TANG [HUMANITAS MEDICINE]

Review

Role of heavy metals in human health and particularly in respect to diabetic patients

Mohammad Asif*

Department of Pharmacy, Guru Ram Das (PG) IMT, Dehradun, (Uttarakhand), India

ABSTRACT

Minerals are individual of the components of foods and are not produced in the body but essential for best possible health. Several essential metals are vital for the appropriate performance of various enzymes, transcriptional factors and proteins that are essential in various biochemical paths. Metals like zinc (Zn), magnesium (Mg), and manganese (Mn) are cofactors of hundreds of enzymes. Zn is involved in the synthesis and secretion of insulin from the pancreatic β-cells. Chromium (Cr) increases the insulin receptors activity on target tissues, mainly in muscle cells. Insulin hormone is required to maintain the blood glucose amount in normal range. Continual increase of blood serum glucose level leads to marked chronic hyperglycemia or diabetes mellitus. Deficiency of insulin or its resistance, blood glucose level exceeds the upper limit of the common range of 126 mg/dl. Poor glucose control and diabetes changes the levels of essential trace elements such as Zn, Mg, Mn, Cr, iron etc. by rising urinary excretion and their related decrease in the blood. The aim of this article to discusses the important roles of essential trace elements in particular perspective of type 2 diabetes.

Keywords diabetes, essential metals, insulin, diabetes mellitus

INTRODUCTION

It has believed that heavy metals possess various adverse health effects. Interest in the significance of trace elements to human health has increased very much during last decades (Horng et al., 2002). Certain elements have been identified as essential trace elements that play vital role in the origin and succession of numerous diseases. Amongst several metals, chromium (Cr), cadmium (Cd), nickel (Ni), and lead (Pb) are of huge significance because these elements are chiefly used in the metal industry together with welders and alloy smelter works. Various factors contributing to the pathophysiology of type II diabetes, some of these factors are trace elements (Kamal et al., 2009). The deficiency and efficiency of some essential trace metals may participates a function in the islet activity and development of diabetes mellitus. Some toxic metals have also shown in high amount in biological samples of diabetes mellitus patients (Chen et al., 2009). The position of trace elements in diabetes patients is also influenced by their diet, drugs administered and by environmental factors (Chłopicka et al., 1995). Pollutants due to the existence of toxic metals in surroundings not only enter the body by breathing, water, and food stuffs but they are collected in hair and skin (Wasiak et al., 1996). Trace elements analysis on hair samples has been extensively used to evaluate wildlife and human exposure to different contaminants exist in the environment (Sreenivasa Rao et al., 2002) and investigated the relationship between the level of zinc (Zn), Pb, Cd, Ni, and Cr in hair samples of diabetic patients.

Macrominerals are the minerals that are required by adults in amounts greater than 100 mg/day. Major (macro) minerals include sodium, potassium, chloride, calcium, magnesium (Mg), and phosphorus. Trace elements (or trace minerals) are the minerals that are required in amounts between 1 to 100 mg/day by adults. Trace mineral group includes iron (Fe), copper (Cu) and Zn. Ultra-trace minerals are the minerals that are required in amounts less than 1 mg/day. They include Cr, manganese (Mn), fluoride, iodide, cobalt, selenium, silicon, arsenic (As), boron, vanadium, Ni, Cd, lithium, Pb, and molybdenum (O'Dell and Sunde, 1997). Metals are naturally occurring inorganic elements which are present in very small amounts in the living tissues but are important for the vital processes of life (Kazi et al., 2008). Some metals are known as macro-metals and found in high amount in the body tissues, therefore they are also called macro-nutrients. At least 100 mg of each macro-nutrient is required in the daily diet (Simsek and Aykut, 2007; Soetan et al., 2010). Some metals like Cu, Zn, Fe, Mn, and Cr etc. are needed in the body in very small amounts, less than 100 parts per million (ppm), hence, these are called trace elements or micro-nutrients (Grivetti, 2000). Metals are concerned in a range of physiological courses like prosthetic groups of several proteins, water balance, cofactors of numerous enzymes etc. (Fraga, 2005). A number of metals role as part of proteins or enzymes as metallo-proteinase or metallo-enzymes (McCall et al., 2000). These proteins lacking metal containing prosthetic groups are incapable to execute their physiological activities (Lu et al., 2009). The parameter of different metallic contents in the body is requires for their appropriate performance (Lutsenko et al., 2007). Metals facilitate the muscles to contract or relax, and also transmit impulses through the nerves. Most

