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Impact of Lifestyle on Metal Exposure, Homeostasis, and Associated Diseases

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Abstract

Unhealthy lifestyle factors (e.g., cigarette smoking, excessive alcohol drinking, long working hours, reduced sleep, physical inactivity, obesogenic diets) and psychological stress contribute to cardiovascular disease, cancer, and other causes of mortality in industrialized countries. Many of these factors correlate with alterations in the homeostasis of trace metals, which play an important role in human health and are essential for human antioxidant defense and immune function. Metal levels consumed by humans are influenced by the mineral composition of soil used to grow food as well as weather conditions, the composition of water for irrigation, and agricultural practices (e.g., types and amounts of fertilizers used). In some cases, major sources of trace metals derive from environmental pollution that results from industrial and other anthropogenic activities (e.g., cadmium from agricultural fertilizers). Food processing and packaging also play a role (e.g., aluminum and tin from canned foods). Although some individuals encounter toxic metals mainly in the workplace, for most people primary exposure of toxic and essential metals occurs through diet. The most common foods in our diet that contain metals are fish and seafood (mercury, copper and zinc), vegetables and grains (cadmium, magnesium, and molybdenum), chocolate and coffee (cobalt, copper, and nickel), fruit (lead), nuts (selenium), and mushrooms (vanadium). This chapter discusses the impact that lifestyle has on exposure to metals, homeostasis, and associated diseases.

Introduction

As of conception and throughout life, humans experience a broad range of physical, chemical, and biological exposures to heavy metals. The health effects of these exposures depend not only on dose but also on how they interact with each other as well as the characteristics of the individual (e.g., age, sex, genotype). Trace metals are ubiquitous environmental pollutants with known toxic properties. Human exposure to these chemicals may occur occupationally, environmentally, or through dietary intake. In the general population, food and water are the most common metal sources, while cigarette smoking is an additional relevant source of exposure to trace metals such as cadmium (Cd) and chromium (Cr). The relationship between chemical elements in rainwater and the frequency of hospitalizations for gastric and duodenal peptic ulcers as well as for chronic myeloid leukemia (CML) was studied on the population of the province of Opole, Poland during the years 2000–2002. A high positive correlation was found between hospitalized cases of gastric peptic ulcers or CML in women exposed to cadmium and lead contained in rainwater (Szygula et al. 2011; Tubek et al. 2011). Gender is a factor that affects the impact of trace metal exposure. For instance, statistically higher amounts of silver (Ag), manganese (Mn), and lead (Pb) have been found in females in some communities. This has been attributed to traditional lifestyles: wearing large amounts of Ag jewelry, cooking with colored Al pots and kitchen utensils glazed with trace metals (Sela et al. 2013). The impact of cooking on trace metal exposure was recently demonstrated through the pan-frying and grilling of fish and shellfish: cooked products had elevated metal concentrations compared to the fresh uncooked specimens (Kalogeropoulos et al. 2012). The cooked marine species studied were shown to be good sources of the essential metals iron (Fe), zinc (Zn), and chromium and also contained low enough levels of the toxic metals cadmium, mercury, and lead so as not to pose a health risk to the consumer.

Fetuses and neonates are especially vulnerable to toxic chemicals because of the immaturity of their detoxification systems. Intake of trace metals per unit of body weight, however, is generally higher in children than in adults (Marti-Cid et al. 2007). A large number of epidemiological studies have associated early exposure to lead, mercury, arsenic (As), and cadmium with infant health effects, including neurological (Wright et al. 2006), developmental (Gundacker et al. 2010), and endocrine disorders (Stasenko et al. 2010). However, micronutrient malnutrition seriously threatens the health and productivity of more than 2 billion people worldwide. Fortification of foods offers one way to address micronutrient deficiencies in a cost-effective manner (Darnton-Hill et al. 2002). In addition, during storage or baking, it does not pose any risk of substantial deteriorative effects on native mineral contents in whole wheat flour—a highly preferred food carrier for the fortification of minerals in the developing world.

