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Current Understanding of the Relationship between Metal Exposures and Risk of Type 2 Diabetes

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Introduction

Type 2 diabetes (T2D) and its complications constitute a major public health problem for both developed and developing countries due to the high rate of morbidity and mortality associated with the disease. More than 400 million people worldwide have T2D, and there has been a rapid increase globally in its burden [1]. In the U.S., the Centers for Disease Control and Prevention reported that 29 million people have diabetes [2] and one in three children born in the US in the year 2000 will go on to develop T2D at some point in their lifetime [3]. In China, a recent national survey reported up to 114 million Chinese adults with T2D [4]. Thus, identification of novel preventable risk factors for T2D beyond those that are already established is an urgent need with significant public health implications. New evidence from both experimental and human studies has resulted in increased interest in studying the relationship between T2D and heavy metal exposures that are ubiquitous in the environment. A heavy metal is any metal or metalloid of environmental health concern, including both toxic metals and essential trace metals. Due to large-scale production and consumption, heavy metals are emitted into the environment in large quantities through solid waste and wastewater disposal, recycling of electronic and electric waste, vehicle exhausts and industrial pollution. Human exposure to heavy metals occurs through inhalation of dust, direct ingestion of polluted soil and water, dermal contact of contaminated soil and water, and consumption of foods grown in contaminated fields as well as tobacco products. Below is a brief review of the current understanding of the relationship between metal exposures and risk of type 2 diabetes and the suggestions for future studies.

Proposed mechanisms linking heavy metal to T2D risk

If heavy metal exposures indeed increase T2D risk, then, how do they affect the risk? The current literature does not seem to allow us to draw a definitive conclusion. Seven potential mechanisms are briefly summarized below. It should be noted that individual heavy metals may increase T2D risk via different biological mechanisms due to the fact that 1) specific toxic metals have varied toxicities in pancreatic islet cells [5-7], 2) essential trace metals at normal levels have varied biological functionsthatare directly involved in glucose homeostasis [7-9], and 3) imbalances of essential trace metals in humanshave different impacts on islet cells and diabetogenic effects [8-10]. Multiple mechanisms may also be involved to work synergistically resulting in islet dysfunction and ultimately dysglycemia [10]. Pancreatic islet β-cell dysfunction and insulin resistance are the hallmark of T2D, and thus heavy metals that reduce the function of insulin producing β-cells are therefore highly relevant to T2D risk.

Toxic metals-induced oxidative stress directly damage pancreatic islet β-cells: It is well known that toxic metals (As, Cd, Hg, Pb) have the ability to induce oxidative stress through the increased production of reactive oxygen species (ROS) such as superoxide radicals, hydrogen peroxide and nitric oxide that are highly reactive [11,12]. The islet β-cells have a high expression of metal transporters and low expression of antioxidants that creates a weak anti-oxidative defense system in pancreatic islet cells that makes the islet cells extremely sensitive to the effects of heavy metals, resulting in pancreatic islet β-cell dysfunction

or destruction or even death [6]. Studies have shown that as increases ROS generation and induces oxidative stress and cell death in pancreatic β-cells [12-14]. Cd can accumulate in pancreatic β-cells and cause β-cell dysfunction, induce degeneration, necrosis, and weak degranulation in the β-cells and decrease β-cell viability and even induce β-cell death through induction of oxidative stress and disruption of islet β-cell function [10,15-17]. The toxicity of Hg in islets is highly related to oxidative stress [18] since Hg-induced oxidative stress can cause islet β-cell dysfunction, apoptosis and death [19-21]. Pb is known to induce production of ROS [12,22,23] and Pb-triggered oxidative stress can lead to the degradation of proteins, nucleic acids and lipid peroxidation [22]. Exposure to Ni, which is considered both toxic and essential metal, also causes production of free radicals impairing islet function and induces glucose deregulation [24-28].

Toxic metal-induced oxidative stress affects insulin gene activities: Toxic metal-induced oxidative stress could also decrease insulin gene promoter activity and insulin mRNA expression in pancreatic islet β-cells [6,7,12,29,30] and, thus, alter the related molecular mechanism in glucose regulations and modify their functions and kinetics by decreasing insulin release; impairing insulin receptor and disrupting the glucose uptake; decreasing peripheral utilization of glucose and inducing gluconeogenesis; increasing hepatic glycolysis and pancreatic glucagon release [6,7,12,31-34]. Hence, the toxic metal exposure and the resulting oxidative attack in insulin gene activity could be an important factor in the pathogenesis of T2D.

