12

Obesity, Trace Metals, and Infection

Jerome O. Nriagu

Abstract

Trace metals are required in small quantities for a wide array of metabolic functions in the body. In terms of obesity, they can enhance insulin action through activating insulin receptor sites, serve as cofactors or components for enzyme systems involved in glucose metabolism, increase insulin sensitivity, and act as antioxidants to prevent tissue oxidation. Chronic hyperglycemia causes significant alterations in the status of many trace metals in the body and consequently increases the oxidative stress which can contribute to the pathogenesis of infectious diseases. Whether obese individuals with trace metal deficiency (or toxicity) are at increased risk for infection is a matter of concern in many developing countries, where a growing segment of the population (exposed to traditional health risks) has embraced Western dietary habits. A better understanding of the roles of different trace metals will undoubtedly facilitate the development of new treatment and prevention strategies that can more effectively reduce the silent burden of comorbid obesity and infectious diseases.

Introduction

This chapter addresses the risk overlap and role of metals at the confluence of First and Third World disease risks. With rapid evolution of the socioeconomic structures and impressive urbanization rates, major chronic degenerative diseases have spread epidemically in many developing countries. We are now witnessing the emergence of a new, highly complex, and challenging pathocenosis in these countries, where comparatively "new" disorders once associated with a "Western" lifestyle (e.g., obesity, diabetes, and immune disorders) coexist rampantly with acute and chronic diseases typical of traditional societies (e.g., malaria, schistosomiasis, viral hepatitis, and other infectious diseases). A matter of critical interest is whether trace metals can play a mediating role when these two nosologic entities are superimposed.

The two strongest selection pressures in human evolution were probably a robust immune response capable of clearing bacterial, viral, and parasitic infection and an ability to store nutrients efficiently to survive times when food sources were scarce (Johnson et al. 2012). These traits have evolved in their relationships over time. Recent studies have shown that the critical proteins necessary for regulating energy metabolism—such as peroxisome proliferator-activated receptors, Toll-like receptors, and fatty acid-binding proteins—also act as links between nutrient metabolism and activation of chronic inflammation in immune cells (Nieman et al. 1999; Keaney et al. 2003; Matsuzawa-Nagata et al. 2008). Expression of these proteins and their metabolism depend on an optimum supply of essential trace elements being available and the absence of large amounts of the toxic metals. Evolutionary selection led to a phenotype characterized by efficient energy storage and the formation of insulin resistance, both of which activate inflammatory cells; this could be considered a protective mechanism that coevolved to repartition energy sources within the body during times of nutritional stress and infection (Johnson et al. 2012; Ruiz-Nunez et al. 2013). The development of insulin resistance could also be considered a survival strategy aimed at reallocating the energy-rich nutrients that result from an activated immune system, limiting the immune response and repairing the inflicted damage, among other things (Ruiz-Nunez et al. 2013). I argue that in ancient times, inflammatory cell activation and insulin resistance were maintained largely by trace metal homeostasis, through regulation by the metabolic cycles of iron and zinc in particular. Modern lifestyles have managed to introduce a number of false inflammatory triggers, characterized by a lack of inflammation-suppressing factors, which have led to an imbalance: energy intake now far exceeds energy output. We have reached a point where a once beneficial adaptive trait has become very detrimental to our health.

The risk factors most commonly proposed for the recent increase in the prevalence of obesity include, but are not limited to, increased availability of energy-dense food items, increased portion sizes (especially in commercially marketed food items), abnormal dietary composition (especially as fast foods), the built environment, and physical inactivity (Poskitt 2014). When an inflammatory disease spreads like an epidemic over a short period of time, it needs to be scrutinized for environmental causes and infectious implications. The changes in environmental exposures and dietary intake from trace metals in Western foods have impacted the obesity epidemic and this deserves some attention. This is especially true considering that systemic low-grade inflammation, altered immune response, and oxidative stress are common features shared by obesity, many infectious diseases, and a dysregulated system of metal homeostasis. What is currently emerging in the scientific literature is that disruption in trace metal homeostasis can impair the immune function of adipose tissue in obesity and, consequently, exacerbate certain infections.

