Role of Vitamins and Minerals in Health and Diseases

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Summary We have adopted the following four topics: 1) dietary phosphorus management in chronic kidney disease (CKD) patients, 2) inadequate nutrient intakes in Filipino schoolchildren and adolescents, 3) clinical and societal implications of vitamin insufficiency, and 4) zinc transporters. Vitamins and minerals play essential roles in health promotion in clinical and societal perspectives with marked advances in understanding the mechanism underlying such effects.

Key Words chronic kidney disease, phosphorus, schoolchildren and adolescents, vitamin insufficiency, zinc transporters

Vitamins and minerals are essential in health promotion, and there have been marked advances in understanding their underlying health promoting effects. In this symposium, we have adopted the following four topics: 1) dietary management of phosphorus in chronic kidney disease (CKD) patients, 2) inadequate nutrient intakes in Filipino schoolchildren and adolescents, 3) clinical and societal implications of vitamin insufficiency, and 4) zinc transporters.

Dietary management of phosphorus in CKD patients

Phosphorus is found in bone, phospholipids, ATP, and nucleic acids, and also is involved in energy production, acid-base homeostasis, and cell signaling. Its blood level is tightly maintained between 2.5 and 4.5 mg/dL in adults. Phosphorus balance is regulated through intestinal absorption, renal reabsorption/excretion, uptake/release in soft tissues, and bone formation/resorption (1). The kidney plays critical roles in maintaining phosphorus balance. Thus, hyperphosphatemia is a major complication in advanced CKD patients, due to impaired urinary excretion.

To maintain phosphorus balance in hyperphosphatemic CKD patients, its dietary intake must be restricted. A low-protein diet is commonly employed, and contributes to improve hyperphosphatemia, since dietary phosphorus and protein intakes are strongly associated, which, however, may cause protein-energy wasting, poor prognosis, and mortality risk. For its avoidance, several alternative dietary managements have been proposed.

i) Phosphorus to protein ratio: The food phosphorus/protein ratio is divergent. For instance, it is 1.4 and 63.3 for egg white and liquid nondairy creamers, respectively. Consumption of foods with a high phosphorus/protein ratio is associated with mortality in end-stage CKD patients. They are often educated to substitute foods with a high phosphorus/protein ratio with foods with lower alternatives.

ii) Plant foods vs animal foods: Phosphorus availability is higher in animal foods than plant foods, because phosphorus exists as phytate, hardly hydrolyzed in the digestive tract in plant foods. An observational study with NHANES III participants showed an association of a higher proportion of protein from plant sources with lower mortality in those with eGFR <60 mL/min/1.73 m² (2). A higher plant foods/animal foods ratio may be beneficial in CKD patients.

iii) Food additives in processed foods: Phosphorus-containing food additives, widely used in many processed foods, are digested to inorganic phosphate and absorbed, with almost 100% availability, higher than for animal and plant foods (1). Such additives may be harmful in advanced CKD patients, and their avoidance must be taught.

iv) Phosphatemic index: Phosphorus availability is determined by intestinal digestion and absorption, tissue distribution, and renal excretion, and is quite different among food groups. It is low in plant foods containing phytate, and high in processed foods supplemented with phosphate-containing food additives. However, exact determination in each food is difficult. Narasaki et al. have proposed a novel index reflecting the phosphorus bioavailability: the phosphatemic index (3). It is based on the postprandial increase in serum phosphorus after ingestion of various foods, like the glycemic index. The phosphatemic index can more accurately evaluate the effect of food phosphorus on serum phosphorus levels than the phosphorus/protein ratio or plant food/animal food ratio, and is applicable to evaluation of the dietary phosphorus load and food choices to prevent hyperphosphatemia or an excessive phosphorus load in CKD patients (3).

Dietary phosphorus management through such approaches is more effective to treat hyperphosphatemia in patients with CKD than phosphorus-lowering drugs.