Imbalanced body levels of essential trace metals adversely affect islet cell functions: Essential trace metals at normal levels play a key role in glucose homeostasis, because they are essential cofactors in glucose metabolic pathways, pancreatic β-cell function and the insulin signaling cascade [6-9]. These essential metals enhance insulin action through activating insulin receptor sites, serving as cofactors or components for enzyme systems involved in glucose metabolism, increase insulin sensitivity [7-9]. However, the proper glucose metabolic functions of the essential metals depend on their normal levels in pancreatic islet. Imbalanced levels (either deficiency or overexposure) of essential metals will adversely affect pancreatic islet cells and cause development of diabetes. For example, Zn at normal levels plays a key role in maintaining the pancreatic islet cell function in the synthesis, storage, and secretion of insulin [7]. Zn deficiency, however, adversely affects the ability of islet cells to produce and secrete insulin [35,36]. Zn at high levels is actually toxic to the islet beta cells because of enhanced oxidative damage [37,38]. Cu deficiency could result in glucose intolerance, decreased insulin response and increase glucose response [9], and might lead to the distortion of mitochondria in pancreatic acinar cells [39]. Se at normal level regulates specific beta cell target genes, promotes improvement in islet function and is a key component of several functional selenoproteins that protect tissues and membranes from oxidative stress [7,9]. Excess Se level has a potential diabetogenic effect possibly by impairing insulin responsiveness; increasing rates of glycolysis; stimulating the release of glucagon and, thus, promoting hyperglycemia or inducing over expression of antioxidant selenoproteins resulting in insulin resistance and obesity [40-42].

Mg plays a key role in regulating insulin action and insulin-mediated glucose uptake. Mg deficiency results in a decrease in insulin mediated glucose uptake [43,44]. Dietary and supplemental Mg has been shown to reduce the risk of T2D [45]. Cr plays an important role in the metabolism of carbohydrates and lipids leading to normalization of the synthesis and secretion of insulin and the optimal glucose uptake by cells [7,46]. Mn is required for normal insulin synthesis and secretion [7]. Altered Mn metabolism was associated with impaired glucose utilization [47]. Elevated body levels of Fe oxidize various biomolecules such as nucleic acids, proteins and lipids which may contribute to T2D development by decreasing insulin secretion from pancreatic beta cells with concomitant increase of insulin resistance [48-50]. Higher Ca concentration impairs carbohydrate and lipid metabolism, while imbalanced Ca levels can have adverse effects on β-cells secretion function and affect normal insulin release [9]. V affects glucose transport, glycolysis, and glucose oxidation and glycogen synthesis [51-53]. Co could cause an increased expression of glucose transporter 1 and inhibition of gluconeogenesis [54]. Thus, while it is indisputable that essential metals at normal levels play an important role in glucose metabolism, imbalanced levels of trace metals, however, could have severe adverse effects on pancreatic islets [6-9,55].

Essential trace metals at normal levels exhibit an antagonistic effect from toxic metal exposures and thus reduce T2D risk induced by toxic metals: Toxic metal-induced oxidative stress causes islet β-cell destruction or dysfunction and increase T2D risk, while essential trace metals with their antioxidant properties at normal levels have the ability to counteract the oxidative stress induced by toxic metals, and thus modulate the toxicity of toxic metals and protect the pancreatic islet β-cells from toxic metal-induced damages. The antagonistic effect existing between essential trace metals and toxic metals plays an important role in maintaining insulin homeostasis and reducing the risk of T2D.Cu together with Zn, for example, is essential for balanced oxidant-antioxidant mechanisms, and Cu and Zn imbalances can increase susceptibility to toxic metal-induced oxidative damage to islet β-cells and thereby lead to the pathogenesis of diabetes [7-10]. Cr is a component or activator of some enzymes, mostly antioxidants. Se is a cofactor of the antioxidant enzyme glutathione peroxidase that enables to reduce the Cd/Pb-induced oxidative stress [56-58].