*Correspondence: Mohammad Asif
E-mail: aasif321@gmail.com
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metals are existed in the soluble salt forms, which control the composition of biofluids. The accurate metabolic working of the trace elements depends on their regular levels in different body tissues (Guidotti et al., 2010). Due to the varied metabolic uniqueness and functions; different metals like Mg, Zn, Cr, Fe, Mn, and Cu are measured as vital for regular human health (Kazi et al., 2008). Some studies have accounted that the imbalance of few essential metals might adversely affect pancreatic islet and cause diabetes (Chen, 2009). It is also noticeable that some reactive oxygen species (ROS) are formed during diabetes due to imbalance of essential metals. This oxidative stress might be reduces the insulin gene supporter action and mRNA expression in pancreatic islet cells due to hyperglycemic situation (Galhardi et al., 2004; Jiang et al., 2004; Valko et al., 2005). On opposite to essential metals, some toxic metals have also been recognized which collect in different biological model of type-2 diabetic patients. Uncontrolled pollution and industrialization might be a possible source to expose human population against toxic metals like Pb, Ni, Cd, and As. Some of the toxic metals are concerned to interrupt the glucose uptake and modify the associated molecular mechanism in glucose regulation (Kazi et al., 2009; Serdar et al., 2009).

ESSENTIAL METALS AND THEIR PHYSIOLOGICAL ROLES (Table 1)

Fe: Fe is an essential transition metal necessary for the production of two important purposeful proteins like hemoglobin and myoglobin, which are involved in the convey of molecular oxygen during respiration (Ganz et al., 2006). It is also essential in the elastin making along with Zn and ascorbic acid and collagen production (Stechmiller, 2010). In blood flow small portion of serum Fe is transported by a glycoprotein, called transferrin into the cells (Wish, 2006). In body tissues, ferritin stores free Fe form, which is raised in diagnosed diabetic patients (Kundu et al., 2013; McClain et al., 2006) and the higher level of ferritin in diabetics as compared to the non-diabetics. A positive correlation between serum ferritin and Fe deposition in tissues is linearly increased with diabetes duration (Raj and Rajan, 2013). The serum ferritin rise is considered as an indicator of Fe overload, which in turn leads to a situation called hemochromatosis (Rajpathak et al., 2006). There is a link between hemochromatosis and type 2 diabetes (Acton et al., 2006; Adams et al., 2005; Worwood, 2002). The rise Fe level oxidizes different biomolecules like nucleic acids, lipids and proteins, may contribute to type 2 diabetes progress by reducing insulin secretion from pancreatic β-cells with related enhancement of insulin resistance (Fernández-Real et al., 2002; Jehn et al., 2004; Jiang et al., 2004; Lee et al., 2006; Papanikolaou and Pantopoulos, 2005) and a strong connection between serum ferritin level and insulin resistance at preclinical stage prior to the expansion of full blown diabetes mellitus (Kim et al., 2011; Sharifi et al., 2008). In addition to the glucose rise, serum ferritin level might become a substitute marker of diabetes to calculate disease onset (Forouhi et al., 2007; Rajpathak et al., 2009). Fe is the most abundant trace element in the body and Fe deficiency anemia is the frequent micronutrient deficiency. Hemoglobin transports oxygen to various tissues. Fe deficiency is linked with impairment in the immune function. Impairment of cell mediated immunity, reduced neutrophil, natural killer cell, myeloperoxidase and bactericidal activity in Fe deficient state has been confirmed. Recommended dietary allowance (RDA) for men and postmenopausal women is 8 mg/day, adolescents 11 mg/day, premenopausal women 15 mg/day and pregnant women 30 mg/day (Mason, 2008). Dietary form of Fe are of two types-heme Fe found in red meat, chicken, sea food and other animal products and non-heme Fe found in dark green leafy vegetables, whole grains, nuts and dried fruits. Intestinal absorption is 15 - 20% for heme Fe and 1 - 8% for non-heme Fe. Absorption is increased by ascorbic acid and decreased by phytates and tannins. Fe deficiency can be caused by raised physiological need, excess menstrual blood loss, poor intake, poor absorption, hookworm infestation and other infections. Fe deficiency causes hypochromic, microcytic anemia linked with easy fatigability, poor cognitive development, pica and occasionally dysphagia. Pallor, koilonychia and glossitis are general on physical test. Fe overload occurs in case of high dietary intake, excessive intestinal absorption or repeated parenteral use. Conditions linked with Fe overload include hemosiderosis and hemochromatosis. Body Fe status can be assessed by estimating serum ferritin, Fe, total Fe binding capacity and bone marrow Fe stores. Negative Fe balance depletes bone marrow stores followed by serum ferritin. As deficiency worsens, serum Fe falls, microcytosis and hypochromasia appear on the peripheral smear.

