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Intervention Strategies for Metal Deficiency and Overload

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Abstract

An increasing amount of evidence shows the linkage between metal ion homeostasis and human disease. Deficiency or overload of metal ions play vital roles in many human diseases, including infectious disease. Nutritional supplementation and metal-based drugs have been suggested as potential intervention strategies to develop treatment for various diseases related to metal deficiency and overload. However, there are numerous forms of metal ion supplementation and metal-based drugs with different features. This chapter provides an overview of the recommended dietary allowance, tolerable upper intake levels, and bioavailability of metal elements and offers perspectives on intervention strategies for metal deficiency and overload. Data for analysis were obtained from research articles, reviews, and reports from the World Health Organization; the National Academic Press websites were another principal source of data.

Introduction

It is well known that some metal ions (iron, zinc, copper, selenium, manganese, molybdenum, nickel, and vanadium) are essential for the proper functioning of living cells. Deficiency of these essential metal ions is often linked with an increased risk for various diseases, including infectious diseases, especially among at-risk populations. Supplementation with metal ions has been shown to prevent, attenuate, and treat a portion of infectious diseases successfully. For example, worldwide, Zn deficiency is responsible for approximately 16% of lower respiratory tract infections, 18% of malaria, and 10% of diarrhoeal disease; Zn supplementation has been recommended by the World Health Organization as the main treatment of choice for diarrhea among children under five years of age (WHO/UNICEF 2004).

Whether essential or not, all metal can be toxic to living cells. Metal overload may cause illness and even death in humans. For example, about 100,000 children born with transfusion-dependent β thalassaemia are currently

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reliant on regular transfusions, and at least 3,000 die annually in their teens or early twenties from uncontrolled Fe overload (Modell and Darlison 2008). Moreover, Fe overload has been demonstrated to be related to some of the world's most common infections: malaria, HIV-1, and tuberculosis (Sazawal et al. 2006; Boelaert et al. 2007; Prentice et al. 2007; Drakesmith and Prentice 2008). Therefore, it is urgent to consider the most appropriate strategies for prevention and treatment of metal overload.

Government agencies in many countries have been providing nutritional (including essential metal elements) advice to the public for several decades. The aim of this chapter is to give an overview of the recommended dietary allowance (RDA), tolerable upper intake level (UIL), and bioavailability of metal elements and present perspectives on intervention strategies for metal deficiency and overload.

Recommended Dietary Allowance

RDA is the daily intake level of a nutrient that is considered to be sufficient to meet the requirements of 97% of healthy individuals for sustenance or avoidance of deficiency states. It was developed during World War II by Lydia J. Roberts, Hazel Stiebeling, and Helen S. Mitchell. They surveyed all available data, created a tentative set of allowances for "energy and eight nutrients," and submitted them to experts for review. The final sets of guidelines were accepted in 1941. The committee established by the U.S. National Academy of Sciences to investigate issues of nutrition was renamed the Food and Nutrition Board in 1941. Since then, this board reviews and revises the RDAs every five to ten years.

The reference daily intake or recommended daily intake (RDI) is based on the RDA from 1968. However, in 1994, at the suggestion of the Institute of Medicine (IOM) of the National Academy, RDA became one part of a new broader set of values known as the dietary reference intake (DRI) system (Flo et al. 2004), which consists of the estimated average requirement (Blackwell et al. 2001), RDA, adequate intake (AI), and tolerable UILs. Hence, newer RDAs have since been introduced into the DRI system, though the RDI is still used for nutritional labeling.

Essential Metal Ions per Individual for Populations in Different Countries

The value of RDA for essential metals varies in different countries. For example, the selenium RDA for the Japanese population is much lower than people in other parts of the world. Here we summarize the RDA for people in the United States, Australia/New Zealand combined, China, Japan, and the European Union for iron (Table 6.1), zinc (Table 6.2), copper (Table 6.3), and

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Table 6.1 Recommended dietary allowances for iron (mg/day) per individual, for populations from different countries: United States, Australia and New Zealand (combined), China, Japan, and the European Union. AI: adequate intake.

