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Nutrition Research and Practice

Review

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Issues pertaining to Mg, Zn and Cu in the 2020 Dietary Reference Intakes for Koreans

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ABSTRACT

In the current years, it has now become necessary to establish standards for micronutrient intake based on scientific evidence. This review discusses issues related to the development of the 2020 Dietary Reference Intakes for Koreans (KDRI) for magnesium (Mg), zinc (Zn), and copper (Cu), and future research directions. Following issues were encountered when establishing the KDRI for these minerals. First, characteristics of Korean subjects need to be applied to estimate nutrient requirements. When calculating the estimated average requirement (EAR), the KDRI used the results of balance studies for Mg absorption and factorial analysis for Zn, which is defined as the minimum amount to offset endogenous losses for Zn and Mg. For Cu, a combination of indicators, such as depletion/repletion studies, were applied, wherein all reference values were based on data obtained from other countries. Second, there was a limitation in that it was difficult to determine whether reference values of Mg, Zn, and Cu intakes in the 2020 KDRI were achievable. This might be due to the lack of representative previous studies on intakes of these nutrients, and an insufficient database for Mg, Zn, and Cu contents in foods. This lack of database for mineral content in food poses a problem when evaluating the appropriateness of intake. Third, data was insufficient to assess the adequacy of Mg, Zn, and Cu intakes from supplements when calculating reference values, considering the rise in both demand and intake of mineral supplements. Mg is more likely to be consumed as a multi-nutrient supplement in combination with other minerals than as a single supplement. Moreover, Zn-Cu interactions in the body need to be considered when determining the reference intake values of Zn and Cu. It is recommended to discuss these issues present in the 2020 KDRI development for Mg, Zn, and Cu intakes in a systematic way, and to find relevant solutions.

Keywords: Magnesium; zinc; copper; Dietary Reference Intakes for Koreans (KDRIs)

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INTRODUCTION

The Recommended Dietary Allowances (RDA) for South Koreans was first established in 1962, and subsequently been updated and revised continuously. In 2005, it was renamed as the Dietary Reference Intakes for Koreans (KDRIs). Since the first publication, the number of nutrients has gradually increased from 10 nutrients in 1962 to 15 nutrients in 1995 through 2000, 34 nutrients in 2005, and 36 nutrients in 2015 [1]. In particular, the growing interest in the health benefits of micronutrients has resulted in an increasingly recognized need to establish guidelines for micronutrient consumption, resulting in expanding the range of micronutrients for which reference intakes for Koreans are established. Accordingly, among minerals, the reference values for zinc (Zn) intake have been established and revised since 1995, and for magnesium (Mg) and copper (Cu) intake since 2005 [1]. In the current review, the issues and limitations for Mg, Zn, and Cu reference values in the 2020 KDRIs have been addressed (**Table 1**), followed by suggestions for future KDRIs of Mg, Zn, and Cu.

Due to the intrinsic physiological functions of the 3 minerals discussed in this review, their intakes are of increasing interest in terms of promoting health. Therefore, accurate assessment of nutrient intakes and reviews of the scientific evidence associating the intakes and health benefits are necessary. However, it is difficult to precisely evaluate the intake amounts due to the lack of databases on the contents of Mg, Zn, and Cu in foods or Korean diets and supplements. Moreover, important additions to scientific literature that are useful in establishing DRIs for health are still lacking. This review discusses the issues and limitations in setting the 2020 KDRIs for Mg, Zn, and Cu, and offers suggestions for establishment of future KDRIs.