Poor and rural adolescents and school children are most affected by inadequate nutrient intake

Nutrition plays critical roles in schoolchildren and adolescents, especially when physical, social, and cogni-
tive growth and development occur. Macro- and micro-nutrient inadequacy may lead to their impairment, for which economic reasons can be the important limiting factor (4). Rural areas have lower socio-economic status associated with food insecurity, lower dietary quality and diversity, and less healthy dietary patterns than urban areas, (5). We have studied the prevalence of inadequate nutrient status among Filipino schoolchildren and adolescents stratified by locality and wealth status.

Food and beverage intakes were evaluated from two 24-h dietary recalls from nationally representative samples of school children aged 6–12 y (N=6,565), and adolescents aged 13–18 y (N=5,446). Distributions of usual energy, nutrient intakes, and the prevalence of inadequate intakes (intakes less than estimated average requirements or acceptable macronutrient distribution ranges) were estimated. Socio-economic, demographic, and anthropometric data were also collected, and wealth status of the families was categorized into five groups.

Data were from the cross-sectional, population-based, nationwide survey with multi-staged stratified sampling. Of the 12,011 study subjects, 42% lived in rural areas, and 51% belonged to the poor and poorest wealth status. Macro- and micronutrient intake inadequacy was highly prevalent for various nutrients including folate, vitamin A, vitamin C and calcium, key nutrients for growth and development (4, 6). The average energy intake was 19–35% lower than the age group’s estimated energy requirement.

In both age groups, the prevalence of inadequate intake of most macro- and micro-nutrients was inversely proportional to wealth status; the poorest having the highest prevalence. Carbohydrate intake is the highest in poor and poorest wealth status, since diets in these groups are mostly composed of rice with scarce intake of meat, fruits vegetables, and milk due to economic reasons. Higher intake of diets with poor nutrient quality is likely to be associated with the high prevalence of obesity in these groups. The prevalence of inadequate intake was higher in schoolchildren and adolescents in rural areas than in urban areas for most nutrients, but was higher in urban areas regarding carbohydrates, vitamin C, folate, and vitamin A.

In conclusion, inadequate nutrient intake is prevalent in Filipino schoolchildren and adolescents, more marked in rural areas and in poor families, rendering them at higher risk for malnutrition and impaired growth and development. Our results suggest the need for government agencies, non-profit organizations, and other policy makers to strengthen the existing policies, and also implement new programs to correct such inadequacies, with cost-effective targeting.

Clinical and societal implications of vitamin insufficiency

Vitamin deficiency causes classical diseases such as beriberi (vitamin B1), which are considered to be mostly overcome in developed countries. However, vitamin insufficiency, milder than deficiency, is associated with the increased risk of various diseases (7). The most fundamental action of vitamin D (VD) is to enhance the intestinal calcium and phosphorus absorption, and its deficiency causes rickets and osteomalacia. In VD insufficiency, secondary hyperparathyroidism, enhanced bone resorption, and increased fracture risk occurs. VD is metabolized to 25-hydroxy VD[25(OH)D] in the liver, then to its active form, 1,25-dihydroxy VD [1,25(OH)2D] in the kidney. VD status is best diagnosed by serum 25(OH)D level: sufficiency (≥30 ng/mL), insufficiency (20 to 30 ng/mL), and deficiency (<20 ng/mL).

Recently, extra-skeletal actions of VD have been discovered. VD is essential in maintaining muscle strength. Most non-vertebral osteoporotic fractures occur at falling. Thus, VD deficiency/insufficiency is likely to increase fracture risk both through impaired bone strength and increased risk of falling. Additionally, VD insufficiency has been reported to be a risk for additional diseases including coronary heart diseases, cancer, and upper respiratory tract infection, and mortality. Recently, a high prevalence of VD deficiency/insufficiency has been reported worldwide (8).

Far less attention has been paid to B vitamin insufficiency. Homocysteine (Hcy), an intermediate in methionine metabolism, is metabolized either to methionine with folate and vitamin B12 as the cofactors, or vitamin B6-dependently to cysteine. Insufficiency of these vitamins causes hyperhomocysteinemia (HHcy), an atherosclerosis risk independent of dyslipidemia. Results from observational studies have been positive with strong association between HHcy and cardiovascular diseases risk, but those from intervention studies are mostly negative.

