Calcium and Magnesium Levels Change in Relationship to Variations in Usual Dietary Nutrient Intake

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Abstract

Objective: Changes in nutrient intake induce changes in calcium and magnesium metabolism. However, studies dealing with these changes were usually performed by addition of one specific nutrient to initiate changes in either calcium or magnesium in only one biological fluid, usually blood plasma or urine. We were interested in evaluating changes in both calcium and magnesium levels in several biological fluids simultaneously in relationship to usual intake of a wide range of dietary nutrients since this type of study has not been previously performed.

Methods: Calcium and magnesium in blood plasma, urine and saliva and magnesium in erythrocytes were measured by flame aspiration atomic absorption spectrophotometry in 253 subjects, 150 women and 103 men in relationship to their usual dietary intake of calcium, magnesium, sodium, potassium, phosphorus, carbohydrate, fat, fiber, protein, vitamin D, vitamin C and total calories. Dietary nutrient intake was calculated by careful, systematic analysis of all food and fluids taken over three typical days by performance of computer based dietary analysis.

Results: Complex changes occurred in calcium and magnesium levels in some but not all biological fluids as usual dietary nutrient intake varied. As sodium, potassium and total calorie intake increased urinary calcium excretion increased. As sodium, potassium, vitamin D and protein intake increased urinary magnesium excretion increased. As sodium intake increased salivary magnesium decreased.

Conclusions: These studies demonstrate that calcium and magnesium levels in blood plasma, urine, saliva and nasal mucus are altered following variations in the usual intake of several nutrients. These results can assist in forming a nutritional foundation upon which variations in the usual dietary intake of several nutrients alter calcium and magnesium levels in several biological fluids.

Keywords: calcium; magnesium; diet; saliva; erythrocytes; nutrient intake;

200mg daily. The unabsorbed secreted calcium and urinary calcium loss together is termed "endogenous loss" over which there is little control. Bone contains 99% of the total body calcium which is approximately 15-18% of the total body weight. About 500mg of calcium enters and exits from bone per day.

The body contains about 20-35g of magnesium of which 55-60% is present as phosphates and carbonates in bone. About 27% is found in muscle and 18% of non-muscle, soft tissues and bodily fluids. Extracellular fluid contains 2% of body magnesium. Magnesium is absorbed by active transport and competes with calcium for carrier sites. Usually 3-5% of magnesium is excreted in urine on a daily basis. However, there is some magnesium excretion via the gastrointestinal tract or in saliva. The recommended daily allowance for magnesium is 350mg daily for adult men and 300mg daily for adult women.

Changes in nutrient intake induce changes in calcium and magnesium metabolism. These changes have been demonstrated by many previous investigators [1-9]. However, these studies were usually performed by addition of one specific nutrient to initiate changes in either calcium or magnesium usually in one biological fluid, usually blood plasma or urine.

Measurements of calcium and magnesium have been made in several biological fluids in humans for many years by use of several methods but more recently by atomic absorption spectrophotometry and inductively coupled emission spectroscopy [10-22]. These measurements have usually been made in reference to physiological changes or pathological conditions in single biological fluids. However, results of these reported studies were also dependent upon many factors not only including measurement methods but also type of subject studied, subject number studied, introduction of specific dietary substances and form of moiety measured, e.g., free[23-25], ionized[14,26] or bound[13,27].

Calcium is involved in many metabolic systems including bone, cardiomyocardial, endocrine, nutritional and neural systems [28-32].

Mild elevations of serum phosphate within the normal range have been associated with cardiovascular risk in healthy

Introduction

Calcium metabolism varies widely among individuals. The recommended dietary allowance for calcium intake in adults is about 800mg daily, but less than 50% is absorbed through the gastrointestinal tract. The remainder, together with an unabsorbed quantity of secreted calcium, passes into the feces. Urinary calcium contributes to a daily loss which is less than

populations [33]. High phosphorus consumption has been shown to reduce bone mass in several species and elevated phosphate can promote calcification of the cellular and matrix components of vascular smooth muscle cells [33,34]. Excess phosphorus intake may disrupt hormonal regulation of phosphorus contributing to diminished mineral metabolism, vascular calcification, bone loss and impaired renal function [34].

Magnesium has been considered important in cardiomyopathy, hypertension, diabetes, nutritional and other systems [27,35-37,38-40]. Clinical hypomagnesemia and dietary magnesium restriction have increased cardiac arrhythmias with inverse association demonstrated between circulation and dietary magnesium and cardiovascular risk[41]. Dietary magnesium restriction adversely affects oxidative metabolism, glucose homeostasis and retention and excretion of other electrolytes [42-44]. Indeed, dietary intake of magnesium in most American adults is below the recommended dietary allowances, as particularly apparent in elderly Americans [45].

