The Effect of Environmental Stressors on β-Cell Dysfunction in Type 1 and Type 2 Diabetes Mellitus

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Abstract

Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM) are currently reaching epidemic proportions as various studies anticipate the rates of such autoimmune conditions to increase in the next decade. Although genetic inheritance and lifestyle choices have been accredited for the occurrence of T1DM and T2DM, recent studies suggest that environmental pollutants are additional inducers for diabetes development as they impair β (beta)-cells, which produce and secrete insulin. Insulin is able to reduce blood glucose levels and maintain homeostasis, and with its impairment, such a tack cannot be achieved. Thus, the present work relies on published peer-reviewed articles in order to establish a better understanding of environmental stressors, and if there is some, if any, effect on β-cell function.

Keywords: T1DM, T2DM, DM, DKA, ATP, Beta-cell, dysfunction, environmental stressors

Introduction

Diabetes Mellitus (DM) is a chronic condition which affects nearly 400 million people globally, with at least 200 individuals being diagnosed per day (Daneman, 2006). Caused by the dysfunctioning of pancreatic islet-β cells, both Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM) leave an individual with either the inability to produce insulin or the resistance to accept the insulin. Without the circulation of insulin throughout the bloodstream, the individual is prone to rising blood glucose levels which can eventually lead to Diabetic Ketoacidosis (DKA), and ultimately, death (Thomas & Elliott, 2009). While various researchers are developing easier mechanisms for insulin uptake by the patient, others are researching the origins of such a disease. Although previously thought to be an either genetically inherited or diet-related condition, many cases of DM are arising with no familial or lifestyle history of such (Wolfsdorf, 2006).

Pancreatic islet beta (β)-cells are one of the four major types of cells found in the islets of Langerhans, areas of cells distributed across the endocrine pancreas. The β-cell is able to secrete insulin, the hormone used to lower high blood glucose levels, in response to nervous and intestinal stimuli. The cell is also able to synthesize the production of more insulin in the process of secretion (Laybutt et al., 2007). The secreted insulin can then travel through the bloodstream and store the excess glucose as energy in the form of Adenosine Triphosphate (ATP). However, these cells are extremely sensitive to oxidative and environmental stressors, induced by the reaction of oxygen and nitrogen. Through

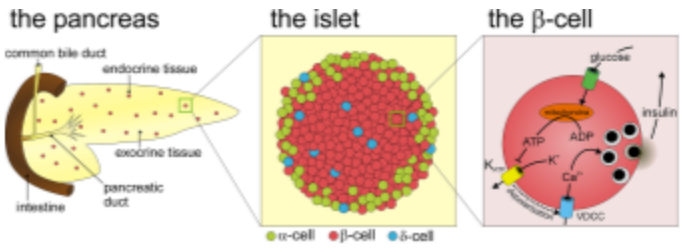

Figure 1: Pancreatic islets in their normal environment. An islet and an individual beta-cell is portrayed (MacDonald, 2006).

the continuous exposure to such oxidative stress, the β-cell can dysfunction and β-cell apoptosis, or cell death, may occur (Bouwens & Rooman, 2005).

Unable to complete the process of mitosis, the β-cells are rapidly depleted as they must carry the function of secreting a large amount of insulin with fewer producers. This exerts too much pressure on the cells, leading to the loss of β-cell function, and thus, the pathogenesis of T1DM and T2DM (Donath & Halban, 2004).

While many researchers believe that such β-cell dysfunction is the result of mutations in the parental DNA transcription, others theorize that the loss of insulin production is rather a result of environmental pollutants and previous underlying health conditions (Rother, 2007). Continuous exposure to materials in one's environment such as arsenic, BPA, pesticides, and nitrates, can lead to β-cell dysfunction. Other health factors, such as viruses, Vitamin D deficiency, ingested microbial toxins, and increased mental stress are also proponents of this phenomenon as such materials interfere with the intrinsic stimuli pathway (Nielsen, Skadhede, & Correll, 2010). This interference from the stressors leads to stress on the β-cell to produce and/or secrete more insulin without the help of stimuli signals. Thus, the DNA is fragmented, and numerous β-cells undergo apoptosis, which renders the other β-cells to experience "overload" (Dahlquist, 2004), and eventually causing a decrease in insulin production.

Background

T1DM and T2DM are complex diseases which are influenced by a variety of factors. The loss of β-cell function, accompanied with a reduced secretory capacity and apoptosis, or programmed cell death, is a key event in the pathogenesis of this condition. Even though β-cell

apoptosis plays a major role in this, the causes leading up to such are still being debated. Some studies have shown that oxidative stress "induced by reactive oxygen and nitrogen species" can cause this. Since β-cells are sensitive to antioxidants, their metabolism and K(ATP) channels are severely affected (Dahlquist, 2004). Other studies have shown that mitochondrial interference with K(ATP) channels is a key cause of β-cell apoptosis as well (Liu, et al., 2012).

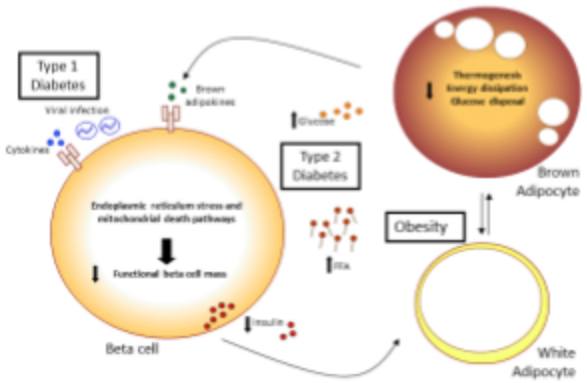

Figure 2: The pathogenesis of both T1DM and T2DM is highlighted. T1DM lose complete beta-cell function, whereas T2DM retain a minimal amount (BetaBat).