Table 1. 2020 KDRIs for Mg, Zn, and Cu

Subject	Age	Mg (mg/d)				Zinc (mg/d)				Copper (ug/d)			
		EAR	RNI	AI	UL[1)]	EAR	RNI	AI	UL	EAR	RNI	AI	UL
Infants	0–5 mon			25				2				240	
	6–11 mon			55		2	3					330	
Children	1–2 yrs	60	70		60	2	3		6	220	290		1,700
	3–5 yrs	90	110		90	3	4		9	270	350		2,600
Males	6–8 yrs	130	150		130	5	5		13	360	470		3,700
	9–11 yrs	190	220		190	7	8		19	470	600		5,500
	12–14 yrs	260	320		270	7	8		27	600	800		7,500
	15–18 yrs	340	410		350	8	10		33	700	900		9,500
	19–29 yrs	300	360		350	9	10		35	650	850		10,000
	30–49 yrs	310	370		350	8	10		35	650	850		10,000
	50–64 yrs	310	370		350	8	10		35	650	850		10,000
	65–74 yrs	310	370		350	8	9		35	600	800		10,000
	≥ 75 yrs	310	370		350	7	9		35	600	800		10,000
Females	6–8 yrs	130	150		130	4	5		13	310	400		3,700
	9–11 yrs	180	220		190	7	8		19	420	550		5,500
	12–14 yrs	240	290		270	6	8		27	500	650		7,500
	15–18 yrs	290	340		350	7	9		33	550	700		9,500
	19–29 yrs	230	280		350	7	8		35	500	650		10,000
	30–49 yrs	240	280		350	7	8		35	500	650		10,000
	50–64 yrs	240	280		350	6	8		35	500	650		10,000
	65–74 yrs	240	280		350	6	7		35	460	600		10,000
	≥ 75 yrs	240	280		350	6	7		35	460	600		10,000
Pregnancy		+30	+40		350	+2.0	+2.5		35	+100	+130		10,000
Lactation		+0	+0		350	+4.0	+5.0		35	+370	+480		10,000

KDRIs, Dietary Reference Intakes for Koreans; Mg, magnesium; Zn, zinc; Cu, copper; EAR, Estimated Average Requirement; RNI, Recommended Nutrient Intake; AI, Adequate Intake; UL, Tolerable Upper Intake Level.
1)Only for non-food magnesium sources.

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Conflict of Interest
The authors declare no potential conflicts of interests.

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MAGNESIUM

Outline for 2020 Mg KDRIs

Reference intakes for Mg, comprising the Estimated Average Requirement (EAR), Recommended Nutrient Intake (RNI), and Tolerable Upper Intake Level (UL), were reestablished in the 2020 KDRIs. In the revision process of KDRIs for Mg, we reviewed several indicators to set reference values for health, and we evaluated 33 out of 1,315 article abstracts (extracted using search engines such as PubMed and ScienceDirect) to discover recent relevant and useful information [1] (**Fig. 1**). Our evaluation revealed that in Korea, there were no updated studies applicable to the revision of the EAR for Mg established in 2015. In addition, assessment of the strength of evidence (SoE) for the relationship between Mg and various health outcomes showed limited strength, and thus, it was not specifically applied to the 2020 DRIs.

The EAR and RNI of Mg in the 2020 KDRIs were established based on the Mg equilibrium experiment. Accordingly, similar to 2015, the Mg intake per body weight for the 2020 KDRIs was calculated based on studies reported in foreign countries by life cycle. In 2020, this was applied to the standard physical characteristics of Koreans to calculate the average Mg requirement [2,3]. Adverse effects from excessive intake of Mg through food have not been reported. Therefore, the UL of Mg was established considering only sources such as supplements, other than food [1].