Results of studies in which calcium and magnesium were changed by intake or administration of one specific nutrient have been variable. Variations in these results have been related not only to a specific nutrient intake but also to several physiological parameters. For example, increased protein intake was reported to increase urinary calcium excretion, although others considered this intake of negligible importance [46,47]. Sodium intake was reported to be a major factor associated with calcium excretion[48]. Although not nutrient-related, some studies reported gender and age influenced changes in these moieties while others did not [49-51,52].

We addressed this variation in a novel, but relevant manner to these prior studies. We assessed the influence of variation of dietary intake of several nutrients over a wide range of usual intakes on simultaneous changes in calcium and magnesium in several biological fluids (blood plasma, urine, saliva and erythrocytes). This type of study has not been previously reported but may provide a foundation of useful information not previously available. These results are particularly useful with respect to previous studies in which single nutrient intake in relationship to a single biochemical marker has been reported.

Methods

Subjects

Subjects were 253 patients, aged 6-91y ($58 \pm 1y$, mean $\pm$ SEM) who presented to The Taste and Smell Clinic in Washington, DC with clinical complaints of smell and/or taste loss [53]. Other than these losses of sensory function patients were overall well and healthy. Subjects were 150 women, aged 11-91y ($58 \pm 2y$) and 103 men, aged 6-86y ($56 \pm 2y$). All studies were approved by the Institutional Review Board of the Georgetown University Medical Center; all subjects gave informed consent to participate in this study.

Nutritional Analysis

All subjects completed a three day dietary record for three

typical days in which all food and drink, their amounts, method of preparation and details of their added condiments were written down on each of three separate data sheets with respect to time of intake of each food or fluid prior to their visit to The Clinic. To prepare each patient for completion of this diet record an extensive telephone conversation about the method to prepare this record was performed. Each patient also received an eight page food instruction booklet containing specific instructions on how to complete the dietary record including lists and pictures of food items, their description and how to estimate amounts taken. During their visit to The Clinic a critical evaluation of these data took place which included detailed assessment of the previously obtained diet history with food and beverage pictures and food models used to assess accuracy of the diets. Assistance of a trained technician discussed each item to verify its quantity and character. Each diet record was then entered into a Nutritionist Pro™ 4.7 program such that intake and quantity of each nutrient was analyzed. After completion of analysis of all data results were sorted by intake of individual patients into groups of 10-20 subjects by each level of intake for each nutrient and mean $\pm$ SEM of nutrient intake in each group were calculated [54]. Levels of calcium and magnesium in blood plasma, urine and saliva and magnesium in erythrocytes were measured in each subject and then compared directly to nutrient intake in each subject and then in each subject group. In this manner variation of changes in levels of calcium and magnesium in each biological fluid was obtained in relationship to nutrient intake.

Dietary nutrient intakes measured were calcium, magnesium, sodium, potassium, phosphorus, carbohydrate, fat, protein, vitamin D, vitamin C and total calories.

Biological Fluid Measurements

At the time of evaluation of dietary history in the morning, in the fasting state, blood plasma was collected by venipuncture, placed into zinc-free tubes containing 100 μ l of zinc free heparin, centrifuged at 3000 rpm for 20 minutes in a refrigerated centrifuge, blood plasma removed and stored at -20°C until assayed. Erythrocytes remaining after plasma removal were washed three times with 10mM Tris-HCl in 0.15M NaCl, pH 7.4 and prepared as previously described [55,56]. Urine from each subject was collected over a 24-hour period in direct timed relationship to collection of blood plasma. Urine volume was measured and a 20ml aliquot was stored at 4°C until assayed. Parotid saliva was collected from each subject immediately after blood collection by placement of a modified Lashley cup over Stensen's duct with lingual stimulation with reconstituted lemon juice (Borden, Real Lemon, Stamford, CT) as previously described [57]. Saliva was collected in plastic tubes on ice over an 8-12 minute period. Samples were stored at 4°C until assayed.

Calcium and magnesium were measured simultaneously in each fluid by flame aspiration atomic absorption spectrophotometry using a Thermo Jarrell Ash flame atomic absorption spectrophotometer modified by Maxwell Instrumentation Company (Salisbury, NC) using a modification

of the technique initially used to measure zinc and copper simultaneously [58]. All analyses were completed within five days of collection. Measurements were obtained in duplicate with values varying <5%. Measurements were made in the same patients over a period of 10 days with a variation of <5%.