Social and environmental epidemiologists underline the synergies between the biochemical environment and the social environment and stress the importance of exploring the role of environmental pollution as a contributing factor in health disparities (O’Neill et al. 2007). The socio-spatial distribution of environmental quality reveals that poor people and deprived communities experience accumulated exposure to multiple, suboptimal environmental conditions (Evans and Kantrowitz 2002): proximity to hazardous waste facilities and busy roads, flood risk, and air quality (Walker and Burningham 2011). For trace metals, negative associations have also been found between socioeconomic status and internal concentrations of lead (Elreedy et al. 1999) and cadmium (McKelvey et al. 2007) in adult populations in the United States. The negative relation between socioeconomic status and cadmium or lead (where higher socioeconomic status equals lower exposure) may largely be explained by age, gender, smoking behavior, and the residential area of the adolescent (Morrens et al. 2012).

Hair is considered a suitable biomarker of chronic exposure to many toxic elements (Ag, Al, As, Au, Cd, Cr, Cu, Fe, Hg, Mn, Ni, Pb, Se, Tl, and Zn) and can thus be applied to environmental biomonitoring and forensic medicine (Ochi et al. 2011). This technique was employed in a recent study by Dongarra et al. (2012), conducted in Sicily, and demonstrates how trace mineral levels measured in children's scalp hair varied as a result of environmental contexts. For example, a significant percentage (10–30%) of hair samples taken from one site was found to contain concentrations of aluminum, rubidium, lead, arsenic, and uranium that exceeded the coverage intervals. This is not surprising, since the rocks and therefore soils from this area contain polymetallic sulphosalt/sulfide mineralizations. Facilitated by the considerable presence of CO_2 in solution, the volcano Mount Etna contains concentrations of chromium, antimony, nickel, uranium, and zinc in concentrations that are far higher than those commonly found in Sicilian groundwater (Dongarra et al. 2012).

It is well known that during infection, along with immune system activation, a sequential series of alterations in metabolism occurs, including changes in trace element balance (Corbin et al. 2008). The host's acute response to infection generally includes increased synthesis of metal-binding proteins and a concomitant flux of trace elements between blood and tissues. Necessary for the proper functioning of the immune system, metal ions may have a significant influence on the interaction between bacteria and host. Below I present a short description of the most common trace metals as well as their relation with dietary intake and, when data are available, lifestyle and human activities.

Arsenic

Human exposure to inorganic arsenic, a known carcinogen, occurs predominately through diet and drinking water. Early in pregnancy, moderate exposure to As-contaminated drinking water has been associated with an increased risk for experiencing nausea, vomiting, and abdominal cramping (Kile et al. 2014). Studies in mice have shown that As exposure during pregnancy reduced the clearance of and exacerbated the inflammatory response to influenza A, and resulted in acute and long-term changes in lung mechanics and airway structure (Ramsey et al. 2013). Long-term exposure to high levels of arsenic is associated with increased risk for cardiovascular disease and mortality, although the risk from long-term exposure to low or moderate As levels (< 100 μg/l in drinking water) is unclear. Dietary exposure to organic forms of arsenic occurs primarily through the ingestion of seafood. Many researchers have reported that urinary dimethylated As levels are increased by seafood intake. In Korea, seaweed is consumed by itself as an ingredient in soup stock and processed foods. Thus, Korean dietary habits may be responsible for the increased urinary dimethylated As levels that have been reported within this population (Lee et al. 2012). Seaweed is also consumed in other Asian countries (e.g., Japan and China). Accordingly, urinary dimethylated As levels may be higher in East Asian countries than in Europe and North America.

Cadmium

Cadmium, a toxic and carcinogenic heavy metal, is released into the environment as a result of industrial and agricultural activities (Jarup and Akesson 2009). Multiple mechanisms potentially link cadmium with carcinogenesis, including oxidative stress and inflammation (Lag et al. 2010), interference with DNA repair (Asmuss et al. 2000), and alterations of DNA methylation (Takiguchi et al. 2003). Recently it was suggested that HIV-infected patients have higher levels of cadmium in their blood when compared to non-HIV infected individuals, although the cause of this accumulation remains undetermined. Increased levels of cadmium in HIV-infected individuals could contribute to the higher prevalence of chronic diseases among these subjects (Xu et al. 2013). In addition, Cd-induced oxidative stress directly increases the ability of influenza virus to replicate in host cells, thus suggesting that exposure to heavy metals could result in increased severity of virus-induced respiratory diseases (Checconi et al. 2013).