The mediating role of metals in comorbidity of obesity and infectious diseases should not be a matter of "if" but rather a question of "how much."

Obesity and Infections

Although obesity is a well-documented risk factor for metabolic and cardiovascular problems, its impacts on susceptibility to infectious diseases are just beginning to receive attention (Anaya and Dellinger 2006; Falagas and Kompoti 2006; Smith et al. 2007). Studies in hospital settings report that obese patients are more likely to develop secondary infections and complications such as sepsis, pneumonia, bacteremia, as well as wound and catheter-related infections (Karlsson and Beck 2010). Hospitalized obese patients have been reported to be at increased risk for pulmonary aspiration and community-related respiratory tract infections (Koenig 2001; Jubber 2004). Increased susceptibility to acute respiratory tract infection has been shown to be associated with body mass index (BMI) in overweight children (Jedrychowski et al. 1998). Obese individuals are at increased risk for *Helicobacter pylori* infection (Arslan et al. 2009), and children with increased BMI have been found to be at greater risk of being asymptomatic carriers of *Neisseria meningitidis* (Uberos et al. 2010). Case control studies have shown an increased risk of cellulitis and skin infections in overweight and obese cases (Karppelin et al. 2010; Bjornsdottir et al. 2005). Morbid obesity has been shown to be an independent risk factor for increased severity of infection and death from a recent H1N1 pandemic influenza strain (Morgan et al. 2010). In addition, increased BMI has been associated with greater risk for several other bacterial infections, including periodontal infections, *Staphylococcus aureus* nasal carriage, and gastric infection by *H. pylori* (Herwaldt et al. 2004; Ylostalo et al. 2008). One study found that obesity was significantly associated with herpes simplex virus 1 infection (Karjala et al. 2011). Reported results (Huttunen and Syrjanen 2013) regarding the association between obesity and the risk and outcome of community-acquired infections (e.g., pneumonia, bacteremia, sepsis, and as well as the course of HIV infection) are still equivocal.

Weber et al. (1985) were the first study to describe a relationship between vaccine response and obesity, and they found that higher BMI was the single best predictor of failure to develop detectable antibody to serum-derived hepatitis B vaccine in health-care workers. Further studies have subsequently confirmed the association between obesity and poor antibody response to hepatitis B vaccines (Roome et al. 1993; Wood et al. 1993; Simo-Minana et al. 1996; Young et al. 2001). Other than responses to hepatitis B vaccines, there have been few studies on vaccine efficacy in the obese host. Eliakim et al. (2006) demonstrated that antibody response to standard tetanus immunization was lower in overweight 13-year-olds compared to age-matched controls.

Dinelli and Moraes-Pinto (2008) reported that an obese female remained non-responsive, even following six doses of hepatitis B vaccine. The fact that there has been no published study of BMI in relation to the efficacy of influenza vaccination is a serious oversight. These studies with hepatitis B suggest that vaccine responses in obese individuals may be very different from vaccine responses in lean individuals (Karlsson and Beck 2010). If obese individuals who are immuno compromised do indeed have poor vaccine responsiveness, then they may not be receiving the full benefits of our current immunization protocols.

