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Trace elements and human obesity: An overview

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Review article

Trace elements and human obesity: An overview

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Abstract

The human body requires certain amount of trace elements to function properly (especially those that are classified as essential to health). Most elements are co-factors in the molecular mechanisms within the body but when in excess can also cause toxicity. Concentrations of some elements in excess (above optimum) or deficient amount can progress to some types of metabolic abnormalities which could lead to obesity. Obesity is a multifactorial condition with multiple pathways including environmental, dietary, and genetic. All these factors, including elemental abnormalities can disrupt the molecular mechanisms. Whilst there is evidence that obesity causes several elemental deficiencies, there is lack of knowledge on how these elemental deficiencies are related to an obese individual. This review examined the literature to determine if there are biological reasons to believe that low or increased concentrations of certain trace elements, namely, copper, magnesium, iodine, cobalt, molybdenum, boron, antimony, aluminium, chromium, selenium, manganese, calcium, zinc and iron might be associated with increased body fat.

Key words: trace elements, toxic metals, obese, obesity, fat disposition, deficiency, diet, nutrition, essential minerals and micronutrients

Introduction

There is an increasing interest in the potential influence of trace elements on the development of not only the brain but also the body of adults and children. Elements play an important part in human health including obesity (Kimmons, Black, Tohill, & Khan, 2006). They are present in many different forms within the human body, namely metalloenzymes, ions, and complexes, (Zitka et al., 2012). A deficiency of an element that will consistently change the biological function and that can be used to prevent or reverse the condition when that particular element is added is essential for the human body (Nielsen, 2000). If the presence of an element produces an adverse effect on the body, by impairing or over stimulation of an important chemical process, that element is considered toxic (Williams, James, & Roberts, 2000). The effects of non-essential elements on the human body are not very well understood (Ward, 2000). Excess exposure of most elements can damage cell membranes causing alteration of normal cellular function, damaging the cellular system such as the enzymes, signalling system, transporters, and deoxyribonucleic acid (DNA). As such, there is evidence that deficiencies or toxicity of certain elements may compromise overall health (Campbell, 2001). Health disorders due to elements may arise from insufficient dietary intake, genetic defects, excessive exposure or impaired excretion (Patriarca, Menditto, Rossi, Lyon, & Fell, 2000). Table one summarizes the elements of interest for this review and their functions.

Obesity is an abnormal or excess fat accumulation in adipose tissues measured using the body mass index (BMI). The BMI is defined as the weight (in kilograms) divided by the height (in metres)^2 and provides an estimate of body fat (Kimmons, Black, Tohill, & Khan, 2006). Confounders such as the gender of the study population, age and ethnicity are usually considered to reduce any bias when using the BMI as there are differences in fat distribution (Sweeting, 2007). Obesity has a complex physiological mechanism with

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multiple factors (environmental and genetics) that can negatively influence the bodily functions, especially due to abnormally low or high concentrations of certain elements (Garcia, Long, & Rosado, 2009; Kimmons, Black, Tohill, & Khan, 2006). The function of elements in human physiology and metabolism in relation to obesity is an area that requires further understanding. The aim of this review is to provide an overview of the literature focused on trace elements, namely, copper, magnesium, iodine, cobalt, molybdenum, boron, antimony, aluminium, chromium, selenium, manganese, calcium, zinc and iron, and obesity in adults and children. It is hoped that this review will motivate further research in this field.

Table 1:
Elements of Interest and Summary of Their Functions in the Human Body

Elements	Function/s in human body
Essential	
Iodine (I)	Synthesis of thyroid hormones
Molybdenum (Mo)	Metalloflavoproteins
Selenium(Se)	Enzyme reactions for glutathione and thyroxine
Zinc (Zn)	Synthesis, storage, release of insulin
Copper (Cu)	Co-factor for numerous enzymes and important role in central nervous system
Nickel (Ni)	Protein structure or function in RNA
Cobalt (Co)	Structure of vitamin B 12.
Iron (Fe)	Expression of genes for receptors of ferritin, trans ferritin and metallothioneins.
Magnesium (Mg)	Co-factor in many enzymatic reactions
Chromium (Cr)	Regulates carbohydrates and fat metabolism
Calcium (Ca)	Many physiological functions
Non-essential	
Aluminium (Al)	No known function
Boron (B)	Increases estrogen, and has an effect on other minerals such as Mg and Phosphorus (P)
Antomony (Sb)	No known function

A literature search using Web of Science and PubMed Ovid was performed using the following terms in various different combinations: trace elements, toxic metals, individual elements of interest (iron, zinc, calcium, magnesium, selenium, chromium, copper, manganese, iodine, cobalt, molybdenum, boron, antimony and aluminium), obese, obesity, fat disposition, deficiency, diet, nutrition, essential minerals, micronutrients and biomarkers. References of selected and electronic links to related articles were also searched. The key references in articles were also identified. All articles and reviews until the year 2014 that investigated the role of elements and obesity were included.