Smoking is a major source for Cd exposure (Bjermo et al. 2013). However, diet can significantly influence Cd uptake. Mollusks, crustaceans, cereals, bread, potatoes, and leafy vegetables have been described as the major dietary Cd sources. Together, vegetables and grains contribute daily, on average, 66% of estimated dietary cadmium. Higher Cd levels have been observed in individuals who consume less discretionary foods (i.e., sweets, bakery products, processed meats, snack foods, etc.) (Bjermo et al. 2013). These individuals may have a healthier lifestyle because of their higher fiber intake, as another observational study (Berglund et al. 1994) demonstrated that high fiber intake inhibited the gastrointestinal absorption of cadmium.

Women are known to be more significantly impacted by Cd exposure than men. Although only approximately 5% of cadmium ingested through food is actually absorbed, Cd absorption is potentiated by low Fe stores. Lower Fe stores of women may, in part, be the reason that women are consistently observed to have higher average urine and blood Cd concentrations (Akesson et al. 2002). Cadmium and Fe homeostasis have been linked by other studies.

For example, plasma ferritin levels were inversely related with cadmium. This is probably due to the up-regulation of transporters caused by low Fe stores influencing Cd absorption (Vahter et al. 2007).

In addition to the gender-specific differential accumulation of cadmium observed by previous studies, Cd levels within the human body are influenced by other biological factors. For example, Cd levels increase with age. This is primarily an effect of the very long half-life at which this element is retained within the human body. A recent study (Ellis et al. 2012) has shown evidence that an NMR-based metabolic profiling strategy in an uncontrolled human population is capable of identifying intermediate biomarkers of response to toxicants at true environmental concentrations. In particular, citrate levels retained a significant correlation to urinary cadmium and smoking status after controlling for age and sex. Oxidative stress (as determined by urinary 8-oxo-deoxyguanosine levels) was elevated in individuals with high Cd exposure, thus supporting the hypothesis that trace metal accumulation causes mitochondrial dysfunction.

Cobalt

Cobalt (Co), an essential element, is a central bonding atom for vitamin B12 (also called cobalamin), which is necessary for the metabolism of folates and fatty acids. The biological functions and activities of cobalt play a role in erythropoiesis, the regulation of various phosphoprotein phosphatases, and as a substitute for zinc in metalloenzymes. Recently, Hoffman et al. (2013) demonstrated that certain Co(II) and Cu(II) metal-based complexes possess antimicrobial action with notable selectivity and marked potency against *Mycobacterium tuberculosis*, including multidrug-resistant strains. These complexes were confirmed to be bacteriocidal and not affected by efflux inhibitors.

In food of animal origin, cobalt is found as cobalamin, whereas in plants it is present in an inorganic form. The gastrointestinal absorption of cobalt in humans is highly variable (18–97%), depending on its chemical form. The highest mean concentrations are found in chocolate (0.139 mg/kg), offal (0.091 mg/kg), and butter (0.046 mg/kg). The mean exposure of a French population to cobalt was estimated at 0.18 μg/kg/day in adults and 0.31 μg/kg/day in children. The main contributor to cobalt intake in adults was coffee (11%). For children, chocolate was the main contributor (12%) (Arnich et al. 2012). While no Co deficiency has been shown in humans, excess Co exposure could be detrimental. In humans, cardiomyopathies were reported in the 1960s in heavy drinkers of beer to which Co had been added as a foam stabilizer. It was calculated that these drinkers had ingested an average of 0.04–0.14 mg Co/kg/day for several years. However, the risk that has been associated with dietary exposure to cobalt does not seem to constitute a major public health issue with regard to threshold effects.

Copper

Copper (Cu) is an essential redox active metal that is potentially toxic in excess. Multicellular organisms acquire copper from the diet and must regulate Cu uptake, storage, distribution, and export at both the cellular and organismal levels. Systemic Cu deficiency can be fatal, as seen in Menkes disease patients. Conversely, Cu toxicity occurs in patients with Wilson disease. In addition, Cu dyshomeostasis has been implicated in neurodegenerative disorders such as Alzheimer disease. It has been reported that smoking increases plasma levels of copper and that these levels are positively correlated with Cu/Zn-SOD activity. Both plasma Cu and Cu/Zn-SOD activities have been shown to increase in response to the chronic inflammation of the respiratory tract found in smokers (Northrop-Clewes and Thurnham 2007).

