeine has been noted to induce calciuria, however, potassium ingestion induces an opposite effect [31-33]. The calcium urinary excretion serves as an indicator of renal health, as a 24-hour calcium urine test is frequently used in the evaluation of kidney stones due to the high incidence of hypercalciuria in patients with calcium oxalate stone formation [34]. Alterations in calcium excretion also serve as a diagnostic test for hyperparathyroidism where a calcium load test (CLT) is conducted [35]. Urinary calcium may hence be used to monitor kidney function in addition to serving as a diagnostic test of disorders of parathyroid, the gland near the thyroid associated with a variety of physiological functions in the body including cognitive function [36].

2.4. Magnesium

Magnesium is a mineral essential for glucose and lipid metabolism, signaling pathways, neurotransmitter release, neuromuscular function, bone development, and energy storage [4]. It can be obtained through the diet from foods such as fruits, vegetables, nuts, dairy, meats, and fortified cereals [4].

2.4.1. Dietary recommended intake

Recommended dietary allowances of magnesium are 30 mg/d for infants up to 6 months and 75mg/d for infants 7-12 months of age [8].

Children from 1 to 3 years of age are recommended 80mg/d of magnesium, children from 4 to 8 years of age are recommended 130mg/d and children from 9 to 13 years of age 240 mg/d [8].

Recommended dietary allowances of magnesium for males aged 14-18 are 410 mg/d, from the age 19-30 this value goes down to 400mg/d, increasing again after the age of 31 to 420mg/d [8]. For females these values are 360mg/d for the ages 14-18, 310mg/d for the ages

18-30, and 320 mg/d for 31 and older [8].

Pregnancy requires a higher magnesium intake in females. Therefore, the RDAs are 400mg/d for the ages 14-18, 350mg/d for the ages 19-30, and 360mg/d for the ages 31-50. Lactation however does not interfere with the general recommended dietary allowances for women [8].

2.4.2. Magnesium handling and human health

Magnesium homeostasis is regulated by the kidneys which either reabsorb or excrete magnesium filtered from the bloodstream [37]. A little over 70% of serum magnesium undergoes glomerular filtration in the kidneys, with only 4% of filtered magnesium being excreted in the urine [38]. Magnesium reabsorption in the proximal tubule happens through the Para cellular shunt pathway, which is dependent on the active reabsorption of sodium, while distal tubule magnesium follows a transcellular pathway [39]. Normal concentrations of magnesium ions in the urine range between 262 (42-1189) umol/mmol creatinine [11]. Urinary magnesium does not correlate with serum levels nor ingested magnesium levels [37]. However, urinary metabolites of magnesium are influenced directly by its dietary intake [37]. There are several factors that can increase or decrease urine magnesium levels. Caffeine for example, has shown to decrease renal capability of magnesium reabsorption, increasing the urinary magnesium loss during post-caffeine period [40]. Calcium oxalate, a by-product of digestion and an indicator of gut dysbiosis or a diet high in salt, protein, and/or oxalate, can also directly lead to decreased urinary levels of magnesium and thus kidney stone formation [41,42]. On the contrary, the chemotherapy agents (cisplatin) and immunosuppressant's (tacrolimus, cyclosporine, rapamycin) can cause abnormally high magnesium excretion with urine magnesium excretion averaging more than 1 mmol/day [38,43]. Diuretics such as loop and thiazide also causes increases in magnesium excretion [38]. The urinary excretion of magnesium is also seen to be altered in some health states. A comparative study with type 2 diabetic patients (38-78 mg/L approximately) has reported a substantial increase in urinary magnesium compared to healthy individuals (approximately 28-47 mg/L) [44]. In general, higher urinary magnesium levels are indicative of renal magnesium wasting that usually accompanies diuretic use or familial magnesium wasting disorders [45]. Other than disease states, some medications such as the antiviral foscarnet, the antifungal amphotericin B, and antibiotic aminoglycosides, increase excretion of magnesium via urine [38]. Whereas the hormones such as PTH, glucagon, calcitonin, vasopressin, aldosterone, and insulin promote magnesium absorption, lowering urine magnesium levels [38]. Urinary magnesium is also generally reduced in case of extra-renal magnesium loss (generally due to malabsorption or laxative use) [38]. Mutations in the CLDN16 and CLDN19 genes, cause familial hypomagnesemia with hypercalciuria and nephrocalcinosis due to faulty encoded proteins in the tight junctions of Henle's loop responsible for Para cellular reabsorption of calcium and magnesium [38]. On the other hand, mutations