2. Trace Elements and Fat Disposition

The new literature has shown that lower concentrations of trace elements or higher concentrations of toxic elements may be related to increased body fat in humans (Padilla, Elobeid, Ruden, & Allison, 2010; Zavala et al., 2012). There is recognition that obesity is one health condition that is a risk factor for elemental deficiencies (Garcia et al., 2009). Obese population of varying age groups and in different parts of the world have been shown to have such elemental deficiencies (Garcia et al., 2009). This may be due to the accumulation of fat tissues in the body that can cause disruptions in the concentrations of essential elements (Zavala et al., 2012). However, elemental deficiencies and its relationship to obesity in adults and children is less understood.

Lower elemental concentrations in obese individuals have been observed than their non-obese counterparts (Bougle, Bureau, & Laroche, 2009; Kimmons, Black, Tohill, & Khan, 2006; Tascilar, Ozgen, Abaci, Serdar, & Aykut, 2010). In certain parts of the world where elemental deficiencies are more prevalent, research has shown that the rate of obesity is increasing more rapidly (Usfar et al., 2010). There are many possible physiological processes that are required in developing obesity (Usfar et al., 2010) and therefore understanding the elemental balance in humans is important. Disruption of elemental intake (deficiencies or toxicity) can lead to "oxidative stress" defined as "a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant

defences" (Rupérez, Gil, & Aguilera, 2014). Evidence is accumulating in the fact that oxidative stress is a leading cause of inflammatory processes. Such elemental abnormalities maybe making individuals susceptible to becoming obese with its associated diseases (Vincent & Taylor, 2006) such as diabetes (Ohkuma et al., 2013), atherosclerosis (Dick, Lesser, Leipsic, Mancini, & Lear, 2013) and inflammation (Vazzana et al., 2012). Chronic or excess oxidative stress has been observed in many studies (Vincent, Innes, & Vincent, 2007). The body's protective antioxidants maybe decreased in obese individuals and hence increase the systematic oxidative stress such that the development to renal cancer may occur (Gago-Dominguez, Castelao, Yuan, Ross, & Yu, 2002). This is an example of another mechanism for development of cardiovascular disease with excess body fatness. In children with oxidative stress, their adipokine levels increases with the progression of obesity (Sun, Ji, Kersten, & Qi, 2012).

2.1. Specific Elements and its Association to Obesity

2.1.1. Iron (Fe): The causal relationship between obesity and concentration of iron in the teenagers was already established as early as 1960s (Wenzel, Stults, & Mayer, 1962). Further to that, a causal association between low blood iron concentrations and adiposity in people has been noted (Azab et al., 2014). The US Studies (such as the National Health and Nutrition Examination Survey (NHANES) III) showed that the likelihood of iron deficiency was higher in children who were overweight or those at a risk of becoming overweight (Nead, Halterman, Kaczorowski, Auinger, & Weitzman, 2004). A case-control study showed serum iron levels to be lower in obese compared to the non-obese children within this study (Azab et al., 2014). As iron deficiency is prevalent in obese individuals, it is likely that there might be several mechanisms involved in causing this deficiency. Obese cases generally have an unhealthy diet leading to low iron intake, possible reduced absorption, and due to the chronic inflammation, the sequestration of iron (Zimmermann et al., 2008). Furthermore, research has shown that women with obesity had a decreased iron absorption rate and therefore were iron deficient (Zimmermann et al., 2008). In addition, they further reported that the children's iron status improved with foods that were fortified with iron (Zimmermann et al., 2008). In contrast, another research has shown that the consumption of iron or other chemicals that is associated with the absorption of iron was not related with obesity related hypoferremi. (Menzie et al.,2008). However, the intake of phytate (phosphorous deposit), oxalic acid, caffeine intake, eggs and zinc among others has been showed a reduction in the absorption of iron (Garcia et al., 2009). In summary, the mechanism that links iron deficiency to obesity is the chemical Hepcidin whereby the regulation of iron homeostasis occurs and hence causes hyppoferremia which leads to fat disposition (Garcia et al., 2009).