All measurements were made without reference to any subject data. Only after all measurements were completed were values matched with subject records and sorted by dietary intake of each nutrient.

Statistical significance of differences between measurements were determined by Student's t-test with $p < 0.05$ considered significant. Correlation coefficients between nutrient intake in calcium and magnesium levels in each fluid were determined by Pearson product moment correlations with $p < 0.05$ considered significant.

Results

Calcium Metabolism: Relationships to Variations in Usual Nutrient Intake

Plasma Calcium: There were no significant correlations between intake of any nutrient and changes in plasma calcium (Figure 1). However, there was an inverted U shape curve of plasma calcium related to intake of calcium, sodium and vitamin D. There was also an initial U shaped curve of change in plasma calcium in relationship to intake of magnesium and protein.

Urine Calcium: There were significant positive correlations between increased intake of sodium ($p < 0.05$), potassium ($p < 0.05$), protein ($p < 0.01$) and total calories ($p < 0.02$) and urine calcium ($p < 0.05$) (Figure 2). As sodium, potassium, protein and total calorie intake increased there were significant increases in urine calcium. A similar trend was also observed with intake of carbohydrate and perhaps fat but these changes were not significant.

Saliva Calcium: There were no significant correlations between intake of any nutrient and saliva calcium (Figure 3). There was a

minimal inverted U shaped pattern in relationship to fat and total calorie intake but these changes were not significant. There was a tendency of increased saliva calcium with vitamin D intake but these changes were also not significant.

Magnesium Metabolism: Relationships to Variations in Usual Nutrient Intake

Plasma Magnesium: There was a significant correlation between intake of sodium and plasma magnesium such that as sodium intake increased plasma magnesium increased ($p < 0.05$) (Figure 4). There were no other significant correlations in relationship to intake of any nutrient and plasma magnesium. However, there was an inverted U shaped curve in plasma magnesium related to increased intake of magnesium, sodium and protein. There was also a variable and irregular increase in plasma magnesium in relationship to increased intake of phosphorus.

Urine Magnesium: There were significant positive correlations between increased intake of sodium ($p < 0.05$), potassium ($p < 0.05$) and vitamin C ($p < 0.01$) and increased urinary magnesium excretion (Figure 5). Urinary magnesium also increased with increased intake of phosphorus, fiber, protein, carbohydrate, vitamin C and total calorie but these increases were not statistically significant. There was an inverted U shaped curve of urine magnesium excretion related to fat intake.

Saliva Magnesium: There was a significant negative correlation between increased intake of sodium ($p < 0.02$) and salivary magnesium with saliva magnesium decreasing as sodium intake increased (Figure 6). There were also decreases in saliva magnesium in relationship to intake of phosphorus, potassium, fiber, carbohydrate, fat, protein and total calories but these decreases were not significant.

Erythrocyte Magnesium: There were no significant changes in erythrocyte magnesium in relationship to intake of any nutrient (Figure 7). However, there was a slight increase in erythrocyte magnesium with increased intake of vitamin D but this change was not significant.

Figure 1: Plasma calcium concentration (in mg/dL) in relationship to usual dietary intakes of calcium (Ca), magnesium (Mg), phosphorus (P), sodium (Na), potassium (K), fiber, carbohydrate (Carb), fat, protein, vitamin D, vitamin C and total caloric intake (calories intake) in 253 people with taste and smell dysfunction without other medical problems. Intake was measured by analysis of three day diet records of usual intake of all food and fluids. Bar heights indicate mean nutrient intake of each subject group. Black lines indicate mean±SEM of intake of each nutrient in each subject group.

Figure 2: Urine calcium excretion (in mg/24hr) in relationship to intake of several nutrients (see Fig. 1 legend for details).

Figure 3: Parotid saliva calcium (in mg/dL) in relationship to intake of several nutrients (see Fig. 1 legend for details).

Figure 4: Plasma magnesium concentration (in mg/dL) in relationship to intake of several nutrients (see Fig. 1 legend for details).

Figure 5: Urine magnesium excretion (in mg/24hr) in relationship to intake of several nutrients (see Fig. 1 legend for details).

Figure 6: Parotid saliva magnesium (in mg/dL) in relationship to intake of several nutrients (see Fig. 1 legend for details).

Figure 7: Erythrocyte magnesium concentration [in mg/gHb (hemoglobin)] in relationship to intake of several nutrients (see Fig. 1 legend for details).

Discussion

There is vast literature on the roles calcium, magnesium and their interactions play in human physiology and disease [1,5,59-73]. The present results can assist in forming a nutritional foundation upon which variations in the changes in the usual dietary intake of several nutrients may alter calcium and magnesium levels in several biological fluids.

