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Assessment of Mercury, Lead and Cadmium Levels among Children with Type 1 Diabetes in Suez Canal Region: Review Article

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ABSTRACT

Background: Type 1 diabetes mellitus (T1DM), a chronic illness requiring lifelong insulin treatment, is on the rise among children and adolescents globally. While, epidemiological studies on childhood T1D in Egypt are limited.

Objective: This study aimed to elucidate potential links between environmental heavy metal exposure [mercury (Hg), lead (Pb), and cadmium (Cd)] and diabetes onset in children diagnosed with T1DM in Suez Canal region.

Methods: In our search for information on T1DM, Mercury, Lead, we used Google Scholar, Science Direct, PubMed, and other internet databases. Additionally, the writers combed through relevant literature for references; however, they only included research that were either very recent or thorough, covering the years 2010–2023

Conclusion: While, the specific mechanisms by which heavy metals contribute to the disease are still being investigated, evidence suggests that these environmental toxins can play a significant role. Further research is crucial to understand the complex interactions between heavy metal exposure, oxidative stress, and autoimmune processes in the development and progression of T1D.

Keywords: Type 1 diabetes, Mercury, Lead, Cadmium.

INTRODUCTION

Type 1 diabetes, a chronic illness requiring lifelong insulin treatment, is rising among children and adolescents globally. While, epidemiological studies on childhood T1D in Egypt are limited, available data suggests that the incidence rates in the Nile Delta region are lower than those reported from neighboring countries like Sudan, Libya, Tunisia, Saudi Arabia, Kuwait, and Turkey [1- 4].

A prevalence rate of 0.7/1000 and an incidence rate of 4.01/100,000 were discovered among children and adolescents in a study carried out in three governorates of Egypt (Fayoum, North Sinai, and Suez). In Menoufia governorate, the prevalence of type 1 diabetes among school-aged children was 3.75 per 1000. In addition, the survey found that there were more men than women (33.3%). There is no consistent trend of type 1 diabetes incidence among age groups. The incidence rises with age, reaching a peak during puberty, according to most registries. There is always a gender effect with this trend; typically, girls reach a peak one or two years before boys do. Between the ages of 0 and 18, the incidence and prevalence of type 1 diabetes in the Nile Delta region rose steadily over the course of 18 years. T1D was more common in rural regions, and women were more likely to be affected than men. Diagnosis of type 1 diabetes also showed a seasonal tendency, with winter being the peak season [2].

The pancreatic beta cells responsible for manufacturing insulin are targeted by the immune system in type 1 diabetes, an autoimmune illness. It is probable that environmental triggers and genetic predisposition work together to generate this, albeit the exact reason is yet unknown [5]. Toxins and food variables are other suspected triggers, in addition to viral infections [5].

The geographical variability in T1D incidence suggests a role for genetic factors, especially within the HLA system [2]. However, the recent rapid increase in T1D incidence worldwide cannot be solely attributed to genetics [2]. Even among ethnically similar populations, T1D incidence can vary significantly, highlighting the influence of environmental factors on disease evolution [2].

Heavy metals effects on health:

Heavy metals, a group of metals with a high atomic density (greater than 6 g/cm^3), are naturally occurring elements. While, some heavy metals, in trace amounts, are essential for human physiology, they can be toxic at higher concentrations [6].

Since the term "metal trace elements" (MTEs) includes both harmful and less harmful heavy metals, it is becoming more popular. There is a concentration threshold above which most MTEs become hazardous. Nickel, zinc, cadmium, copper, lead, mercury, and even trace amounts (less than 0.01 mg/kg) can cause harm to people [6].

Reduced energy levels are only one of the many health issues that heavy metal exposure can cause. Injury to the central nervous system, respiratory system, kidneys, liver, and blood type, Discouraging neurological, muscular, and skeletal degeneration that mimics the course of illnesses such as cancer, MS, PD, Alzheimer's, and muscular dystrophy. Some heavy metals can have toxicity levels that are slightly higher than environmental background amounts. Consequently, in order to execute effective preventive measures, it is essential to have thorough understanding of heavy metals. In addition to lowering water quality,

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heavy metals provide a significant health risk by interfering with central nervous system, renal, hepatic, and respiratory system functions [7, 8].

