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Review

The role of cadmium in obesity and diabetes☆

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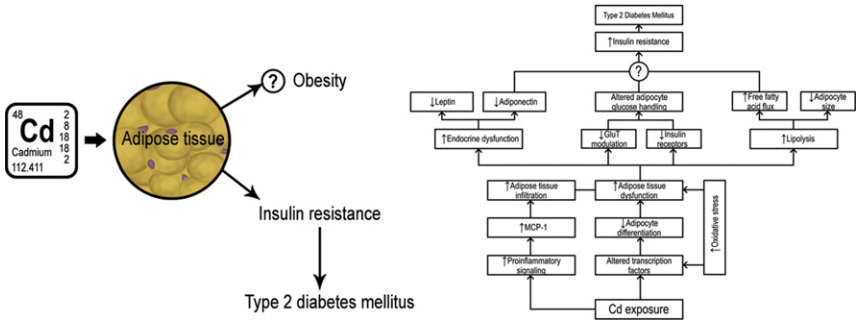
HIGHLIGHTS

- Human data on the association between Cd exposure and obesity are contradictory.
- Laboratory studies demonstrate that Cd exposure causes adipose tissue dysfunction.
- Cd-induced adipose tissue dysfunction promotes insulin resistance without obesity.
- Human and laboratory studies indicate the role of Cd in diabetes.

GRAPHICAL ABSTRACT



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ABSTRACT

Multiple studies have shown an association between environmental exposure to hazardous chemicals including toxic metals and obesity, diabetes, and metabolic syndrome. At the same time, the existing data on the impact of cadmium exposure on obesity and diabetes are contradictory. Therefore, the aim of the present work was to review the impact of cadmium exposure and status on the risk and potential etiologic mechanisms of obesity and diabetes. In addition, since an effect of cadmium exposure on incidence of diabetes mellitus and insulin resistance was suggested by several epidemiologic studies, we carried out a meta-analysis of all studies assessing risk of prevalence and incidence of diabetes. By comparing the highest versus the lowest cadmium exposure category, we found a high risk of diabetes incidence (odds ratio = 1.38, 95% confidence interval 1.12–1.71), which was higher for studies using urine as exposure assessment. On the converse, results of epidemiologic studies linking cadmium exposure and overweight or obesity are far less consistent and even conflicting, also depending on

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Insulin resistance
Obesity
Diabetes

differences in exposure levels and the specific marker of exposure (blood, urine, hair, nails). In turn, laboratory studies demonstrated that cadmium adversely affects adipose tissue physiopathology through several mechanisms, thus contributing to increased insulin resistance and enhancing diabetes. However, intimate biological mechanisms linking Cd exposure with obesity and diabetes are still to be adequately investigated.

Contents

1. Introduction

Obesity and diabetes mellitus type 2 have reached epidemic proportions on the border between XX and XXI centuries (James et al., 2001; Lam and LeRoith, 2012). In particular, the prevalence of obesity among American adults has doubled from 1980 to 2000, accounting for one third of the population (Ogden et al., 2014). Moreover, in 2013, every third person worldwide had excessive body weight (overweight or obesity) (Hruby and Hu, 2015). Correspondingly, the number of diabetics in 2013 was neatly 382 million, and it is expected to increase to 592 million in 2035 (Winer and Sowers, 2004). Due to an extremely high prevalence and association with metabolic disturbances, obesity has a significant socioeconomic impact, being associated with 21% of all health expenditures in the USA ($190 billion/year) (Hruby and Hu, 2015). In turn, according to 2012 estimates, the total cost of DM2 in USA was $245 billion, being characterized by a 41% increase in comparison to the 2007 (ADA, 2013).

Obesity is associated by increased adipose tissue mass and adipocyte dysfunction (Hajer et al., 2008), being accompanied by increased production of proinflammatory adipokines (Fantuzzi, 2005; Weisberg et al., 2003; Wellen and Hotamisligil, 2003), oxidative stress (Furukawa et al., 2004), endoplasmic reticulum stress (Özcan et al., 2004), and insulin resistance (Maury and Brichard, 2010). Such mechanisms mediate a tight interaction between obesity and diabetes, that resulted in the introduction of the term “diabesity” (Farag and Gaballa, 2011; Schmidt and Duncan, 2003). Moreover, a complex of pathologies including obesity, hyperglycemia, arterial hypertension and dyslipoproteinemia was clustered and termed “metabolic syndrome” (Eckel et al., 2010).

Multiple attempts have been made to assess the causes of diabesity and metabolic syndrome epidemics. In particular, it has been proposed that the increased incidence of both diabetes and obesity may be associated with the increased number of sweeteners, sedentary lifestyle, stress, nutrient deficiencies (Hyman, 2014). These observations are in general in agreement with the initial hypothesis of the role of positive caloric balance in obesity, diabetes, and metabolic syndrome in general (Hyman, 2014; Roberts et al., 2013). However, recent studies have revealed a significant association between environmental pollution and obesity epidemics (Madrigano et al., 2010). The possible role of certain chemical toxins of environmental in the etiology of obesity epidemics was proposed recently in the latest years (Baillie-Hamilton, 2002). Further studies have demonstrated the impact of environmental pollution on the incidence of diabetes and metabolic syndrome (Andersen et al., 2012; Eze et al., 2015). Moreover, it has been proposed that differential response of the human organism to environmental pollution even in terms of similar exposure patterns is indicative of the presence of gene-environment interaction that may promote the development of metabolic syndrome (Andreassi, 2009).

Toxic metals and metalloids also seem to be involved in MetS pathophysiology (Wang et al., 2014). Thus, it has been demonstrated that metabolic syndrome is associated with mercury (Chung et al., 2015; Eom et al., 2014; Park et al., 2013; Tinkov et al., 2015), lead (Lee et al., 2013; Park et al., 2006; Rhee et al., 2013), and arsenic (Chen et al., 2012; Wang et al., 2007; Wang et al., 2010) exposure.

Cadmium is a heavy metal that also refers to endocrine disrupting chemicals, having a special impact on the functioning of reproductive organs, including testes, placenta (Takiguchi and Yoshihara, 2005), and ovaries (Henson and Chedrese, 2004). The mechanisms of toxicity of Cd also include induction of oxidative and endoplasmic reticulum stress, inflammatory response (Moulis and Thévenod, 2010; Thévenod and Lee, 2013), genotoxicity (Filipič, 2012; Schwerdtle et al., 2010), and interference with essential metals (especially zinc) (Moulis, 2010).

Despite the well-documented role of endocrine disrupting chemicals, oxidative, endoplasmic reticulum stress, and inflammation in pathogenesis of obesity, diabetes and metabolic syndrome, the association between Cd exposure, diabetes, and especially obesity, as well as the underlying mechanisms are still unclear.

Therefore, the primary objective of the study was to review the existing clinical and experimental data on the association between Cd exposure, body burden and obesity and diabetes in clinical and experimental studies, and the mechanisms linking Cd to these pathologies.

2. Cadmium as an environmental toxicant

Cadmium (Cd) is released in the environment by natural and anthropogenic activities. It is utilized for corrosion protection of steel (cadmium plating), as solder and weld metal in alloys, polyvinyl chloride plastics, as pigments in paint colours, different types of paint and glazes,