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Paper Title: Occupational Blood Lead (Pb) Exposure and Type 2 Diabetes Incidence: A Literature Review of possible biological mechanisms and epidemiological evidence linking environmental lead exposure to Type 2 Diabetes risk and an ecological study on occupational blood lead (Pb) exposure on Type 2 Diabetes in Adults >18 years old in all states in the United States from 2000 to 2012.

Summary: Maneeza Khan

Date: August 2022

Professor: Dr Caryl Waggett

About the Student:

Maneeza Khan is a student studying in the International Baccalaureate Diploma Programme at The Heritage School, Kolkata, India. This paper was written by her as a part of the Summer 2022 Scholarly program: LS190 Introduction to College-Level Research in Biology. This course was instructed by Professor Caryl Waggett from Allegheny College and covered topics on Eco-Health, Pathophysiology, and Toxicokinetics. Due to the student's interest in molecular epidemiology on metabolic diseases and the role of xenobiotic heavy metals on their incidence, she chose a relevant public health topic on the effect of Occupational Blood Lead (Pb) Exposure on Type 2 Diabetes Incidence. She explored her research topic by conducting an ecological study of the United States spanning 12 years and a literature review to propose possible biological mechanisms and epidemiological evidence linking environmental lead exposure to Type 2 Diabetes risk. Maneeza noticed a persistent research gap in linking the effect of environmental factors on the incidence of Type 2 Diabetes, which is why she chose a research topic that merges the two disciplines.

Research Question: To what extent does occupational blood lead (Pb) exposure ≥25 μg/dL affect the risk of Type 2 Diabetes in Adults >18 years old in all states in the United States from 2000 to 2012 and what are the possible biological mechanisms and epidemiological linking environmental lead exposure to Type 2 Diabetes Risk?

Keywords: Type 2 Diabetes (T2D), Occupational blood lead (Pb) exposure, endocrine disrupting chemicals (EDCs), pancreatic islet β-cell dysfunction

Abstract

Type 2 Diabetes (T2D) is a persistent health problem in the United States and is caused by a multitude of

lifestyle and environmental factors. While the increased incidence of T2D has been attributed to lifestyle factors, very little is known about the effect of environmental pollutants on the incidence of chronic metabolic diseases such as T2D. Occupational lead exposure is of particular interest in this regard. Even though there has been a consistent decline in overall environmental lead exposure levels, occupational lead exposure has been identified as the most common source of lead poisoning in non-pregnant adults. Lead, being a xenobiotic heavy metal, has severe ramifications on overall metabolic health. Firstly, an ecological study was conducted to understand the extent to which occupational blood lead (Pb) exposure ≥25 μg/dL affects the risk of Type 2 Diabetes in Adults >18 years old in all states in the United States 2000 to 2012. Diabetes Data was obtained from the CDC United States Diabetes Surveillance System and Lead Exposure Data was obtained from the CDC report "Elevated Blood Lead Levels Among Employed Adults — the United States, 1994–2012" by State Adult Blood Lead Epidemiology and Surveillance (ABLES). It was found that there is a strong negative correlation between Total Diagnosed Type 2 Diabetes in Adults and the Number of cases of employed adults with blood lead levels ≥25 μg/dL nationally from the years 2000 to 2012. Limitations of the study were also considered: there were not very optimized datasets, the incidence of lead exposure were deeply underestimated as only lead exposure ≥25 μg/dL was surveyed and synergistic effects of occupational exposure to many other environmental compounds were not considered. Considering the limitations and the fact that our understanding of the metabolic health effects of lead exposure is incomplete, a literature review of proposed epidemiological evidence and biological mechanisms linking environmental lead exposure to T2D risk was conducted. It is well known that even very low doses of lead exposure have harmful effects, so it is worthwhile to understand the mechanisms by which lead affects biological systems and to determine the exact role it plays in T2D risk. This paper supports the existence of a link between lead and T2D risk, but more research needs to be conducted to provide a clear mechanistic pathway for how a limited exposure to lead might lead to diseases like T2D.