In addition to environmental factors, such as smoking, there are several significant dietary sources of copper. In a recent study, Cu, Mn, Se, and Zn levels were determined in fresh, canned, and frozen fish and shellfish products (Olmedo et al. 2013). The highest concentrations of copper were found in crustacean species (shrimp and prawn), as they have hemocyanin (a Cu-containing protein) which functions as an oxygen transport molecule. Data from the Nutrient Data Laboratory of the U.S. Department of Agriculture indicate that dark chocolate ranges from 1.0 to 1.8 mg Cu/100 g, depending on the content of cocoa solids. Thus 100 g of dark chocolate can provide more than the recommended dietary allowance (RDA) of copper (0.9 mg), and the darkest chocolate can double that amount. Even when diluted with sugar and milk, chocolate can provide an appreciable supplement of copper.

Copper plays an important role in public health. A considerable body of evidence from laboratory-based studies demonstrates that Cu alloys are efficacious against a diverse range of pathogenic microorganisms. Early studies demonstrated a rapid killing of *Escherichia coli* O157, *Listeria monocytogenes*, and methicillin-resistant *Staphylococcus aureus* in the presence of copper (Noyce et al. 2006; Wilks et al. 2006; Warnes et al. 2012). This was followed by observations that both vegetative cells and spores of virulent toxin-producing *Clostridium difficile*, which is responsible for numerous hospital-acquired infections, were destroyed after Cu treatment (Weaver et al. 2008).

It was previously demonstrated that a family of small peptides called trefoil factors (TFFs), implicated in the maintenance of the integrity of gastrointestinal tissue, are able specifically to bind Cu ions at the carboxy-terminus and that Cu binding favors the homodimerization of the peptide, thus enhancing its motogenic activity (Tosco et al. 2010b). The finding that copper can influence expression (Tosco et al. 2010a), biological activity, and structure of TFF1 prompted researchers to use copper to investigate the effect of homodimerization of TFF1 on the interaction between *Helicobacter pylori* and the peptide (Montefusco et al. 2013). Thus, it was demonstrated that the Cu-TFF1 complex promotes *H. pylori* colonization of gastric epithelial cells and a mucus-secreting cell line (Montefusco et al. 2013).

Iron

The adult human body contains 3–4 g of iron, approximately 70% of which is present in hemoglobin (Hb) in red blood cells and myoglobin in muscle. Iron is instrumental for the transport of oxygen around the body and is an essential component of many enzymes, such as cytochromes, where it plays a role in electron transport, respiration, and hormone synthesis. Iron deficiency affects almost 50% of the population worldwide, making it the most common nutritional deficiency (Zimmermann and Hurrell 2007). Iron-deficiency anemia is the end state of Fe deficiency, and there is a clear gender difference with Fe deficiency being most prevalent among women (Zimmermann and Hurrell 2007). Recently, it was demonstrated that *H. pylori* infection in children influences the serum ferritin and Hb concentrations, markers of early depletion of Fe stores and anemia, respectively (Queiroz et al. 2013). In addition, Fe overload is associated with significant morbidity and mortality. Abnormal accumulation of brain iron has been detected in various neurodegenerative diseases, but the contribution of Fe overload to pathology remains unclear (Rouault 2013).

Good food sources of iron include meat and meat products that contain heme Fe, especially red meat and offal as well as dark poultry meat, oily fish (e.g., tuna and sardines), cereal products (e.g., fortified breakfast cereals), eggs, and dark green vegetables. Since vegetarians do not consume meat, their main sources of iron must come from fortified cereals, soybeans, tofu, lentils, kidney beans, chickpeas, baked beans, and dark green vegetables. Bread, potatoes, and dried fruit are also a useful source of iron. For elderly people, obtaining an adequate supply of iron may be a challenge due to impaired absorption, reduced food intake associated with lower physical activity, and changes in dietary patterns that result in a more limited diet.