Mg: Mg is the most copious macro-nutrient which is vital for the continuation of proper health. It is needed for the activity of more than 300 enzymes, which serve several essential physiological functions in the human body (Lopez-Ridaura et al., 2004). The Mg containing enzymes are concerned in the glucose homeostasis, nerve transmission, DNA and RNA production (Swaminathan, 2003). Studies were examined between Mg utilization through diet and the risk of type 2 diabetes. The Mg deficiency might lead to a decrease in insulin mediated glucose uptake (Afridi et al., 2008; Lopez-Ridaura et al., 2004). The Mg supplementation prevented insulin resistance and also reduced the development of diabetes in animals (Mooren et al., 2011). The low level of Mg in the blood serum and an improved urinary excretion of Mg in the diabetics comparative to their healthy control subjects (Afridi et al., 2008).

Mn: Mn is located mainly in the mitochondria and acts as a cofactor in several enzymes including those involved in bone marrow production, and metabolism of carbohydrates, proteins and fats (Orbea et al., 2002). It is a part of many important metalloenzymes like pyruvate carboxylase, arginase, superoxide dismutase and glycosyl-transferase. It plays an essential role for the proper use of choline, thiamine, biotin, vit C and vit E. The Mn as a cofactor of enzymes is also involved in mitochondrial glycoproteins synthesis (Serdar et al., 2009). It is absorbed in small intestine, then bound to albumin in circulation and is transported to liver and excreted in bile. Impaired activity of these enzymes, due to Mn deficiency causes abnormal cartilage formation (Rico et al., 2000). The Mn is a cofactor of pyruvate carboxylase, which plays a role in the change of various non-carbohydrate compounds into glucose by gluconeogenesis for their use. RDA in females is 1.2 mg/day and males are 2.3 mg/day (Mason, 2008). Dietary sources are whole grain, leafy vegetables, nuts, soya and tea. Deficiency of Mn causes hypercholesterolemia, dermatitis, impaired glucose tolerance, skeletal abnormalities, changes in hair colour, infertility, impaired synthesis of vit K dependant clotting factors and deafness. The toxic exposure to Mn including dust causes psychosis, hallucinations, neurological symptoms like Parkinson's disease (Berdanier, 1998). The Mn is also necessary for normal insulin synthesis, its secretion, and change its metabolism has been concerned in diabetes development (Kazi et al., 2008). The Mn deficiency in type 2

diabetic patients with respect to their control subjects (Forte et al., 2013).

Cu: Cu is an essential metal, which is required for several biological activities. It is required for the catalytic funtions of superoxide dismutase (SOD) that play a role in the defense of cells from superoxide radicals (Olivares et al., 2000). The Cu imbalance is concerned in cholesterol increase by disturbing normal high density lipoproteins (HDL) and low density lipoproteins (LDL) equilibrium (Jackson et al., 2010). The Cu also activates cytochrome oxidase which is involved in the electron transport chain of the mitochondria (Kako et al., 2004). In case of Cu deficiency, cytochrome oxidases decrease its activity which might lead to the distortion of mitochondria in metabolically active tissues such as pancreatic acinar cells, hepatocytes etc. (Lin et al., 2006; Quilliot, 2001). The Cu deficiency is one of the reasons for the progress of cardiovascular diseases (Klevay, 2000) and Cu is also beneficial to prevent arthritis linked inflammation and epilepsy (Chwiej et al., 2008). The disturbances in Cu levels in various biofluids and tissues are linked with defects implicated in metabolic pathways of diabetes and its problems (Eaton and Qian. 2002). Cu as well as Zn metals play roles in order to protect oxidative damage of body tissues (John et al., 2010; Zheng et al., 2006). Cu is the third largest trace element found in human body after Fe and Zn. It is a part of many enzymes like cytochrome-c oxidase, superoxide dismutase, tyrosinase, dopamine beta hydroxylase ferro-oxidases and amine oxidase (Farell, 2010). Cu is involved in neurotransmitter regulation, nutrient metabolism, collagen synthesis, cellular respiration and immune function. RDA of Cu is 900mcg/day for males and females (Mason, 2008). Cu is absorbed in the small intestine by a specific transport mechanism. It is bound to ceruloplasmin in circulation. It is stored mostly in the liver and muscle. Total Cu in adult human is 50 - 80 mg. Liver has 30 - 50 µgm of Cu/gm of dry tissue. Excretion is mainly through faeces, biliary and GIT secretions. Rich sources of Cu include liver, nuts, shellfish, chocolate and seeds. Cu deficiency is rare except in malnutrition, prolonged parenteral nutrition, and malabsorption disorders. Clinical features include osteoporosis, microcytic anemia, skeletal abnormalities, neutropenia, neurologic symptoms, depigmentation of hair and skin (Olivares and Uauy, 1996). Menke's and Wilson's diseases are two major disorders of Cu metabolism. Menke's syndrome is a rare X linked recessive defect of Cu absorption that has its clinical onset by 3 months of age. Patients have brittle, kinky hair, poor skin and hair pigmentation, skeletal problems, poor mental development, degenerative changes in the aorta, hypothermia and seizures. Wilson's or hepatolenticular degeneration is an autosomal recessive disorder due to impaired biliary Cu excretion. Excess Cu is deposited in the basal nuclei of brain and liver. Patient may have acute, chronic or fulminant hepatitis at presentation. Other physical signs are Kayser Fleischer ring, neurological disorder and cirrhosis of liver. The parameters of urinary Cu > 100 mcg/day, serum ceruloplasmin < 20 mg/land liver Cu > 250 mcg/g dry weight is diagnostic of Wilson's disease. Chelation is an effective therapy. Acute Cu toxicity can cause hepatic necrosis and coma in severe cases. Marked Cu deficiency can be assessed by low serum ceruloplasmin, serum Cu and RBC superoxide dismutase activity.