in gene encoding claudin-10 protein, enhances the permeability of calcium and magnesium, leading to a higher reabsorption of these two minerals resulting in hypermagnesemia and nephrocalcinosis [38]. The urinary magnesium assessment is generally recommended post detection of serum magnesium, calcium and/or potassium levels alterations, as the excretion and absorption of magnesium is tightly linked to the handling of calcium and potassium by the body [38]. Urinary magnesium is thus an earlier and more reliable indicator of an evolving magnesium deficiency, providing an objective estimate of the amount of magnesium that is systematically absorbed [46].

2.5. Phosphorus

The second most abundant mineral in the body, phosphorus is a major part of the body's buffer system, essential to ATP production and constitutes as an important structural component [22]. Phosphorus is ubiquitous in diet as a component of cell walls and membranes or is used as a preservative in processed foods [4].

2.5.1. Dietary recommended intake

Recommended dietary allowances of phosphorus for infants up to 6 months after birth are 100mg/d and 275mg/d for infants 7-12 months after birth [8].

Children from 1 to 3 years of age are recommended 460mg/d of phosphorus, while children from 4 to 8 years of age are recommended 500mg/d [8].

This value goes up to 1,250mg/d for males and females aged 9-18, and for males and females aged 19 and older the RDA is 700 mg/d [8].

2.5.2. Phosphorus handling and human health

Phosphorus is mainly present in the body in the form of phosphate and excess of it is excreted by the kidneys as phosphate ions [47]. The rate of glomerular filtration of phosphorus is directly proportional to its serum levels at about 7g per day, only 15-25% of which is excreted in urine, and rest is reabsorbed by renal tubules [38,47]. Urinary levels of phosphate can vary around 1799 (221-4936) umol/mmol creatinine, fluctuating heavily with diet [11]. The amount of phosphate reabsorbed in the kidneys is directly proportional to the availability of co-transporters in the renal tubules [38]. Therefore, some hormones and diet can modulate the urine excretion of phosphate by changing the availability of sodium phosphate cotransporters [38].

Renal phosphate handling is regulated by the PTH, vitamin D, calcitonin, fibro genic growth factor 23 (FGF23) and Klotho coreceptor [22,47]. PTH promotes phosphorus excretion via urine but is inhibited by hypercalcemia, which consequently induces phosphate retention

[48]. Calcitonin released by the thyroid gland, acts similarly to PTH by decreasing the renal tubular capacity for phosphate reabsorption [48]. Vitamin D promotes calcium ions absorption by the cells which leads to a lower level of calcium circulating in the blood and consequently raises PTH release inducing phosphorus renal excretion [47]. FGF23 released by osteocytes and osteoblasts inhibits calcitriol, vitamin D's active form, in the kidneys which consequently repress renal phosphorus excretion [47]. FGF23 activation is mediated by the co-factor Klotho released by the kidneys. Patients with tumoral calcinosis have presented hyperphosphatemia due to high levels of fragmented FGF23 in the blood [47]. Glucocorticoids, estrogen, and dopamine promote phosphaturia [38]. Glucocorticoids act inhibiting proximal tubule synthesis and changes to the lipid brush border membrane [38]. Estrogen decreases availability of sodium phosphate cotransporters and increase production of FGF23 [38]. Dopamine promotes internalization of sodium phosphate cotransporters from the proximal tubule [38].