In addition to dietary sources impacting Fe stores within humans, other environmental and biological factors affect Fe levels. For example, it is known that serum Fe decreases during active training; this is probably due to the inflammatory response of physical activity (Peeling et al. 2008). Intense physical training can induce a two- to threefold increase in proinflammatory cytokine levels of tumor necrosis factor alpha and interleukin (IL)-1b (Ostrowski et al. 1998) as well as the cytokine IL-6 (Helge et al. 2003). The increase in inflammatory cytokines, especially IL-6, stimulates the synthesis of hepcidin, a key regulator of Fe metabolism (Peeling 2010), thus leading to lower levels of iron and transferrin. In a recent report, Kim et al. (2014) describe the mechanism of Fe homeostasis in response to *Salmonella enterica* var. Typhimurium (*S. typhimurium*) infection, an intramacrophage bacterium. They showed that the estrogen-related receptor γ (ERRγ) modulates the intramacrophage proliferation of *S. typhimurium* by altering host Fe homeostasis, therefore demonstrating an antimicrobial effect of an ERRγ inverse agonist.

Manganese

Manganese is an essential nutrient involved in the metabolism of amino acids, proteins, and lipids. In excess, however, manganese can be a potent neurotoxicant. Occupational and environmental exposure to airborne manganese has been associated with neurobehavioral deficits in adults and children (Riojas-Rodriguez et al. 2010). Manganese is commonly found in groundwater because of the weathering and leaching of Mn-bearing minerals and rocks into aquifers. Within these waters, Mn concentrations can vary by several orders of magnitude; however, exposure to manganese at levels commonly found in many groundwater sources has been associated with intellectual impairment in children (Bouchard et al. 2011).

Previous studies have reported a relationship between the concentration of manganese in drinking water and the Mn levels present in hair (Bouchard et al. 2007). In addition, it was recently found that the biological samples (scalp hair, blood, and urine) of male HIV-1 patients contained significantly lower concentrations of manganese and chromium compared to control subjects (Afridi et al. 2014). Hence, the lower levels of these trace elements may be predictors for secondary infections in HIV-1 patients. The chemical form of manganese, notably the valence state and solubility, might modify its toxicity (Michalke et al. 2007). Moreover, Mn absorption is decreased in the digestive system with concurrent intake of dietary fiber, oxalic acids, tannins, and phytic acids (Gibson 1994). Gender differences of Mn levels show contradictory results: in Korean populations, men show higher levels compared to women (Lee et al. 2012) whereas in Caucasian populations, women have higher blood Mn levels than men (Clark et al. 2007).

Within a human host, Mn levels are likely to impact microbial growth during infection. It has been shown that manganese is sequestered from sites of infection through the action of a host-derived immune-associated protein known as calprotectin in a murine model of staphylococcal infection (Corbin et al. 2008). The antimicrobial effect of this Mn sequestration is further highlighted by the fact that the staphylococcal Mn acquisition systems MntABC and MntH were required for *S. aureus* survival in mice expressing calprotectin, but were expendable in calprotectin-deficient animals (Kehl-Fie et al. 2013).

Molybdenum

Molybdenum (Mo) is a trace element and an essential nutrient in the human diet. It is a cofactor for the enzymes xanthine oxidase, sulfite oxidase, and aldehyde oxidase, which are involved in the metabolism of sulfur-containing amino acids, purines, and pyrimidines. A dose-dependent trend between molybdenum and declined sperm concentration and normal morphology has been reported (Meeker et al. 2008). Significant sources of molybdenum (as soluble molybdates) in the human diet are leafy vegetables, legumes, organ meats, grain products, cow's milk, and eggs. The Mo content in food sources varies, depending on the amount that has been taken up from the soil. Before weaning, an infant's primary Mo sources derive from breast milk and infant formula (both cow-milk and soy-based types). In an ongoing study of premature, hospitalized infants, Abramovich et al. (2011) recorded daily intake of formula and breast milk. Based on the intake data and the infants' average weight measured midterm of the hospitalization stay, mean Mo intakes per day and per kilogram bodyweight were calculated. Abramovich et al. (2011) report that the mean Mo content in soy-based and cow-milk formulas intended for the feeding of full-term or premature infants is higher than in human milk. Despite lower bioavailability of molybdenum from formula compared with human milk, the high intake may pose health risks, especially for premature infants due to immaturity of their compensatory mechanisms.