Carcinogenicity is a concern with most MTEs. Additionally, they have the potential to interfere with bioregulatory systems, stunt development, and amplify the symptoms of neurodegenerative diseases including Alzheimer's and Parkinson's as well as chronic fatigue syndrome. Mercury and lead are among the heavy metals that, when ingested, can cause the immune system to launch an attack on its own cells, a condition known as an autoimmune response. Diseases of the joints, such as rheumatoid arthritis, as well as those of the kidneys, blood vessels, and neurological system, can result from this. A variety of human health issues have been linked to heavy metal exposure [9, 10].

There are a number of mechanisms by which heavy metals bioaccumulate in living things, including humans. Metals enter cells and tissues via their respective compartments; once there, they attach to macromolecules like proteins and nucleic acids, potentially damaging them and interfering with their function. This has the potential to cause a range of outcomes, such as: Mental disorders due to central nervous system dysfunction, damage to blood constituents, damage to vital organs like the lungs, liver, and kidneys, and promotion of various disease conditions [7].

Multiple investigations have established a connection between heavy metals' carcinogenic and mutagenic effects and their ability to induce oxidative stress. Redox processes can be triggered in biological systems by cadmium, nickel, vanadium, cobalt, and arsenic ions, among others. Proteins and DNA are oxidatively damaged by the free radicals that are produced. These reactions can also activate redox-sensitive transcription factors and act as mitogenic signals, both contributing to carcinogenic effects. Heavy metals can also interfere with DNA repair processes, further contributing to carcinogenicity [11].

Continued exposure to heavy metals can disrupt the body's internal balance. Heavy metals can accumulate and replace essential elements, such as lead replacing calcium, cadmium replacing zinc, and aluminum replacing other trace elements. These accumulated heavy metals can disrupt major metabolic processes, create an imbalance in antioxidants, and interfere with hormone function and enzyme activity. These disruptions can alter carbohydrate, protein, and lipid metabolism, leading to increased susceptibility to infections. The alterations in neurotransmitter synthesis and function further disrupt central nervous system functions [12].

Certain enzymes involved in metabolism, detoxification, and damage repair can be inhibited by heavy metals, along with the cell membrane, mitochondria, lysosomes, endoplasmic reticulum, nuclei, and other cellular organelles and processes. They have the ability to bind to DNA, altering its structure in ways that trigger cell cycle regulation, cancer development, or cell death. In terms of public health, systemic toxicants including mercury, lead, cadmium, and barium are at the top of the priority list due to their extremely toxic levels [13].

MERCURY

Mercury is a naturally occurring, shiny, silver-white liquid metal that becomes a colorless and odorless gas when heated. Mercury is highly toxic and bioaccumulative, posing a significant threat to the marine environment. Mercury is the only metal that exists in liquid form at room temperature. The US Environmental Protection Agency (USEPA) has set a safe limit of 10 nm for mercury ions in drinking water to prevent serious health problems. Mercury's toxicity stems from its prolonged half-life, lack of decomposition, and its ability to interact with enzymes and proteins. Mercury exists in three main forms in the environment: Elemental mercury: Found in the atmosphere and present as a liquid at room temperature. Used in thermometers and fluorescent bulbs. Inorganic mercury: Includes metallic (Hg), mercurous (Hg^{+}), or mercuric (Hg^{2+}) forms. Found in crystalline form and used in pesticides and antiseptics. Organic mercury: Includes aryl and alkyl forms. Methylmercury, the most common example, readily enters the food chain [7, 14].