Genetic mutations that cause hypophosphatemia rickets also disturb phosphorus metabolism by inducing phosphate excretion due to elevated serum levels of PTH [49]. Potassium deficiency leads to phosphaturia due to modifications in the composition of the lipid membrane of the proximal tubule which inhibits the activity of sodium potassium cotransporters [38]. Hypertension and metabolic acidosis stimulate phosphaturia by removal and inhibition of sodium phosphate cotransporters in the proximal tubule, respectfully [38]. A 24-h urine test for phosphate concentration has been noted to be the most accurate method for estimating short-term ingestion of phosphorus [50]. A phosphate urine test can also be indicated in the investigation of kidney disease [51].

2.6. Sulfur

Sulfur is an essential mineral constituent of amino acids, enzymes, vitamins, and proteins [52]. Sulfur can be obtained in the diet through the ingestion of sulfur containing amino acids such as methionine and cysteine, as well as cruciferous and alliaceous vegetables [53].

2.6.1. Dietary recommended intake

Recommended dietary allowances for sulfur have not been established, however, the World Health Organization has determined 13mg/kg per 24h as the recommendation for sulfur-containing amino acids intake in healthy adults [54].

2.6.2. Sulfur handling and human health

Sulfur containing amino acids (SAA) methionine and cysteine are catabolized into sulfate and taurine as the two main S-containing end products which are excreted almost entirely in the urine and can be a marker of SAA catabolism and whole-body amino acid catabolism [55]. Normal concentrations of sulfate in urine are 2407.89 (2171.05-2697.36) umol/mmol

creatinine fluctuating slightly with diet [55]. Sulfur containing amino acids are converted into sulfate in the body through an oxidation process known as sulfoxidation pathway [56]. The penultimate product of this pathway is sulfite which is then further converted into sulfate in the kidneys and liver by sulfite oxidase (SO) and molybdenum [56]. Therefore, in conditions where this sulfite is unable to be cleared, due to a mutation in the SO gene (SO deficiency) or any of the several genes involved in the synthesis of molybdopterin's (as in molybdenum cofactor deficiency (MoCD)), toxic sulfite and a secondary metabolite, S-sulfocysteine (SSC) accumulates in the brain creating neurological damage which progresses rapidly leading to a high infant mortality rate [55-59]. The serum sulfite levels in healthy individuals stay within 4–5 nmol/L, but increases due to inability or ineffective clearance by kidney, such as chronic renal diseases [56].

Gender and age differences, growth and thyroid hormones, dietary sulfate, vitamins, and non-steroid anti-inflammatory drugs (NSAID) can affect sulfate reabsorption in the kidneys and consequently affect excreted urinary sulfate [60]. Men have shown a significantly higher 24-h urine excretion of inorganic sulfate than women, while children and infants have been reported to have a lower sulfate excretion than adults [30]. This can be explained by the elevated levels of sodium/sulfate cotransporters located in the kidneys of infants, young children, and pregnant women, which promote sulfate reabsorption by the kidneys [30]. Various factors increase urinary sulfate levels. Decreased sodium/sulfate cotransporter has been reported after the use of glucocorticoids and NSAIDs, excess ingestion of methionine, vitamin D deficiency, potassium deficiency, and hypothyroidism, thus inducing increased urinary sulfate levels [30].

Reabsorption capability of sulfate in kidney transplant receptors and kidney donors is greatly decreased ultimately increasing urinary sulfate excretion [60]. Sulfate excretion increases for some health conditions like Type 1 diabetes and burns. Type 1 diabetes patients have demonstrated a high urinary sulfate excretion due to progressive decline in glomerular filtration rate, a risk factor for kidney nephropathy [61]. Burn victims present higher excretion of sulfate during the catabolic phase [62]. Urinary sulphate is a reflection of dietary protein intake of foods like meat and fish that are rich in the Sulphur containing amino acids methionine and cysteine [63]. It may be used as an index of protein-induced calciuria, stones like calcium oxalate in urine and impaired renal function [63-65].