1. Introduction

Type 2 Diabetes (T2D) is a rising global health problem due to the high rate of morbidity and mortality associated with the disease (Global Burden of Disease, 2021). It is a metabolic disease characterized by hyperglycemia, resulting from a progressive loss of insulin secretion on the background of insulin resistance. T2D is the leading cause of death, blindness, and renal failure and poses a major risk factor for vascular diseases such as myocardial infarction and stroke (WHO, 2019). According to the Centers for Diseases Control And Prevention (CDC), in the US, more than 37 million Americans have diabetes, of which approximately 90-95% have type 2 diabetes (CDC, 2019). This is why there is an urgent need for the identification of novel preventable risk factors for T2D beyond those that are already established. The increased incidence of T2D since the 1950s has been attributed to concurrent variations in lifestyle factors, including an increase in caloric consumption, a change in the quality of the nutrients, and a general decline in physical activity. However, in recent years, there has been growing epidemiological evidence that exposure to environmental pollutants and industrial chemicals can also affect the incidence of chronic metabolic diseases such as diabetes (Jun Ho Ji et al., 2020). The incidence of numerous environmental toxicants has increased at the same rate as diabetes incidence. Additionally, it has been demonstrated that several of these frequently used compounds interact with biological systems and have negative effects on the endocrine and/or metabolic systems (Adegoke et al.,2021). Environmental substances that cause endocrine disruption have been defined as endocrine disrupting chemicals (EDCs) by the U.S. Environmental Protection Agency. There is growing evidence that exposure to some of these EDCs increases the risk of developing diabetes (Min Kyong Moon et al.,2022).

EDCs such as phthalates, dichlorodiphenyldichloroethylene (DDE), and perfluoroalkyl substances (PFAS) lead to the development of Type 2 Diabetes in people. Animal studies have found that some EDCs directly target alpha and beta cells in the pancreas, fat cells, and liver cells, which causes insulin resistance and an excess of the hormone insulin in the body – risk factors for T2D.
An important class of environmental toxicants that pose human health risks and are also termed EDCs are heavy metals. They are defined as metals with relatively high densities, atomic weights, or atomic numbers. Heavy metals and metalloids can affect hormonal activity and overall physiology and a subset of them are considered xenobiotic, which means that they have no role in human physiology.

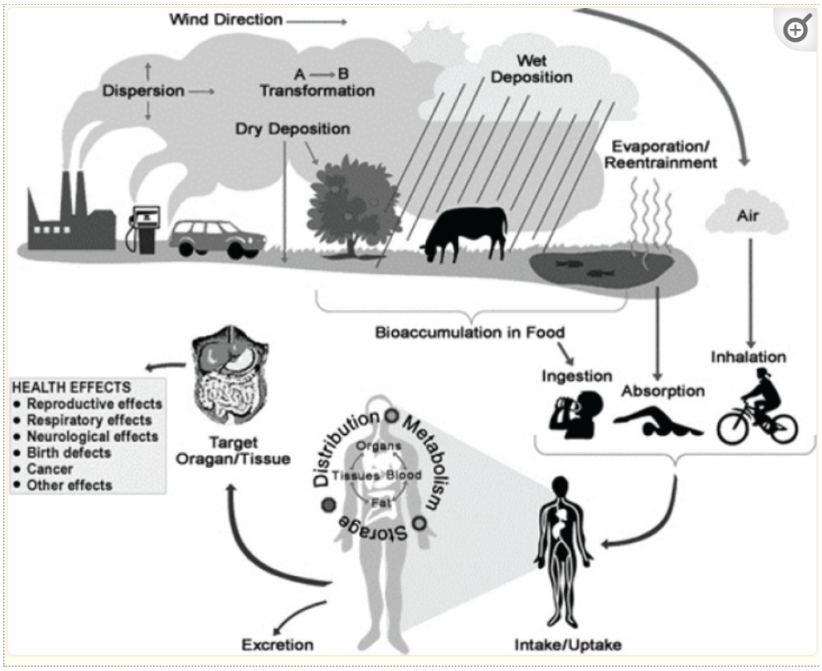

Figure 1: Illustration showing how humans are exposed to environmental toxicants and chemicals (NCBI, 2015)

