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REVIEW PAPER

ROLE OF HEAVY METALS IN THE DEVELOPMENT OF OBESITY: A REVIEW OF RESEARCH*

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Abstract

Obesity is an excessive accumulation of body fat, above its physiological needs and adaptive capacity. Causes of obesity are overeating, lack of physical activity, genetic factors, damage to the hypothalamus and abdominal-medial hypothalamic nuclei, some medications, mood disorders and stress. Results of some studies imply that trace heavy metals may represent significant risk factors for the development of obesity, especially in areas that the degree of metal pollution is considerable. Our aim has been to present results of recent research into the role of heavy metals in the development of obesity. There are many studies on the relationship of exposure to heavy metals such as manganese, barium, cobalt, cadmium, lead, zinc, iron, or copper and obesity. The relationship between cadmium and its effects on obesity has been demonstrated. Exposure to cadmium results in a meaningful increase in hepatic GluT2, glucokinase, carbohydrate regulatory element binding protein (Chrebp), and pyruvate kinase mRNA. At the same time, activation of lipogenic proteins was discovered. Cadmium exposure resulted in a significant increase in free fatty acids and serum glucose level. Fat cells exposed to this metal significantly decreased dose-dependent cell viability after Cd2+ exposure. Adipocytes exposed to cadmium are characterized by an elevated rate of lipogenesis from glucose. As for the other heavy metals, further research is needed because not every study has linked these elements, especially cobalt and lead, to obesity. It has been shown that a lower concentration of zinc and a higher concentration of copper in blood can increase the risk of obesity. However, it is necessary to recognize the mechanisms of action of these elements on the process of obesity.

Keywords: obesity, zinc, cadmium, lead.

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INTRODUCTION

Obesity is an excessive accumulation of body fat, above its physiological needs and adaptive capacity, which can lead to adverse health effects. Obesity is considered to be a state in which adipose tissue represents more than 20% of total body weight in men and 25% in women. Obesity is accompanied by overweight, which is excess body weight above the optimal weight. Obesity has been found to increase the risk of certain diseases, including cardiovascular disease, type 2 diabetes, obstructive sleep apnea, cholelithiasis, kidney diseases, certain types of cancer, osteoarthritis, and thus to shorten the life expectancy (Haslam et al. 2005). Excessive obesity leads to disability. Obesity in high-growth countries is a social problem, it can take on epidemic proportions in the future and is already considered one of the civilization threats among developed societies. The Polish Central Statistical Office showed that 44% of men and 30.1% of women were overweight in Poland in 2014, while 18.1% of men and 15.6% of women suffered from obesity. The percentage of overweight and obese people is constantly growing. In Poland, it was 27.7% in 1996, rising to 29.6% in 2004 and reaching 53% in 2009. Overweight and obesity also occur among children and adolescents. According to the results of the study 'Health Behavior in School-aged Children (HBSC)' carried out in the 2013/2014 school year, the proportion of 11-15-year-olds with overweight and obesity in Poland was 14.8% (12.4% and 2.4% respectively) (Zgliczyński. 2017).The most common causes of obesity are likely to be overeating (excessive energy intake versus body requirement) and lack of physical activity. Genetic factors may play a role in the development of obesity or increase susceptibility to its development. Non-genetic biological agents also play a role in the development of obesity. Damage to the hypothalamus (inflammatory or neoplastic process) and abdominal-medial hypothalamic nuclei can cause obesity. At this time, excessive food intake and autonomic disorders may occur. The cause of obesity may also be some medications, mood disorders and stress (Adam et al. 2007). Moreover, there is a wealth of evidence supporting the link between environmental exposure to dangerous chemicals including toxic metals and obesity, diabetes and the metabolic syndrome (Tinkov et al. 2017). Trace heavy metals may represent decisive risk factors for the development of obesity, especially in areas with considerable metal pollution (Shao et al. 2017).The relationship between the concentration of some metals in blood and body mass has been investigated in children, adolescents and adults. However, the fundamental mechanisms still need exploration (Fan et al. 2017).

MATERIAL AND METHODS

We searched several electronic databases, such as PubMed, Web of Science, Cochrane Library and Medline, to find papers relating to the role of heavy metals in the development of obesity. A keyword approach was used. The search terms were "heavy metals obesity/ BMI," "cadmium obesity/ BMI", "cobalt obesity/ BMI", "zinc obesity/ BMI" "iron obesity/ BMI" and "lead obesity/ BMI". The search was conducted in October 2017. Initial screening of reports was based on a review of titles. Abstracts and/or full texts were also checked when necessary. The search took into account publications written in English or Polish.