All diabetics, regardless of type, undergo some type of β-cell dysfunction. While Type 1 Diabetics experience complete loss of β-cell function, Type 2 Diabetics still retain a minimal amount of insulin production, yet the protein produced is mutated, thus unacceptable by the body. Despite having different effects of β-cell dysfunction, both Type 1 and Type 2 Diabetics are significantly affected. They must consume medications on a daily basis and undergo diet and lifestyle modifications. As previously stated, both conditions, once thought to be solely genetically inherited, are now theorized to be the result of external stress induced upon the β-cells. By examining the causes and effects of such, parameters about the causes of DM can drawn, potentially leading to a decreased number of diagnoses (Dahlquist, 2005).

In the past decade, more cases of TIDM are occurring in individuals with no previous history of such (ADA, 2017). Although no studies can completely confirm the distinct causes for this phenomenon, many are blaming everyday environmental toxins, such as Bisphenol A (BPA)

and arsenic for inducing β-cell apoptosis.

β-Cell Apoptosis:

Weir and Bonner (2004) identified five specific stages of β-cell dysfunction. The first stage is compensation. In this phase, overall insulin secretion is elevated through acute glucose-stimulated insulin secretion (GSIS). This results in a dramatic increase in β-cell mass, as the β-cells prepare to die (Butler et al., 2003). Individuals can remain in this phase for many years, and thus, such a phase is often marked by an increase in weight as there is less glucose circulation in the blood. Decreased glucose concentrations result in frequent hunger and thirst. The second stage is stable adaptation, in which fasting glucose levels see slight increases [between 5.0-7.3 mmol/l], and the β-cells can no longer be regarded as compensating, as normal blood glucose levels cannot be maintained. Despite this, the decline towards DM is minute, as seen by Knowler (2002), in which only 5% of the studied population rapidly progressed towards a complete loss of β-cell function. Weir and Bonner hypothesize that these unstable glucose levels cause a loss of specialized gene expression, eventually leading to GSIS disruption. The third stage is unstable early decompensation, where blood glucose levels increase at a much faster rate [7.3 mmol/l to 16-20 mmol/l] and β-cell mass is rapidly depleted. Due to this increase in glucose concentration in the bloodstream, the glucotoxic effect on insulin target tissues (liver, muscle, and fat) worsens, and glucose levels rise to stage four. The fourth stage is called stable decompensation, in which the individual retains enough β-cell function to secrete insulin, but the amount released is not sufficient. Typically, this stage lasts a lifetime for Type 2 Diabetics, whereas Type 1 Diabetics progress onto stage 5. The fifth and final stage is called severe

decompensation, in which complete function of β-cells is lost and individuals become "truly ketotic and dependent on insulin for survival". In this phase, glucose levels are typically above 22 mmol/l. All of these stages, as a result, lead to the pathogenesis of DM, offset by a certain stressor.

Gender and Ethnicity:

Although Diabetes may be affected by a variety of different factors, gender and ethnicity, or a person's geographic location, plays a role in the development of the disease. Statistically, the United States reports the highest rates of T2DM whereas northern European countries such as Norway, Finland, and Sweden, report one of the highest rates of T1DM globally (ADA, 2018).

Upon analysis, it was found that cases of DM are far higher in women than in men. One speculation over this relationship is that BPA is commonly known as an estrogenic disruptor and traces of the chemical can be found in cosmetics. Such products can be readily found in first world countries, where the rate of T1DM and T2DM is coincidentally higher. Cases of T1DM are also far more common in children living in such countries as there are higher amounts of BPA found in toys, and exposure to heat can cause BPA to leak, thus increasing exposure (Kotwal, Upreti, Kumar, & Nachankar, 2017).

In some Asian countries, such as China, men from below the poverty line exhibited weight gain. One study found that Chinese men over the age of 40 had a higher chance of acquiring the disease as they were more exposed to chemicals through their workplace in factories (Wang, et al., 2012; Hao et al., 2017). One study of Chinese girls found that they had a

higher rate of developing T1DM as they were exposed to BPA and organophosphate pesticides through the schools, especially those near agricultural sectors (Li, et al., 2013). T2DM has also been linked to exposure through the contamination of water. Various third world countries, such as India, reported high rates of pollutants in their drinking water, possibly explaining the high rate of DM (ADA, 2018).

Prenatal/Postnatal:

Some studies examined the effect on the offspring of a pregnant mother exposed to certain chemicals, known as prenatal (before birth) exposure. Various studies concluded that the exposure of a pregnant rat to certain chemicals did not have an effect on her, but rather affected the offspring and their development in later life (Valvi, 2013). Many of these studies found that prenatal exposure resulted in offspring developing obesity in later life. As seen in Figure 3, those rats whose mothers were exposed to BPA during their gestational period became far larger than those whose mothers remained in a controlled environment.