Toxic metals compete with essential metals for various physiological function and affect T2D risk: Toxic metals compete with essential metals for absorption and excretion; transport of metals in the body; binding to target proteins;

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metabolism and sequestration of toxic metals [59-61]. Part of Pb toxicity, for example, comes from its ability to mimic other essential metals (such asCa, Fe, and Zn), as it binds to and interacts with many of the same enzymes as these essential metals and, thus, interferes with the enzyme's ability to catalyze its normal reactions [12]. Cd and Pb have similar chemical and physical properties to Zn, and compete for the binding sites of metal absorptive and enzymatic proteins. Therefore, in case of Zn deficiency and increased exposure to these toxic metals, the body will use Cd and Pb instead of Zn [62]. Cd also competes with Fe for access to intestinal metal uptake transporters [63]. Deficiency of Fe can lead to greater absorption and toxicity of Cd and Pb [64,65]. Se at low concentration can decrease as toxicity via excretion of As-Se compounds, but excessive Se can enhance As toxicity [66]. Ca and Mg also compete with Pb or Cd for intestinal absorption to reduce the toxic metal burden and prevent toxic metal induced tissue damage by competitive binding to active sites of the enzymes [67,68].

Heavy metals increase the risk of diabetes through endocrine disruption: Toxic metals (As, Cd, Pb, Hg) and some of the essential metals (Co. Cu, Cr, Ni, Se) are metalloestrogens and may increase the risk of diabetes through endocrine disruption [69,70]. For example, as was shown to mimic the action of insulin by phosphorylation of PKB/Akt-mediated GLUT4 expression in vitro [6]. Se sustains improvement of glucose homeostasis by exerting insulin like actions in diabetic rats [71]. Cu also possesses an insulin-like activity and promotes lipogenesis [9]. Cr enhances the insulin receptor activity on target tissues [46]. V acts primarily as an insulin mimetic agent affecting glucose transport and glucose oxidation [9].

Heavy metals affect diabetes risk through body weight changes: Low-level Pb exposure during development resulted in later life obesity in adult mice [72]. Pb intake during development caused higher food intake, higher body weight and body fat, and higher insulin response [73]. A study reported that Hg, Mn and Co affect lipid metabolism in the adipose tissue and Hg may accelerate the development of obesity-related diseases in mice [74]. Human studies also found that toxic metals could contribute to weight changes and associated with obesity. A U.S. NHANES study found that Ba and Tl were positively associated while Cd, Co and Pb negatively associated with BMI and waist circumference [75]. U.S. adults who had a higher BMI had lower levels of Hg in their blood [76]. Cd levels in adults were found to be negatively associated with being overweight [77]. Overweight/obese women were found to have a high prevalence of Ni allergy and a low-Ni diet could help loss weight [78].

Epidemiological Evidence of Metal Exposures and T2D Risk

Consistent with findings from experimental studies, epidemiologic studies have provided provocative, albeit inconsistent, evidence supporting the hypothesis that heavy metal exposures increase the risk of T2D as briefly summarized below.

Heavy metal exposures and T2D risk

Previous epidemiological studies have reported statistically significant associations between T2D and exposure to As [79-102], Cd [91,103-105], Hg and Pb [91,105-107], while other studies found no significant association between these toxic metals and T2D risk [77,80,104,108,107-126]. Studies also reported a significant association between imbalances in essential metals and risk of T2D. Specifically, imbalanced levels of Zn [80,91,107,110,117,127-131], Cu [80-117], Mn [107,123,128,129,132,133], Cr [107,128,129], Co [107], Mg [127,134], Mo [80], Ni [80,123,128,133,135-137], W [80,108], and V [129] were associated with an increased risk of T2D. Other studies, however, failed to establish a significant association between these essential metals and T2D risk [80,91,105,107,108,116-118,123,127,129,133-135,138-143].