Zn: Zn is an essential trace element which is required for normal cell processing e.g. cell division and apoptosis. Zn participates in multiple biochemical pathways such as in transcription, translation and cell divisions (Karamouzis et al., 2002). More than 300 enzymes need Zn for their catalytic activities. On the other hand, removal of Zn from catalytic site leads to the loss of enzymatic activity (Jansen et al., 2009). About 70% of the Zn is bound to albumin and any pathological alteration of albumin affects the serum Zn levels (Droge, 2002). Zn malabsorption results in various types of disorders like dermal, gastrointestinal, neurological and immunological abnormalities (Wapnir, 2000). The type 2 diabetic patients have suboptimal Zn status in blood due to its increased urinary depletion (Forte et al., 2013). Hypozincemia and hyperzincuria are developed in diabetics (Wapnir, 2000). Zn plays a key role in the storage and secretion of insulin, which then increases the uptake of glucose (Kazi et al., 2008; Rungby, 2010). The decreased plasma level of Zn adversely affects the ability of islet cells to produce and secrete insulin (Brender et al., 2010; Rungby, 2010). The Zn transporter (ZnT8) is a key protein for the regulation of insulin secretion from the pancreatic β-cells. Recently a mutation in ZnT8 transporter has been associated with T2D (Wijesekara et al., 2010). Briefly all these evidences show the importance of Zn in the continuation and integration of insulin hexamer and its role in the metabolic regulation (Rungby, 2010).

It is the most common catalytic metal ion in cell cytoplasm. It is a component of more than 100 enzymes like DNA polymerase, RNA polymerase, transfer RNA synthetase, reverse transcriptase, carbonic anhydrase, superoxide dismutase, alcohol dehydrogenase, thymidine kinase and alkaline phosphatase. It constitutes Zn finger proteins which are looped sequence specific DNA binding proteins those act as transcriptional mediators for nucleic acids. Zn also plays a role in all stages of insulin metabolism. The beneficial effects of Zn supplementation in common cold and diarrhea in children (Natchu et al., 2008). RDA of Zn is 8 mg/day for females and 11 mg/day for males. The highest level of Zn is found in choroid of eye and optic nerve followed by in muscle and bone. Liver has a small pool of 170 mg which is mobilised in deficiency state. Symptoms manifest within a week of deficiency. Natural sources of Zn include meat, sea food, eggs, soya beans, peanuts, wheat bran, yeast, cheese and oysters. Zn deficiency is generally in alcoholics and diabetics, and in malabsorption syndrome, liver and kidney diseases, burns, sickle cell disease, inflammatory bowel disease, and HIV infection. Mild deficiency causes growth retardation in children. Severe deficiency leads to dwarfism and cardiomyopathy in children, teratogenicity, hypogonadism, infertility, loss of taste, poor wound healing, dermatitis, alopecia, deformed bones, diarrhea, night blindness, skin striae and nail changes. Acrodermatitis enteropathica is an inherited autosomal recessive disorder with impaired intestinal absorption and transport of Zn. Patient suffers with postural and bullous dermatitis, alopecia, growth retardation, diarrhea, secondary infection, lethargy, irritability and depression. Oral Zn supplementation leads to remission. Cu and Zn compete for intestinal absorption. Toxicity of Zn leads to reduced Cu absorption, gastritis, sweating, fever, nausea and vomiting. Plasma level of Zn is 70 - 120 mcg/dl. No single test is indicative of Zn stores in the body. Zn in RBC and hair provides a long term assessment of body Zn status.