One particular heavy metal of interest is lead (Pb). According to a new study published in the *Proceedings of the National Academy of Sciences,* more than 170 million Americans were exposed to harmful levels of lead as children, which is equivalent to half of U.S. adults. Most lead exposure occurs in home or childcare facilities built before 1978 as a result of the chipping and peeling of lead-based paint and the lead-tainted dust the infrastructure creates. Other than that, occupational lead exposure is also a growing concern. According to the New York State Health Department, the most commonly identified source of lead poisoning in non-pregnant adults is occupational lead exposure in the construction industry. In fact, some studies suggest that the current OSHA Permissible Exposure Limit (PEL) - a Time Weighted Average of 50 micrograms per cubic meter of air (µg/m3) over 8 hours - and NIOSH Permissible Exposure Limit (PEL) - a Time Weighted Average of 30 µg/m3 over 8-hours - is too high to protect against certain health effects. (CDC, nd)

Lead exposure has decreased dramatically following the decline of lead compounds used in the 1970s. However, substantial amounts of lead are still utilized in industrial products. It is interesting to note that even though lead exposure had decreased over the years while diabetes exposure has increased, this

does not suggest a causal relationship. A few population-based studies have focused on the association between metal exposure and diabetes, showing inconsistent results.

Even though the biological pathways of lead toxicity have been well documented, current studies have not been able to go further than speculating potential mechanisms linking individual heavy metals to T2D risk. As pancreatic islet β-cell dysfunction and insulin resistance are the main bases of T2D, studies have concluded that focus must be given to heavy metals that reduce the function of insulin-producing β-cells. Therefore, further research must be conducted on whether Pb might be one of those heavy metals.

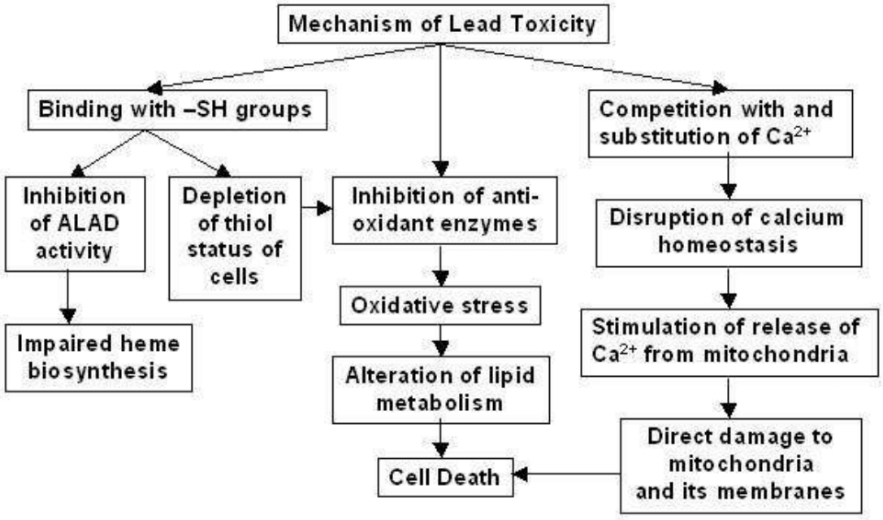

Figure 2: The mechanisms of lead toxicity (NCBI, 2012)

My research paper will aim to answer the research question "To what extent does occupational blood lead (Pb) exposure ≥25 μg/dL affect the risk of Type 2 Diabetes in Adults >18 years old in all states in the United States from 2000 to 2012 and what are the possible biological mechanisms and epidemiological linking environmental lead exposure to Type 2 Diabetes Risk?" through two components: firstly, an ecological study and secondly, a literature review.

2. Ecological Study

An ecological study was conducted to look for a temporal correlation between occupational blood lead exposure and T2D risk for adults aged 18+ years old in the United States. Based on the findings of the study, a further literature review will be conducted and recommendations for future research studies will be given.

Procedure:-

1. National Database for Diagnosed Diabetes for Adults aged 18+ years and National Database for adult blood lead levels were identified.
2. Raw Data and prevalence rates per 100,000 were acquired from the databases.