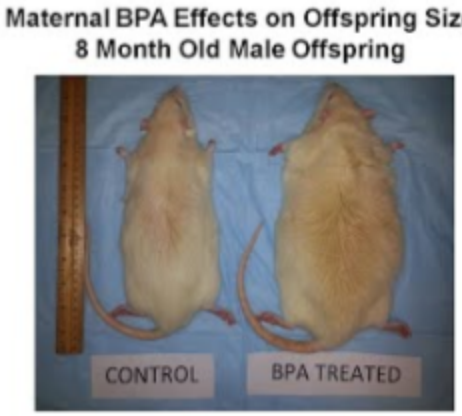

Figure 3: Rat exposed to BPA prenatally has gained much more weight and has become larger than rat not exposed.

Other studies examined how immediate postnatal exposure affected growth and development (Snijder, 2013). In one study, rats were exposed to BPA everyday for 8 weeks directly following birth, and they later went on to experience weight gain at a later point in their lives (Desai, 2013). These rats did not begin to gain weight immediately like prenatally exposed rats, but the

amount of weight gained was significant. Thus, postnatal effects are not as severe but dependent on how much they were exposed to and how long after birth the exposure began. It is to be noted, however, that weight gain is an indicator of T2DM.

Prenatal exposure is far more lethal as the developing pancreas and β-cells are extremely vulnerable to external stimuli and stressors and their immune systems have not been fully developed.

BPA:

According to Bodin, Stene, and Nygaard (2015), the endocrine disruptor, BPA, had the highest likelihood for T1DM influence out of a wide array of chemical subgroups such as metals, nitroso compounds, and air pollution factors.

BPA, which is used to develop polycarbonate place and epoxy resin coatings, can be found in various everyday products, such as the inner lining of metal soda cans and food containers. This substance, thus, is able to penetrate the food consumed by an individual. Although more than 99% of the ingested BPA is metabolized and secreted from the body via urine in less than four hours (Vandenberg et al., 2010), any long-term exposure to it, whether that is postnatal or prenatal, can greatly increase one's risk for impaired insulin secretion (Bodin, 2015). Bodin also suggests that an extremely high BPA exposure [15 mg/kg/day] impairs macrophage function, leading to, "the clearance of apoptotic cells, a feature common for several autoimmune diseases" (Bodin, Stene, & Nygaard, 2015). Other similar studies have shown that

BPA exposure has induced insulin resistance in various mice species (Perreault et al., 2013).

The Environmental Protection Agency (EPA) illustrates their lowest observed adverse effect level (LOAEL) of BPA at 0.05 mg/kg/day, according to a 2010 Bisphenol A action plan. Despite this, exposure less than the EPA limit has been found to induce insulin resistance as well (Alonso-Magdalena, Morimoto, Ripoll, Fuentes, & Nadal 2006).

The most critical time of exposure is during fetal development and BPA exposure leads to an increase in β-cell mass (compensation) in the fetal pancreas, but later decreases, an indicator of sudden β-cell apoptosis (Liu et al., 2012). Another study found, that alongside prenatal exposure, peripubertal exposure was potentially harmful (Rubin et al., 2016).

Phthalates:

Phthalates, used as plasticizers, are commonly found in a variety of cosmetic products and paint substances. This toxic chemical is a highly biodegradable endocrine disruptor and is mainly ingested through the diffusion of parabens in food or through inhalation of dust or air. Some studies show that phthalate uptake is also facilitated through cosmetic application to the skin. Epidemiological studies have indicated that exposure to this substance over prolonged periods of time has led to insulin resistance in many individuals (Song et al., 2012).

According to the EPA 2012 Phthalate Action Plan, the maximum contaminant level to prevent harmful exposure is 0.006 mg/kg/day. According to Feige et al. (2007), women have higher exposure rates to phthalates as compared to men as this chemical can be found in various

cosmetics.

Organophosphate Pesticides:

Organophosphate pesticides are hazardous chemicals commonly used for agricultural purposes. Studies have shown that the continuous exposure to such a substance inhibits the enzyme acetylcholinesterase (AChE), which is able to catalyze the breakdown of acetylcholine, a neurotransmitter (Costes, Langen, Gurlo, Matveyenko, & Butler, 2003).

Since AChE receptors facilitate the secretion of insulin and glucagon-like peptides from the islet of Langerhans (where all pancreatic β-cells are located), exposure to organophosphate pesticides, primarily through farming, interfere in the intrinsic pathway, leading to insulin impairment (Duttaroy, Zimliki, Gautam, Cui, Mears, & Wess, 2004).

Arsenic:

Arsenic is a toxic chemical which is most often found to in contaminated drinking water. Soil erosions, volcanic emissions, natural weathering reactions, and geochemical reactions have all been found to diffuse into drinking water (Mohan, Jaydip, & Deepa, 2007). High levels of arsenic are found predominantly in South-East Asia, Latin-America, and in various parts of the United States and Australia, all of which, coincidentally, have one of the highest rates of individuals with DM globally (Dangleben, Skibola, & Smith, 2013).

While there are no direct studies examining the effects of arsenic exposure on TIDM development, the substance has been found to impair the immune system in both humans and

animals (Ahmed et al., 2014). Other studies have found that arsenic inhibits the glucose-stimulated insulin release intrinsic pathway (Douillet et al., 2013).

Purpose

There are approximately 400 million Diabetics worldwide, out of which there are 1.5 million deaths globally due to complications from the condition and the lack of the availability of medication. With this number drastically increasing each year, it is predicted that by the year 2025, 1 in 4, or 25%, of people will either have T1DM or T2DM, and only 40-50% will be able to financially afford any type of medication (ADA, 2018). Predominantly found in young children, T1DM is an autoimmune disease, where the pancreas begins to fail due to the antibodies attacking themselves (Bodin, Stene, & Nygaard, 2015). Those affected must maintain healthy eating and exercise habits, while also injecting themselves with daily insulin shots to keep their blood sugar levels stable. T2DM is rather caused by unhealthy eating habits and fosters itself in one's later years, with most Type 2 cases appearing after the age of 40 (Chatterjee, Khunti, & Davies, 2017).