Major gaps in current epidemiologic studies linking heavy metals to T2D risk

Prior epidemiologic studies have some major limitations in studying the relationship between heavy metal exposures and T2D that could be used to explain the observed inconsistent findings linking heavy metals to T2D as summarized below

Most previous studies were based on cross-sectional designs: For example, among the heavy metals associated with the risk of T2D, As has received earliest and special attention. Out of 34 studies of As exposure and T2D risk, 23 were cross-sectional studies [57,79-91,97-99,109-111,116,124,125], 3 case-control studies used blood samples collected after diagnosis [92,112,115]; 3 were retrospective studies, 1 a nested case-control study, and 4 were prospective studies of which 3 studies only measured drinking water As levels [93-96,100-102,113]. Out of 14 studies of Zn exposure and T2D risk, 13 studies were either cross-sectional or case-control studies using blood samples obtained after T2D diagnosis [80,107,110,115,116,122,126-128,130,132,137,138]. Most of the studies linking other heavy metals to T2D risk were also cross-sectional. It is well known that toxic metals could cause renal tubular dysfunction in patients with established T2D, and that dysfunctional kidneys lose metals through increasing renal excretion that results in their concomitant decrease in the blood [144]. Thus, findings from cross-sectional studies may actually reflect disease consequences, rather than disease causes. A recent large cross-sectional study from U.S. NHANES data reported an increased risk of diabetes associated with metal exposures and concluded that prospective studies are urgently needed to further evaluate metals as risk factors for diabetes [108].

Most previous studies focused on individual metals, rather than the joint effects of multiple metals and ignored possible antidiabetic effects of essential metals in reducing toxic metal toxicity: Despite experimental studies which have shown that heavy metal exposures may increase T2D risk and that essential metals at normal levels could counteract the

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toxicity from toxic metal exposures on T2D risk, few human studies have directly and comprehensively investigated the effects of multiple metal exposures and the alleged antagonistic effect between essential and toxic metals on T2D risk. Nevertheless, essential trace metals are recommended by some as potential beneficial supplements for the prevention of T2D [22,145-147]. But the fact is that no epidemiologic study has actually investigated the antagonistic effect of essential metals in reducing toxic metal effects nor the optimal levels of essential metals to mitigate the toxic metal effect. Thus, it is considered by some to be immature at this stage to recommend mineral supplementation as a means of prevention of T2D, and additional and methodologically comprehensive prospective follow-up studies are needed to further determine the significance and the optimal levels of the anti-diabetogenic effects of essential metals [7,8,18,45,108,143,148-151]. Establishing optimal body levels of essential metals that reduce the adverse effect of toxic metal exposure could lead to simple, safe, readily available, acceptable and highly affordable nutrition intervention for the prevention of T2D that will have both clinical and public health significance worldwide.

Most previous studies have relied on self-reported T2D: Studies have shown that the undiagnosed T2D rate is high, as 28% of all T2D cases are undiagnosed even in the US [2]. The prevalence of prediabetes, which is associated with an increased risk of T2D, is also high, reaching 37% in U.S. adults [152]. Epidemiologic studies relying on self-reported T2D status and not considering undiagnosed diabetes and prediabetes in their selection of study subjects could cause serious misclassification of disease status in epidemiologic studies, leading to attenuated estimates of the association between metal exposures and T2D risk. Small sample size few epidemiologic studies conducted to date have had the power to study effect modification between essential trace metals and toxic metals in reducing T2D risk.

Suggestions for Future Studies

Due to the inconclusive nature of the reported association and the widespread exposure to heavy metals, there exists an urgent need for large prospective cohort studies to investigate the alleged association. In addressing the major gaps in the current literature, we suggest that future prospective studies or nested case-control studies should:

1. Simultaneously evaluate the role of multiple heavy metal exposures on T2D risk;

2. Assess the antagonistic effect of essential metals in reducing toxic metal effect on T2D;

3. Determine the optimal body levels of essential metals that could mitigate the risk of T2D from toxic metals;

4. Nested case-control study should select both cases and the controls based on physical examinations and clinical biochemistry tests both at baseline and during follow-up. This allows the studies to 1) avoid recruiting cases relying on self-report; 2) identify all incident T2D cases from the cohort; and 3) avoid selecting controls with undiagnosed diabetes and prediabetes that would attenuate associations of metal exposures with T2D.

In summary, there is a general consensus that large and high-quality prospective studies of well-characterized populations are urgently needed to further investigate heavy metal exposures as risk factors for T2D, an association that is biologically plausible.

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