Mechanisms of mercury toxicity:

Mercury ions entering the body cause toxic effects through several mechanisms, including: Generalized oxidation, where mercury ions can induce oxidative stress leading to cellular damage. Enzyme inhibition: Mercury ions bind to proteins, including those with amine, amide, carboxyl, and phosphoryl groups, rendering them inactive. Protein precipitation: Mercury ions can bind to proteins, altering their structure and function. The chemical form and oxidation state of mercury determine its toxicity. Mercury, an element, quickly crosses cell membranes and is very soluble in lipids. When compared to its monovalent counterpart, divalent mercury (Hg^{2+}) is far more poisonous. The gastrointestinal mucosa is more sensitive to organic mercury compounds, and they are 90% absorbed compared to 10% inorganic versions [13].

Effect of mercury on health:

The toxic effects of mercury on humans are influenced by factors such as the chemical form of mercury, age, overall health status, and the type of exposure. Particularly in younger children, mercury poisoning can cause harm to the neurological system [14].

The impact of mercury exposure in children:

Mercury exposure in children is concerning due to its potential impact on development: Fetal exposure: Maternal mercury intake through contaminated shellfish and fish can impair neurological development in children [14].

Neurotoxicity: Mercury's neurotoxicity can lead to impaired nervous and cognitive development, resulting in lower verbal IQ scores, social developmental delays, fine motor skill deficits, and prosocial behavior issues [13]. Exposure can also result in mental retardation.

Mercury poisoning in children can cause a variety of other health issues, including but not limited to: developmental delays, epilepsy, abnormal saliva production, abnormal limb development, dysarthria, damage to the cerebellum, improper eye alignment, and primitive reflexes [13].

LEAD

In dry environments, lead takes on a bluish tint and appears as a shiny silvery metal. The Earth's crust contains this poisonous element, which occurs naturally. Depending on the surrounding conditions, lead tarnishes when exposed to air, creating a diverse variety of chemicals [7, 14].

Mechanisms of lead toxicity:

Toxic effects of lead on human health are mainly caused by: Damage to cells and oxidative stress occur when the body's antioxidant defenses are overwhelmed by an increase in free radical production [15]. Glutathione is rendered inactive and oxidative stress is intensified when lead attaches to its sulfhydryl group. Lead further reduces glutathione levels by inhibiting the action of enzymes such as δ-aminolevulinic acid dehydratase (ALAD), glutathione reductase, glutathione peroxidase, and glutathione-S-transferase. Haemolytic anemia can be caused by lipid peroxidation, which can disrupt cell membranes at high lead levels [15].

Ionic mechanism: One way lead ions might interfere with cellular metabolism is by replacing other bivalent cations (Ca^{2+}, Mg^{2+}, Fe^{2+}) and monovalent cations (Na^{+}). Neurotransmitter release, ion transport, cellular adhesion, signaling, protein folding, maturation, and death are all impacted by this ionic system. Protein kinase C is an essential enzyme for neuronal excitation and memory storage, and even at picomolar doses, lead can substitute calcium in this enzyme [7].

Sodium ion disruption: Lead toxicity can interfere with sodium ion concentrations, disrupting cell-to-cell communication and neurotransmitter uptake. Even low levels can affect protein kinase C, leading to prolonged neural excitation and memory storage [15].

Health effects of lead exposure on children:

Young children are particularly vulnerable to lead poisoning due to their higher absorption rates of lead (four to five times higher than adults). Their hand-to-mouth behavior also increases their likelihood of ingesting lead-contaminated soil, dust, or paint chips. Children with pica, a psychological disorder involving the craving of non-food substances, are at an even higher risk of ingesting lead-containing paint. The effects of lead exposure on humans depend on the severity of exposure. High lead levels in children can cause: Decreased attention span, increased irritability, seizures, headache, coma, and death. Lower levels of lead exposure have been linked to: Reduced intelligence and increased impulsivity in school-aged children [15].

CADMIUM

The heavy metal cadmium is extremely poisonous and has no recognized physiological use. It is the fifth most poisonous heavy metal, according to research. Although it is present as a combination, cadmium does not exist in nature as an element. Three of cadmium's most prevalent chemicals are oxide, carbonate, and sulfide. The hydrochemical characteristics of cadmium make it a mobile element in groundwater [16].