When β-cells lose their ability to produce insulin, the blood glucose levels in the individual's body remain high. If not treated soon thereafter, complications may arise, including but not limited to blindness, neuropathy, coma, and death. Thus, these individuals are labeled as "Diabetics".

Diabetics, thus, must remain dependent on insulin/medication to control blood glucose levels. However, since the number of such cases is increasing, more and more people are becoming dependent on medication, which is also increasing in its costs. Identified to be caused by a variety of environmental and internal factors, measures can be taken to ensure others limit

the amount of exposure they have to hazardous chemicals as well as maintaining their personal health.

Beyond the personal effects that DM may have on the individual, the expenses of such a condition reach far beyond everyday life. It is estimated those with either T1DM or T2DM have medical expenses that are almost double as compared to those without DM. This, in turn, costs the United States government over $174 Billion annually. The ever-increasing expenses result in even more taxpayer dollars, proving that DM affects not just the patient, but all factions of life (Herman, 2012; Williams, 2015)

Thus, the purpose of this study is to highlight which chemicals, if any, result in β-cell dysfunction.

Hypotheses

DM is occurring at a rapid speed, and researchers, who previously thought it was passed onto offspring genetically, believe it is actually a result of stress on insulin-producing β-cells. Such stressors range from environmental pollutants to internal viruses and microbial toxins. There is a need to pinpoint the causes of this chronic condition so further diagnoses may be prevented. Thus, this study examines how environmental stressors affect β-cell dysfunction.

a. ALTERNATIVE: Environmental stressors interfere with normal β-cell function and can lead to the pathogenesis of Diabetes Mellitus through their dysfunction.
b. NULL: Environmental stressors have no effect on β-cell function and exposure does not lead to the pathogenesis of Diabetes Mellitus.
c. DEPENDENT VARIABLE(S): Change in weight, Change in glucose levels, and Plasma insulin secretion

d. INDEPENDENT VARIABLE(S): environmental stressors exposure

e. CONTROL: No exposure to environmental stressors

f. TEST: Systematic data analysis

Data Sources and Methods

For this study, peer-reviewed articles were utilized. These articles were mainly obtained from online electronic bases such as EbscoHost and Google Scholar. PLOS One and BioMed Central also had useful databases providing applicable papers. The bibliographical references were also used to find additional, related papers. The data range dated from 2004-2018. 2004 has been established as the baseline year for systematic data analysis collection as the study of β-cells needs to be recent, as to match with new technologies. The language of all source publications remained in English but could have been translated from another language. Search terms for journal articles included the following: "β-cell", "β-cell dysfunction", "oxidative stress", or "environmental stress and diabetes". Keywords for electronic databases included the following: "β-cell", "diabetes", "causes of diabetes", " oxidative stress", or "dysfunction/degeneration". This researching strategy was the most appropriate, as it provided the most usable and applicable data as compared to other methods of research such as surveys or interviews.

Explanation for Data Collection

Data collection was done by examining a variety of sources, such as peer-reviewed papers and review articles. All data presented in the articles was reviewed collectively and

analyzed. Various pieces of quantitative data were applicable as well. Data was analyzed based on how the researchers of that specific article drew conclusions. The statistical results determined how the indicated variable related to β-cell dysfunction.

Data

The Effect of Chemicals on Weight in Humans

STUDY TESTING AFFECTS OF:	AMOUNT EXPOSURE (24 HRS.)	TOTAL EXPOSURE TIME	CONTROL (NO EXPOSURE): TOTAL CHANGE IN WEIGHT [LBS.]	TEST (EXPOSURE): TOTAL CHANGE IN WEIGHT [LBS.]	P-VALUE
BPA (Diet); n=12	0.057 mg/kg	6.4 months	+3.4	+11.9	0.04
ARSENIC (Inhalation); n=8	0.0043 mg/kg	5.2 months	+2.3	+3.7	0.062
ORGANOPHOSPHATE PESTICIDES (Inhalation); n=9	0.93 mg/kg	8.3 months	+3.9	+4.3	0.06
PHTHALATES (Diet); n=9	17.4 mg/kg	3.3 months	+1.8	+6.5	0.04