3. An inclusion and exclusion criteria were developed according to the availability and type of raw data.

Inclusion Criteria:-

Total Diagnosed Diabetes cases for Adults Aged 18+ years old nationally from the years 2000-2012 were taken as-

- Age-Adjusted Crude Percentage
- Crude Number in 1000s

Total number of cases of employed adults with blood lead levels ≥25 µg/dL nationally from years 2000-2012 was taken as:-

- Number of cases of employed adults
- National prevalence rates per 100,000 employed adults

Exclusion Criteria:-

Gestational and Pre-Pregnancy Diabetes Mellitus, Diabetes Medication Use, Influenza Vaccination Last Year, Received Pneumococcal Vaccination, Diabetes-Related Complications, Lower Extremity Diseases, End-stage Renal Diseases (ESRD), Risk Factors for Complications

4. Raw data was processed accordingly and graphs were plotted using Google Excel.

Safety, Environmental and Ethical Considerations:-

The data for Total Diagnosed Diabetes cases for Adults Aged 18+ years old nationally from the years 2000-2012 was taken from the United States Diabetes Surveillance System (CDC, nd) and the data for the Total number of cases of employed adults with blood lead levels ≥25 µg/dL nationally from years 2000-2012 was taken from the report "Elevated Blood Lead Levels Among Employed Adults — the United States, 1994–2012" by State Adult Blood Lead Epidemiology and Surveillance (ABLES) (CDC, 2016)

As these were government databases, all personal details of patients are kept confidential according to the regulations. Attribution of the databases have also been given in this paper so copyright laws have not been violated.

Data collection and processing:-

Table 1: Data showing Total Diagnosed Diabetes in Adults aged 18+ years as an age-adjusted percentage and National prevalence rates per 100,000 employed adults with blood lead levels ≥25 µg/dL

Year	Diagnosed Diabetes - Total, Adults Aged 18+ Years, Age-Adjusted Percentage, National	National prevalence rates per 100,000 employed adults with blood lead levels ≥25 µg/dL
2000	6.0	11.9

2001	6.4	10.9
2002	6.5	9.2
2003	6.6	8.7
2004	7.0	7.9
2005	7.3	7.5
2006	7.6	7.7
2007	7.5	7.8
2008	7.9	7.4
2009	8.6	6.3
2010	8.7	7.0
2011	8.4	6.6
2012	8.4	5.7

Figure 3: National prevalence rates per 100,000 employed adults with blood lead levels ≥25 µg/dL vs Diagnosed Diabetes - Total, Adults Aged 18+ Years, Age-Adjusted Percentage, National

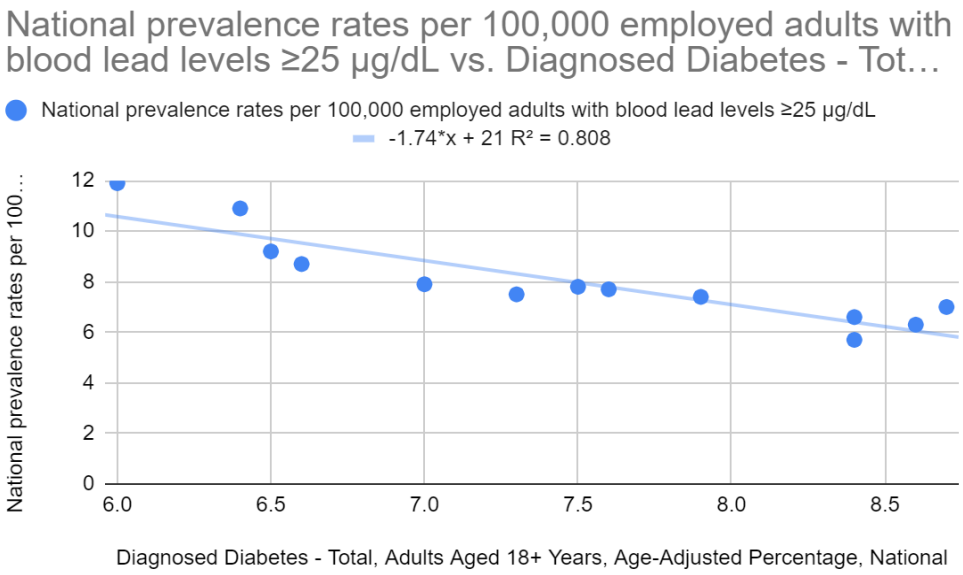

Table 2: Pearson's product moment correlation test. Variable X is the Diagnosed Diabetes - Total, Adults Aged 18+ Years, Age-Adjusted Percentage, National mentioned in Table 1 and Variable Y is National prevalence rates per 100,000 employed adults with blood lead levels ≥25 µg/dL. N denotes the number of years. The squares of X and Y and the product of X and Y was calculated and the sum of all columns was calculated in the last row.