Cr: The activity of Cr depends on its valence state and chemical complexes it forms (Guidotti et al., 2010; Guidotti et al., 2008; Tudan et al., 2011). Trivalent form of Cr has high biological activity which is necessary for the optimal glucose uptake by cells (Belinda and O'Connell, 2001; Tudan et al., 2011). Cr regulates insulin and blood glucose levels by stimulating insulin signaling pathway and metabolism by up-regulating glucose transporter (GLUT4) translocation in muscle

cells (Qiao et al., 2009). Cr deficiency results in the elevation of blood glucose levels and if it is continued for longer period, it may lead to the progress of diabetes (Wiernsperger and Rapin, 2010). The Cr supplements decrease the blood sugar level in diabetes (Lai et al., 2006). Prolonged hyperglycemia increases Cr urinary excretion (Forte et al., 2013). The roles of these essential metals are for upholding the normal human physiology. While their imbalance predisposes to glucose intolerance which subsequently converts to diabetes related complications (Kazi et al., 2008).

Key role of Cr in human body is to potentiate interaction of insulin with its receptor on the cell surface. It is a basic of glucose tolerance factor and is synergistic with insulin in promoting carbohydrate, fat and lipid metabolism (Bender, 2008). The Cr exists in trivalent state in biological system and in hexavalent state in industrial pollutants. Dietary Cr is absorbed from the intestine, circulates in plasma bound to transferrin and is intense in the liver, spleen, soft tissue and bone. RDA in males is 35 µg/day and in females 25 µg/day (Mason, 2008). Dietary sources are whole grains, broccoli, meat, green beans and spices. The Cr deficiency is seen in patients on total parenteral nutrition. Hyperglycemia, neuropathy, encephalopathy, impaired glucose tolerance, elevated plasma free fatty acid concentration and abnormalities in nitrogen metabolism have been reported in patients with Cr deficiency. However, the value of Cr supplements for diabetics is controversial (Ryan et al., 2003). Industrial pollutants containing hexavalent Cr are carcinogenic. Leather tanning, dyestuff industries produce waste containing hexavalent Cr which can contaminate soil. Air- borne exposure causes contact dermatitis, skin ulcers, eczema, asthma, renal and hepatic necrosis and bronchogenic carcinoma. Plasma Cr levels are useful if the values are markedly above or below normal. Increased urinary Cr indicates recent environmental exposure to excess Cr.

Toxic metals and health: Toxic metals e.g. Pb, Ni, Cd, and As deposit in tissues and are non-degradable. Hence, these metals remain in the tissues for a long period, and it is often difficult to eliminate metal-based problem. Body tissues can tolerate a certain level of metals, and beyond such limits tissues get damaged due to metal toxicity. Some of the toxic metals including Ni, As etc. are marked as carcinogens (Chiu et al., 2004; Valko et al., 2005; Yabe et al., 2011). The mechanism of metal induced carcinogenesis is elusive, which might be due to complex nature of interactions of metals in biological systems (Valko et al., 2005). The essential metals also have carcinogenic effects if present in excess amounts than they are needed. For example, Cr^{3+} is essential while Cr^{4+} behaves as carcinogenic agent (Chiu et al., 2004). Similarly, hemo-chromatosis increases the risk of hepatocarcinoma (Kowdley, 2004). Prevalence of these toxic metals in the environment is potentially alarming and harmful for human health (Schwarzenbach et al., 2010). They are common in the nature and present in air, water and soil, which increases the probability of human exposure (Serdar et al., 2009). Toxic metals react with various proteins in the body that may modify their functions and kinetics. Moreover, when diet is low in essential metals, the body absorbs and makes use of more toxic metals. Several human populations are exposed to high levels of toxic metals including Pb, Cd, As, and Ni (Yabe et al., 2011). An abundance of a toxic metal competes with vital metal for enzymes activity and various body physiological functions (Flora, 2009). For example, Zn is required for the activity of many enzymes. In case of Zn deficiency and enlarged exposure to toxic metals such as Pb, body will use Pb instead of Zn (Duruibe, 2007). Some toxic metals including Pb, Cd, As and Ni are elevated in biological samples of diabetic patients, which adversely affect health status of an individual by disrupting organ functions. Free Pb in blood plasma is rapidly transferred to soft body tissues (Afridi et al., 2010). Ni is needed by certain enzymes used in anaerobic energy production in the cell (Berdanier, 1998). Cd is nephrotoxic in large doses. Pb and mercury are mostly known for their toxicity. As can cause acute and chronic toxicity. However, in animals, As deprivation affects growth and reproduction.