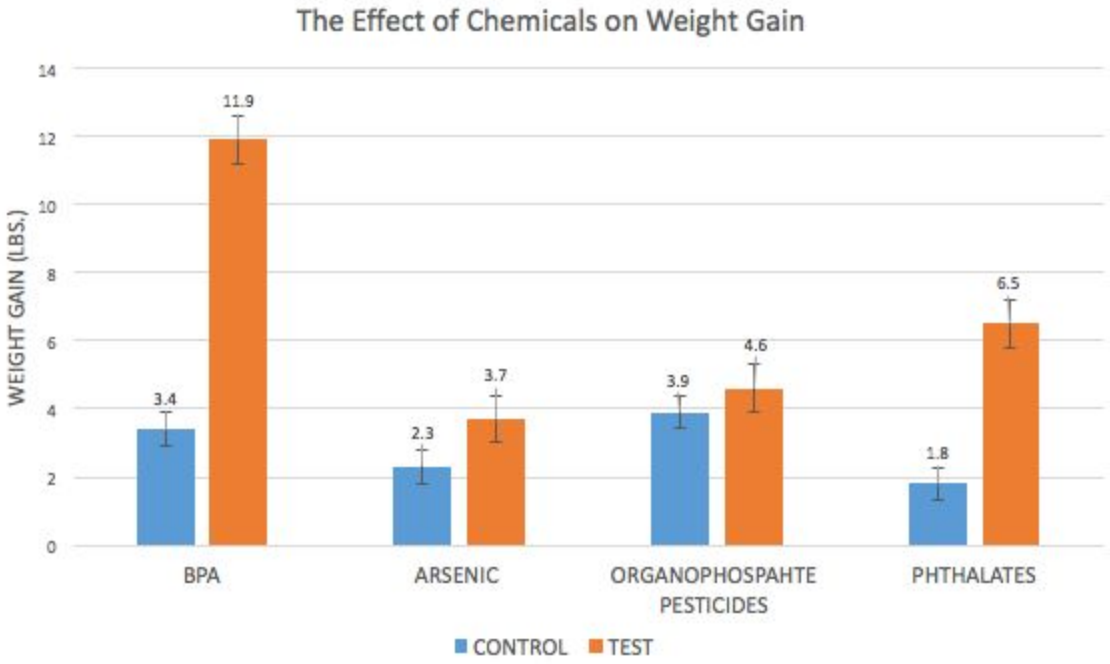

Figure 4 (Above): This data table and graph show the association between exposure to different chemicals and the total change in weight (in humans) at the end of the study. A control was included for comparison.

The Effect of Chemicals on Glucose Levels in Humans

STUDY TESTING AFFECTS OF:	AMOUNT EXPOSURE (24 HRS.)	EXPOSURE TIME	CONTROL (NO EXPOSURE): CHANGE IN BG	TEST (EXPOSURE): CHANGE IN BG	P-VALUE
BPA (Diet); n=9	0.052 mg/kg	4.5 Months	+2.6 mg/dL	+18.7 mg/dL	0.03
ARSENIC (Inhalation); n=8	0.005 mg/kg	3.7 Months	+1.3 mg/dL	+ 5.7 mg/dL	0.04
ORGANOPHOSPHATE PESTICIDES (Inhalation) n=11	0.85 mg/kg	8.6 Months	+1.7 mg/dL	+3.5 mg/dL	0.06
PHTHALATES (Diet); n=7	12.5 mg/kg	3.1 Months	+1.1 mg/dL	+10.6 mg/dL	0.03

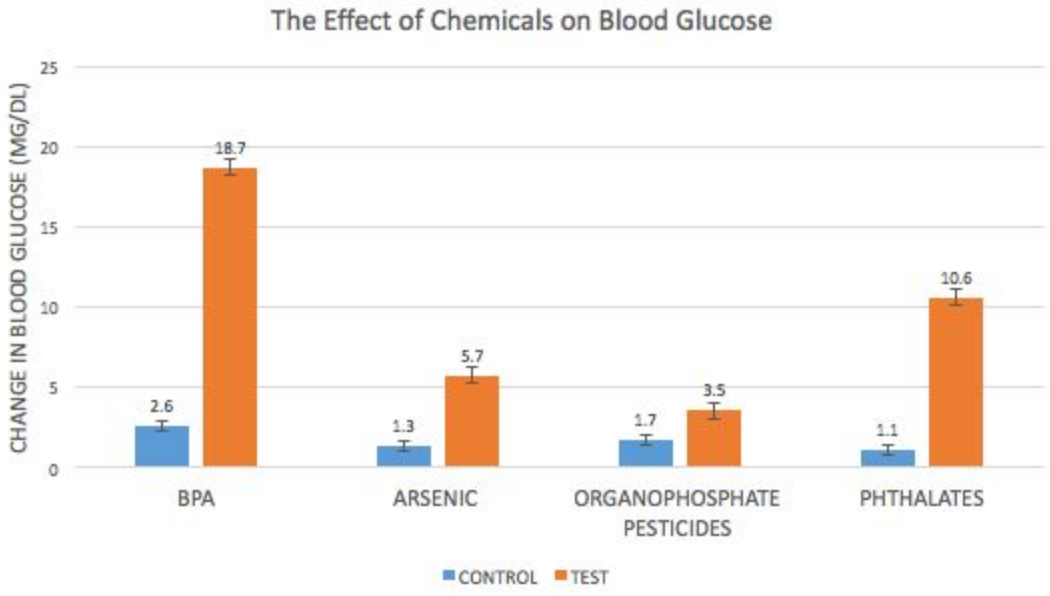

Figure 5 (Above): This data table and graph show the association between exposure to different chemicals and the total change in blood glucose (in humans) at the end of the study. A control was included for comparison.