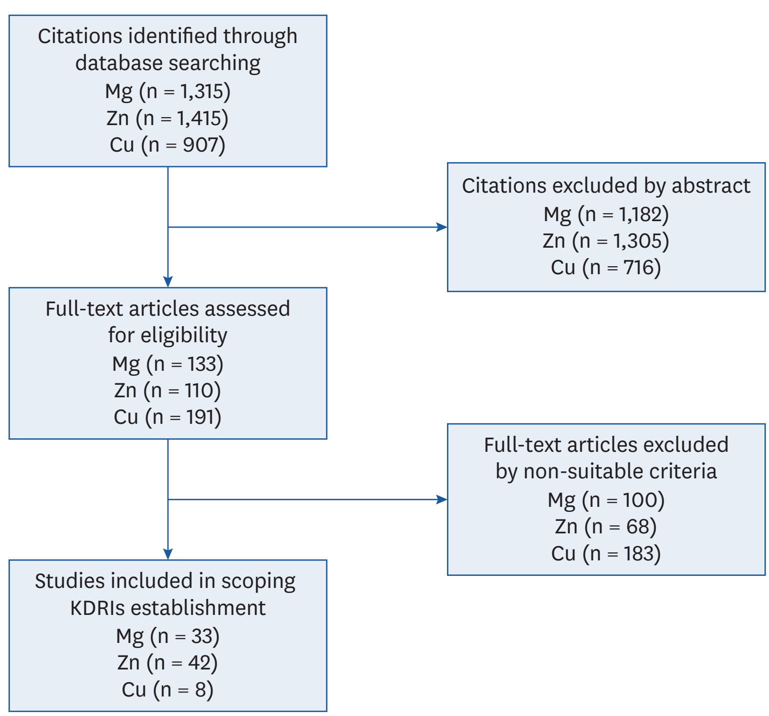

Fig. 1. Literature review process for the 2020 KDRIs, for Mg, Zn, and Cu.
Citations identified in PubMed and ScienceDirect search for Mg and Zn, and in PubMed, Web of Science, RISS and DBpia databases for Cu, for studies published between 2014 and April 2019. The literature reviews up to 2013 has already been updated for the 2015 KDRIs, and studies after 2013 were cited and updated for the 2020 KDRIs.
KDRIs, Dietary Reference Intakes for Koreans; Mg, magnesium; Zn, zinc; Cu, copper.

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Issues and topics for 2020 Mg KDRIs

Mg intake from Korean diet

Mg is abundant in green leafy vegetables, nuts, legumes, and grains, and is also found in dairy products, meat, fish and shellfish, eggs, and fruits [4]. Therefore, sufficient intake of various food groups and plant-based foods could generally avoid concerns about Mg deficiency. Traditional Korean meals consist of rice and soup/stew as staple foods, a protein-based main dish, and vegetable side dishes that are rich in minerals and vitamins. In South Korea, numerous Mg-rich vegetables (such as leafy, stem, and tubal vegetables) are consumed using various recipes such as seasoning raw vegetables, seasoning cooked vegetables, stir-frying, and blanching [5]. However, the consumption of high-energy foods, high-fat animal-based foods, and high-sugar foods has increased due to recent Westernized and global dietary lifestyle comprising busy work and life schedules, while the consumption of plant-based foods has relatively decreased [6,7]. Due to the recent downward trend of plant-based food intake, the adequacy of Mg intake needs to be assessed. Previously, few studies have evaluated Mg intake in healthy Korean adults. In a previous study of healthy adults, Mg intake for subjects aged 19–64 yrs was about 250–270 mg per day, and the percentage of subjects consuming Mg below the EAR was 50–55% [8]. In a recent study conducted on healthy adults aged 21–69 yrs (n = 80), Mg intake was determined to be 319 mg/day for males and 277 mg/day for females [9]. The percentage of subjects consuming Mg below the EAR was 50% for males and 67.5% for females, indicating a severe deficiency of Mg intake [9]. If more intake evaluations are performed applying the 2020 KDRIs, accumulation of the intake evaluation data over the years and changing trends in Mg intake might be examined in a more comprehensive way.

To date, there has been no report on any representative study investigating Mg intake using the 2020 KDRIs. This may to be due to the lack of database on the Mg content in foods. The insufficient Mg database in foods has been problematic for determining the adequacy of Mg intake and examining the health benefits of Mg. Therefore, establishment of an ongoing database on the Mg contents in natural and commercial foods in Korea is necessary. This will facilitate a representative assessment of Mg intake, similar to other micronutrients such as calcium (Ca), phosphorus (P), sodium (Na), potassium (K) and iron (Fe), which are currently evaluated in representative Korean population groups.