RESULTS AND DISCUSSION

The study investigating the association between serum metallic elements with obesity in U.S children and adolescent showed that the highest concentrations of manganese in the blood was associated with obesity and there was a negative association between blood zinc and obesity. (Fan et al. 2017). Scientific research analyzing the urinary level of nine trace heavy metals, including barium, cadmium, cobalt, cesium, molybdenum, lead, antimony, thallium, and tungsten in U.S children revealed that there was a remarkable association between barium exposure and prevalence of obesity. A negative association was observed between cobalt, lead and cadmium and the obesity. These results suggest that trace heavy metals can be critical risk factors for the development of obesity (Shao et al. 2017).The Polish study conducted on children of age 6-17 years showed positive correlation between the cobalt content in plasma and BMI in obese boys. Also, a negative association between BMI and zinc in blood, iron in urine and copper in plasma was discovered for girls (Błażewicz et al. 2013).

Cadmium is a chemical element which has a high concentration in soil, water and air (Czeczot et al. 2010). Many scientific papers have confirmed the negative impact of this element on human health (Skolarczyk et al. 2018). Exposure to this chemical element can lead to various health results, such as lung diseases, peripheral artery disease, diabetes, diabetic nephropathy, arterial hypertension, itai-itai disease, immune system disorders, problems with reabsorption of vitamins or minerals and different types of cancer (Satarug et al. 2010). Scientific work about the impact of cadmium exposure and status on the risk and potential etiological mechanisms of obesity and diabetes showed that cadmium adversely affects adipose tissue physiopathology through several mechanisms that cause increased insulin resistance and higher probability of diabetes (Tinkov et al. 2017). Exposure to cadmium results in a meaningful increase in hepatic GluT2, glucokinase, carbohydrate

regulatory element binding protein (Chrebp), and pyruvate kinase mRNA. At the same time, activation of lipogenic proteins was also discovered. Cadmium exposure resulted in a significant increase in free fatty acids andserum glucose level. Treatment with cadmium purposefully altered the gut microbiome, increased the level of LPS in serum and transcriptional status of LPS target genes, finally causing induction of inflammatory response via elevation of IL-1ß, TNFa and IL-6 mRNA (Zhang et al. 2015). An *in vitro* study of cadmium toxicity in 3T3-L1 adipocytes showed that fat cells exposed to this metal significantly decreased dose-dependent cell viability after Cd2+ exposure (Kawakami et al. 2010). One study also demonstrated a significant cadmium-induced increase in carbon dioxide (CO2) formation from glucose in fat cells. This study also showed that adipocytes exposed to cadmium were characterized by an increased rate of lipogenesis from glucose (Yamamoto et al. 1986). One study revealed that cadmium-induced glucose uptake in adipocytes is related to altered Ca2+ signaling rather than to insulin signaling. It is implicated that the observed enhancement in cadmium-induced glucose uptake in 3T3-L1 adipocytes is mediated through the modulation of GluT1 activity (Harrison et al. 1991). An *in vitro* study showed that exposure to cadmium resulted in a significant dose-dependent decrease in lipid accumulation in differentiating 3T3-L1 cells on the stage of preadipocyte differentiation. It is also suggested that exposure to this metal may significantly alter the expression of adipogenesis activators, CCAAT/enhancer-binding protein alpha (C/EBPα) and peroxisome proliferator-activator receptor gamma (PPARγ) (Lee et al. 2012). A study carried out in 2013 on mice revealed that cadmium reduced adipocyte size and increased macrophage infiltration of white adipose tissue through up-regulation of Monocyte Chemoattractant Protein-1 (MCP-1) expression in metallothionein-null mice (Kawakami et al. 2013). In the same study, Kawakami study demonstrated meaningfully lowered adiponectin and leptin expression as well as a decreased adipocyte size in MT-null mice in response to cadmium treatment. Interestingly, the adipocyte size recovered in 6 weeks after cadmium withdrawal in MT-null mice, but the expression of adiponectin and leptin remained low (Kawakami et al. 2012). A Chinese study investigating the association between blood cadmium levels and obesity showed that blood levels of this metal had a negative relationship with the prevalence of overweight (Nie et al. 2016). Research into the link between blood cadmium and metabolic syndrome in South Korea demonstrated that blood cadmium levels were robust risk factors for the metabolic syndrome in examined men. Also, a relation of the metabolic syndrome and blood cadmium level was significant, regardless of the type of a variable (categorical or continuous), among men with lower blood cadmium levels (Lee et al. 2013). What is important is that the existing epidemiological data do not clearly support the role of cadmium exposure in obesity (Tinkov et al. 2017). A review of studies dealing with the influence of cadmium on obesity is summarised in Table 1.