	USA		AUS/NZ		China		Japan		EU	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0–6 mon	0.27 (AI)		0.2 (AI)		0.3		0.4		–	
7–12 mon	11		11		10		6		6.2	
1–3 yr	7		9		12		5.5	6	3.9	
4–8 yr	10		10		12		6.5	8.5	4.2	
9–13 yr	8	8	8	8	16	18	11	13	9.7	21.8
14–18 yr	11	15	11	15	20	25	10.5	11	12.5	20.7
19–30 yr	8	18	8	18	15	20	7.5	10.5	9.1	19.6
31–50 yr	8	18	8	18	15	20	7.5	10.5	9.1	19.6
50–70 yr	8	8	8	8	15	15	7.5	10.5	9.1	7.5
> 70 yr	8	8	8	8	15	15	6.5	10.5	9.1	7.5
Pregnancy:										
< 18 yr		27		27		15		24		30
19–30 yr		27		27		25		24		30
31–50 yr		27		27		35		24		30
Lactation:										
< 18 yr		10		10		25		13.5		10
19–30 yr		9		9		25		13		10
31–50 yr		9		9		25		13		10

selenium (Table 6.4). These tables provide an overview of the RDA for people in different life stages and gender groups as well as data for pregnant and lactating women.

Perspectives

Normal dietary levels of various essential metal ions are required to prevent the occurrence of metal deficiencies. The RDA provides the public nutritional advice. Used properly, it can also inform intervention strategies to address metal deficiency and achieve metal ion sustenance as well as to reduce the risk of some diseases, including infectious diseases.

The important point that we wish to emphasize is that it is necessary for RDA users to have a thorough knowledge of major concepts in the DRI system. For example, estimated average requirements is a concept used to represent the estimated median requirement (half of healthy individuals) and is particularly appropriate for applications related to planning and assessing intakes for groups of persons. RDA is derived from the estimated average requirement

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Table 6.2 Recommended dietary allowances for zinc (mg/day) per individual, for populations from different countries: United States, Australia and New Zealand (combined), China, Japan, and the European Union.

	USA		AUS/NZ		China		Japan		EU	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0–6 mon	2 (AI)		2 (AI)		1.5		2		–	
7–12 mon	3		3		8		3		4	
1–3 yr	3		3		9		4		4	
4–8 yr	5		4		12		5		6	
9–13 yr	8	8	6	6	18	15	6	7	9	9
14–18 yr	11	9	13	7	19	15.5	8	7	9	7
19–30 yr	11	8	14	8	15	11.5	9	7	9	7
31–50 yr	11	8	14	8	15	11.5	9	7	9	7
50–70 yr	11	8	14	8	11.5	11.5	9	7	9	7
> 70 yr	11	8	14	8	11.5	11.5	8	7	9	7
Pregnancy:										
< 18 yr	12		10		11.5		10		7	
19–30 yr	11		11		16.5		10		7	
31–50 yr	11		11		16.5		10		7	
Lactation:										
< 18 yr	13		11		21.5		10		12	
19–30 yr	12		12		21.5		10		12	
31–50 yr	12		12		21.5		10		1	

(EAR) and covers requirements for 97% of the population. UIL is the highest average intake that is likely to pose no risk of adverse health effects to almost all individuals (discussed in detail below), whereas average intake is used when an EAR/RDA cannot be developed; average intake level is based on observed or experimental intakes.

Despite the emphasis on the population basis of the RDA, RDA has often been misused to assess dietary adequacy in individuals. In fact, RDA is a general guide designed to assist the public or nutrition and health professionals in assessing the dietary requirements of individuals. The recommendations are used for healthy people and may not meet the specific nutritional requirements of all individuals.

Tolerable Upper Intake Levels

Tolerable UILs are defined as the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UIL, the risk of adverse

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Table 6.3 Recommended dietary allowances for copper (mg/day) per individual, for populations from different countries: United States, Australia and New Zealand (combined), China, Japan, and the European Union.