A number of studies with genetically obese animals consistently find reduced resistance to bacterial and viral infections, consistent with observations in human subjects. These studies often use mouse models lacking leptin (ob/ob), an important adipokine, or the leptin receptor (db/db). Experiments with ob/ob mice have found increased susceptibility to a number of different bacterial infections including *Mycobacterium abscessus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, and *M. tuberculosis* (Wieland et al. 2005; Hsu et al. 2007). Other studies, however, have found no differences in bacterial growth in ob/ob mice challenged with the *K. pneumoniae* and *S. pneumoniae* strains (Mancuso et al. 2002; Wieland et al. 2005; Hsu et al. 2007; Ordway et al. 2008). Experiments with db/db mice have reported increased susceptibility to *S. aureus* and *H. pylori*, and increased susceptibility to *Listeria monocytogenes* has been reported in both ob/ob and db/db mice (Ikejima et al. 2005; Wehrens et al. 2008; Park et al. 2009). Increased susceptibility to viral myocarditis induced by coxsackievirus B468 as well as encephalomyocarditis virus has been reported in studies with ob/ob mice (Kanda 2004). Diet-induced obese animal models have been used to assess the effects of chronic overnutrition, and such studies have yielded confirmatory results. As with the genetically obese model, diet-induced obese mice are more susceptible to bacterial infection, including infection with *Porphyromonas gingivalis* and *S. aureus*-induced sepsis (Amar et al. 2007; Strandberg et al. 2009).

Studies over the past three decades also suggest that some microbes may promote obesity in animals and humans, a phenomenon called "infectobesity" (Dhurander 2011). Germ-free mice are resistant to diet-induced obesity, suggesting that specific microbes may cause adiposities (Backhed et al. 2007; Nathan 2008). Induction of obesity in mice experimentally infected with canine distemper virus was the first report of infectobesity (Lyons et al. 1982; Dhurander 2011). Subsequent studies have shown that several viruses, bacteria, parasites, and scrapie agents can cause obesity in chicken, rodents, and nonhuman primates (Cani et al. 2007). In addition, a number of microbes, including *Chlamydia pneumoniae*, *Selenomonas noxia*, *H. pylori*, and herpes simplex virus 1 or 2, have been associated with human obesity (Dart et al. 2002; Fernandez-Real et al. 2007; Arslan et al. 2009). Adenoviruses are, however, the only human pathogens that are causatively and correlatively linked

with animal and human obesity and seem to directly influence the adipose tissue (Hegde and Dhurander 2013).

Obesity and Trace Metals

Recent studies of early life exposure to environmental chemicals are beginning to provide interesting information on the potentially important role of pre- and perinatal metabolic programming as a risk factor for obesity later in life (Merrill and Birnbaum 2011). A review of metabolic programming and how early life exposure to the "obesogenic" trace metals might be setting the stage for weight gain later in life was recently published by Merrill and Birnbaum (2011). From this review, the two most important obesogenic "metals" that have been identified are organotins and lead. Male mice and male rats exposed to tributyl tin (TBT) during puberty were found to show increased body mass, associated with increased relative fat mass (Makita et al. 2005; Si et al. 2011; Zuo et al. 2011). Two other studies, however, found opposite effects of TBT exposure on the body weights of female rats (Cooke et al. 2004). Cell culture models support a role of developmental exposure to organotins in obesity. TBT also induces adipogenesis in multipotent stem cells of mice and humans, while both TBT and triphenyltin (TPT) induce differentiation of 3T3-L1 adipocytes (Kirchner et al. 2010).

Although some evidence suggests that Pb exposure may also influence the risk of obesity, most of the human data on the association between developmental Pb exposure and obesity is equivocal. Lead levels in the teeth of male and female children in the United States are positively associated with BMI measured at the same time (Kim et al. 1995). A cross-sectional study found no association between blood Pb levels and obesity in 11-year-olds (Merrill and Birnbaum 2011); however, another study of adults showed a marginally significant inverse dose-response relationship between age-adjusted patella Pb levels in adulthood and abdominal obesity (Hu et al. 1998; Park et al. 2006). Results of animal research are consistent with an early-life susceptibility to Pb-associated adiposity and suggests there is a gender effect (Leasure et al. 2008).