2.1.2. Zinc (Zn): Zinc a metalloenzyme has a role in controlling appetite. It is also known to synthesis, store and release insulin (Payahoo et al., 2013). Zinc deficiency causes resistance to insulin and intolerance of glucose but has also shown a link to obesity (Garcia et al., 2012). As insulin resistance leads to pathological conditions such as metabolic disorder and obesity, understanding these effects becomes important (Mikhail, 2009). Further, pervious research has shown a lower plasma zinc levels in obese individuals (Azab et al., 2014). A study in the United States of America (USA) established that a higher consumption of zinc supplements had a reduction in the risk of type 2 diabetes (Sun, van Dam, Willett, & Hu, 2009). In contrast, zinc supplementation in patients with type 2 diabetes, reduced triglyceride while increasing high density lipoprotein cholesterol (Kelishadi et al., 2010). Furthermore, a randomised cross-over trial showed that insulin resistance reduced when 20 mg of zinc was given to those children that exhibited a metabolic syndrome, (Kelishadi et al., 2010). Addition of 30 mg per day of zinc showed an improvement in weight as well as BMI categories in one study (Payahoo et al., 2013). Additionally, low concentrations of zinc in children who were obese were associated with high lipids, inflammation and insulin resistance in a recent Mexican cross-sectional study (Zavala et al., 2012).

2.1.3. Calcium (Ca): Calcium is a major essential nutrient found in the bones and teeth in humans (Shills, Shike, Ross, Caballero, & Cousins, 2006). Calcium has a role in many physiological functions in the body; including hormones and enzyme processes, blood clotting and neuro muscular functions (Straub, 2007).

Vitamin D and parathyroid hormone is produced with calcium intake as it influences the body weight (Zemel, 2004). During calcium metabolism (in "adipocytes" and "thermogenesis") a dose-response association is observed between fat disposition and the amount of calcium (Garcia et al., 2009). In the presence of low calcium intake, there is a reduced plasma calcium levels associated and this can lead to "a calcitriol (1, 25-dihydroxyvitamin D) mediated increase in intracellular ($[Ca^{2}+]i$) concentrations" (Groff, Gropper, & Gropper, 1995). The opposite effect is seen in the presence of higher "intracellular ($[Ca^{2}+]i$)" concentrations, as this process increases physiological activates (such as "expression" and fatty acid synthesis) which in turn hinder lipolysian" (Zemel, 2004). Induced obesity can be curbed by increasing the intake of calcium through dairy products, such as milk or yogurt. This stops the lipogenesis process and hence promotes lipolysis and lipid oxidation (Zemel, 2004). In hindsight, previous research has shown that calcium intake can increase the breakdown of fat which in turn decreases the production of fatty tissues. Another mechanism in the reduction of body fatness, is that calcium has been shown to increases faecal fat excretion (Heaney, 2011). Similarly, a review (Heaney & Rafferty, 2009) and a meta-analysis (Onakpoya, Perry, Zhang, & Ernst, 2011) stated that calcium helps in reduction of fat disposition. A few previous studies did not find a positive result in lowering obesity with increased calcium intake (Bowen, Noakes, & Clifton, 2005). Supplementing calcium had no positive effect on body weight or fat content in a systematic review (Heaney, 2011). In addition, if calcium is taken with proteins, the fat content in faeces increases with a high excretion rate (350 kJ/per day) (Jacobsen, Lorenzen, Toubro, Krog-Mikkelsen, & Astrup, 2005). Diets that are rich in calcium,, increases energy release by suppressing "calcitrio-mediated inhibition" of adipocyte uncoupling binding protein 2 (UCP2), which is implicated in thermogenesis and hence keeps the body weight regulated (Shi, Dirienzo, & Zemel, 2001).

2.1.4. Magnesium (Mg): Several studies have shown a lower concentration of magnesium in obesity and hence this may be associated with metabolic diseases (Neilson, 2010). In a comparative study, a lower plasma magnesium concentrations in obese/diabetic individuals than non-obese individuals was observed, whilst normotensive obese people did not (Corcia, Allegra, Lentile, & Buemi, 1997). Similar findings were observed in a Korean study whereby blood pressure was lowered when magnesium supplement was given but not in those individuals with normal blood pressures, nor in those adults who were overweight (Lee, Park, Son, Lee, & Kim, 2009). Another study found that magnesium in serum was significantly lower in obese children than their matched controls (Huerta et al., 2005).