Pb: Some toxic metals including Pb were reported in higher level in the blood plasma and urine of diabetics than the non-diabetics (Afridi et al., 2008). The Pb is harmful to most of the human body organs, and obstructs with metabolism and cellular activities (Martinez-Finley et al., 2012). A linear relationship is reported between blood Pb level and renal dysfunction in age-related diseases. This is due to the recurrent exposure to Pb (Yu et al., 2004) and badly affects the antioxidant pathways (Yabe et al., 2011). The metal induced toxicity may cause derangement of antioxidant mechanisms in living tissues; as a result highly ROS are produced. This antioxidant discrepancy might lead to the degradation of proteins, nucleic acids and lipid peroxidation. An oxidative attack of cellular components by ROS is concerned in the pathogenesis of numerous human diseases including diabetes (Beyersmann and Hartwig, 2008; Kazi et al., 2009).

Cd: Cd is a heavy metal which is broadly detected in air, water and soil. Increased Cd level in water is absorbed by plants, animals and humans (Afridi et al., 2010). Frequent exposure to Cd supplied to its excess addition in kidney, which causes renal damage and nephropathy (Kazi et al., 2009). The high level of Cd reduces calcium absorption, which becomes an approaching cause of bone and kidney losses, called *Itai-Itai* disease. The Cd might down-regulate glucose transporter-4 (GLUT4) translocation by insulin and improved the stimulation of pancreatic β-cells interference in diabetes (Chen et al., 2009).

As: As is a naturally occurring toxic semi-metal, which is mostly used in Cu alloys and Pb batteries. It is also used in the herbicides, insecticides and pesticides formation. Ground water pollution with As is an alarming threat for human lives all around the world (Afridi et al., 2008; Valko et al., 2005). Regular exposure to As associated to different diseases together with certain types of cancers and diabetes. It connect in the disruption of glucose metabolism due to an modification in cell signaling tranduction factors like tumor necrosis factor-α (TNF-α), mitogen-activated protein kinase (MAPK) etc., then GLUT4 translocation to membrane might be arrested. The connection of As in β-cell dysfunction is also reported (Chen et al., 2009; Kazi et al., 2009).

Ni: Ni is ferromagnetic component which is generally used in Ni-Cd batteries. The majority of the human populations are exposed to Ni by different means like drinking polluted water, air and eating Ni polluted food (Das et al., 2008). Kidney is the major organ for Ni accumulation and contributes in renal dysfunction (Kubrak et al., 2012). The type 2 diabetic patients have 0.89 ng/ml of Ni in the blood relative to 0.77 ng/ml in the control patients. Various biofluids such as blood serum/plasma, urine, hair, etc. are known to altered metabolism of metals in different diseases including diabetes. In these biological samples, urine was distinctive because it is readily available and noninvasively sampled. Some research have shown urinary levels of metals which correspond to their blood serum status

Table 1. Clinical implications of nutritional trace elements

Trace Element	Functions	Deficiency	Toxicity
Iron	Component of hemo-globin, metallo-protein, oxygen transport	Iron deficiency anemia	Hemosiderosis hemochromatosis
Zinc	Protein synthesis, zinc finger protein, component of enzymes	Ageusia, Growth retardation Dermatitis, Hypogonadism Acrodermatitis enteropathica	Copper deficiency Nausea, vomiting
Copper	Cellular respiration, collagen synthesis, component of enzymes, Antioxidant	Menke's kinky hair syndrome, Hypochromic anemia, Skeletal defects	Wilson's disease
Chromium	Glucose tolerance factor	Hyperglycemia, neuropathy, ence-phalopathy	Dermatitis, eczema, bron-chogenic carcinoma
Fluorine	Prevents tooth decay	Dental caries	Fluorosis, mottled enamel
Manganese	Component of metallo-enzymes, Manganese superoxide dismutase	Hypocholesterolemia, Hair and nail changes, impaired clotting factors	Parkinsonism like features
Molybdenum	Cofactor for xanthine and sulfite oxidase	Hypercuprinemia, Low sulfate excretion, hypouricemia	Risk of gout, Anemia Thyrotoxicosis
Selenium	Component of glutathione peroxi-dase, superoxide dismutase	Keshan's disease, Kashin-Beck Disease, Myxedematous, Endemic Cretinism	Hair and nail loss, neuro-pathy, liver failure
Iodine	Component of thyroid hormone	hypothyroidism	Thyrotoxicosis
Cobalt	Component of vitamin B12	vitamin B12 deficiency anemia	Cardiomyopathy, heart failure, goiter, hypo-thyroidism vomiting and diarrhea
Boron	calcium, magnesium, vitamin D metabolism	Osteoporosis, low estrogen, testos-terone levels	-
Germanium	Immuno-stimulant	hypertension and heart disease	-
Vanadium	Insulin signal enhancer, lipid metabolism	-	Greenish tongue, nephron-toxic, Silicosis of lungs
Silicon	Bone and connective tissue formation	Risk of osteoporosis	