	USA		AUS/NZ		China		Japan		EU	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0–6 mon	0.2 (AI)		0.2 (AI)		0.4		0.3		–	
7–12 mon	0.22		0.22		0.6		0.3		0.3	
1–3 yr	0.34		0.7		0.8		0.3		0.4	
4–8 yr	0.44		1		1		0.4		0.7	
9–13 yr	0.7	0.7	1.3	1.1	1.8	1.8	0.7	0.7	0.8	0.8
14–18 yr	0.89	0.89	1.5	1.1	2	2	0.9	0.7	1	1
19–30 yr	0.9	0.9	1.7	1.2	2	2	0.8	0.7	1	1
31–50 yr	0.9	0.9	1.7	1.2	2	2	0.8	0.7	1	1
50–70 yr	0.9	0.9	1.7	1.2	2	2	0.8	0.7	1	1
> 70 yr	0.9	0.9	1.7	1.2	2	2	0.8	0.7	1	1
Pregnancy:										
< 18 yr	1		1.2		2		0.8		1.1	
19–30 yr	1		1.3		2		0.8		1.1	
31–50 yr	1		1.3		2		0.8		1.1	
Lactation:										
< 18 yr	1.3		1.4		2		1.3		1.4	
19–30 yr	1.3		1.5		2		1.3		1.4	
31–50 yr	1.3		1.5		2		1.3		1.4	

effects (including any significant alteration in the structure or function of the human organism or any impairment of a physiologically important function) increases. Therefore, UIL is used to examine the possibility of excessive intake of nutrients that can be harmful in large amounts. The term "tolerable" indicates a level of intake that can, with high probability, be tolerated biologically by individuals. However, it does not imply acceptability of that level in any other sense, which indicates that upper intake levels do not mean that nutrient intakes greater than the RDA or AI are recommended as being beneficial to an individual.

Essential Metal Ions per Individual for Populations in Different Countries

The value of the UIL for the essential metal ions varies in different countries. The scientific data used to develop the UIL derive, in fact, from observational and experimental studies of different countries; life stages and gender of the population were also considered to the fullest extent possible. Here we

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Table 6.4 Recommended dietary allowances for selenium (μg/day) per individual, for populations from different countries: United States, Australia and New Zealand (combined), China, Japan, and the European Union.

	USA		AUS/NZ		China		Japan		EU	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0–6 mon	15 (AI)		12 (AI)		15		16		–	
7–12 mon	20		15		200		19		8	
1–3 yr	20		20		20		9	8	10	
4–8 yr	30		30		25		15	15	20	
9–13 yr	40	40	50	50	40	40	20	20	35	35
14–18 yr	55	55	70	60	50	50	30	25	45	45
19–30 yr	55	55	70	60	50	50	30	25	45	45
31–50 yr	55	55	70	60	50	50	35	25	45	45
50–70 yr	55	55	70	60	50	50	30	25	45	45
> 70 yr	55	55	70	60	50	50	30	25	45	45
Pregnancy:										
< 18 yr		60		65		50		29		55
19–30 yr		60		65		50		29		55
31–50 yr		60		65		50		29		55
Lactation:										
< 18 yr		70		75		60		45		70
19–30 yr		70		75		60		45		70
31–50 yr		70		75		60		45		70

summarize the UIL for people in the United States, Australia/New Zealand combined, China, Japan, and the European Union for iron (Table 6.5), zinc (Table 6.6), copper (Table 6.7), and selenium (Table 6.8). These tables provide an overview of the UIL for people in different life stages and gender groups as well as data for pregnant and lactating women.

Perspectives

The UIL is the highest level of daily consumption that current data have shown to cause no side effects in humans when used indefinitely without medical supervision. It is thus an important part of the intervention strategies for metal overload. Many individuals self-medicate with nutrients for curative or treatment purposes. However, it is impossible to identify a "risk-free" intake level for a nutrient that can be applied with certainty to all members of a population. Despite its inclusion of sensitive individuals (e.g., pregnant and lactating women), the UIL is a general guide for most members of the general population. It should be applied properly, especially for those who live in areas with metal pollution.

