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Neurological Impact of Diabetes, and Stem Cell as a Course of Action

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ABSTRACT

A large, and ever growing population has diabetes. Research needs to be conducted to help this population maintain a healthy life. The study focused in particular with regards to neurodegeneration. Multiple connections between diabetes and neurodegeneration were found such as in neuropathy, which is nerve damage due to oxidative and other stress due to high blood sugars, which could eventually escalate to motor dysfunction. Other conditions were also looked at, such as the impact of hypoglycemia low blood sugar conditions on neurodegeneration. FJB+ cells, biomarkers for neurodegeneration, were seen in severe hypoglycemic conditions potentially due to excitotoxicity damaging nerve cells. Multiple solutions were then looked into in an attempt to find a cure for diabetes and neuropathy. Stem cells were evaluated as a potential cure for diabetes. A recent use of stem cells in diabetes was evaluated, and there is promise in this technique for curing diabetes but further research is required. A method called TMS was explored as a cure for neuropathy, and current research shows promising results.

Introduction

Diabetes can be a life changing disease that can result in various, potentially life threatening complications. Diabetes can cause one to have to change many aspects of their life including diet and exercise, in order to prevent damage to the body. It may still be difficult at times in order to properly manage diabetes for various reasons ranging from simply a lack of knowledge of potential complications, lack of access to medication, or even lack of knowing that one has the disease. Due to these reasons, among others, over long periods of time, uncontrolled blood sugars have the power to cause currently incurable damage to someone. This also includes the nervous system. In order to help this population, research should be conducted to understand the neurological impacts that diabetes can have on the brain and other parts of the nervous system, how they impact the body and daily activities, how to manage diabetes, and also how to potentially cure diabetes. According to the Mayo Clinic, high blood sugars can result in various forms of diabetic neuropathy, which potentially have the ability to interrupt neurons from sending signals (Mayo Clinic, 2022b). With excessive damage to certain nerves, it could be possible for one to lose motor control from diabetic neuropathy. With a loss of motor control, one may have trouble being active and exercising, which is not only beneficial for managing diabetes, but also preventing other complications from arising as one ages.

Complications, such as diabetic neuropathy, resulting from diabetes is somewhat common amongst the diabetic population, and it has been seen that it can have significant impacts on the nervous system. Research by Akhtar S., et al., Akhtar who studied in the University of Haripur, Pakistan, has found that out of approximately 8500 diabetic patients in Pakistan, in a meta-analysis, around 43% of them developed diabetic neuropathy (Akhtar et al., 2023). Al-Sayyar A., et al., Al-Sayyar who works at the Dasman Diabetes Institute in Kuwait, sheds more light on the specific impacts of diabetes. They found that high blood sugar levels due to Type 2 Diabetes(T2D) results in damage to nerves through the activation of NMDA receptors (Al-Sayyar et al., 2023). These receptors are glucose receptors found in the brain, and are associated with multiple functions such as memory (Jewett & Thapa, 2022). Damaging these receptors may then lead to one struggling to form new memories.

Furthermore, additional studies demonstrate the impact of diabetes on cognitive decline. For example, research by A. Staniago J., et al., found that people with T2D had around a 40% more chance of Parkinson's disease compared to those without the condition(Santiago et al., 2023). This demonstrates the impact that diabetes can have on brain function in the long run. This also demonstrates the importance of insulin in the brain, and demonstrates why initiative should be taken to find a cure for diabetic conditions.

Other studies further correlate diabetes with neurodegeneration. J. Bree, A., et al., conducted a study utilizing rats. 10 of these rats were experimental and experienced diabetic conditions while the other 7 were control, and had normal pancreas functioning. The researchers induced a hypoglycemic, or low blood sugar condition onto both groups of rats (Bree et al., 2009). Hypoglycemia can be a dangerous condition as there is not enough energy for the body to properly function and in severe cases could lead to coma. Both groups of rats had similar hypoglycemic reactions and experienced seizures. An interesting outcome of the study was that diabetic rats had more than two times the number of FJB+ cells, markers for neurodegeneration, compared to the control group (Bree et al., 2009).

With the implications of diabetes and its relation to the nervous system and neurodegeneration being established, multiple actions must be taken. Research should be conducted on this topic in an attempt to better understand the connection between diabetes and the nervous system and how it relates to neurodegeneration. Gaining a deeper understanding on why correlations between diabetes and FJB+ cells, for example, would help to show what exactly is the cause of this problem. This would help to provide information on how to prevent neurodegeneration from diabetes and potentially help to establish a base going forward to determine if there is any pathway to be taken that could lead to a cure for nerve damage. In addition, this research would help to bring awareness to the far reaching impacts of diabetes. This research is also going to look at stem cells and how they could potentially lead to a cure for diabetes, helping to altogether prevent neurodegeneration from diabetes.