of this metal (Kazi et al., 2008; Kazi et al., 2009). The existence of connection between the levels of toxic metals and essential trace metals (Barany et al., 2005).

Molybdenum: Molybdenum is included in several metallo-enzymes like xanthine, sulfite and aldehyde oxidase. It competes with Cu at absorption sites. RDA is 45 µ/day (Mason, 2008). Dietary sources are liver, grains, legumes, and nuts. Deficiency of molybdenum trace element is exceptionally rare. Medical features of deficiency are low sulfite excretion, hyper-cuprinemia, flawed keratin construction, cretinism, goiter, growth depression, hypouricemia and neurological defects. Excess intake causes to Cu deficiency thyrotoxicosis, anemia, hyperuricemia and risk of gout (Blake, 2007).

Selenium: Selenium is a part of various enzymes like glutathione peroxidase and superoxide dismutase. This reported as antioxidant role to selenium as the enzymes protect against oxidative and free radical damage of cell structure. Antioxidant activity of selenium balances that of vit E. Besides its antioxidant action, selenium also gives to protection of normal immune function (Morse and High, 2009). It also controls change of thyroxine to triiodothyronine. RDA of selenium is 55 mcg/day (Mason, 2008). Dietary sources are whole grain, seafood, egg, lean meat, mushrooms, and garlic. Deficiency in widespread area causes cardiomyopathy called as Keshan's disease in some parts of China, Kashin-Beck disease linked with osteoarthropathy and Myxedematous Endemic Cretinism, a form of hypothyroidism with mental retardation. Toxicity causes hair loss, irritability, nail damage, garlic odour to breath and peripheral neuropathy. The parameters to assess selenium include RBC glutathione peroxidase activity and whole blood selenium level (Mason, 2008).

Iodine: Dietary Iodine is ingested as iodide and it is the vital part of thyroid hormones which are formed by pairing of iodinated tyrosine residues within the thyroglobulin in the follicular lumen. Proteolytic breakdown of thyroglobulin liberates the thyroid hormones into circulation. Thyroid hormones participates a main role in growth and metabolism. RDA of iodine is 150 mcg/day (Mason, 2008). Dietary sources include iodised salt, saltwater fish, egg, meat and milk. Maternal deficiency causes congenital hypothyroidism, mental retardation and cretinism. Moderate deficiency in adults causes goiter and myxedema in hypothyroid adults is distinguished by hypotension and coma. Intake of large doses more than 2000 mcg/day can block thyroid hormone formation (Mason, 2008). Iodine status of a people can be predictable by occurrence of goiter and urinary iodide excretion can also be calculated.

Cobalt: Cobalt is a part of the vit B12 as cobalamin and has no other identified role in humans (Farell, 2010). Free cobalt cannot be used in body's vit B12 pool and hence diet has to supply body's vit B12 needs. Dietary sources are organ meat, yoghurt, sea food etc. A deficiency in cobalt is finally a deficiency in vit B12. Patient has anemia, depression and anorexia. Cobalt toxicity causes cardiomyopathy, heart failure, hypothyroidism, goiter, vomiting and diarrhea.

Boron: Boron has a control in calcium and Mg metabolism

(Nielsen, 1990). It is necessary to convert vitamin D to its active form in the kidneys. Boron deficiency emphasizes vit D deficiency. Dietary sources are dried fruits, dark green leafy vegetables, nuts and grains. Supplementation of boron in the diets has been linked with raised testosterone and estradiol levels (Naghii et al., 2011). Boron deficiency may affect to osteoporosis.