While much remains to be learned about early life exposure to obesogenic metals and infectious diseases, numerous studies have reported on the influencing effects of deficiencies in essential trace metals in obese individuals in many parts of the world. A few studies have even suggested that adiposity increases the susceptibility to metal toxicity (Huang et al. 2007; Wildman and Mao 2001; Guerrero-Romero et al. 2006; Komolova et al. 2008). An interesting trend that has been noted is that the rates of obesity are increasing more rapidly in regions of the world where micronutrient deficiencies are more prevalent (Monteiro et al. 2004). This pattern could suggest that (a) the micronutrient deficiencies of individuals in these communities may be contributing to the increase in obesity rates or that (b) the correction of native deficiencies with

Western metal-enriched foods itself is the risk factor for obesity. It is not clear whether such deficiencies in obese individuals are the result of inadequate intake relative to overall body mass and/or are due to alterations in the metabolism and excretion of the trace metals. This question is further complicated by the uncertainty as to how to assess and define the optimal status of trace elements in obese individuals.

Documentation of the influencing factor of Zn status on obesity has come from studies of animal models and human subjects (reviewed by García et al. 2009). A number of epidemiological studies have reported that low Zn intake and low Zn concentrations in blood and other biological fluids are associated with increased prevalence of obesity and diabetes (common comorbid conditions). Obesity has been associated with hypozincemia in Italian (Di Martino et al. 1993), Turkish (Ozata et al. 2002), Thai (Tungtrongchitr et al. 2003), Indian (Singh et al. 1998), and Taiwanese (Chen et al. 1996) adult populations, as well as in Turkish children (Yakinci et al. 1997). A study in Guatemala found that Zn-deficient children were more obese than children with adequate Zn nutrition (Cavan et al. 1993), and a study by Arsenault et al. (2007) reported a higher increase in fat-free mass among a subset of children with mild-to-moderate stunting who received liquid zinc compared to children who were not stunted and who also received zinc.

Zinc is an antioxidant, hence its deficiency has been associated with increased oxidative stress and the inflammatory response in obese individuals (Sprietsma 1999; DiSilvestro 2000; Ozata et al. 2002; Tungtrongchitr et al. 2003; Cunningham-Rundles et al. 2005). Suboptimal Zn intake has been associated with low superoxide dismutase (SOD) activity in overweight and obese individuals (Tungtrongchitr et al. 2003). Another study found that blood concentrations of zinc, SOD, and glutathione peroxidase were significantly lower in obese men compared to a control group (Ozata et al. 2002). The available literature thus implicates Zn deficiency as influencing inflammation. Animal models suggest that Zn deficiency can lead to reduced lean body mass and increased body fat, which may be risk factors for obesity (García et al. 2009). During the initial stage of an infection, levels of zinc (and other essential trace metals) decline rapidly as the metals are redistributed to the point of infection, to boost immunity, and into tissues (especially liver), so as to deny bioavailable trace metals to the infecting pathogens. Furthermore, mobilization of zinc into the cellular compartment may be required to facilitate gene transcription and protein production, including the synthesis of adipocytes (especially leptin and adiponectin), insulin-degrading enzymes, and acute phase proteins (APPs) (Liu et al. 2013). These are also common presentations in obesity.

In obese individuals, Fe deficiency may result from low Fe intake, reduced Fe absorption, and the sequestration of Fe as a result of chronic inflammation (Yanoff et al. 2007; Zimmermann et al. 2008). One of the common pathologic conditions observed in obesity is systemic Fe deficiency and hypoferremia

(Nikonorov et al. 2014). Along with a large number of studies that indicate disturbed Fe homeostasis in obesity, recent data point to a cause–effect relationship between Fe status and obesity-related pathologies (Nead et al. 2004; Pinhas-Hamiel et al. 2003). Although the possibility of obesity-induced Fe-deficient anemia was debated for a long time, this hypothesis has not been confirmed through experimental data (Ausk et al. 2008; Anna et al. 2009). An association between reduced Fe concentrations in human biomarkers and obesity has been reported in a number of epidemiological studies (Seltzer and Mayer 1963; Nead et al. 2004; Chambers et al. 2006; Lecube et al. 2006; Moayeri et al. 2006). An analysis of the NHANES III data showed that children who were overweight or at risk of being overweight were twice as likely to be Fe deficient (Nead et al. 2004); another study of adults found an inverse correlation between serum Fe concentration with BMI, waist circumference, and fat mass in Hispanic women living in the United States (Chambers et al. 2006). A study of obese and nonobese postmenopausal women found significantly higher concentrations of transferrin receptors in serum of the obese women (Lecube et al. 2006). A cross-sectional study of children by Pinhas-Hamiel et al. (2003) found that low Fe concentration in blood and Fe-deficiency anemia were more common in obese children and adolescents than among normal-weight children. Zimmerman et al. (2008) showed that high BMI Z-scores were associated with decreased Fe absorption in women and reported improvement of Fe status in Fe-deficient children following intake of Fe-fortified foods.