Changes in Calcium

Calcium Intake: Although there are many reports of changes in calcium intake with a variety of nutrient intakes we did not observe significant changes in plasma calcium with usual dietary intakes (Figure 1). There are many reports of increased renal stone formation with increased calcium intake [74]. Prior results have complex antecedents but have been related to the form of exogenous calcium taken, to genetic and other factors, e.g., obesity [75-77]. With increased calcium intake in our studies there was an initial increase in plasma calcium which decreased as calcium intake increased (Figure 1). This phenomenon was also observed by others with calcium intake [78]. Other investigators investigated changes in plasma and saliva calcium and magnesium in milk-fed calves [79,80].

Sodium Intake: Many investigators demonstrated increased urinary calcium excretion with increased dietary sodium intake [1,63-66] as we did also (Figure 2). Some investigators related this effect to genesis of hypertension and bone loss [1,4,73]. This phenomenon has been related to a sodium-calcium exchange mechanism which takes place at the renal tubule with the gradient reflected in calcium excretion [81]. This effect may be due to competitive binding of calcium and sodium at the cellular membrane of the renal tubule. Conversely, with decreased sodium intake a concomitant decrease in urine calcium has been reported [66].

Potassium Intake: Some previous investigators demonstrated decreased urinary calcium excretion with increased dietary intake of potassium whereas others demonstrated the opposite effect, potassium administration increasing and potassium deprivation reducing urinary calcium excretion [82-86]. Our results demonstrate an increase in urinary calcium with increased potassium intake (Figure 2).

Phosphorus Intake: Previous investigators disagreed on the role of phosphorus in calcium metabolism. Some reported increased urinary calcium related to reduction in tubular reabsorption of calcium due to phosphorus intake whereas others reported urinary calcium decreased significantly during phosphorus supplementation [87-89]. With intake of a high phosphorus diet plasma calcium decreased in ponies but little overall effect was observed in our studies (Figure 1) [90]. Some studies considered different dietary sources of calcium important [91]. In our studies there was little change in urinary calcium with increased phosphorus intake although calcium excretion increased at the highest phosphorus intake (Figure 2).

Protein Intake: Many previous investigators demonstrated that as dietary protein increased urinary calcium excretion increased although excess intake of dietary protein may not affect bone health [67,92-100]. Investigators also reported that the hypercalciuria associated with high dietary protein was not due to an acid load [101]. Consistent with this finding hypocalciuria was reported with low protein intake [67]. Amino acid supplementation was reported to increase urinary calcium excretion [102]. However, urinary calcium was reported independent of protein intake in one study whereas increasing protein intake was reported not to alter urine calcium excretion in a group of healthy older men and women [96,99]. These relationships have been suggested by some investigators to adversely affect bone function but not by others [98,99,100]. This effect may be due to a competitive binding effect of protein and calcium at the renal tubule with the converse effect of decreased calcium excretion with decreased protein intake [67]. Results in our study indicate increased calcium excretion at the highest protein intake (Figure 2).

Fiber Intake: Fiber intake has been associated with negative calcium balance and decreased plasma calcium and phosphorus [103]. Diets rich in cereals have been reported to have a decalcifying action in rats [104]. In our studies there was a tendency to increase urine calcium excretion as fiber increased although not at the highest fiber intake (Figure 2).

Carbohydrate Intake: In previous studies increased carbohydrate intake was associated with hypercalciuria and this result was also shown in our studies (Figure 2) [105-107]. Intake of specific carbohydrates, e.g., fructose, has been considered relevant to this effect with a presumed increased risk of developing renal stones [108]. This was postulated as due to an increase in glomerular filtration rate and a consequent decrease in filtered load [107].

Vitamin D Intake: The relationship between vitamin D intake and calcium metabolism has been well established since vitamin D is necessary to maintain calcium absorption although one study reported that vitamin D repletion did not alter urinary calcium excretion in post menopausal women [106,109,110]. In our study there was little change in calcium excretion with increased vitamin D intake but our subjects were not vitamin D deficient (Figure 2).

Changes in Magnesium

Magnesium Intake: Investigators reported little or no change in serum magnesium with magnesium intake [111,112]. Subjects taking average or even high levels of diets enriched with magnesium were reported not to demonstrate significantly elevated plasma magnesium; however, decreased magnesium intake was reported to decrease both plasma and erythrocyte membrane magnesium, to increase urinary phosphorus excretion and decrease potassium excretion [45,112,113]. With magnesium depletion serum magnesium and calcium have been reported to decrease [113-116]. We demonstrated an inverted U shaped curve of magnesium excretion with increased magnesium intake (Figure 4).