N	X	Y	X2	Y2	XY

1	6.0	11.9	36	141.61	71.4
2	6.4	10.9	40.96	118.81	69.76
3	6.5	9.2	42.25	84.64	59.8
4	6.6	8.7	43.56	75.69	57.42
5	7.0	7.9	49	62.41	55.3
6	7.3	7.5	53.29	56.25	54.75
7	7.6	7.7	57.76	59.29	58.52
8	7.5	7.8	56.25	60.84	58.5
9	7.9	7.4	62.41	54.76	58.46
10	8.6	6.3	73.96	39.69	54.18
11	8.7	7.0	75.69	49	60.9
12	8.4	6.6	70.56	43.56	55.44
13	8.4	5.7	70.56	32.49	47.88

The following equation was used to calculate the Pearson's correlation value:

$$r = \frac{n(\sum xy) - (\sum x)(\sum y)}{\sqrt{[n\sum x^2 - (\sum x)^2]\,[n\sum y^2 - (\sum y)^2]}}$$

r = -0.899 (3sf)

The r value calculated above signifies that there is a strong negative correlation between Total Diagnosed Diabetes in Adults aged 18+ years as an age-adjusted percentage and National prevalence rates per 100,000 employed adults with blood lead levels ≥25 µg/dL from the years 2000 to 2012.

Following the Critical Value Table for the correlation coefficient r, the critical value for a correlation with 11 degrees of freedom (found by the number of trials, 13 minus 2), and a level of confidence of 0.05, is 0.553 (Statistics Solutions, n.d.). The r value obtained from this investigation has a higher absolute value than this meaning that the results are statistically significant.

Table 3: Data showing Total Diagnosed Type 2 Diabetes in Adults aged 18+ years (Numbers in 1000s) and Number of cases of employed adults with blood lead levels ≥25 µg/dL nationally

Year	Total Diagnosed Type 2 Diabetes in Adults 18+ Years (Numbers in 1000s)	Number of cases of employed adults with blood lead levels ≥25 µg/dL - National
2000	11863	10,718
2001	13006	9,517
2002	13391	10,690
2003	14012	10,404
2004	15126	9,530
2005	16186	9,235
2006	17110	9,880
2007	17273	10,190
2008	18651	9,709
2009	20490	7,992
2010	20974	8,738
2011	20589	8,567
2012	21319	7,529

Figure 4: Graph showing Total Diagnosed Type 2 Diabetes in Adults aged 18+ years (Numbers in 1000s) and Number of cases of employed adults with blood lead levels ≥25 µg/dL - National

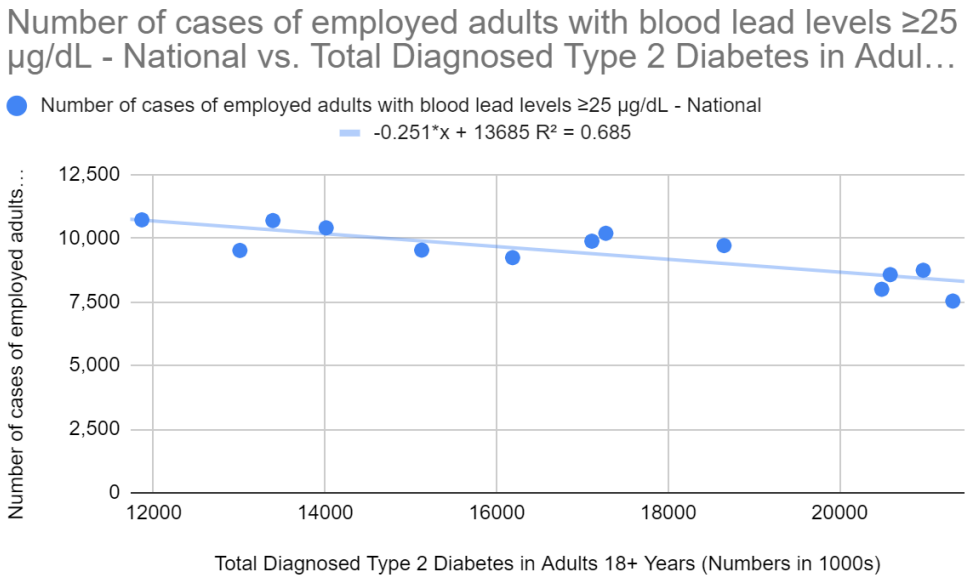

Table 4: Pearson's product moment correlation test. Variable X is the Total Diagnosed Type 2 Diabetes in Adults 18+ Years (Numbers in 1000s) and Variable Y is Number of cases of employed adults with blood lead levels ≥25 µg/dL - National. N denotes the number of years. The squares of X and Y and the product of X and Y was calculated and the sum of all columns was calculated in the last row