Mg intake from supplements for health and functional purpose

Among the many roles attributed to this mineral, Mg maintains the bone integrity as a component of bone and teeth, stabilizes cell membranes, acts as a coenzyme of diverse enzymes within our body, delivers neural stimulation, and takes part in the synthesis of fat, protein, and nucleic acid [3,10-12]. Based on these physiological functions, numerous studies have shown that Mg is related to non-communicable diseases such as hypertension [13], dyslipidemia [14], diabetes [15], and metabolic syndrome [16], in addition to maintaining the skeletal health. However, most previous studies [13-26] examining the relationship between Mg intake and chronic diseases have been conducted outside Korea. Studies applying KDRIs, or national studies that can be used as scientific evidence for establishing KDRIs, are very limited.

With increasing consumer interest in the relationship between food intake and health status, consumption of dietary supplements is popular worldwide, and their use has been steadily increasing. The use of dietary supplements has been reported in 52% adults in the USA [27], 45.1% females and 25.2% males in the UK [28], and 49% adults in Italy [29]. In South Korea, use of dietary supplements among adults was 57.3% using the 2019 Korea National

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Health and Nutrition Examination Survey (KNHANES) data [30]. With increasing intake of dietary supplements, there is a corresponding increase in the intake of vitamin and mineral supplements, which are difficult to be sufficiently obtained through food consumption [31]. Growing numbers of healthy people are taking dietary supplements, although there is little evidence supporting that they provide protection against non-communicable diseases [32]. Mg is also consumed as a dietary supplement since various health functions of Mg have been reported [10-26]. However, there is insufficient evidence for the necessity or a guideline of Mg intake for health functionalities.

Considering that no harmful effects of excessive intake through foods have been reported, the UL in the 2020 KDRIs was set through sources other than foods, including dietary supplements [1]. However, in South Korea, there has been no study on Mg intake through dietary supplement sources other than foods, neither is there any reference value for adequate intake. Since the health function of Mg must be verified not only through dietary Mg intake but also through intake of dietary supplement sources other than foods, a study to evaluate Mg intake through dietary supplements needs to be conducted. In the future, accumulation of these scientific evidences will help in establishing the reference values of Mg for UL and/or prevention of chronic diseases.

Suggestions for future Mg KDRIs

Research subjects required for the next revision of Mg KDRIs are as follows: 1) Although the equilibrium experiment is used as scientific evidence for EAR of Mg, most evidence is obtained from studies conducted in foreign countries long time ago. Therefore, Mg equilibrium experiment by life cycle targeting Korean people needs to be conducted; 2) The UL of Mg intake is determined from dietary supplement sources other than food. To estimate the Mg intake from dietary supplements as non-food sources, it is necessary to establish the Mg content database of dietary supplements. Studies that evaluate the Mg intake from dietary supplements by life cycle are also required; 3) Studies that examine the relationship between Mg intake and chronic disease-related health indicators for the Korean population are needed, since the association between Mg intake and chronic health problems (such as cardiovascular diseases, hypertension, type 2 diabetes, skeletal growth retardation, and osteoporosis) has been continuously reported. However, most studies reporting the relationship were conducted outside South Korea, while studies conducted in Korea are very limited.

ZINC

Outline for 2020 Zn KDRIs

For determining Zn intakes for the 2020 KDRIs, factorial analysis considering various factors for Zn requirement was performed first. For adequate Zn intake, we need to consider 1) physiological Zn absorption, metabolism and excretion, 2) clinical effects of inadequate Zn intake, and 3) selection of various Zn indicators for estimating the Zn requirement. These include factors such as Zn concentration in human milk for infants, requirements for growth, endogenous zinc loss, intestinal and urinary loss, fractional absorption of dietary Zn, and semen and menstrual losses. To develop the SoE for Zn studies, published Zn studies were retrieved and reviewed using the PubMed and ScienceDirect searching engine database for the period 2014–2019, which updated and covered sufficient material for Zn studies since the 2015 KDRIs revision. Randomized controlled trials (RCTs) were originally included and, also observation studies were additionally included, due to the limited RCT reports. In all, 1,415 articles were screened, from which 110 articles were reviewed entirely, and finally 42 articles were attributed to having adequate strength of evidence for establishing the DRI [1] (**Fig. 1**).