2.7. Chloride

Chloride is the body's major extracellular anion. It is necessary for maintaining fluid and electrolyte balance, muscle contraction, and digestion [4]. Chloride is obtained in the diet, most commonly in the form of table salt [4]. Additionally, it is present in processed foods, meats, milk, eggs, and vegetables [4].

2.7.1. Dietary recommended intake

Recommended dietary allowances of chloride for infants up to 6 months after birth are 0.18g/d and 0.57g/d for infants 7-12 months after birth [8].

Children from 1 to 3 years of age are recommended 1.5g/d of phosphorus, while children from 4 to 8 years of age are recommended 1.9g/d.8 This value goes up to 2.3g/d for males and females aged 9-50, then goes down to 2.0g/d for the ages 51-70, and finally 1.8g/d for the ages of 71 and older [8].

2.7.2. Chloride handling and human health

Chloride concentrations are regulated by the kidneys, with reabsorption occurring in the distal and proximal tubules through both active transcellular transport and passive paracellular transport [66]. Excess filtered calcium is excreted via urine [22]. Normal ranges for urinary chloride vary around 8881.6 (5263.2-17763.2) umol/mmol creatinine [55]. Urinary chloride excretion mirrors sodium excretion with accordance to dietary intake [21]. Urinary chloride test can be done to help diagnose acid-base and osmolar disorders, as well as to be used in formulas such as the anion gap, strong anion gap, strong ion difference, and chloride/sodium ratio used to assess metabolic acid-base disorders in emergency and critically ill patients [4,67]. For instance, the anion gap is a sum of the concentrations of chloride and bicarbonate subtracted from the concentration of sodium, which helps assess bodily chloride/sodium ratios [68]. A high chloride and low sodium chloride ratio indicates the presence of a competitor cation in the urine, usually ammonium, which forces chloride out of the body even in a hypochloremic state [21]. This is usually due to diarrhea, which causes hypokalemia and metabolic acidosis [21]. Excessive chloride loss can happen in patients with renal failure, which leads to hypochloremia and metabolic alkalosis [4]. In this case, urine chloride levels can be an indicator to whether the alkalosis is responsive or resistant to treatment with chloride-containing solution [21]. Low urine chlorine, less than 15 mEq/L, means a responsive metabolic alkalosis while a high urine chloride, more than 15 mEq/L, means a resistant metabolic alkalosis [21]. Excessive renal bicarbonate loss due to medications that promote bicarbonate excretion increases renal chlorine reabsorption, leading to hyperchloremia and metabolic acidosis [4]. It has also been found that mutations in with-no-lysine (WNK) kinase impact body homeostasis by modifying chloride transport chains and promoting sodium and chloride renal retention [69]. In general, urinary chloride is an indicator of fluid balance and acid-base homeostasis. In the absence of acid-base disturbances, urinary chloride reflects chloride taken mainly in the form of sodium chloride [70].

3. Conclusion

The urinary mineral parameters are thought to be reflective of an individual's dietary

habits and there are ongoing research efforts dedicated to assessing the diagnostic value of these urinary mineral levels as biochemical indicators of nutritional status. Another area where these levels are being useful is as indicators of mineral metabolism associated disorders, especially in conjunction with disorders in the renal system.

4. References

1. Dubey P, Thakur V, Chattopadhyay M. Role of minerals and trace elements in diabetes and insulin resistance. Nutrients. 2020;12(6):1864. doi: 10.3390/nu12061864

2. Varela-López A, Giampieri F, Bullón P, Battino M, Quiles J. A systematic review on the implication of minerals in the onset, severity and treatment of periodontal disease. Molecules. 2016;21(9):1183. doi: 10.3390/molecules21091183

3. Suzuki A, Minamide M, Iwaya C, Ogata K, Iwata J. Role of metabolism in bone development and homeostasis. Int J Mol Sc. 2020;21(23): 8992. doi:10.3390/ijms21238992