The mutual interaction between Fe homeostasis and obesity-related pathogenesis leads to hypoferremia and results in increased adipose tissue Fe content being stored in either adipocytes or adipose tissue macrophages. The inflammation of obesity and obesity-related hepcidin and lipocalin 2 hyperproduction seem to be the most probable cause of obesity-related hypoferremia, since oversecretion of these proteins leads to Fe sequestration in reticuloendothelial system cells (Nikonorov et al. 2014). The latter also leads to increased adipose tissue Fe content, which produces preconditions for adverse effects of local Fe overload. Being a redox-active metal, iron is capable of inducing oxidative stress as well as endoplasmic reticulum stress, inflammation, and adipose tissue endocrine dysfunction. It is presumed to increase the levels of the pro-inflammatory cytokines interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α), which, in turn, increase the expression of hepcidin (McClung et al. 2009; García et al. 2009). Thus, the disturbance in Fe homeostasis (including both systemic hypoferremia and local adipose tissue Fe overload) and obesity pathogenesis seem to interact mutually in ways that can also influence host–pathogen interactions.

Arsenicism, from intake of inorganic arsenic in water and food, is a major health problem that is found especially in areas with high prevalence rates for infectious diseases and a growing epidemic of obesity (Nriagu et al. 2007). In recent years, increasing epidemiologic evidence from multiple countries

supports the role of inorganic arsenic in the development of diabetes (reviewed by Huang et al. 2011; Wang et al. 2014). A recent meta-analysis pooled 17 published articles that reported on 2,243,745 participants and found a 13% increase in risk of type 2 diabetes mellitus for every 100 mg/l increment in concentration of inorganic arsenic in drinking water (Wang et al. 2014). Biologic evidence in support of obesogenicity of arsenic includes the fact that arsenic could affect β cell function and insulin sensitivity through several mechanisms, including oxidative stress, glucose uptake and transport, gluconeogenesis, adipocyte differentiation, and calcium signaling (Tseng 2004; Davey et al. 2007; Diaz-Villasenor et al. 2007; Maull et al. 2012; Douillet et al. 2013). Arsenic can also act as an endocrine disrupter affecting the function of hormone receptors, including glucocorticoid, androgen, estrogen, and thyroid hormone in cell culture and animal models (Bodwell et al. 2006; Davey et al. 2007). In addition, arsenic may also impact diabetes through epigenetic mechanisms, including hyper- and hypomethylation of diabetes-related genes (Smeester et al. 2011; Kuo et al. 2013).

Copper is a pro-oxidant that participates in metal-catalyzed formation of free radicals; together with zinc, copper also acts as a structural and catalytic component of some metalloenzymes (Viktorinova et al. 2009). Copper is necessary for the catalytic activity of Cu/Zn-SOD, which is involved in the protection of cells from superoxide radicals (Viktorinova et al. 2009). Zinc, on the other hand, acts as an antioxidant by protecting the sulfhydryl groups of proteins and enzymes against free radical damage in the body (DiSilvestro 2000). The protective and toxic effects of copper and zinc in the pathogenesis of obesity and diabetic complications have been documented (Walter et al. 1991; Galhardi et al. 2004; Forbes et al. 2008). In particular, the relationships of serum Cu and Zn levels with obesity and diabetes have been extensively studied; results generally show that serum Cu levels are significantly increased (reflecting oxidative status of the adipose) and Zn levels are significantly decreased in obese and diabetic adults (Zargar et al. 1998; Basaki et al. 2012; Ferdousi and Mia 2012; Naka et al. 2013).