The Zn EAR was calculated to be 8 and 7 mg/day for male and female adults, respectively. The RNI was determined to be 10 and 8 mg/day for male and female adults, respectively. The UL for adults was established at 35 mg/day. The values in the 2020 Zn KDRIs were similar to those obtained in the 2015 Zn KDRIs; however, RNI levels for male children (5 mg for 6–8 years, −1 mg compared to the previous 2015 KDRIs) and for older male and female subjects (10 and 8 mg, respectively, for 50–64 years, +1 mg compared to the 2015 KDRIs) were modified by considering the 2020 body weight KDRIs. EAR for Zn was also reestablished in the three age groups as follows, based on calculations for the increased body weight: 9 mg/day for the 19–29 years male group, 8 mg/day for the 65–74 years male group, and 7 mg for the 9–11 years female group [1]. The 2020 KDRIs included not only the major food sources of Zn for Koreans, but also Zn contents per serving size of foods. This information helps to determine the daily Zn intake from major food sources [33].

Issues and topics for 2020 Zn KDRIs

Zn intakes from foods and supplements, and establishment of the UL

The 2020 KDRIs provide the major food sources of Zn and Zn contents per serving size from Zn rich foods. However, since reports and study results on real Zn intakes of Koreans are limited, the available data are insufficient to accurately determine the DRI levels for Zn. Moreover, the Zn intakes from supplements are yet to be analyzed. Also, the KNHANES does not provide Zn intake levels in South Korea [34,35]. The mean and median Zn intakes from foods and supplements would be useful for estimating Zn intakes more accurately. In the USA, Zn RDA values for male and female adults are 11 and 8 mg/day, respectively, while the median Zn intakes from only foods are 14 and 10 mg/day, respectively, which considered to lower UL level as lowest level of 23 mg/day on considering Zn supplements. Zn UL for KDRIs is established as 35 mg/day [36,37]. The primary reason that Zn UL for South Koreans are higher than the USA levels is because Zn intake from foods and Zn supplements is lower in South Koreans as compared to Americans, which results in obtaining higher Zn UL (35 mg/day). Currently, the UL for Zn needs to be reconsidered since insoluble mineral toxicity is of concern for public health. Particularly, Zn intake from supplements needs to be cautiously considered for children and the elderly due to potential sensitivity to extra high Zn intake. Also, the pattern of food consumption in South Korea has transformed from plant- and grain-oriented foods to animal-oriented foods rich in Zn [6,34]. Therefore, future KDRIs for Zn need to be prepared based on actual food consumption and Zn supplement data.

Limitations for Zn human studies

The most difficult aspects for estimating the Zn KDRIs are limited human and clinical Zn studies in South Korea and globally. In the past decade, while knowledge about the biochemical and molecular function of Zn has developed and expanded worldwide, reports on large-scale human Zn studies remain limited since the late 1990s [38].

Major clinical outcomes of Zn deficiency include growth retardation, immune dysfunction, the altered cognition ability, altered host defense properties, defects in carbohydrate utilization, etc. This implies the necessity of human studies to elucidate Zn functions and intake levels, in addition to animal studies [39-41]. Any indications of Zn deficiency and outcomes of Zn balance studies on human subjects are 'factors' that need to be considered when estimating the Zn requirement. Without sufficient data and study results, there are limitations for determining accurate Zn requirement. Particularly, dietary Zn human studies for Koreans are very limited and hence insufficient for the accurate determination of Zn intake levels. There are two comprehensive Zn expert working groups for Zn requirements: the Zn group in European Micronutrient Recommendations Aligned (EURRECA) network [42,43], and the Zn group of the Biomarkers of Nutrition for Development (BOND) project [44]. Reports from both groups provide best practice guidelines for assessing dietary Zn intake and Zn status. Moreover, both groups provide valuable data for establishing the dietary Zn recommendation, including its factorial approach and physiological requirements [45]. However, there are only a few studies capable of compiling Zn intake for a global large-scale human subject study [46,47].