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Table 6.5 Tolerable upper intake levels for iron (mg/day) per individual, for populations from different countries: United States, Australia and New Zealand (combined), China, Japan, and the European Union.

	USA		AUS/NZ		China		Japan		EU	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0–6 mon	40		20		10		–		–	
7–12 mon	40		20		30		–		–	
1–3 yr	40		20		30		25	–	–	
4–8 yr	40		40		30		30	8.5	–	
9–13 yr	40	40	40	40	50	50	35	35	–	–
14–18 yr	45	45	45	45	50	50	50	50	–	–
19–30 yr	45	45	45	45	50	50	50	50	50	50
31–50 yr	45	45	45	45	50	50	55	55	50	50
50–70 yr	45	45	45	45	50	50	50	50	50	50
> 70 yr	45	45	45	45	50	50	45	45	50	7.5
Pregnancy:										
< 18 yr		45		45		50		50		50
19–30 yr		45		45		50		50		50
31–50 yr		45		45		50		50		50
Lactation:										
< 18 yr		45		45		50		50		50
19–30 yr		45		45		50		50		50
31–50 yr		45		45		50		50		50

Most metals, whether essential or not, can produce adverse health effects if intakes are excessive. Metal ions can be obtained from any combination of food, water, or nonfood sources (e.g., nutrient supplements and pharmacologic agents). Moreover the setting of the UIL is based on nutrients as part of the total diet. Therefore, nutrient supplements, which are usually taken separately from food, require special consideration due to wide-ranging factors surrounding their intake. As a result, nutrient supplements may produce toxic effects. The addition of essential metal ions to a diet—through the ingestion of large amounts of highly fortified food or nonfood sources such as supplements—may pose a risk for adverse health effects.

Bioavailability

Bioavailability, one of the essential tools in pharmacology and nutritional science, is a subcategory of absorption and is defined as the fraction of an administered dose of unchanged drug that reaches the systemic circulation. In general, it can be described as absolute bioavailability or relative bioavailability.

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Table 6.6 Tolerable upper intake levels for zinc (mg/day) per individual, for populations from different countries: United States, Australia and New Zealand (combined), China, Japan, and the European Union.

	USA		AUS/NZ		China		Japan		EU	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0–6 mon	4		4		–		–		–	
7–12 mon	5		5		13		–		–	
1–3 yr	7		7		23		–		7	
4–8 yr	12		12		23		–		11	
9–13 yr	23	23	25	25	37	34	–	–	18	18
14–18 yr	34	34	35	35	42	35	–	–	22	22
19–30 yr	40	40	40	40	45	37	30	30	25	25
31–50 yr	40	40	40	40	45	37	30	30	25	25
50–70 yr	40	40	40	40	37	37	30	30	25	25
> 70 yr	40	40	40	40	37	37	30	30	25	25
Pregnancy:										
< 18 yr	34		35		35		30		25	
19–30 yr	40		40		35		30		25	
31–50 yr	40		40		35		30		25	
Lactation:										
< 18 yr	34		35		35		30		25	
19–30 yr	40		40		35		30		25	
31–50 yr	40		40		35		30		25	

Absolute bioavailability compares the bioavailability of an active drug in systemic circulation following non-intravenous administration (such as oral, rectal, transdermal, subcutaneous, or sublingual administration) with the bioavailability of the same drug following intravenous administration. It is the fraction of the drug absorbed through non-intravenous administration compared with the corresponding intravenous administration of the same drug. Therefore, a drug given by the intravenous route will have an absolute bioavailability of 100%, whereas drugs given by other routes usually have an absolute bioavailability of less than 100%, due to incomplete absorption and first-pass metabolism.

Relative bioavailability measures the bioavailability of one formulation of a certain drug when compared with another formulation of the same drug, usually an established standard, or through administration via a different route. By definition, when the standard consists of intravenously administered drug, this is known as absolute bioavailability.

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Table 6.7 Tolerable upper intake levels for copper (mg/day) per individual, for populations from different countries: United States, Australia and New Zealand (combined), China, Japan, and the European Union.