Biologically speaking, cadmium and, to a lesser degree, mercury should be of interest in the biology of insulin-secreting β cells, because of their similarity to zinc and the importance of zinc in the physiology of β cells (Afridi et al. 2008; Eddins et al. 2008). Given that zinc is co-secreted with insulin and that β cells have to maintain a high metabolic turnover of zinc, these cells are highly vulnerable to changes in Zn homeostasis (Muayed et al. 2012). Impairment in function of insulin-producing pancreatic β cells has been proposed to be one of the underlying causes of diabetic complication in obesity (Huang and Arvan 1995). The recent study by Muayed et al. (2012) reported that mouse β cells accumulated cadmium in a dose- and time-dependent manner over a prolonged period of time. In this study, Cd uptake led to a functional impairment of β cell function (including inhibition of glucose-stimulated insulin secretion) without

inducing general cell toxicity or oxidative stress. The results of such *in vitro* experiments have yet to be validated in human studies.

Obesity, Trace Metal Homeostasis, and Infection

Modern lifestyles have fundamentally changed the types, amounts, and forms of trace metals to which people are routinely exposed, and the consequences for human health have yet to be fully assessed. A large number of studies suggest that these changes can significantly influence the pathogenesis of obesity and infectious diseases as separate entities (see above). The question as to whether obese individuals with trace metal deficiency or toxicity (growing traits in the developing countries) are at increased risk for infectious diseases has not received much attention. For this review, I have relied on a "weight of evidence" approach to make suggestive inferences.

There are multiple cellular and biochemical pathways in the homeostasis of trace metals which can influence metabolic disorders (including insulin resistance, obesity, and diabetes) and infections. The three potential processes in metal metabolism that can simultaneously influence the pathogenesis of obesity and many infections are:

1. nutritional trace metal deficiency or excessive exposure to toxic metals, which can compromise immune function;
2. elevated blood volume as a function of increased adipose tissue mass, which increases the trace metal requirements and can potentially dysregulate the systemic distribution of many metals; and
3. formation of systemic inflammation and oxidative status common through trace metal homeostasis.

The proposed mechanisms behind obesity and infectious diseases include immune system dysregulation, decreased cell-mediated immune responses, obesity-related comorbidities, respiratory dysfunction, and pharmacological issues (Huttunen and Syrjanen 2013). As to be expected, however, most studies on obesity and susceptibility to infections in humans and animals have focused on the role and functionality of the immune system. The immune system cells and adipocytes show similarities in structure and function, such as the production of various inflammatory mediators (Marti et al. 2001; Huttunen and Syrjanen 2013). Adipose tissue itself has its own immune function and can also interact by secreting adipokines, such as leptin (Nave et al. 2011). In some respect, obesity can be regarded as a violation of the well-balanced system of adipocytes and immune cells, which can lead to a disturbance to the immune surveillance system and dysregulation of the immune response, impairment of chemotaxis, and alteration in macrophage differentiation (Nave et al. 2011; Huttunen and Syrjanen 2013). The homeostatic cycle of many trace metals is closely linked to these processes.