4. Morris A, Mohiuddin S. Biochemistry, Nutrients. In: StatPearls [Internet]. StatPearls Publishing: 2021. Accessed October 20, 2021. https://www.ncbi.nlm.nih.gov/books/NBK554545/

5. Kies A, Gerrits W, Schrama J, et al. Mineral absorption and excretion as affected by microbial phytase, and their effect on energy metabolism in young piglets. J Nutr. 2005;135(5):1131-1138. doi:10.1093/jn/135.5.1131

6. Miller IJ, Peters SR, Overmyer KA, Paulson BR, Westphall MS, Coon JJ. Real-time health monitoring through urine metabolomics. NPJ Digit Med. 2019;2(1):1-9. doi: 10.1038/s41746-019-0185-y

7. Stanhewicz AE, Larry Kenney W. Determinants of water and sodium intake and output. Nutr Rev. 2015;73(2):73-82. doi:10.1093/nutrit/nuv033

8. National Academies of Sciences, Engineering and Medicine. Sodium: dietary reference intakes for adequacy. In: Oria M, Harrison M, Stallings VA, eds. Dietary Reference Intakes for Sodium and Potassium. National Academies Press; 2019:30844154. doi: 10.17226/25353

9. Muñoz-Durango N, Fuentes CA, Castillo AE, González-Gómez LM, Vecchiola A, Fardella CE, Kalergis AM. Role of the renin-angiotensin-aldosterone system beyond blood pressure regulation: molecular and cellular mechanisms involved in end-organ damage during arterial hypertension. Int J Mol Sci. 2016;17(7):797. doi: 10.3390/ijms17070797

10. Simko F, Hrenak J, Adamcova M, Paulis L. Renin–angiotensin–aldosterone system: friend or foe—the matter of balance. Insight on history, therapeutic implications and COVID-19 interactions. Int J Mol Sci. 2021;22(6):3217. doi:10.3390/ijms22063217

11. Bouatra S, Aziat F, Mandal R, et al. The human urine metabolome. PLoS One. 2013; 8(9):e73076. doi:10.1371/journal.pone.0073076

12. Spital A. Diuretic-induced hyponatremia. Am J Nephrol. 1999;19(4):447-452. doi:10.1159/000013496

13. Schrier RW. Diagnostic value of urinary sodium, chloride, urea, and flow. J Am Soc Nephrol. 2011; 22(9):1610–1613. doi:10.1681/asn.2010121289

14. Reynolds RM, Padfield PL, Seckl JR. Disorders of sodium balance. BMJ. 2006; 332(7543):702–705. doi:10.1136/bmj.332.7543.702

15. Kim SY. Diagnosis and treatment of hypopituitarism. Endocrinol Metab. 2015; 30(4):443-455. doi:10.3803/EnM.2015.30.4.443

16. Munit S, Quintanilla Rodriguez BS, Waseem M. Addison Disease. In: StatPearls [Internet]. Stat Pearls Publishing: 2021. Accessed October 20, 2021. https://www.ncbi.nlm.nih.gov/books/NBK441994/

17. Pantalone KM, Hatipoglu BA. Hyponatremia and the thyroid: causality or association? J Clin Med. 2014; 4(1):32-36. doi:10.3390/jcm4010032

18. John S, Thuluvath PJ. Hyponatremia in cirrhosis: pathophysiology and management. World J Gastroenterol. 2015; 21(11):3197-3205. doi:10.3748/wjg.v21.i11.3197

19. Lastra G, Syed S, Kurukulasuriya LR, Manrique C, Sowers JR. Type 2 diabetes mellitus and hypertension: an update. Endocrinol Metab Clin North Am. 2014; 43(1):103-122. doi:10.1016/j.ecl.2013.09.005

20. Grant P, Ayuk J, Bouloux P, et al. The diagnosis and management of inpatient hyponatraemia and SIADH. Eur J Clin Invest. 2015;45(8), 888–894. doi:10.1111/eci.12465