	USA		AUS/NZ		China		Japan		EU	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0–6 mon	–		–		–		–		–	
7–12 mon	–		–		–		–		–	
1–3 yr	1		1		1.5		–		1	
4–8 yr	3		3		2		–		2	
9–13 yr	5	5	5	5	5	5	–	–	4	4
14–18 yr	8	8	8	8	7	7	–	–	4	4
19–30 yr	10	10	10	10	8	8	10	10	5	5
31–50 yr	10	10	10	10	8	8	10	10	5	5
50–70 yr	10	10	10	10	8	8	10	10	5	5
> 70 yr	10	10	10	10	8	8	10	10	5	5
Pregnancy:										
< 18 yr		8		8		8		10		5
19–30 yr		10		10		8		10		5
31–50 yr		10		10		8		10		5
Lactation:										
< 18 yr		8		8		8		10		5
19–30 yr		10		10		8		10		5
31–50 yr		10		10		8		10		5

Bioavailability of Different Forms of Metal Elements

Supplements of metal elements are available in a wide variety of forms: inorganic salts, organic salts, amino acid chelates, and yeast form. Inorganic salts (such as sulfates and carbonates) and organic salts (such as citrates and gluconates) are the most commonly used forms. In contrast, the amino acid chelates are formed by hydrolysis of protein. The reaction of the resulting amino acids with an inorganic salt supposedly forms a chelate of the metal with the ligands of the amino acids. The resulting yeast is produced by growing yeast in a nutrient medium containing the inorganic salt. In theory, the yeast absorbs the element by forming a natural chelate between the metal ions and the proteins or amino acids of the yeast.

Table 6.9 summarizes the bioavailability of different forms of iron, zinc, copper, selenium, and manganese in the blood and liver from humans and/or rats.

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Table 6.8 Tolerable upper intake levels for selenium (mg/day) per individual, for populations from different countries: United States, Australia and New Zealand (combined), China, Japan, and the European Union.

	USA		AUS/NZ		China		Japan		EU	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0–6 mon	45		45		55		–		–	
7–12 mon	60		60		80		–		–	
1–3 yr	90		90		120		200		60	
4–8 yr	150		150		180		200		90	
9–13 yr	280	280	280	280	300	300	300	300	200	200
14–18 yr	400	400	400	400	360	360	400	350	250	250
19–30 yr	400	400	400	400	400	400	450	350	300	300
31–50 yr	400	400	400	400	400	400	450	350	300	300
50–70 yr	400	400	400	400	400	400	450	350	300	300
>70 yr	400	400	400	400	400	400	400	350	300	300
Pregnancy:										
<18 yr	400		400		400		350		300	
19–30 yr	400		400		400		350		300	
31–50 yr	400		400		400		350		300	
Lactation:										
<18 yr	400		400		400		350		300	
19–30 yr	400		400		400		350		300	
31–50 yr	400		400		400		350		300	

Perspectives

Treatment of metal deficiency or overload often involves supplementation of missing metal ions or metal ion chelating agents. Bioavailability is one of the key factors in the assessment of supplementation effects. For dietary supplements, the route of administration is nearly always oral. Therefore, bioavailability influences a nutrient's beneficial effects at the physiological level of intake. It may also affect the nature and severity of toxicity due to excessive intake.

Bioavailability varies from individual to individual. There are many factors that influence the utilization of metal elements, including the concentration and chemical form of the metal elements, the nutrition and health of the individual, the gut flora, and excretory losses. Some metals may be less readily absorbed when they are part of a meal than when they are ingested separately. Most importantly, supplemental forms of some metals (e.g., magnesium) may require special consideration due to their higher bioavailability and may therefore present a higher risk of producing adverse effects than equivalent amounts from the natural form found in food.

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Table 6.9 Relative bioavailability of different forms of common trace metal elements. Note: for all studies, the inorganic salt is defined as 100% bioavailable.