Sepsis, the syndrome of microbial infection complicated by systemic inflammation, provides an exaggerated illustration of the mediating effects of zinc on obesity and infection. An association between obesity and the increased morbidity and mortality from sepsis has been documented in a number of studies (Cheng et al. 2008; Sander et al. 2010), and both conditions share a number of important clinical and pathophysiological features. A characteristic feature of obesity is the induction of a chronic inflammatory state characterized by increased cytokine production by adipocytes or macrophages infiltrating adipose tissue (Oteiza 2012). An exaggerated inflammatory response to microbial infection is a prominent feature of sepsis (Bao et al. 2010b). Adipose tissue secretes proinflammatory adipokines such as interleukin-6, TNF-α, and calcitonin, which are commonly associated with sepsis pathophysiology (Knoell et al. 2009). Adipocytes also express Toll-like receptors, which are responsive to endotoxin; these are also critical factors in sepsis (Andreini et al. 2006a). Another feature of obesity is systemic lipotocixity that results from adiposity, leading to the production of toxic metabolites and overactivation of oxidative pathways (Calvano et al. 2005). Oxidative stress and high lipid concentrations may lead to apoptosis and endothelial dysfunction (Ho et al. 2003; Calvano et al. 2005). Relatedly, Liu et al. (2014) recently made the important observation that Zn deficiency significantly increases mortality in a mouse model of polymicrobial sepsis due to overactivation of the inflammatory response. They showed that during the initial stage of sepsis, Zn deficiency can induce rapid release of cytokines, such as TNFα, IL-1β, and IL-6, which rapidly activate the acute phase response (APR) and lead to the production of APPs. They also report that the upregulation of APR under Zn deficiency was accompanied by enhanced JAK-STAT3 signaling and a corresponding increase in serum amyloid A production. Further, Liu et al. (2014) report that adding zinc to the experimental system reduced the JAK-STAT3 signaling and APR activity, indicating that zinc plays a pivotal role in balancing the host response through the APR and enhanced expression of APPs during the severe infection associated with sepsis.

In recent years, it has become clear that chronic systemic low-grade inflammation, altered immune response, and oxidative stress are the basis for many, if not all, Western diseases centered around the metabolic syndrome (Keaney et al. 2003; Furukawa et al. 2004; Matsuzawa-Nagata et al. 2008; Fernández-Sánchez et al. 2011). These features are also commonly associated with trace metal deficiencies (or toxicity) and infections. The adverse impact of obesity on immunity is particularly striking in tuberculosis, a disease that may have shaped recent human evolution. In premodern times, type 1 diabetes was observed to predispose individuals to tuberculosis (Nathan 2008). It is now becoming clear that obesity-associated prediabetes and type 2 diabetes are risk factors that affect the contagiousness of tuberculosis and prolonged posttreatment of the infection (Alisjahbana et al. 2007; Restrepo 2007; Stevenson et al. 2007). Suppression of the ability to generate interferon (IFN)-α has been implicated in increasing susceptibility (Stalenhoef et al. 2007): IFN-α enhances

the antimicrobial capacity of macrophages (Nathan 2008), and deficiencies in its production or signaling underlie most syndromes of susceptibility to mycobacterial infection (Fortin et al. 2007). In India, the case burden of tuberculosis attributable to obesity and/or diabetes has been estimated to exceed markedly that attributable to infection by HIV (Alisjahbana et al. 2007; Restrepo 2007). Coincidentally, the prevalence of zinc, iron, and other trace metal deficiencies in India is among the highest in the world (see Ackland et al., this volume). Both obesity and deficiencies in trace metals lead to the expression of copious amounts of the inflammatory cytokines seen in tuberculosis patients, and it is most likely that all three conditions share common pathogenic features. The likelihood that the superposition of the growing vulnerabilities of obesity into endemicity of trace metal deficiencies may be involved in the changing presentation of tuberculosis and other infectious diseases in some parts of India cannot be discounted.