Vitamin B1 (VB1) deficiency causes beriberi: dry beriberi causing peripheral neuropathy, and wet beriberi causing heart failure. We have recently reported that plasma brain natriuretic peptide (BNP) concentration, a sensitive marker for heart failure, inversely correlated with blood VB1, which was confirmed by logistic regression analysis after adjusting for the various confounding variables in the institutionalized elderly. With the ageing society, the prevalence of elderly heart failure is rapidly increasing, and has become a serious societal problem. It was considered likely that VB1 insufficiency is a modifiable risk factor for elderly heart failure, and VB1 can play an important role both clinically and societally for its primary prevention (9).

Since the number of subjects with low to intermediate risk is large, an absolute number of events occurs in them, despite the lower risk in each subject, to which drug intervention is unsuitable considering the cost and possible adverse events. Vitamin insufficiency is a significant risk for various diseases, and its correction is of great societal significance.

Zinc transporter

Zinc (Zn) plays important roles as a structural, catalytic, and signaling component in proteins (10). It is involved in various physiological processes, and its adequate dietary intake is essential for maintaining health. Cellular Zn homeostasis is maintained by coordinated
function of two of the Zn transporter families, Zrt-/Irt-like protein (ZIP) and Zn transporter (ZNT), and the cytosolic zinc-binding protein; metallothionein (MT) (11). Fourteen, 10, and 11 isoforms of ZIP, ZNT, and MT function in humans, respectively. ZIPs, mostly localized to the plasma membrane, mediate the Zn uptake into the cytoplasm; specific ZIPS localize to intracellular compartments and mediate the Zn release from the lumen of these compartments. Increased cytosolic Zn concentrations are counteracted through ZNT-mediated mobilization of Zn either out of the cells or into the lumen of intracellular compartments; therefore, ZNTs function in removing cytosolic Zn. Zn efflux from the cell is mediated solely by ZNT1, the only ZNT localized at the cell surface. In addition, the sequestration of Zn by MTs can also reduce cytosolic free ionic Zn levels. Thus, coordination of these processes is essential to maintain intracellular Zn levels near homeostatic set-points in each cell type and must be accomplished in a spatiotemporally appropriate manner.

In intestinal cells, coordinated expression of ZIP4 and ZNT1 is crucial for dietary Zn absorption (12). ZIP4 is an essential component for dietary Zn uptake, and thus its mutations result in acrodermatitis enteropathica (AE), a rare genetic recessive disorder with Zn deficiency. ZIP4 protein accumulates on the apical membrane at Zn deficiency, which, however, is rapidly internalized by endocytosis and degraded by the ubiquitin proteasome pathway at Zn excess. Zn taken up into intestinal epithelial cells is thought to be excreted into portal blood by ZNT1 localized in the basolateral membrane, although this is not yet directly proven. Kambe et al. aimed to determine how ZNT1 and MT expression responds to changes in ZIP expression under normal cell culture conditions without Zn supplementation, particularly focusing on how increased apical surface ZIP4 expression affects basolaterally-localized ZNT1 expression. They used a Tet-regulatable promoter, allowing induction of ZIP by doxycycline (Dox) treatment, which enabled them to control ZIP expression with or without Dox (13). Using this system, they found that ZNT1 expression is sophisticatedly regulated by the expression status of ZIP4. Thus ZIP4-mediated ZNT1 expression operates in intestinal cells and is essential for vectorial intercellular Zn transport in its absorption, possibly helping to achieve systemic Zn homeostasis.

Zn absorption does not require redox reactions during membrane transport, unlike iron or copper. Therefore, strict spatiotemporal regulation of ZIP4 and ZNT1 expression is critical for membrane transport of Zn for systemic and cellular Zn homeostasis. The findings of ZIP4-driven ZNT1 expression also provide new molecular insights into how Zn homeostasis is maintained when ZIP expression is altered by physiological and pathological stimuli.

**Conclusion**

Vitamins and minerals play essential roles in health promotion in clinical nutrition, public health nutrition, and also from societal perspectives. There have been marked advances in understanding the mechanism underlying such effects.

**Disclosure of state of COI**

We declare no conflicts of interest.

**REFERENCES**