The Effects of Chemicals on Weight and Plasma Insulin in Rats

STUDY TESTING AFFECTS OF:	AMOUNT EXPOSURE (24 HRS.)	EXPOSURE TIME	CONTROL (NO EXPOSURE): TOTAL CHANGE IN WEIGHT	TEST (EXPOSURE): TOTAL CHANGE IN WEIGHT	MAXIMUM PLASMA INSULIN SECRETION AT END OF STUDY (CONTROL): mIU/L	MAXIMUM PLASMA INSULIN SECRETION AT END OF STUDY: mIU/L	P-VALUE
BPA (injection); n=4	0.067 mg/kg	8.4 Months	+0.97 oz	+5.60 oz	166	152	0.03
ARSENIC (inhalation); n=3	0.007 mg/kg	7.7 Months	+1.12 oz	+1.20 oz	156	155	0.04
ORGANOPHOSPAHTE PESTICIDES (inhalation); n=3	1.03 mg/kg	6.1 Months	+1.03 oz	+0.98 oz	169	169	0.06
PHTHALTES (diet); n=3	19.4 mg/kg	5.9 Months	+0.88 oz	+4.48 oz	159	147	0.03

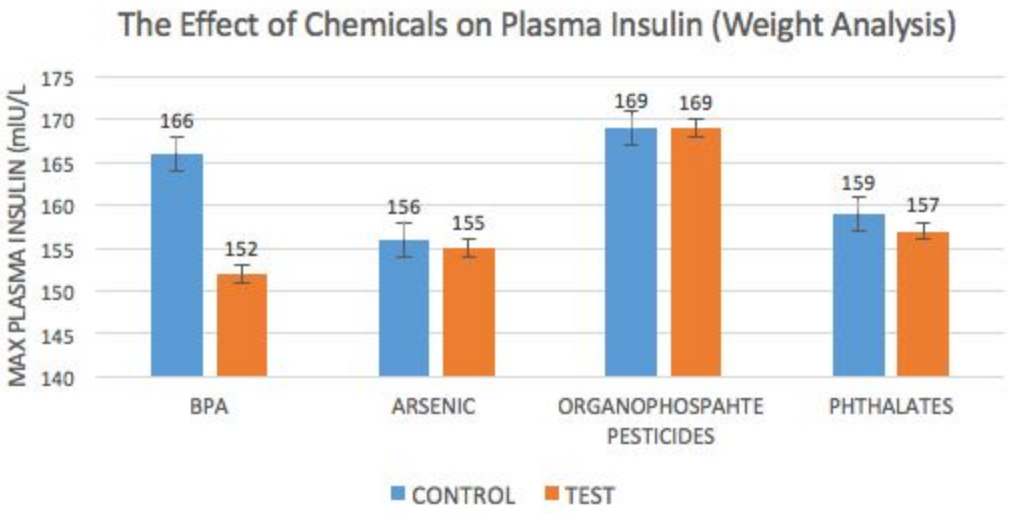

Figure 6 (Above): This data table and graph show the association between exposure to different chemicals and the total change in plasma insulin secretion and change in weight in rats at the end of the studies. Only plasma insulin is graphed. A control was included for comparison.

The Effect of Chemicals on Glucose and Plasma Insulin in Rats

STUDY TESTING AFFECTS OF:	AMOUNT EXPOSURE (24 HRS.)	EXPOSURE TIME	CONTROL (NO EXPOSURE): CHANGE IN BG	TEST (EXPOSURE): CHANGE IN GLUCOSE	MAXIMUM PLASMA INSULIN SECRETION AT END OF STUDY (CONTROL): mIU/L	TEST (EXPOSURE) MAXIMUM PLASMA INSULIN SECRETION AT END OF STUDY: mIU/L	P-VALUE
BPA (injection); n=3	0.071 mg/kg	7.1 Months	+1.6 mg/dL	+22.9 mg/dL	162	102	0.04
ARSENIC (inhalation); n=3	0.006 mg/kg	8.7 Months	+1.4 mg/dL	+9.7 mg/dL	147	144	0.05
ORGANOPHOSPAHTE PESTICIDES (inhalation); n=3	0.98 mg/kg	5.8 Months	+2.7 mg/dL	+2.4 mg/dL	153	154	0.06
PHTHALTES (diet); n=4	17.6 mg/kg	4.3 Months	+2.1 mg/dL	+15.6 mg/dL	164	114	0.04

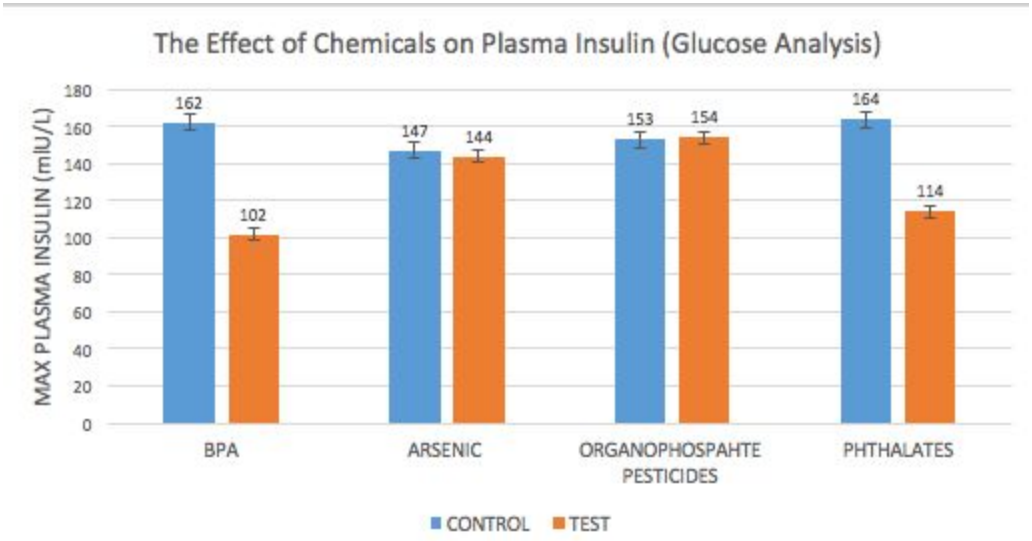

Figure 7 (Above): This data table and graph show the association between exposure to different chemicals and the total change in plasma insulin secretion and change in glucose in rats at the end of the studies. Only plasma insulin is graphed. A control was included for comparison.