21. Palmer BF, Clegg DJ. The use of selected urine chemistries in the diagnosis of kidney disorders. Clin J of Am Soc Nephrol. 2019;14(2):306–316. doi: 10.2215/cjn.10330818

22. Shrimanker I, Bhattarai S. Electrolytes. In: StatPearls [Internet]. StatPearls Publishing: 2020. Accessed October 20, 2021. https://pubmed.ncbi.nlm.nih.gov/31082167/

23. Brooks G. Potassium additive algorithm for use in continuous renal replacement therapy. Nurs Crit Care. 2006;11(6):273-280. doi:10.1111/j.1478-5153.2006.00185.x

24. Jędrusik P, Symonides B, Wojciechowska E, Gryglas A, Gaciong Z. Diagnostic value of potassium level in a spot urine sample as an index of 24-hour urinary potassium excretion in unselected patients hospitalized in a hypertension unit. PLoS One. 2017; 12(6):e0180117. doi: 10.1371/journal.pone.0180117

25. Schöfl C. Update – Calcium metabolism. Dtsch Med Wochenschr. 2019;144(16):1125–1132. doi:10.1055/a-0833-9674

26. Jeon US. Kidney and calcium homeostasis. Electrolyte Blood Press. 2008;6(2):68-76. doi:10.5049/EBP.2008.6.2.68

27. Fleet JC. The role of vitamin D in the endocrinology controlling calcium homeostasis. Mol Cell Endocrinol. 2017;453:36–45. doi: 10.1016/j.mce.2017.04.008

28. Black CE, Berg RL, Urquhart AC. 24-hour urinary calcium in primary hyperparathyroidism. Clin Med Res. 2013; 11(4), 219–225. doi: 10.3121/cmr.2013.1164

29. Foley KF, Boccuzzi L. Urine calcium: laboratory measurement and clinical utility. Lab Med. 2010;41(11):683–686. doi:10.1309/lm9so94znbhedntm

30. Morris ME, Sagawa K. Molecular mechanisms of renal sulfate regulation. Crit Rev Clin Lab Sci. 2008;37(4):345–388. doi:10.1080/10408360091174240

31. Barghouthy Y, Corrales M, Doizi S, Somani BK, Traxer O. Tea and coffee consumption and pathophysiology related to kidney stone formation: a systematic review. World J Urol. 2021;39(7):2417-2426. doi: 10.1007/s00345-020-03466-8

32. Sellmeyer DE, Schloetter M, Sebastian A. Potassium citrate prevents increased urine calcium excretion and bone resorption induced by a high sodium chloride diet. J Clin Endocrinol Metab. 2002;87(5):2008–2012. doi: 10.1210/jcem.87.5.8470

33. Teucher B, Dainty JR, Spinks CA, et al. Sodium and bone health: impact of moderately high and low salt intakes on calcium metabolism in postmenopausal women. J Bone Miner Res. 2008;23(9):1477–1485. doi:10.1359/jbmr.080408

34. Kustov AV, Strelnikov AI. Quantitative mineralogical composition of calculi and urine abnormalities for calcium oxalate stone formers: a single-center results. Urology. 2018;15(3):87–91. doi:10.22037/uj.v010.3910

35. Keller EX, de Coninck V, Pietropaolo A, Somani B, Haymann JP, Daudon M. Metabolic evaluation: place of the calcium load test: how, when, for whom, and why? Eur Urol Focus. 2021;7(1):26–30. doi:10.1016/j.euf.2020.12.019

36. Arshad MF, McAllister J, Merchant A, Rab E, Cook J, Eastell R, Balasubramanian S. Urinary calcium indices in primary hyperparathyroidism (PHPT) and familial hypocalciuric hypercalcaemia (FHH): which test performs best? Postgrad Med J. 2021;97(1151):577-582. doi: 10.1136/postgradmedj-2020-137718