Mechanisms of cadmium toxicity:

Cadmium's toxicity stems from its ability to: Disrupt enzymatic systems where cadmium significantly impacts cellular enzymatic systems. Induce oxidative stress: Cadmium is known to trigger oxidative stress in cells. Cause nutritional deficiencies: Cadmium can disrupt nutrient uptake in plants. Its effects on cells are well-established, although the exact process of cadmium toxicity remains unknown. Metallothionein and other cysteine-rich proteins can enhance cadmium concentrations by a factor of three thousand. Hepatotoxicity is caused by the cysteine-metallothionein complex in the liver, while nephrotoxicity is caused by cadmium accumulation in renal tissue when it circulates to the kidneys. Additionally, cadmium can cause an iron deficit by binding to ligands that are histidine, cysteine, glutamate, or aspartate. The scavenging capabilities of metallothionein are diminished when cadmium is used instead of zinc because the two metals have the same oxidation states. Catalase, copper-zinc superoxide dismutase, and manganese superoxide dismutase are antioxidant enzymes that cadmium can inhibit. Metallothionein is a protein that binds zinc and also scavenges free radicals. Cadmium toxicity can be mitigated in cells that have metallothioneins, but it can be fatally poisonous in cells that do not produce these proteins. When cells are exposed to cadmium, the expression of the metalloprothin one gene determines whether they undergo apoptosis or necrosis [7, 16].

Among cadmium's effects on mitochondria is its ability to cause oxidative stress, which in turn causes the production of cell-damaging reactive oxygen species (ROS). Programed cell death (apoptosis) is activated when cadmium is present. Damage to mitochondrial function may result from cadmium's ability to alter mitochondrial DNA. Cadmium has the ability to change the way genes are expressed within mitochondria. Cadmium has the ability to hinder complexes of respiratory chains, which are essential for the synthesis of energy within mitochondria. The creation of cellular energy is affected by cadmium because it decreases ATP synthesis. Cadmium changes the permeability of the inner mitochondrial membrane, which adds to

mitochondrial dysfunction. A number of clinical illnesses can be traced back to these mitochondrial abnormalities [17].

Cadmium-associated health effects:

Acute intoxication: Acute exposure to cadmium can cause severe health problems. Inhaling cadmium fumes can damage the respiratory system, leading to shortness of breath, mucous membrane irritation, and pulmonary edema [11].

Chronic exposure: Chronic exposure to cadmium can lead to a variety of adverse effects, including renal and hepatic dysfunction, pulmonary edema, testicular damage, osteomalacia, adrenal damage, and hemopoietic system damage. Cadmium is a known human carcinogen (Group 1 of the International Agency for Research on Cancer classification) [17].

Osteoporosis Risk: Cadmium is recognized as a potential risk factor for osteoporosis, although the exact mechanisms and critical exposure levels remain unclear [17].

Heavy metals (Mercury, lead, and cadmium) and type 1 diabetes:

Autoimmune disease causes the pancreas to lose its insulin-producing beta cells, leading to type 1 diabetes (T1D). The identification of environmental triggers for type 1 diabetes is still a challenging issue, despite the fact that there has been great strides in treating the disease, reducing complications, and improving the quality of life for people with diabetes. The current methods for predicting the likelihood of type 1 diabetes include testing for islet cell antigens using autoantibody screening, family history, and genotyping for the HLA class II loci HLA-DR and HLA-DQ. Epigenetic and environmental variables likely play a role in determining an individual's risk of type 1 diabetes, since the vast majority of people with a hereditary predisposition do not actually get the disease. The significance of environmental triggers is further underscored by the fact that type 1 diabetes is heterogeneous, with beta cell loss showing age-related variability. A person's genetic susceptibility may be reflected in the age at which type 1 diabetes begins to manifest. In Finland, for example, a lower cumulative incidence of type 1 diabetes in children was observed when parents' onset of diabetes was delayed. As people aged, the likelihood of type 1 diabetes decreased in Italy when either parent had Sardinian ancestry. Nutrition, pollution, chemicals, pollutants, and infectious diseases in childhood are only a few examples of how environmental risk factors, as shown in epidemiological research, can alter dramatically over time. These factors might speed up the death of beta cells or promote autoimmunity, both of which are involved in the pathophysiology of type 1 diabetes [5].