Animal studies have shown that where there is severe magnesium deprivation, the extracellular magnesium is decreases rapidly and these resulted in metabolic symptoms such as inflammation (Mazur et al., 2007). Magnesium acts as a calcium antagonist and therefore, the inflammation response is most likely caused by an increase in intracellular calcium and the priming of phagocytic cells, which releases inflammatory cytokines (Mazur et al., 2007). Severe deficiency in magnesium that may cause inflammation in humans is highly unlikely. In order to understand the role of magnesium in relation to body weight and comorbid conditions further research is required (Neilson, 2010).

2.1.5. Selenium (Se): This element plays an important part in enzymes and selenoproteins, and is known for protecting individuals against cancer, infections of viral origin in immune functions and in the origin of fibrinogen disorders (a disorder that affects the immune system) (Combs & Lu, 2001; Rayman, 2002). The case-control study conducted in Egyptian children found lower levels of serum selenium in obese children than the controls (Azab et al., 2014). Similarly, a Madrid study on 573 school children found that obese children had lower selenium levels than normal weight children and children with central adiposity had even lower selenium levels (Ortega, Rodriguez-Rodriguez, & Aparicio, 2012). In people with sufficient selenium levels, a reduction in body fatness was observed (Savoury et al., 2011). In contrast, no associations between gender and ethnicity along with other covariates in young adults in relation to toenail selenium and inflammation (as measured by fibrinogen, hs-CRP and IL-6) was found (Xun et al., 2010). Similar results were observed in a small case-control of Turkish children where selenium levels were not different in the obese or non-obese groups (Tascilar

et al., 2010). A randomised control trial on selenium supplementation showed a benefit of selenium intake to reduce lipid hydroperoxide in overweight individuals than the placebo group (Savoury et al., 2011).

2.1.6. Chromium (Cr): This element is very similar to the properties of manganese in that it has a role in carbohydrates and fat metabolism (Padmavathi et al., 2010). Chromium supplementation has a role in hunger management, helps in the reduction of body weight, as well as reduction in body fat when investigated in humans and animal models (Mertz, 1969). With increased high density lipoprotein (HDL) cholesterol and decreased plasma total cholesterol and triglycerides, a reduction in body weight of diabetic people were observed when chromium was supplemented (Mertz, 1969). In animal studies chronic chromium deficiencies in females during pregnancy increased visceral fat and offset the fatty tissues in their offspring (Padilla et al., 2010). This study suggested that the pre and postnatal chromium deficiency is an important period that influences the developmental and functional aspects of fatty tissues in offspring. Hence, such deficiency may predispose them to insulin resistance as well as fat accumulation in later life. Systematic review and meta-analysis showed that a chromium supplement reduced body weight, however, the magnitude of the effect was small (Onakpoya, Posadzki, & Ernst, 2013). In contrast a recent study on Egyptian children found no significant difference in serum chromium levels between the normal weight and obese children in their case-control study (Azab et al., 2014).

2.1.7. Other elements: There is very little research on copper, iodine, manganese, molybdenum, boron, cobalt, antimony and aluminium in relation to fat disposition in humans. Diseases such as anaemia and neutropenia in adults are known to be caused by copper deficiencies (Mertz, 1969). Furthermore, copper deficiency and obesity seems to be connected (Relling et al., 2007). A recent study showed copper levels to be lower in obese individuals than non-obese individuals (Gonzalez-Reimers et al., 2014). Similarly, in an Egyptian case control study of children found lower levels of serum copper in children who were obese (Azab et al., 2014). However, in genetically obese mice, with sufficient copper intake, lower hepatic copper content was observed (Kennedy, Failla, & Smith, 1986). Further research is required to determine a causal relationship between copper and its possible link to obesity and in People.

Manganese is another essential element which has health benefit in the right amount in the human body (Aschner, Guilarte, Schneider, & Zheng, 2007). It has a major role in bone structure and metabolism, glucose regulation, reproductive health and it acts as a co-enzyme as well (Aschner et al., 2007). A high level of blood sugar, which is possibly caused by low manganese levels can cause an increase in body fat (Aschner et al., 2007). However, no direct studies have been conducted to suggest manganese as a causal agent for obesity. Antimony occurs in nature and has similar chemical and toxicological properties to arsenic. Lead products like batteries use antimony to harden the products in industries. People are exposed to antimony via tap water and a research has shown that it can cause cancer (Gebel, 1997). However, very few studies investigated antimony and its role on adiposity. For example, a US study found that BMI was associated with antimony (Padilla, Elobeid, Ruden, & Allison, 2010); however, further research is required to understand how antimony may or may not have a role on the development of fat disposition in humans.