37. Workinger JL, Doyle RP, Bortz J. Challenges in the diagnosis of magnesium status. Nutrients. 2018;10(9):1202. doi:10.3390/nu10091202

38. Blaine J, Chonchol M, Levi M. Renal control of calcium, phosphate, and magnesium homeostasis. Clin J Am Soc Nephro. 2014;10(7):1257–1272. doi:10.2215/cjn.09750913

39. Curry JN, Yu ASL. Magnesium handling in the kidney. Adv Chronic Kidney Dis. 2018; 25(3):236-243. doi:10.1053/j.ackd.2018.01.003

40. Bergman EA, Massey LK, Wise KJ, Sherrard DJ. Effects of dietary caffeine on renal handling of minerals in adult women. Life Sci. 1990;47(6):557–564. doi:10.1016/0024-3205(90)90616-y

41. Kustov AV, Strelnikov AI. Quantitative mineralogical composition of calculi and urine abnormalities for calcium oxalate stone formers: a single-center results. Urology. 2018;15(3):87–91. doi:10.22037/uj.v010.3910

42. Liebman M, Costa G. Effects of calcium and magnesium on urinary oxalate excretion after oxalate loads. J Urol. 2000;163(5):1565-1569.

43. Swaminathan R. Magnesium metabolism and its disorders. Clin Biochem Rev. 2003;24(2):47–66.

44. Xu J, Xu W, Yao H, Sun W, Zhou Q, Cai L. Associations of serum and urinary magnesium with the pre-diabetes, diabetes and diabetic complications in the Chinese northeast population. PLoS One. 2013;8(2):e56750. doi:10.1371/journal.pone.005675

45. Fleming CR, George L, Stoner GL, Tarrosa VB, Moyer TP. The importance of urinary magnesium values in patients with gut failure. Mayo Clin Proc. 1996;71(1):21-24. doi:10.4065/71.1.21

46. Joosten MM, Gansevoort RT, Mukamal KJ,et al. Urinary magnesium excretion and risk of hypertension: the prevention of renal and vascular end-stage disease study. Hypertension. 2013;61(6):1161-1167.

47. Prasad N, Bhadauria D. Renal phosphate handling: physiology. Indian J Endocrinol Metab. 2013;17(4):620. doi:10.4103/2230-8210.113752

48. Zalups RK, Knox FG. Calcitonin decreases the renal tubular capacity for phosphate reabsorption. Am J Physiol Renal Physiol. 1983;245(3):F345–F348. doi:10.1152/ajprenal.1983.245.3.F345

49. Jagtap VS, Sarathi V, Lila AR, Bandgar T, Menon P, Shah NS. Hypophosphatemic rickets. Indian J Endocrinol Metab. 2012;16(2):177-182. doi:10.4103/2230-8210.93733

50. Sakuma M, Morimoto Y, Suzuki Y, et al. Availability of 24-h urine collection method on dietary phosphorus intake estimation. J Clin Biochem Nutr. 2017;60(2):125–129. doi:10.3164/jcbn.16-50

51. Hinkle J, Cheever K. Calcium, serum; calcium and phosphates, urine. In: Lippincott Williams & Wilkins. UrinBrunner & Suddarth's Handbook of Laboratory and Diagnostic Tests. 2nd Ed. Wolters Kluwer Health; 2014:118–119.

52. Komarnisky LA, Christopherson RJ, Basu TK. Sulfur: its clinical and toxicologic aspects. Nutrition. 2003;19(1):54-61. doi:10.1016/s0899-9007(02)00833-x

53. Doleman J, Grisar K, Van Liedekerke L, Saha S, Roe M, Tapp H, Mithen R. The contribution of alliaceous and cruciferous vegetables to dietary sulphur intake. Food Chem. 2021;234:38-45. doi:10.1016/j.foodchem.2017.04.098

54. van de Poll MCG, Dejong CHC, Soeters PB. Adequate range for sulfur-containing amino acids and biomarkers for their excess: lessons from enteral and parental nutrition. J Nutr. 2006;136(6):1694-1700. doi:10.1093/jn/136.6.1694S