Insulin resistance and other diabetes problems may arise when metal status changes cause oxidative stress [18].

Heavy metals, nutritional supplements, pesticides, hydrocarbons, and hundreds of pharmaceutical compounds are just a few of the environmental agents that have the potential to cause or worsen autoimmune symptoms in vulnerable people. Over the past forty years, reports of glomerulonephritis caused by heavy metals including mercury and cadmium have surfaced [5].

The imbalance between the body's generation and neutralization of reactive oxygen species (ROS) leads to oxidative stress. Increased ROS production or decreased ROS scavenging capacity can both contribute to oxidative stress, which in turn can cause tissue damage. Many diseases, including diabetes, cardiovascular disease, and neurological problems, have oxidative stress as one of their underlying causes [19].

Mercury and type 1 diabetes:

As a heavy metal, mercury is a worldwide problem, especially in its organic form, methylmercury. The kidneys, astrocytes, lymphomas, human gums, alveolar epithelium, and pancreatic islet beta cells are just some of the cell types that can be damaged by organic and inorganic mercury compounds [14, 20]. Mercury poisoning can cause beta cell loss and malfunction due to oxidative stress. Oxidative stress is a key component in mercury's harmful effects on beta cells. A biomarker of oxidative DNA damage, 8-hydroxy-2'-deoxyguanosine (8-OHdG) is found in higher concentrations in urine samples from places contaminated with mercury, according to studies. People exposed to mercury had elevated levels of many antioxidant enzymes, including glutathione peroxidase, superoxide dismutase, and total protein thiols, in comparison to those in the control group. In vivo and in vitro, mercury can affect beta cell survival and function via oxidative stress pathways. Beta cell apoptosis and death induced by oxidative stress can be induced by methylmercury. In light of these findings, mercury might be an environmental determinant of diabetes [20].

The formation and function of pancreatic beta cells can be negatively impacted by methylmercury. Hyperglycemia, insulin resistance, and decreased pancreatic function are all risk factors for developing diabetes [21].

Additionally, methylmercury destroys the endoplasmic reticulum and ribosomes by interfering with translation and transcription. Additionally, it causes free radicals to be formed, which in turn impacts cellular integrity [7].

Mercury toxicity has numerous adverse effects, including:

Mercury has a number of negative effects on cells, including: enzyme inhibition (particularly sulfhydryl-

containing enzymes), increased reactive oxygen species (ROS) production, lipid peroxidation, cell membrane damage, and mitochondrial dysfunction (as a result of mercury's inhibition of mitochondrial enzymes, which causes depolarization and damage to the mitochondrial membrane and further contributes to ROS production). Methylmercury can drastically change DNA even at low concentrations. Pancreatic beta cells are vulnerable to oxidative stress and its effects on insulin production, suggesting that elevated methylmercury exposure may exacerbate diabetes pathogenesis in a roundabout way. Apoptosis and cell signaling are two of the many cellular activities that rely on mitochondria, the principal generator of ATP. People with a history of diabetes in their family also tend to have altered mitochondrial activity and lower ATP production. The DNA of mitochondria is extremely vulnerable to oxidative damage because it is situated near locations that produce ROS. Mutations in mitochondrial DNA produced by oxidative damage may account for around 1% of diabetic cases, according to researchers' hypotheses [22].

Lead and type 1 diabetes:

Currently, there is no acknowledged causal link between lead and type 1 diabetes. Lead levels in diabetic patients' blood, serum, and hair were found to be considerably greater than those in healthy control groups [18].