Suggestions for future Zn KDRIs

Considering all the issues and limitations described above, 2 aspects are suggested for future Zn KDRI determination. First, the database for Zn contents in foods and mean Zn intake studies are needed for establishing accurate Zn requirement in South Koreans. These studies would be more reliable when they are included in national-level studies such as the KNHANES. Secondly, reasonable and large-scale human studies on Zn are needed, both globally and in Korea. Randomized control human clinical and balance studies on Zn would be useful for the accurate determination of Zn requirement.

COPPER

Outline for 2020 Cu KDRIs

Literature search was conducted in the PubMed, Web of Science, RISS and DBpia databases to identify eligible studies published from January 2014 to August 2019. The following keywords were used: dietary Cu intake, human studies, clinical studies, observational studies, double-blinded studies, cross-sectional studies, case-control studies and randomized controlled studies. Totally, 907 articles were retrieved and screened for abstracts; subsequently, 191 articles were selected, and full-text review was performed, and 8 articles were finally selected for the SoE analysis (**Fig. 1**). However, all 8 articles failed to meet inclusion criteria in the study. As a result, scientific evidence is lacking to justify the modification of KDRIs for Cu.

Therefore, as in the 2015 KDRIs, results from the USA/Canada studies have been used to determine Cu requirement for the 2020 KDRIs [48]. The criteria used for determining the EAR include plasma Cu and ceruloplasmin concentrations, erythrocyte superoxide dismutase activity (SOD), and platelet Cu concentration in humans [49-51]. The Cu EAR for adult males is set at 700 µg/day in the USA and Canada. For Korea, the USA EAR was extrapolated based on average body weight. In the 2020 KDRIs, EAR for Korean adult male was established at 650 µg/day.

In the USA, the same EAR value has been applied to females and people aged 65 years and over, due to lack of scientific data that would indicate differences in Cu metabolism among gender and age groups. Previous KDRIs were also established using the same principle. However, in 2020, EARs for females and older age groups have been extrapolated from the adult male EAR, based on their body weights.

Issues and topics for 2020 Cu KDRIs

Reliability of Korean Cu intake assessment

A limited number of studies have assessed the amount of Cu intake by Koreans. The KNHANES, a national survey that evaluates the nutritional status of Koreans, has only evaluated intakes of Ca, P, Na, K, and Fe among minerals. This is because of the paucity of information and incomplete database of Cu content for frequently consumed foods. Currently, the national food composition table of Korea provides Cu information for only 1,639 (54.6%) of the 3,000 food items consumed [33]. Also, this database has adopted information from foreign databases, which might be different in Cu content due to geographical variations in soil and water [52].

Most studies using available Cu database in Korea have reported excess intake over RNI [52-55]. In a study using data from the 2007–2008 KNHANES, Cu intakes for males and females over the age of 19 years were found to be 1.4 mg/day and 1.1 mg/day, respectively [53]. In a study on Cu consumption by age groups, Cu intakes of Korean males were 1.17, 1.10, 1.33, 1.33, and 1.34 mg/day for the age groups 19–29, 30–39, 40–49, 50–59, and 60 years and over, respectively [55]. In the same study, Cu intakes by Korean females were determined to be 1.07, 1.06, 1.20, 1.29, and 1.36 mg/day for the age groups 19–29, 30–39, 40–49, 50–59, and 60 years and over, respectively, exceeding the recommended intake for both genders [55]. However, since the Cu database covered only 59.2% of food items investigated by Lee *et al.* [55], it is highly likely that Cu was underestimated due to incomplete data. Considering that most studies report Cu consumption above the RNI, it can be speculated that Cu insufficiency is scarce in Korea.