One of the enzymatic functions of bacteria enabled by molybdenum is anaerobic respiration. Anaerobic respiration has been shown to contribute to intestinal disease due to the fact that anaerobically respiring pathogens can outcompete beneficial gut microorganisms when alternative electron acceptors are provided during intestinal inflammation. This process has been disrupted in mutant pathogens with dysfunctional Mo homeostasis (Winter et al. 2013). These findings indicate that dietary molybdenum may play a role in gut disease associated with inflammation-induced dysbiosis.

Nickel

Exposure to nickel (Ni) increased significantly during the twentieth century because of its common applications (Vahter et al. 2007). Typically, nickel is utilized in metallurgical processes for the production of alloys such as stainless steel (Sharma 2007). The release of nickel into the environment occurs from various sources: metallurgy and refining industries, coal combustion, diesel and fuel oil as well as sewage. Nickel and its compounds are bioaccumulated by the human body through inhalation, ingestion, and dermal absorption. It is considered a carcinogenic agent and is the fourth most frequent contact allergen (Nohynek et al. 2004). Humans are exposed to nickel through food, jewelry, coins, and dental restorations (Vahter et al. 2007). Food which contains considerable amounts of nickel include cacao, dark chocolate, nuts, almonds, soya beans, oatmeal, spinach, tea leaves as well as fresh and dried legumes (Sharma 2007). In addition, Torjussen et al. (2003) report that cigarette smoking is a possible source of Ni exposure and conclude that Ni exposure from smoking is greater than occupational or workplace exposure. Other sources of Ni exposure included photocopiers, PVC and Cu pipes, and amalgam fillings (dental amalgam contains about 50% Hg as well as other toxic metals—Sn, Cu, Ni, and Pd). The literature reports that females more frequently suffer from Ni-induced dermatitis than males (10–20%, 1–5%, respectively) (Picarelli et al. 2011). In a recent study from Poland, Michalak et al. (2012) demonstrated that the type of water-supply system influenced Ni content in hair. The highest content was observed when PVC pipes were present, followed by Cu and finally steel pipes. Gender differences have also been recorded: the hair of females contained statistically higher Ni levels than the hair of males.

One of the most established links between Ni exposure and infection is that of *H. pylori* colonization of the human stomach. The *H. pylori* eradication rate with standard triple therapy is very low. *H. pylori* is known to require the Ni-containing metalloenzymes urease and NiFe-hydrogenase to survive the low pH environment in the stomach. Very recently, the addition of a Ni-free diet to standard triple therapy was shown to significantly increase *H. pylori* eradication rates (Campanale et al. 2014). The reduction of *H. pylori* urease activity due to the Ni-free diet could expose the bacterium to gastric acid and increase the susceptibility of *H. pylori* to amoxicillin treatment.

Selenium

In terms of its nutritional value and pathophysiological effects, more controversies are associated with selenium (Se) than with any other trace element. The history of its research is a continuous twist between toxicity and essentiality (Stathopoulou et al. 2012). Some studies have suggested a role of selenoproteins in the prevention of chronic degenerative disorders, including Parkinson and Alzheimer diseases, cancer, cardiovascular disease, atherosclerosis, stroke, and infertility. Children with recurrent wheezing were found to have lower hair Se levels than healthy children, thus suggesting a potential link between Se and infection (Razi et al. 2012). In antiretroviral therapy-naive HIV-infected adults, 24-month supplementation with a mixture containing multivitamins and selenium was shown to reduce the risk of immune decline and morbidity significantly (Baum et al. 2013). Concerns, however, have been raised about a possible association between Se supplementation and an increased risk of developing insulin resistance and type 2 diabetes (Sabino et al. 2013).

Dietary Se intake is determined by its content in different foods, the bioavailability of its chemical forms, and the dietary patterns adopted by different populations. The Se content of foods varies according to soil concentration of selenium. Several physicochemical properties of soil (e.g., pH and moisture) can also affect the entrance of selenium into the food chain. Geochemical mapping of selenium has revealed areas that are poor in selenium (e.g., Scandinavia, New Zealand, certain parts of China) and seleniferous areas (e.g., certain parts of United States, Canada, China and South America). The corresponding dietary intakes vary respectively: from 3 µg/day in Se-poor areas of China to 350 µg/day in Colombia (Rayman 2008). However, the enrichment of soils with Se-containing fertilizers and the use of supplements in animal agriculture have partially overcome low intakes due to Se-poor soils (Combs 2001). Nevertheless, the determination of daily Se intake by food frequency questionnaires is almost impossible because the amount of selenium differs greatly among the same foods, and nutritional tables are unreliable for this trace element. Beef, white bread, pork, chicken, eggs, and fish seem to be the main contributors of selenium in a typical Western diet; Brazil nuts have the highest Se content among all foods (Navarro-Alarcon and Cabrera-Vique 2008). The contribution of fish and shellfish products to the RDA and adequate intakes of copper, manganese, selenium, and zinc range from 2.5% (Mn) to 25.4% (Se) (Olmedo et al. 2013).