55. Wishart D, Feunang Y, Marcu A, et al. HMDB 4.0: the human metabolome database for 2018. Nucleic Acids Res.2018;46(D1):D608-D617. doi: 10.1093/nar/gkx1089

56. Vincent AS, Lim BG, Tan J, Whiteman M, Cheung NS, Halliwell B, Wong KP. Sulfite-mediated oxidative stress in kidney cells. Kidney Int. 2004;65(2):393–402. doi: 10.1111/j.1523-1755.2004.00391.x

57. Atwal PS, Scaglia F. Molybdenum cofactor deficiency. Mol Genet Metab. 2016;117(1):1-4. doi:10.1016/j.ymgme.2015.11.010r

58. Mechler K, Mountford WK, Hoffmann GF, Ries M. Ultra-orphan diseases: a quantitative analysis of the natural history of molybdenum cofactor deficiency. Genet Med. 2015;17(12):965-970. doi:10.1038/gim.2015.12

59. Veldman A, Santamaria-Araujo JA, Sollazzo S, et al. Successful treatment of molybdenum cofactor deficiency type A with cPMP. Pediatrics. 2010;125(5):e1249-e1254. doi:10.1542/peds.2009-2192

60. Post A, Minović I, van den Berg E, et al. Renal sulfate reabsorption in healthy individuals and renal transplant recipients. Physiol Rep. 2018; 6(8):e13670. Doi:10.14814/phy.13670

61. Andrésdóttir G, Bakker SJL, Hansen HP, Parving HH, Rossing P. Urinary sulphate excretion and progression of diabetic nephropathy in Type 1 diabetes. Diabet Med. 2013;30(5):563–566. doi:10.1111/dme.12131

62. Larsson J, Liljedahl SO, Mårtensson J, Nordström H, Schildt BO, Sörbo BO. Urinary excretion of sulfur amino acids and sulfur metabolites in burned patients receiving parenteral nutrition. J Trauma Inj Infection Crit Care. 1982;22(8):656–663.doi:10.1097/00005373-198208000-00002

63. Magee EA, Curno R, Edmond LM, Cummings JH. Contribution of dietary protein and inorganic sulfur to urinary sulfate: toward a biomarker of inorganic sulfur intake. Am J Clin Nutr. 2004;80(1):137-142. doi:10.1093/ajcn/80.1.137

64. Rodgers A, Gauvin D, Edeh S, et al: Sulfate but not thiosulfate reduces calculated and measured urinary ionized calcium and supersaturation: implications for the treatment of calcium renal stones. PLoS One. 2014;9(7):e103602 doi: 10.1371/journal.pone.0103602

65. Houterman S, van Faassen A, Ocke MC, et al: Is urinary sulfate a biomarker for the intake of animal protein and meat? Cancer Lett. 1997;114:295-296

66. Planelles G. Chloride transport in the renal proximal tubule. Pflugers Arch. 2004;448(6):561-570. doi:10.1007/s00424-004-1309-y

67. Artero CT. A quick reference on anion gap and strong ion gap. Vet Clin North Am Small Anim Pract. 2017;47(2):191-196. doi:10.1016/j.cvsm.2016.10.006

68. Ayala-Lopez N, Harb R. Interpreting anion gap values in adult and pediatric patients: examining the reference interval. J Appl Lab Med. 2020;5(1):126–135. doi:10.1373/jalm.2019.029496

69. McCormick JA, Yang CL, Ellison DH.WNK kinases and renal sodium transport in health and disease: an integrated view. Hypertension. 2008;51(3):588–596. doi:10.1161/HYPERTENSIONAHA.107.103788

70. Merrill AE, Chambliss AB. Water and electrolyte balance. In: Clarke W, Markinze MA, eds. Contemporary Practice in Clinical Chemistry. 4th ed. Academic Press; 2020: 651-663.