Metal Elements	Model	Forms	Relative Bioavailability (%)	
			Blood	Liver
Iron	Rat	Inorganic Salt	100	100
		Chelate	57	72
		Yeast	101	121
Zinc	Rat	Inorganic Salt	100	100
		Chelate	101	129
		Yeast	172	187
	Human	Inorganic Salt	100	
		Organic Salt	111	
		Yeast	175	
Copper	Rat	Inorganic Salt	100	100
		Organic Salt	93	130
		Yeast	124	195
	Human	Inorganic Salt	100	
		Chelate	101	
		Yeast	144	
Selenium	Rat	Inorganic Salt	100	100
		Chelate	60	146
		Yeast	122	226
	Human	Inorganic Salt	100	
		Chelate	122	
Manganese	Rat	Inorganic Salt	100	100
		Chelate	111	142
		Yeast	156	163

Implications and Future Areas for Attention

Although metal deficiency and overload have gained worldwide attention, finding effective intervention strategies to prevent and treat the matter is still an arduous task for the government, scholars, and general public.

> *Advocacy and training strategies are powerful tools to increase public knowledge of metal homeostasis and decrease the morbidity and mortality related to metal deficiency and overload.*

Indeed, many individuals are self-medicating with nutrients for health or treatment purposes. Although government agencies in many countries have been providing nutritional advice (RDI system) to the public for several decades, most people misuse the data on the RDA, UIL, and bioavailability (discussed above), due to lack of a full understanding of the guidelines, or even without any knowledge of the guidelines. This situation makes it urgent

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for governments and academic institutions to provide related information, including recent developments in nutritional research, through various publicity approaches such as media, websites, and training programs. To this end, in 2013 we organized the first "Westlake Frontiers in Nutrition Research Training Program" in Hangzhou, China. Designed to provide a perennial platform of exchange for Chinese and overseas nutritional professionals, the program was a huge success. It is hoped that it will become an instrumental component to advance the health of all Chinese people.

Environmental influences on both metal deficiency and overload cannot be ignored.

Minamata disease, endemic in Japan, is a typical example of metal overload: large-scale food poisoning is caused by methylmercury. In November 2010, 2,271 patients were officially diagnosed as having Minamata disease; estimates, however, place the number of people from affected areas, who exhibit neurologic signs of methylmercury poisoning, in the tens of thousands (Yorifuji et al. 2013). The bioaccumulation and biomagnifications of heavy metals such as mercury, lead, and cadmium pose a serious, continuous risk for human health because they are nondegradable. Therefore, given the fast growth of the economic industry (e.g., the market of fluorescent lamps that use mercury as an essential component), heavy metal exposure is expected to gain a high degree of public attention.

Keshan disease, an endemic heart disease in China, is a typical example of metal deficiency. Extensive cross-sectional epidemiological studies have shown that low Se concentrations in cereal grains and low Se status of local residents are associated with the occurrence of Keshan disease. Several large population-based intervention trials, using oral administration of sodium selenite tablets, have shown significant reduction in the incidence of Keshan disease (Chen 2012). It is thus imperative to identify deficiencies of essential metal elements in different areas, especially mild levels of metal deficiencies, which are more difficult to recognize than severe and moderate deficiencies. Certainly, data from these endemic diseases provide a scientific basis for identifying the minimum requirement, RDA, or UIL for certain metal elements.

Metal–metal interaction is an important matter of concern.

The metabolism and transport of metal ions is a complex process that takes place in numerous transporters in mammals. An example of a typical metal ions transporter can be found in the divalent metal ion transporter 1 (DMT1), which transports not only iron but also zinc, copper, manganese, cobalt, nickel, and the toxic metal ions lead and cadmium. Therefore, any strategy designed to address metal deficiency and overload must take DMT1 into account. Excessive intake or deficiency of one metallic element may interfere with absorption, excretion, transport, storage, function, or metabolism of other metals. Recently, Graham et al. (2012) showed that Fe deficiency—the most common

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metal deficiency affecting nearly 2 billion people worldwide—may be due to underlying zinc and other trace metal deficiencies. Moreover, Fe deficiency has become a risk factor for cadmium toxicity since it causes increases in tissue cadmium levels (Min et al. 2008). Nutrition and health status may vary from individual to individual, and especially between people living in different areas, due to variations in environmental influence. People obtain metal ions from any combination of food (including highly fortified food), water, and nonfood sources (e.g., nutrient supplements and pharmacologic agents). Imbalances among the concentrations of metal elements may pose a risk for adverse health effects in almost every individual. In addition, the bioavailability and effect of fortified foods or supplements may differ from the natural constituents of foods.