Results

All data collected in the scope of this study was derived from peer-reviewed papers which assessed a variety of individuals with T1DM or T2DM or those predisposed to such. A latter part of data collection relied on evidence from rats to indicate a loss in insulin production as such was not possible within humans due to ethical restrictions. All data indicating the different chemicals is an average of approximately 8-12 peer-reviewed papers studying the effects of that specific chemical amongst a variety of other parameters. In studies assessing humans, age, ethnicity, and medication were taken into account. All subjects being assessed under "Type 1 Diabetes" were 18 years of age or younger and all being assessed under "Type 2 Diabetes" were 18 years of age or older. All parameters were kept consistent between both conditions as the chemical and amount and time of exposure are crucial to determining β-cell loss in both scenarios. Thus, the controls in this experiment were the time the individual was exposed to the chemical and the amount of exposure they were subject to. The only altered parameter was the indication of the loss of β-cell function. It is to be noted, however, that the amount and time of exposure varied between *different chemicals*. Significant changes in blood glucose levels were measured in individuals exposed to the chemicals who later went on to be diagnosed with DM. Blood glucose levels were measured as Type 1 Diabetics cannot easily control their blood sugar levels with simply exercise and diet alone, unlike Type 2 Diabetics, and

thus, must rely on insulin. Significant blood glucose rises, in both humans and rats, are defined as the blood glucose increase exceeding approximately 9 mg/dL over a time period of three months (Drews, 2010). Those exposed indicated losses of β-cell function by weight gain, a common indicator of insulin resistance and risk of developing T2DM. Significant weight gain in humans is described as gaining more than 6 to 7 pounds over a period of three months, or approximately 1-2 pounds per month (Mayo Clinic) and gaining more than 0.5 oz per month in rats.

All subjects were exposed to a certain amount of each pesticide through differing means. All studies were in close range to the LOAEL of that specific chemical as indicated by the EPA action plan. Those within the scope of the human organophosphate pesticide and arsenic studies were exposed through inhalation in a certain enclosed environment, or through certain materials laced with pesticides. Phthalates and BPA were exposed to the human subject through the diet they consumed over the length of the studies. Within the rat studies, test subjects were injected with BPA, inhaled arsenic or organophosphate pesticides, or consumed phthalates as a part of their diet.

Analysis

In figure 4, all human subjects were exposed to the chemicals for a differing amount of time, ranging from 3 months to 8.5 months. Across all studies in correlation to the change in weight, the control, or those not exposed, gained about an average of about 0.5 pounds per month, a normal and steady increase within a healthy individual (Bodin, 2013). Those exposed to BPA saw an increase of approximately 12 pounds in 6.5 months, or a little under 2 pounds per

month. This gain accounts for a significant increase in weight and correlates to BPA having some type of influential factor upon such. Arsenic and organophosphate pesticides, both administered through inhalation, did not witness a significant increase in body weight. In fact, across both the control and test studies, both subject groups only gained approximately 0.5 pounds per month, making the control and test values relatively equal. The high p-value and close proximity across both groups show that there is not a significant correlation between those stressors and weight gain. Phthalates, on the other hand, also administered through diet (similar to BPA), did witness a significant increase in weight. As compared to the control, the test group gained nearly 2 more pounds per month, making this chemical even more effective at weight gain than BPA.

Due to ethical restrictions of measuring insulin secretion in humans, rats have been subsidized as a similar alternative due to their comparable metabolic processes and anatomy. As seen in figure 6, rats injected with BPA saw a significant total increase in weight as compared to those under the control group, gaining approximately 0.67 oz. per month. Comparatively, the maximum plasma insulin secretion under the BPA test did see a decrease as well. Although not a large drop, the reduction in insulin production indicates some form of β-cell apoptosis is occurring. Under the arsenic and organophosphate pesticide studies, there was only a gain of 0.15 and 0.16 oz. respectively, and the maximum plasma insulin secretion remained relatively similar to the control. This indicates there was not much, if any, loss in β cell function. Rats exposed to phthalates through diet saw a significant increase in weight. The rats exposed to such gained approximately 0.75 oz. per month and also saw a decline in insulin secretion.

In adolescents, blood glucose levels were measured as an indicator of T1DM. In the study testing the effects of BPA, the exposed subject group saw a significant increase in blood glucose levels of approximately 4.1 mg/dL per month. Arsenic and organophosphate pesticides did not show a substantial increase in overall blood glucose levels and, thus, the p-value was high. Subject exposed to phthalates through diet saw an increase of 3.5 mg/dL in blood glucose per month, conveying that the outcome was a potential factor of the chemical. In similarity, the rat studies assessing glucose (figure 7) also witnessed a significant increase in glucose levels of those exposed to BPA and phthalates. BPA subjects saw an increase of 3.2 mg/dL per month and phthalate subjects saw an increase of 3.6 mg/dL per month. The maximum plasma insulin secretion of these groups also decreased rapidly, whereas the plasma insulin levels of the arsenic and organophosphate pesticide groups stayed relatively similar to the control groups. In fact, the overall glucose levels of the pesticide group dropped and the insulin secretion increased. Despite these assertions, the arsenic group saw an increase in blood sugar levels that was not indicated as significant as per the derived p-value, yet the blood sugar did increase far more than any other study with a higher p-value.