Vanadium

Vanadium (V) is an important trace element responsible for maintaining normal biological systems and body functions in humans. It has been reported that V compounds exhibit an insulin-like function or an antidiabetic effect in rats (Domingo 2002). The best food sources of vanadium are mushrooms, shellfish, black pepper, parsley, dill weed, beer, wine, grain and grain products, and artificially sweetened drinks. Vanadium exists in several forms, including vanadyl sulfate and vanadate. Vanadyl sulfate is most commonly found in nutritional supplements. The average diet provides 6–18 mg per day. Dietary vanadium in excess of 30 mg/kg can alter the amount and diversity of intestinal bacteria in avian broilers, implying that the structure and initial balance in the intestinal microbiota are disrupted (Wang et al. 2012b). These findings could have significant implications to human health because many foodborne infectious diseases originate from the gut microbiota of food animals. If these findings extend to humans, a similar V-induced dysbiosis in the human gut microbiota could lead to intestinal disease. As vanadyl sulfate, vanadium is a trace mineral associated with sugar regulation. It is believed to regulate fasting blood sugar levels and improve receptor sensitivity to insulin (Boden et al. 1996; Schulz et al. 1998). Based on available research, vanadyl sulfate appears to be a useful intervention for type 2 diabetic individuals with insulin resistance.

Zinc

Zinc is an essential trace element for all organisms, and its content in the human body is 2–3 g. The greatest amount is stored in skeletal muscle and bones:

11% of the total-body zinc is localized in the liver and skin, and only 0.1% is found within the plasma (Tuerk and Fazel 2009). Zinc is present in all food groups, yet the main dietary sources include oysters, red meat, poultry, fish, seafood, legumes, nuts, whole grains, and dairy products. The RDA for zinc is 8 and 11 mg for adult women and men, respectively; however, these values can range from as high as 12–14 mg for women during pregnancy and breastfeeding to as low as 2–9 mg during childhood and adolescence (Trumbo et al. 2001). Zinc homeostasis is regulated via the gastrointestinal tract, including the coordinated functions of many transporters. All Zn transporters have transmembrane domains and are encoded by two gene families: ZnT and Zip (Sandstrom and Cederblad 1980). Zinc homeostasis is impaired in diabetic animals and humans; type 2 diabetes is associated with decreased plasma Zn levels (Jansen et al. 2009). In a European cohort, Marcellini et al. (2006) found that psychological functions were related to Zn deficiency that resulted from a reduced intake and less variety of foods rich in zinc. This phenomenon was more evident in Greece and Poland than in other European countries (Italy and France) (Marcellini et al. 2006). Consistent findings from several Zn supplementation trials in humans and animal models support the idea that zinc offers protection against cellular oxidation and type 2 diabetes (Mariani et al. 2008).

In addition, Zn deficiency may play an important role in susceptibility to infections, since zinc is essential for numerous immune functions (Ibs and Rink 2003). Although nutritional deficiencies are often associated with inadequate food intake and poor dietary quality, many studies have shown that other factors (e.g., intestinal parasites) play an important role as predictors of such deficiencies (Hesham et al. 2004). A consistent change in Zn level in the blood of children infected with *Giardia lamblia* has been noted and eradication of *G. lamblia* led to a significant improvement in the mean serum Zn levels six months after treatment in school children (Quihui et al. 2010). This intestinal parasite causes a generally self-limited clinical illness characterized by diarrhea, abdominal cramps, bloating, weight loss, and malabsorption. However, for reasons that remain obscure, asymptomatic giardiasis with high reinfection rates occurs frequently, especially in developing countries (Cotton et al. 2011).