Potassium Intake: Previous studies reported increased plasma and urine magnesium with increased potassium intake whereas others reported increased potassium intake decreased magnesium absorption and that serum magnesium decreased with potassium infusion [117-120]. Another study reported decreased magnesium related to potassium deficiency and refractory to potassium repletion [121]. Excessive potassium intake was reported to have no effect on muscle magnesium in calves whereas it was reported to decrease magnesium excretion and increase calcium excretion, the latter effect similar to our results. Increased potassium intake was associated with decreased serum magnesium in calves and increased magnesium excretion [118,122-124]. However, in another study serum magnesium was depressed with increased dietary potassium [125]. In our studies as potassium intake increased there was an increase in urine magnesium excretion, a decrease in saliva magnesium and an initial and final increase in plasma magnesium (Figure 5).

Carbohydrate Intake: Previous studies reported increased urinary magnesium excretion with increased dietary carbohydrate [126]. Still others reported that increased carbohydrate improved availability of dietary magnesium with apparent increased absorption of magnesium although serum magnesium was not affected [127]. We also found increased magnesium excretion with increased dietary carbohydrate but no changes in saliva magnesium.

Fiber Intake: In previous reports increased fecal losses of both calcium and magnesium occurred with increased intake of refined cellulose [128]. We found a slight increase in urinary magnesium as fiber intake increased with a slight decrease in salivary magnesium and no change in erythrocyte magnesium (Figure 5).

Fat Intake: In a previous report short chain fatty acids stimulated net magnesium efflux from isolated rumen of sheep [129]. In our studies there was no change in plasma or erythrocyte magnesium with increased fat, an inverted U shaped pattern of urinary magnesium excretion and a decrease in salivary magnesium (Figure 5).

Phosphorus Intake: As serum concentrations of phosphorus increased serum magnesium reportedly decreased and with an exogenous load of phosphate urinary magnesium was reported to decrease [130]. In our studies there was an initial increase in plasma magnesium with increased phosphorus intake which leveled off at higher intakes of phosphorus (Figure 5). In our studies there was a slight increase in urinary magnesium excretion as phosphorus intake increased whereas there was a slight decrease in saliva magnesium and no change in erythrocyte magnesium.

Calcium Intake: Other investigators reported a high intake of calcium induced a decrease in magnesium utilization and excretion [131]. Increased caloric intake in a previous study reported a rapid rise in excretion of both magnesium and calcium [132]. In our studies increased calcium intake induced no

changes in plasma or erythrocyte magnesium but a decrease in salivary magnesium.

Sodium Intake: We demonstrated increased urinary magnesium excretion with increased sodium intake, an effect not previously reported (Figure 5).

Vitamin D Intake: Other investigators reported increased vitamin D intake increased urinary magnesium excretion and intestinal absorption of magnesium [133]. Others reported an interaction between vitamin D and parathyroid hormone on magnesium homeostasis [134]. We demonstrated little or no change with increased vitamin D intake although our subjects were vitamin D replete at the time of study (Figure 5).

The present results indicate calcium and magnesium in plasma, erythrocytes, saliva and urine change in relationship to intake of some nutrients but not to others. These changes relate to complex interactions among the various nutrients and the physiological compartments into which calcium and magnesium are transported, stored and released. Although compartmented analysis has been utilized to understand basic aspects of human calcium and magnesium metabolism the details of how variations in nutrient intake affect these relationships are complex and conclusions about these relationships are not definitive [135-139]. However, the present studies supply a useful foundation for promulgation of these relationships.

There are limitations to this study. The subjects of the study were patients with taste and/or smell dysfunction. While sensory abnormalities were present among these patients measurements of their blood plasma, urine and saliva calcium and magnesium and erythrocyte magnesium did not differ from those measured in normal volunteers with data obtained from studies of others before us or from our own work (not reported here). Diets of these subjects did not differ significantly from those we have previously measured in normal volunteers.

Conclusions

The present studies demonstrate that changes in calcium levels in blood plasma, urine, saliva and erythrocytes, and magnesium in erythrocytes change in specific ways in relationship to intake of varying amounts of dietary nutrients. The novel aspect of this study is that these changes are related to this varying intake of nutrients in relationship to what may be considered usual dietary intake. These changes relate to the complex roles each nutrient, both individually and together, plays in calcium and magnesium transport, storage and excretion. These results may assist in interpretation of calcium and magnesium levels in these biological fluids in relationship to usual dietary intake of several nutrients.

Declarations

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Robert I. Henkin is a member of the board of directors of Cyrano Therapeutics.

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