Discussion

Assessments across all studies examining the effects of various chemicals on β-cell function have been compiled above. As per the data collected, it can be seen only BPA and phthalates pose a significance in the weight, glucose, and plasma insulin subgroups. Arsenic and organophosphate pesticides do not imply a significant change as compared to other data, but the change that is present is occurring very minimally.

In the studies assessing the effect of chemicals on weight in humans, BPA and phthalates resulted in a rapid increase in weight, a common indicator that β-cell dysfunction is underway. Comparative to the rat study examining weight and plasma insulin, the test subjects also experienced weight gain under those two categories, and coincidentally, saw a decrease in insulin secretion. Even though plasma insulin decreased by a small amount, the drop indicates that β-cell apoptosis is slowly occurring. This would be an indicator that those rats, and most likely, the human subjects also experienced onset DM. Coupled with a gain in weight and a slow decrease in insulin (a signal of insulin resistance, not insulin production loss), BPA and phthalates can be associated with β-cell dysfunction.

Similar effects could be seen under the BPA and organophosphate pesticide subgroups as well when examining glucose levels in both rats and humans. Blood glucose levels, unlike weight, are supposed to remain constantly stable over the course of one's lifetime. However, when assessing glucose in humans, it was seen that BPA and phthalates led to significant increase in glucose levels, and this same effect could be seen in the rat studies as well. Surpassing the threshold of 3 mg/dL per month, both subgroups accounted for a significant change, and, similarly, the rat assessments resulted in a dramatic decline in plasma insulin secretion, further indicating the loss of β-cell function. Interestingly, however, there was a significant effect on glucose levels and plasma insulin in humans and rats, but such a correlation could not be seen in the weight studies. This may be an indicator that some error occurred during experimentation since no correlation can be drawn. Pesticides, again, yielded no correlation in humans and rats, but in rat experiments, the change in blood sugar levels was *lower* than the control and plasma insulin also increased. Although no conclusions can be drawn from this

observation, it may be an indicator that arsenic could potentially help regenerate apoptotic β-cells, but further research is required. Despite these assertions, BPA and phthalates are consistent across both rat and human studies as increasing glucose, and decreasing plasma insulin can be seen amongst both categories, indicating rapid β-cell apoptosis and the pathogenesis of DM.

Interestingly, it can also be seen that BPA and phthalates, in the human studies, were given to the test subjects through their diet, but the other two chemicals were inhaled. BPA and phthalates resulted in a greater significance in correlation to β-cell dysfunction across both rat and human assessments. While no further conclusion can be drawn from this observation, it indicates a need for further research into the methods of exposure as well.

The effect of both BPA and phthalates may be attributable to competitive inhibition of insulin and the receptors on cells. Thus, both BPA and phthalates may be labeled as endocrine disruptors, as they alter the normal functioning of the endocrine system. An endocrine disruptor mimics a naturally occurring hormone, in this case, insulin, and prevents the original hormone from binding to the receptors on the cells, rendering it ineffective. The competitive inhibition of the hormone alters the shape of the cell by binding to the substrate site before the hormone is able to do so. Although this is the likely mechanism occurring on the molecular level, further research is needed to evaluate this proposal.

Addressing the Limitations

This study relied on papers from various countries in order to compile a comprehensive review of the effects of different chemicals. Due to the different times at which each study was

conducted, it may have had an effect on the outcome. Furthermore, most studies did not address β-cell mass, but rather the amount of insulin produced by the β-cells. While insulin can be a correct representation of β-cell function, the mass of such cells provides a more accurate image into the molecular effects. However, due to the expenses and time restraints of measuring the mass, studies rely on plasma insulin levels. Additionally, the environment may, at times, not be the only factor contributing to the pathogenesis of DM. Factors such as lifestyle, eating habits, and genetics may interfere with the correct interpretation of the data. Thus, it should not be assumed the environment is the sole cause of DM, but instead, plays a major role within it.

Conclusion

The prevalence of DM is currently at epidemic proportions and is a cause of great concern, not only for human health but also because of its social and economic implications. Although genetic predisposition, obesity, diet, and lack of exercise are commonly accepted causes of the development of T1DM and T2DM, it is argued that these factors alone cannot fully explain the rapid rise in the prevalence of Diabetes. The environment, and more specifically, environmental pollutants, are mentioned as major interfering factors. Although a large variety of compounds have been shown to be correlated with the occurrence of Diabetes, detailed mechanistic information on how these pollutants interfere with insulin metabolism is lacking. Therefore, the present research gives an overview of the available information connecting environmental stressors with T1DM and T2DM, with adept focus given to the β cell, a crucial factor in the pathogenesis, indicating a strong correlation between BPA and phthalates and dysfunction but not between arsenic and organophosphate pesticides.

Further Work

Any further work should aim to highlight other potential sources of pollutants leading to β-cell impairment, especially those found in the air and groundwater, as it the easiest way pollutants can spread. Further studies should also examine other methods of exposure such as transdermal absorption as pollutants may be found in various objects throughout the house. Further work should also focus on diet exposure as compared to other methods of exposure in order to identify which method is most detrimental. Additional studies should also research how β-cell dysfunction may be prevented, even if already in the initial apoptosis phases so as to prevent any further cases of both T1DM and T2DM. Studies should also study further examine the correlation between arsenic and pesticides, and check to see if long-term exposure renders any significant results.

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