Cu intake from supplements

Cu intake through food and/or supplement is suggested to be associated with prevalence of certain diseases such as cardiovascular disease and diabetes [56,57]. However, data on the actual consumption in Korea, through sources other than food, are very limited. Although the risk of excessive Cu intake from diet is very low, it is currently premature to exclude the possibility of excessive Cu intake from supplements. Therefore, establishment of a complete database of Cu in commonly consumed foods and various dietary supplements is needed for a reliable evaluation of Cu intake in Korea, and investigating the relationship between Cu intake and the risk of various chronic diseases.

Suggestions for future Cu KDRIs

Reliable biomarkers for Cu status assessment are necessary

To date, KDRIs have mainly relied on insufficient and outdated scientific evidence from 1980's [58]. In the absence of 'gold standard' biomarkers to assess marginal or short-term Cu deficiency, it has been challenging to determine the Cu status. In order to accurately determine adequate Cu consumption and intestinal absorption, there is an immediate requirement of intensive practical and clinical Cu-depletion and/or Cu-repletion studies. Since sensitive clinical biomarkers to determine marginal Cu deficiency or excess Cu have yet to be identified [59], clinical and pre-clinical trials are required to find reliable markers for the Cu status. Several biological markers (ceruloplasmin activity, erythrocyte SOD1, Cu chaperone for SOD1 [CCS] in red blood cells, and peptidylglycine alpha-amidating monooxygenase [PAM]) might be useful for determining moderate to severe Cu deficiency [60,61]. In the future, we may determine the biological sensitivity of Cu assessing markers to determine the marginal and excess Cu status.

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Associated biological relationships between Cu and other divalent metals

In the future, significant scientific effort is required not only to discover robust biological markers for dietary Cu status, but also to understand the physiological interactions between dietary or supplemental Cu and other divalent metals. To date, Cu homeostasis is known to be closely associated with other divalent metal ions such as Zn and Fe. High levels of Zn exposure result in decreased Cu absorption and perturb the whole-body Cu homeostasis [62,63]. Excess Zn in enterocyte induces metallothionein expression, which inherently possesses higher affinity for Cu than Zn. Therefore, bioavailability of Cu may be significantly suppressed due to metallothionein-mediated Cu being entrapped in enterocytes.

Fe is another divalent metal that strongly interacts with dietary Cu. In Fe deficiency, Cu absorption and utilization are remarkably increased due to elevated intestinal Cu transport and hepatic ceruloplasmin synthesis [59], both clinically [64] and pre-clinically [65,66]. Conversely, excess Fe exposure suppresses the Cu homeostasis in infants [64,67,68] and rapidly growing rodents [65,66,69,70]. Due to competitive interactions among divalent minerals in their intestinal absorption, distribution, and metabolism, the dietary Cu absorption and distribution might be enhanced or reduced by other divalent metal consumptions. Due to limited literature, current Cu KDRIs solely relied on the extrapolation from a sole clinical report [71]. Therefore, to determine the optimal potential Cu DRI, there is a requirement to update Cu repletion/depletion studies by considering interactions with other minerals.

CONCLUSION

In conclusion, based on issues and limitations for Mg, Zn, and Cu reference values in the 2020 KDRIs, we suggest three aspects for future KDRIs of these three minerals. First, human studies, particularly in Koreans, are needed for more accurate estimation of EAR. Second, more comprehensive and reliable databases on Mg, Cu, and Zn contents in foods are needed to estimate their intakes. Without assessment data of real intakes from foods and supplements for these minerals, it is difficult to establish an accurate EAR. Third, mineral intakes from supplements and foods should be considered for the estimation of UL, since any potential mineral toxicity needs to be considered in the prevailing scenario.

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