Iodine in the human body is an important element as it involves the synthesis of thyroid hormone secreted by the thyroid gland. There have been no reports identified in the causal association c between iodine on body fatness. Molybdenum is an essential element and is known to have a function with the enzymes in the body (Novotney, 2011). Molybdenum deficiency has resulted in headaches, mental health disturbances and ultimately coma (Gupta, Srivastava, & Gupta, 2011). However, molybdenum and its possible effect on obesity need to be explored further. Aluminium and its possible association with obesity has not been previously studied except a research recently done on the comparison between obese and control groups of children, no difference in serum aluminium levels was observed (Tascilar et al., 2010). Cobalt is part of vitamin B12 and at high concentrations, it is known to damage the lungs and heart (Registry AfTSaD., 2004). In order to treat pregnant women with anaemia, cobalt is given as it is known to stimulate red blood cells (Registry AfTSaD., 2004). However, the possible association

cobalt may have on fat disposition is still unknown. The effects of boron on obesity is not well established apart from a recent study which found no significant association between boron and obesity (Tascilar et al., 2010) and another found lower concentrations of boron in obese people in comparison to the non-obese group (Hasbahceci, Cipe, Kadioglu, Aysan, & Muslomanoglu, 2013). In animal studies boron had an influence on reproduction, both from toxicity and deficiency plus bone and brain health benefited from sufficient boron intake (Neilson, 2008).

Conclusion

The study of trace elements and the health status of adults and children could provide an insight into the role of specific or groups of trace elements in protecting against obesity. The evidence shown in the literature proves that the role of essential elements in developing obesity is possible but there is a lack of evidence for non-essential elements. Specifically, there seems to be some evidence for iron and zinc, and mixed results for calcium and selenium. Further research is required for manganese, antimony and iodine as there were limited information on these. There were no studies that were identified which investigated cobalt, iodine, molybdenum, aluminium or boron in relation to fat disposition in adults or children. There was only one study on cobalt and obesity but this was carried out on mice only. The effect of a group of trace elements in relation to obesity had not been explored in those studies identified in this review nor did they investigate a combination of elements (as a single factor) in relation to obesity. For example, zinc and copper are known to have an inter-relationship that can be either synergetic and/or antagonistic (Dessoki, Raafat, Blaurock-Busch, & Rabah, 2012). Copper toxicity can be exasperated when zinc concentrations are lower in the body (Dessoki, Raafat, Blaurock-Busch, & Rabah, 2012). Therefore, studying the relations of Cu-Zn as a factor (or other combined elements known from the literature) in relation to obesity could be investigated. Furthermore, other nutrients such as vitamins need to be considered in elemental studies as certain vitamins (such as vitamin D) may have a role in adiposity (Koszowska, et al., 2014).

In addition, there are many difficulties comparing the literature in this area of research due to differences in the choice of biomarker used, different ages studied, health conditions, place/area of studies and study design. Furthermore, obesity is defined differently in different studies (Azab et al., 2014; Tascilar et al., 2010). For example, some have used visceral adiposity (Padillah et al., 2010), others have used waist height circumference or BMI (Padilla, Elobeid, Ruden, & Allison, 2010) and many studies have used other biomarkers as determinants of obesity (such as chronic inflammation responses) (Bougle, Bureau, & Laroche, 2009). Of note, most of the population studies reviewed are cross-sectional/descriptive and thus cannot determine causality or temporality. Additionally, there is no mention of the reliability/validity of biomarkers used or the chemical methods that were employed. This makes the comparison between studies difficult as well as the interpretation of their results. Lastly, most of the studies reviewed only studied the body burden or dietary intake of trace elements in relation to obesity. However, it would be interesting to explore other factors such as genetic defects or impaired excretion within populations in order to understand the role of elements and obesity.

Further investigation is warranted to understand the complex mechanisms of elements and obesity in both people (children and adults) in different age groups, ethnicity, and gender. It will also be interesting to investigate the affects toxic metals (including lead, cadmium, mercury and arsenic) may have on obesity in both children and adults. Understanding the role of trace elements on overall health and its sources is an important aspect that should be further investigated.

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