Germanium: Organic germanium, bis-carboxyethylsesqui-oxide germanium (Ge-132) has enhanced γ-interferon and activates macrophages and natural killer cells (Kaplan et al., 2004). Distant from enclosing immunostimulant effect, its deficiency may have a role in causation of hypercholesterolemia, hypertension and heart disease. Dietary sources are garlic, siberian ginseng, mushroom and other medicinal plants.

Vanadium: Vanadium is an insulin signal enhancer, which enhances translocation of GLUT4 to the cell membrane. The vanadium may develop insulin sensitivity, preserve pancreatic cells, and encourage an insulin-independent phosphorylation (Sakurai, 2002). Vanadium deficiency has not been illustrated in humans. Rarely, vanadium can cause nausea and greenish discoloration of the tongue and high doses are nephrotoxic..

Silicon: Silicon is a part of certain glycosamino-glycans and poly-uronides and may effective as a biological cross linking compound and participated to protection of structural design and toughness of connective tissue. It also develops bone health, maybe by synthesis of collagen and its stabilization and matrix mineralization (Berdanier, 1998). Silicon supplementation decreases absorption of toxic aluminium. Dietary sources are cereals, wheat bran, oat and vegetables. More level of silica inhalation may be causes toxic silicosis of lungs.

Flourine: Fluoride is an ionic form of fluorine. It is included in the crystalline composition of bone and helps in dental enamel development. RDA is 4 mg/day in males and 3 mg/day in females (Mason, 2008). Dietary sources are fluoridated drinking water, sea food, meat, cheese, and tea. Deficiency of fluorine causes dental caries. Fluoride toxicity may be acute or chronic and acute intake of more than 30 mg/kg body weight is expected to be fatal. Chronic toxicity due to extended intake of more than 0.1 mg/kg/day originates fluoride deposition in teeth and bones leading to fluorosis (Mason, 2008). Dental fluorosis is described by pitting and mottling of teeth. Skeletal fluorosis causes stiffness and pain in joints, brittle bones, calcification of tendon and ligaments. No high-quality laboratory test exists to evaluate toxicity. Treatment includes drinking water with safe fluoride levels, deflouridation of drinking water and stoping children from ingesting fluoridated toothpaste.

DISCUSSION

Trace elements are micronutrients necessary in the body for its regular function especially through different enzymes, hormones, vitamins etc. where they are the vital components. Major among them are Fe, Zn, Cu and cobalt. Insufficiency of each one gives rise to particular clinical quality. In addition Fe deficiency causing Fe deficiency anemia, Zn deficiency causes ageusia and skin changes, Cu deficiency hair changes, cobalt deficiency vit B12 deficiency and selenium deficiency cardiomyopathy. Carbohydrates, fats and proteins are macronutrients which act as metabolic fuel in our body. Vitamins and minerals are micronutrients essential for various biochemical reactions. Minerals can be subdivided into two groups, macro or major and trace minerals based on their body store and daily dietary requirement. The normal levels of essential metals are disturbed in type 2 diabetic patients. The status of crucial trace elements in different body tissues is influenced by renal excretion. Modification in the level of one metal may control normal levels of other metals. The toxic metals like Pb, Ni and Cd may have a function to stimulate renal tubular dysfunction in diabetics. Consequently dysfunctional kidneys may become a possible source for the loss of some essential trace elements through urine excretion rather than their retention in blood plasma in order to retain the homeostasis of blood and other tissues. The high urinary excretion of Zn results in its low levels in blood plasma which disrupt Zn based antioxidant mechanism. Therefore, urinary analysis of different essential and toxic metals, may help to have scientific implications in accepting and controlling diabetes or its obstacles like diabetic nephropathy. Metals pollutants damage organ utilities and interrupt physiological homeostasis. Some toxic metals have been shown to be high in biological samples of diabetes mellitus patients. Deficiency and efficiency of various essential trace metals may play a role in the islet function and progress of diabetes mellitus. Cd, Pb, and Ni are toxic elements that have link with diabetes. Cd and Pb exposure might cause diabetes. The Cr and Zn are decrease in diabetic patient. There is important relationship between the levels of chromium, Zn and Cd in diabetic and control group (Dutta and Mukta, 2012; Khan and Awan. 2014; Tadayon et al., 2013). There was no major link between the levels of Ni and Pb in diabetic and control group. The correlation between these elements was positive.

CONCLUSION

Certain elements have been recognized as important trace elements that contribute an important role in the origin and development of several diseases. Several toxic metals have been shown to be important in diabetes mellitus patients. The category of trace elements in diabetes patients is also influenced by their diet, drugs used or used to a large extent and by environmental factors.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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