Compared to other metal ions with similar chemical properties, zinc is

Table 1

Review of studies into the influence of cadmium on obesity

Review	Year of study	Subject of study	General conclusion
1	2	3	4
Yamamoto et al.	1984	observing glucose uptake in adipocytes	exposure to $CdCl_2$ was described by an increased rate of lipogenesis from glucose
Kang et al.	1986	increase in 2-deoxyglucose uptake by 3 T3-L1 adipocytes	proposing that Cd-induced glucose uptake in adipocytesis is related to changed Ca2+ signaling rather than to insulin signaling
Yamamoto et al.	1986	effect of Cd on carbohydrate metabolism in adipocytes	Significant Cd-induced growth in CO_2 composition from glucose in adipocytes
Harrison et al.	1991	observing glucose uptake in adipocytes	Cd induced glucose uptake in 3T3-L1 adipocytes is mediated through shaping of GLUT1 activity
Lachaal et al.	1996	observing glucose uptake in adipocytes	Cd induced glucose uptake in 3T3-L1 adipocytes is mediated throughmodulation of GLUT1 action, simultaneous increase in GLUT4 activity
Levy et al.	2000	observing of adipocytes incubated with $CdCl_2$	dose-dependent loss in leptin production in adipocytes incubated with $CdCl_2$
Huzior-Bałajewicz et al.	2001	observingsurvey	no correlation between body mass and blood Cd level in children living in the territories with high and low rate of pollution
Ficková et al.	2003	observing of *in vitro* exposure of adipocytes to Cd	no significant result of Cd exposure on GLUT4 content on adipocyte membranes
Han et al.	2003	observing level of GLUT4, GLUT2 and GLUT 1 inducing by CdCl2	decreased 3-O-methy-D-glucose uptake in insulin-stimulated adipocytes
Zhang et al.	2003	oral cadmium treatment in female rats	significantly lower body weight as compared to the control animals
Haswell-Elkins et al.	2007	population survey	significant direct correlation between cadmium levels and waist circumference but not BMI
Moon and Yoo	2008	incubation of adipocytes and progenitor cells with cadmium	significantly decreased dose-dependent cell viability after Cd2+ exposure as assessed by MTT-assay and colony forming efficiency assay

cont. Table 1

1	2	3	4
Akinloye et al.	2010	population survey	blood Cd levels were significantly related with BMI in type 2 diabetes mellitus patients
Kawakami et al.	2010	observing of accumulation of Cd in adipose tissue	Cd exposure significantly decreased adipocyte gene1/mesoderm-specific transcript, PPARγ, and CCAAT/enhancer-binding proteinαmRNA expression levels
Padilla et al.	2010	population survey	the level of cadmium was inversely linked to the anthropometric indices of obesity
Qin et al.	2010	population survey	significantly higher levels of Cd were observed in adipose tissue of patients with uterine leiomyomas as compared to the control values, association of adipose tissue metal levels with BMIwas not meaningful
El-Soud et al.	2011	population survey	the weight reduction was associated with a significant reduction in urinary Cd levels
Yen et al.	2011	population survey	observing diabetic hemodialysis patients shows that people with different blood Cd levels were not characterized by a significant group difference in BMI
Adnan et al.	2012	population survey	no significant association between BMI and urinary cadmium levels
Lee et al.	2012	observing of adipocytes exposed to $CdCl_2$	Cd exposure significantly modified the expression of adipogenesis activators, CCAAT/ C/EBPα and PPARγ
Kawakami et al.	2013	observation of *in vitro* exposure of adipocytes to Cd	significant decrease in leptin, adiponectin, and resistin expression, being associated with decreased fatty acid synthesis and lipid degradation mediated by perilipin
Kelishadi et al.	2013	population survey	no dependency between blood cadmium levels and BMI
Kurzius-Spencer	2013	population survey	negative interaction between Cd exposure and anthropometric indices of obesity, but not after adjustment for total energy intake, sex, age, ethnicity and smoking
Riederer et al.	2013	population survey	significant inverse association between urinary Cd and BMI values in children, teenagers, and smoking adults, but not in the non-smoking ones