N	X	Y	X2	Y2	XY
1	11863	10,718	140730769	114875524	127147634
2	13006	9,517	169156036	90573289	123778102
3	13391	10,690	179318881	114276100	143149790
4	14012	10,404	196336144	108243216	145780848
5	15126	9,530	228795876	90820900	144150780
6	16186	9,235	261986596	85285225	149477710
7	17110	9,880	292752100	97614400	169046800
8	17273	10,190	298356529	103836100	176011870
9	18651	9,709	347859801	94264681	181082559
10	20490	7,992	419840100	63872064	163756080
11	20974	8,738	439908676	76352644	183270812
12	20589	8,567	423906921	73393489	176385963
13	21319	7,529	454499761	56685841	160510751

The following equation was used to calculate the Pearson's correlation value:

$$r = \frac{n(\sum xy) - (\sum x)(\sum y)}{\sqrt{[n\sum x^2 - (\sum x)^2]\,[n\sum y^2 - (\sum y)^2]}}$$

r = -0.828 (3sf)

The r value calculated above signifies that there is a strong negative correlation between Total Diagnosed Type 2 Diabetes in Adults aged 18+ years (Numbers in 1000s) and Number of cases of employed adults with blood lead levels ≥25 µg/dL nationally from the years 2000 to 2012.

Following the Critical Value Table for the correlation coefficient r, the critical value for a correlation with 11 degrees of freedom (found by the number of trials, 13 minus 2), and a level of confidence of 0.05, is 0.553 (Statistics Solutions, n.d.). The r value obtained from this investigation has a higher absolute value than this meaning that the results are statistically significant. This matches the results obtained in the previous Pearson Correlation test.

Limitations of the study:-

- There are not very optimized datasets provided by CDC
    - Specific segregation of Type 1 and Type 2 Diabetes was not available on the CDC United States National Diabetes Surveillance System Database
    - There was not very good surveillance of occupational lead exposure on the ABLES report
- Only Lead exposure ≥25 µg/dL was surveyed for adults aged 18+ years old. This shows that the implications of lead exposure, especially at low levels, are deeply underestimated.
- There may be occupational exposure to many other environmental compounds which may lead to synergistic effects.
- More geographically specific county and state levels over a longer window of time would yield a more accurate analysis.

Discussion of Results:-

The results obtained from the ecological study matches the trends observed for both T2D prevalence and lead exposure patterns in the United States. In the US population lead exposure, as measured by blood lead levels, has been declining for several decades. This is due in large part to the removal of lead from gasoline in the 1980s, which is regarded by many as one of the major public health triumphs of the 20th century. However, there are several glaring evidence that run counter to the view that lead toxicity is no longer a health issue. Firstly, as mentioned in the introduction, current OSHA Permissible Exposure Limit (PEL)is too high to protect workers against certain health effects. Additionally, the examination of the rates of childhood blood lead exposures between 1997 and 2015 reveals a persistent fraction of children (about 0.5% of those tested) diagnosed with significantly elevated blood lead (<10 µg/dL). The CDC estimates that there are currently about 500,000 children ages 1–5 in the US with blood lead levels above 5 µg/dL, the reference level at which CDC currently recommends public health actions be initiated. In addition, current, seemingly low, average blood lead levels in the United States are thousands of times higher than estimated prehistoric levels, and even low levels of lead can be detrimental to many biological systems. Given that it can have severe remafinifcations on metabolic health, it is clear that environmental lead exposure remains a significant public health concern.

Consequently, a literature review was conducted to better understand and possibly bring into light the biological mechanisms linking environmental adult lead exposure to T2D risk.

3. Literature Review

Proposed epidemiological evidence and biological mechanisms linking environmental adult lead exposure to T2D risk

Current literature seems to only propose mechanisms linking heavy metal exposure to T2D risk, but there is a major gap in linking environmental adult lead exposure to T2D risk. Four potential biological mechanisms are briefly summarised below. As emphasized in the introduction, a special focus was given to the biological mechanisms linking lead exposure and pancreatic islet cell dysfunction and insulin resistance as these conditions are the distinguishing features of T2D.