Ionic pathways and oxidative stress are the two main ways that lead toxicity manifests in live cells. An excess of free radicals relative to antioxidant defenses is what causes oxidative stress. Glutathione and other antioxidants shield cells from harmful free radicals. But lead can lower antioxidant levels and raise ROS levels. There are two forms of glutathione: reduced (GSH) and oxidized (GSSG). The reduced form stabilizes reactive oxygen species (ROS) by donating electrons to them. By attaching to the sulfhydryl group of glutathione, lead renders the enzyme inactive and raises levels of oxidative stress, therefore interfering with this process. Lead further lowers glutathione levels by inhibiting the function of enzymes such as ALAD, glutathione reductase, glutathione peroxidase, and glutathione-S-transferase. Cellular stress can be caused by high lead concentrations, which can harm proteins, nucleic acids, membranes, and lipids [15].

Cadmium and type 1 diabetes:

There is substantial evidence linking cadmium exposure to an increased risk of prediabetes and type 2 diabetic mellitus (T2DM). Experimental animals exposed to cadmium, either for a short or extended period of time, develop hyperglycemia and have their glucose homeostasis disrupted, according to multiple in vivo models. It remains unknown how exactly cadmium disturbs glucose homeostasis. The exact mechanism by which cadmium lowers serum insulin levels in humans and animals has not been determined, despite numerous investigations in this area. Here are some potential biological mechanisms: Energy metabolism disruptions where cadmium has the ability to interfere with how cells use energy. The induction of oxidative stress in a variety of cell types and tissues is a well-documented property of cadmium. Cadmium has the potential to disrupt the normal functioning of calcium channels. Cadmium has the potential to interfere with the attachment of cells to one another. Several experimental investigations have shown that cadmium affects a number of organs, including adipose tissue, the pancreas, and the liver. These organs are vulnerable to the diabetogenic effects of cadmium. There may be a correlation between cadmium exposure and diabetes, since cadmium exposure has been associated with pancreatic cancer. The results of a cross-sectional study showed that elevated cadmium levels in urine were associated with reduced fasting glucose. Research on the link between cadmium exposure and diabetes in rats found that the metal accumulated significantly in pancreatic tissue when animals were subjected to doses ranging from 0.2 to 2 mg/kg/day. According to these research, insulin release from beta cells in the pancreas was diminished, and glucose homeostasis was disturbed [17].

According to the findings of **Chang *et al.* [23],** pancreatic beta cells undergo apoptosis when exposed to cadmium, which triggers oxidative stress and activates the c-Jun N-terminal kinase (JNK) pathway. There is new evidence that mitochondrial DNA abnormalities caused by cadmium can cause beta cell death, which in turn can contribute to type 1 diabetes. Heavy metal exposure is associated with mitochondrial malfunction, which is believed to have a role in cell death [17]. Cadmium causes a cascade of events that culminate in cell death by disrupting matrix metalloproteinases (MMPs), which in turn increases the release of mitochondrial death effectors such cytochrome c, endonuclease G (EndoG), and apoptosis-inducing factor (AIF) [11, 23].

All of these things suggest that cadmium might be a metabolic disruptor. Studies in humans have demonstrated that it can accumulate in the pancreas, lending credence to the idea that it has direct pancreatotoxic effects. There has been evidence of a dose-dependent accumulation pattern in rats, which is consistent with the findings in animal studies. The buildup of cadmium in insulin-producing beta cells is dose- and time-dependent, according to in vitro investigations. According to a plethora of animal research, cadmium exposure damages beta cells and alters pancreatic shape, which in turn affects glucose metabolism. Accumulation of cadmium is also associated with oxidative damage, which is a major contributor to the onset of diabetes [11, 17].

CONCLUSION

The present state of knowledge on type 1 diabetes in Egypt and the possible involvement of heavy metals

in the onset of T1D is thoroughly summarized in this document. Environmental pollutants like heavy metals may play a major part in the disease, but the exact ways they do so are still a mystery. To fully comprehend the intricate interplay between oxidative stress, autoimmune processes, heavy metal exposure, and type 1 diabetes, additional research is essential. To effectively manage and prevent this crippling condition, it is crucial to understand these complicated relationships.

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