cont. Table 1

1	2	3	4
Tellez-Plaza et al.	2013	population survey	significant negative association between urinary Cd levels and BMI values
Park and Lee	2013	population survey	no significant relationship between blood cadmium level and body fat was revealed
Gonzalez-Reimers et al.	2014	study of human hair Cd levels	no effect on obesity
Simmons et al.	2014	influence on adipose tissue physiology	increased predisposition to diabetes and metabolic syndrome
Skalnaya et al.	2014	population survey	a weak but meaningful correlation between hair Cd content and BMI values in women aged 22-35 years
Berglund et al.	2015	population survey	non-smoking overweight female are described by slightly raised urinary Cd levels than those with normal body weight but also with obesity
Choi and Han	2015	population survey	blood cadmium levels in obese males were significantly associated with osteoporosis,while such relationship was not significant in non-obese ones
Kim et al.	2015	population survey	blood Cd levels were associated with higher BMI, waist and hip circumference in girls aged 8-15 years
Romano et al.	2015	population survey	women with normal pre-pregnancy BMI values with high urinary cadmium concentration were characterized by increased risk GDM
Son et al.	2015	population survey	significant negative association between blood but not urinary Cd levels and BMI values
Ahn et al.	2016	study of human hair Cd levels	no effect on obesity

relatively innocuous. However, in the scientific literature there are reports of toxic zinc activity on the human body. Exposure to this chemical element causes an impaired immune response and the lowering of HDL cholesterol levels in blood (Piontek et al. 2014).The study exploring the zinc level in 706 individuals demonstrated that the level of zinc was significantly decreased in obese subjects, while the level of copper was increased in these individuals. Also, the superoxide-dismutase levels were lower in obese patients, which shows a reduced antioxidant response in this group (Torkanlou et al. 2016). Research dealing with relationships between zinc, iron and vitamins A, C, E versus obesity in children proved that children who were overweight had lower concentrations of zinc and vitamins C and E in blood. Moreover, these results of laboratory tests in obese children were associated with lipids, inflammation and insulin resistance (Garcia et al. 2013).

In recent years, many studies have examined the effects of lead on adult human organisms. It is believed that lead can indirectly cause elevated blood pressure. Lead is nephrotoxic, it may cause renal dysfunction and development of renal hypertension (Goch et al. 2005). Exposure to this chemical element can be a reason of ventricular arrhythmias, myocardial infarction, atherosclerotic plaque formation, bone marrow damage, lead neuropathy, fertility disorders, and even cancer (Krzywy et al. 2010). Research investigating the relationship of blood lead level (BLL) with body mass index (BMI) and obesity convinced the researchers that BLL was independently associated with BMI in women, but not in men. Increased quartiles of blood lead levels were related to meaningly increased odds ratios of obesity in women. (Wang et al. 2015). A study examinating if detectable BLL ($\geq$1 μg dL^{-1}) is linked to the body size in very early childhood (ages 2-3 years) showed that children with a detectable blood lead level had a 43% lower risk of body mass index ≥85th percentile and a 0.35-unit lower BMI. (Cassidy-Bushrow et al.2016). Further research into the link between lead exposure and body weight in children, adolescent and adults also demonstrated that blood lead levels are related to a lower BMI and obesity in children, adolescents and adults (Scinicariello et al. 2013).

CONCLUSIONS

There are many studies about relationships of heavy metals such as manganese, barium, cobalt, cadmium, lead, zinc, iron, or copper with the formation of obesity. Until now, the relationship and the mechanism of action of cadmium leading to obesity have been demonstrated. As for other heavy metals, further research is needed as not every study demonstrates the association of these metals with obesity, especially in the case of cobalt and lead. It has been shown that the presence of a lower concentration of zinc and a higher concentration of copper in blood has the potential to

increase the risk of obesity. However, it is necessary to know the mechanisms of action of these elements leading to obesity.

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