Epidemiological Evidence that Lead promotes T2D

Epidemiologic research has offered provocative, albeit conflicting, data in support of the idea that exposure to lead increases the incidence of T2D, which is aligned with results from experimental trials. For example, previous epidemiological studies have reported statistically significant associations between T2D and lead, while other studies found no significant association between lead and T2D risk.

Biological Mechanisms linking environmental adult lead exposure to T2D risk

Oxidative stress, a risk factor for Diabetes, is induced by lead which directly damages pancreatic islet β-cells

Oxidative stress is considered to be a risk factor for Diabetes as it directly affects cellular signaling pathways that influence insulin signaling. This mechanism is done by highly reactive oxygen species (ROS) such as superoxide radicals, hydrogen peroxide, and nitric oxide that activate intracellular signaling through JNK/SAPK, p38 MAPK, and NF-κB. Firstly, the activation of JNK "results in serine phosphorylation and inhibition of IRS (Insulin Receptor Substrate) 1 and 2 ". Secondly, the decrease in insulin signaling and insulin resistance is a result of the phosphorylation of IRS1 and IRS2 by JNK, and these insulin receptor substrates are required for downstream signaling through additional serine/threonine kinases. (Afridi et al., 2008)

A common property of lead is to induce oxidative stress in biological systems and generate ROS species. Oxidative stress is a significant factor when firstly, considering its role in the development of lead-mediated diseases and secondly, the weak anti-oxidative defense system of pancreatic islet β-cells.

Firstly, recent studies have shown that there is a strong association of blood lead with markers of oxidative stress in the general population, even among people with relatively low environmental exposure to lead (i.e. <10 μg/dL). The third U.S. National Health and Nutrition Examination Survey showed a strong association of blood lead levels with oxidative stress markers in the surveyed population. This suggests that oxidative stress should be considered in the pathogenesis of lead-related diseases even among people with low environmental exposure to lead. Secondly, pancreatic islet β-cells have a weak anti-oxidative defense system due to the high expression of metal transporters and low expression of antioxidant enzymes, including SOD, catalase, and GPx in the pancreatic cells. This increases the susceptibility of islet cells to the negative effects of heavy metals, including pancreatic islet β-cell dysfunction. For instance, lead (Pb) is known to induce the production of ROS, and Pb-triggered oxidative stress can lead to the degradation of proteins, nucleic acids, and lipid peroxidation. This increased ROS generation and induction of oxidative stress can even lead to cell death in pancreatic β-cells.

Toxic lead-induced oxidative stress affects insulin gene activities

As seen in the discussion above, lead (Pb) induces oxidative stress, which in turn influences insulin mRNA expression and gene promoter activity of islet β-cells. In T2D, oxidative stress has been found to decrease the insulin mRNA expression of islet β-cells and insulin gene promoter activity under hyperglycemic conditions (Javaid et al., 2021). Therefore, this alters the related molecular mechanisms in glucose regulations by modifying their functions and kinetics. These include decreasing peripheral utilization of glucose and inducing gluconeogenesis; impairing insulin receptors and disrupting glucose uptake; increasing hepatic glycolysis and pancreatic glucagon release. These drastic alterations provide strong evidence that the oxidative attack in insulin gene activity after toxic lead exposure is an important yet undermined factor in the pathogenesis of T2D.

Lead is an endocrine disrupting chemical (EDC) thus increases the risk of diabetes through endocrine disruption

As previously stated in the introduction, lead, being a heavy metal, acts as an EDC as it is a metalloestrogen and therefore may increase the risk of diabetes through endocrine disruption (Adegoke et al., 2021). According to some animal studies, some EDCs directly target beta and alpha cells in the pancreas, fat cells, and liver cells - therefore, elevated blood or urinary concentrations of EDCs may be related to an increased risk of type 2 diabetes (Tyrell et al., 2021). EDCs alter metabolic balance through multiple mechanisms including alterations in peroxisome proliferator-modulated pathways, adipogenesis, hypothalamic neuropeptides, and most notably pancreatic β-cell function. Moreover, there is well-documented evidence of the effect of EDCs on the incidence of diabetes as there is confirmed evidence that exposure to EDCs such as bisphenols, pesticides, and dioxins leads to the development and progression of diabetes and obesity.