A large volume of literature reports that the disruption of the homeostasis of redox-active metals (including iron, copper, chromium, cobalt among others) may lead to oxidative stress—a state where increased generation of reactive oxygen species (ROS) overwhelms the body's antioxidant protection and subsequently induces DNA damage, lipid peroxidation, protein modification, and other effects associated with numerous diseases, including obesity and diabetes and related metabolic syndrome (reviewed by Jomova and Valko 2011). Redox-active metals are quintessentially involved in the formation of superoxide radical, hydroxyl radical (mainly via Fenton and Haber–Weiss reactions), nitric oxide, and other ROS species in biological systems, which can subsequently activate the formation of other organic free radicals. Redox-inactive metals including cadmium, arsenic, lead, and mercury, on the other hand, moderate the biological redox cycles via bonding to sulphydryl groups of proteins and depletion of antioxidant species such as glutathione. An alternative mechanism leading to the formation of hydrogen peroxide by oxidation of As(III) to As(V) under physiological conditions has been proposed (Mishra and Flora 2008). As a redox-inert metal, zinc occupies a special position among the metals in that it is an essential component of numerous proteins involved in defense against oxidative stress. Under a normal homeostatic mechanism, the metal-induced formation of free radicals is tightly influenced by the action of cellular antioxidants with many low molecular weight antioxidants, such as ascorbic acid (vitamin C), alpha-tocopherol (vitamin E), glutathione, carotenoids, flavonoids, and other antioxidants, being formed which are capable of chelating metal ions, thus reducing their catalytic activity with respect to ROS (Jomova and Valko 2011). The capacity of these metabolites to prevent the harmful effects of hypoxia is limited and can be overwhelmed by habitual intake of energy-dense and antioxidant-poor diet (Ruiz-Nunez et al. 2013).

Some evidence suggests that excessive zinc in energy-dense food causes excessive accumulation of body fat both in rodents and humans, thereby implicating the involvement of zinc in the etiology of obesity (Prentice 1993; Chen et

al. 1996; Taneja et al. 1996; 2012). The current understanding of a Zn effect on obesity is that zinc positively modulates secretion of insulin from pancreas and certain adipocites (including leptin, adiponectin) from adipose cells (Song et al. 2009). Zinc deficiency alters Zn transporter expression in adipose tissue (see above) and is associated with reduced serum leptin concentrations in healthy humans and rats (Mantzaros et al. 1998; Baltaci et al. 2005). Obese humans and mice, however, show higher concentrations of circulating leptin hyperleptinemia as well as hyperglycemia and hyperinsulinemia in tandem with lower Zn concentrations (hypozincemia) in blood or adipose tissue, suggesting interesting interrelationships between these factors in obesity (Taneja et al. 2012; Liu et al. 2013). Leptin is essential for normal development of both innate and adaptive immune responses, and the lack of this hormone or its receptor results in severe immune abnormalities and greater susceptibility to viral, bacterial, mycobacterial, and fungal infections (Mancuso 2013). Recent studies show that ob/ob mice exhibit increased pulmonary bacterial burdens and reduced survival following an intratracheal challenge with either *K. pneumoniae* or *S. pneumoniae* (Mancuso et al. 2002; Hsu et al. 2007). The extent to which leptin and other adipokines are involved in mediating the role of zinc and other trace metals in the comorbidity of obesity and infectious diseases is unknown at this time.

Conclusions

Modern lifestyles have fundamentally changed the types, amounts, and forms of trace metals to which people are routinely exposed, and a growing number of studies suggest that these changes can significantly influence the pathogenesis of obesity and infectious diseases as separate entities. This review uses a weight of evidence approach to suggest that obese individuals with deficiency or toxicity (growing traits in the developing countries) in some trace metals are at increased risk for infectious diseases. Multiple cellular and biochemical pathways are involved in the homeostasis of trace metals, which can influence metabolic disorders (including insulin resistance, obesity, and diabetes) and host–pathogen interactions. Redox-active metals are quintessentially involved in the formation of superoxide radical, hydroxyl radical (mainly via Fenton and Haber–Weiss reactions), nitric oxide, and other ROS species in biological systems, which can subsequently induce DNA damage, lipid peroxidation, protein modification, and other effects associated with numerous diseases, including obesity and diabetes and related metabolic syndrome. The proposed mechanisms linking trace metals to obesity and infection include (a) nutritional trace metal deficiency or excessive exposure to toxic metals, which can compromise immune function; (b) elevated blood volume as a function of increased adipose tissue mass, which increases the trace metal requirements and can potentially dysregulate the systemic availability of many metals to infecting pathogens; and (c) formation of systemic inflammation and oxidative

status common through trace metal homeostasis. In truth, our understanding of the trace metal-obesity-infection nexus remains very limited and a fertile area for future research.