Regulating the endogenous distribution of metal ions is a vital therapeutic strategy for treating diseases with metal homeostasis imbalance.

It must be kept in mind that some diseases related to metal deficiency or overload are caused by an inappropriate distribution of metal ions in organs or cell compartments. Using Alzheimer disease as an example, an increasing amount of evidence has demonstrated abundant distribution of Zn ions in the plaques of brains of people with the disease; this indicates an overload of Zn ions in the brain. Metal chelator treatment with clioquinol has provided significant evidence of slowing cognitive deterioration (Adlard et al. 2008). Surprisingly, metal chelator treatment increased the brain Zn level (Cherny et al. 2001); in contrast, low dietary zinc caused a significant 25% increase in total plaque volume in Alzheimer mice using stereological measures (Stoltenberg et al. 2007). Further studies demonstrated that clioquinol and PBT are ionophores that promote the transport of zinc, iron, and copper across cell membranes (Adlard et al. 2008). Furthermore, an imbalance between "soluble" and "insoluble" metal ions (such as Cu^{2+}) is also a likely cause for diseases with metal homeostasis imbalance (Faller 2012). Therefore, any strategy for treatment of diseases related to metal deficiency and overload should take this into account.

Further understanding of metal elements and the mechanisms of metal deficiency or overload is of great importance to the development and design of metal-based drugs.

Knowledge of metal–metal interactions has been used successfully as a treatment strategy. In the case of Cu overload in Wilson disease, treatment with zinc has been demonstrated as very effective in preventing symptoms. Take iron for example: the identification of hepcidin as a key regulator of Fe absorption and Fe distribution in health and disease has greatly advanced our understanding of Fe homeostasis in humans and, in turn, has promoted the development of drugs aimed at decreasing Fe overload. Hepcidin mimetics, minihepcidins, have been shown to be effective in reducing Fe overload (Ramos et al. 2012).

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Natural plant extracts may provide opportunities for a new intervention strategy to address metal deficiency and overload.

It is generally more difficult to absorb metal ions (e.g., iron) from plant matter than it is from animal sources. Since ancient times, empirical dietary therapies for treating a wide variety of diseases, including Fe-deficiency anemia, emerged in both traditional Chinese medicine and dietary culture. The contradiction between absorption from plant and animal sources indicates a mechanism that requires analysis. It may account for significant sources of dietary metal and play a key role in regulating the metal homeostasis. To pursue this, we recently screened 16 different medicinal plant extracts used to treat anemia-related disorders in traditional Chinese medicine and identified the extract of Caulis Spatholobi (also called Jixueteng, the stem of *Spatholobus suberectus* Dunn) as a novel, potent hepcidin-encoding gene (HAMP) expression inhibitor. This extract could be modified and optimized into a dietary supplement or a therapeutic option for the amelioration of hepcidin-overexpression-related diseases, including Fe-deficiency anemia (Guan et al. 2013). Of further interest, recent studies in our laboratory on the molecular mechanisms of "black foods" (i.e., foods that are black in color) inducing erythropoiesis have shown that the black soybean extract regulates Fe metabolism by inhibiting the expression of hepcidin (Mu et al. 2014). These findings reveal the potency of natural plants in regulating Fe homeostasis and are bound to attract valuable research into natural plants and their regulation of other metal ions in homeostasis, hence, the prevention and treatment for diseases related to metal deficiency and overload.

In conclusion, metal deficiency and overload have become a major problem affecting billions of people worldwide. Whether metal deficiency and overload are seen as the cause or result of infectious, neurodegenerative, or immune system diseases, intervention strategies offer new insights into the prevention and treatment of these diseases.

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