EDCs bind to the estrogen receptors α and β and thereby act like estrogen. Long-term exposure to xenoestrogen EDCs hyperactivates the β-cells, leading to hyperinsulinemia (Fioresi et al.,2014). This leads to the condition of insulin resistance/glucose resistance which is a significant cause of diabetes. However, these studies do not provide strong evidence that lead increases the risk of diabetes through endocrine disruption, as not enough studies have been conducted to study their relation. However, a comparative ecological study to determine an association between blood levels of lead, blood pressure, and risk of diabetes and heart disease in workers in Al-Ain, Abu-Dhabi Emirate, UAE showed that there is a positive association between lead exposure, high blood pressure, and risk of diabetes and heart disease (Bener A et al., 2015). This suggests that there is some merit to the fact that lead, being an EDC, follows the biological mechanisms established above. However, for future studies, more research needs to be conducted on the specific role of lead as an endocrine disrupting chemical on endocrine disruption.

Lead competes with essential metals for various physiological functions and alters intracellular Signaling Pathways affecting T2D risk

Toxic metals compete with necessary metals for metabolism, sequestration, binding to target proteins, absorption, and excretion of metals in the body. For instance, lead (Pb) mimics other necessary metals (such as Ca, Fe, and Zn), and as a result, interacts and binds to several of the same enzymes that these essential metals do. Zn-like chemical and physical characteristics are shared by Cd and Pb, which compete with Zn for the binding sites of enzyme- and metal-absorbing-proteins. As a result, the body will switch to using Cd and Pb in place of Zn in the event of a zinc deficit and increased exposure to these hazardous metals. (Zheng et al., 2018)

So why is this concerning? Essential trace metals (listed above) are crucial cofactors in the insulin signaling cascade, β cell activity, and glucose metabolic pathways - therefore, imbalanced body levels of essential trace metals can adversely affect islet cell functions. Zinc, at normal levels, enhances insulin action by serving as crucial cofactors in the insulin signaling cascade, β cell activity, and glucose metabolic pathways. Therefore, zinc deficiency can adversely affect the ability of islet cells to secrete insulin. Therefore, Pb, by leading to Zn deficiency can affect islet cell function, therefore increasing T2D risk.

Secondly, lead alters intercellular signaling pathways by increasing Resting Intracellular Ca^{2+}. Pb^{2+} and Ca^{2+} have very similar electron orbitals. As a result, Pb^{2+} can disrupt a number of intracellular activities where Ca^{2+} would typically be active. Although the effects of an increase in intracellular Ca^{2+} caused by Pb^{2+} have not been thoroughly investigated, they clearly have a substantial impact on calmodulin (CaM)-dependent events, such as the activation of calcineurin. Prolonged activation of calcineurin by an increased resting Ca^{2+} concentration could result in a sustained oxidative inactivation of calcineurin since oxidants are only efficient calcineurin inhibitors when the enzyme is active. Lead is expected to have a direct impact on the action of calcineurin due to the effects of Pb^{2+} on it in the low nM range. This could affect calcineurin-dependent cellular activities in, for example, insulin-producing pancreatic -cells.

4. Conclusions and Future Prospects

It is tempting to view the declining rates of environmental lead exposure as a positive factor and dismiss its link with Type 2 Diabetes due to the increase in diabetes incidence that has occurred in the last decades. Although the range is relatively limited and they have been performed at higher blood lead levels than typically seen in human exposures (14–74 μg/dL compared to the human alert level of 5 μg/dL), studies that have been conducted support the idea that at some level of exposure, perhaps in combination with other metabolic stresses, lead promotes the development of diabetes. Considering that even very low doses of lead are likely to have harmful effects and that there is a significant portion of the population that is exposed to lead in the environment, especially the working population, it is clear that the effects of lead exposure on the metabolic health of the population remain an important research topic.

5. Acknowledgments

I would like to thank Dr. Caryl Waggett for her mentorship and guidance throughout writing my research paper. Moreover, I am grateful for her insightful classes on epidemiology and eco-health over the past eight weeks. As a result, I am more interested in molecular epidemiology and integrative biology. I would also like to thank my parents and my sister for their constant encouragement in writing my research paper and for always believing in me.

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