Methodology

The purpose of conducting this study was to gain a better understanding of the impacts that diabetes can have on the body, specifically on the nervous system. To study this topic, research was conducted by analyzing online literature with no physical sources or experimental study. The sources used mainly consist of research articles published by scientists from around the world. Some sources were located from databases such as the National Institute of Health. A few news articles and medical blogs were gathered to help fill gaps in the research that were not readily available through other research articles. Medical blogs came from credible organizations such as the Mayo Clinic and the Centers of Disease Control. The information found in any other news article was checked for by utilizing any available research. No physical sources were used, and no participants were involved in any experiment or process. After research was gathered, sources were analyzed in order to gain a better understanding of the topic. To prevent bias, multiple sources were consulted in making conclusions to make sure any conclusions are well supported by evidence. The sources were from people from different locations around the world, such as the U.S., Pakistan, and China to name a few.

What is Diabetes?

Diabetes in general relates to the hormone insulin and how the body produces and makes use of it (World Health Organization, 2023). NIDDK defines that insulin is created in the pancreas and is used to signal bloods to intake glucose. They state that a lack of this hormone would result in glucose building up in the bloodstream (NIDDK, 2023). Large quantities of glucose result in hyperglycemia, or high blood sugars (World Health Organization, 2023). The opposite of this would be hypoglycemia, or low blood sugars. InformedHealth.org defines the general range between hypoglycemia and hyperglycemia as between 60-140 mg/dl. Anything below this or above this is hypoglycemia or hyperglycemia respectively (InformedHealth.org, 2023). These levels can vary depending on certain conditions such

as when one last ate, but show the general ranges of normal blood sugars. Both hyperglycemia and hypoglycemia are conditions which have various effects on the body. Generally, hyperglycemic effects take longer to form and long term damage occurs after longer periods of time. According to the Mayo Clinic, usually the conditions of hyperglycemia form over days or weeks at blood glucose levels of 180 to 200 mg/dl. Some symptoms range from feeling weak or tired to being confused or losing consciousness (Mayo Clinic , 2022). Hypoglycemia on the other hand can have fast acting impacts on a person and severe cases of this condition could result in multiple conditions such as a coma. There are also multiple different types of diabetes that impact insulin production and usage in multiple ways but for this paper, type 1 and type 2 diabetes are going to be discussed in detail, and their relationship to the nervous system is going to be analyzed.

Background on Type 1 and Type 2 Diabetes

Type 1 and type 2 diabetes are two different conditions that can impair the body from utilizing this sugar by causing some interference. In type 1 diabetes, the body is not able to produce insulin. The cause of this is related to an autoimmune activity where the nervous system attacks insulin producing cells in the pancreas (CDC, 2024). Currently, the cause of this autoimmune reaction is unknown. This could be fatal to a person if left untreated since the body would not make use of sugar, and could potentially leave cells malnourished. In addition, as will be discussed in detail later on, if cells are not utilizing sugar, it will remain in the bloodstream, which could then lead to complications in the nervous system. Type 2 diabetes is more related to insulin resistance (Mayo Clinic, 2023). Due to the insulin resistance, cells do not respond to insulin, resulting in a lower intake of sugar. Another difference between type one and type two diabetes is that type 1 is not related to lifestyle practices such as diet (CDC, 2024), whereas type 2 diabetes has been correlated with obesity or inactivity (Mayo Clinic, 2023a).

The Pancreas and Beta Cells

The pancreas is a bodily organ that is responsible for the production of insulin. The pancreas is closely related to digestion through the secretion of multiple types of enzymes which are released through the major pancreatic duct (Elzouki et al., 2012). In addition, the Beta cells on the pancreas are responsible for the production of insulin (Elzouki et al., 2012). These cells respond to Ca^{2+} ions that enter through a channel, activating these cells (Rorsman & Ashcroft, 2018). These Ca^{2+} ions increase in response to glucose (Sabatini et al., 2019). This means that as the amount of sugar increases in the bloodstream, more Ca^{2+} channels would activate, releasing Ca^{2+} to the beta cells, resulting in the beta cells secreting more insulin. If damage occurs in a Ca^{2+} ion channel, it could prevent Ca^{2+} from crossing the channel and activating the beta cells, resulting in higher blood sugars. This could be a possibility, since damage to ion channels has been seen to result in other diseases. For example, myokymia, which is an involuntary twitching of muscles, usually in the eyes (Cooper & Jan, 1999; Mayo Clinic Staff, 2023). This may result from mutations in ion channels decreasing the repolarization after an action potential (Cooper & Jan, 1999). Repolarization is the return to a resting state after an action potential occurs (Grider et al., 2023). After a chemical signal is fired, it resets before another one is fired again. With the mutation in the ion channel, it causes it to take a longer time for the chemical signal resets. Furthermore, Cooper & Jan described how new action potentials form much more easily. So not only are action potentials lasting longer than normal, spontaneous action potentials are sent resulting in a twitching motion (Cooper & Jan, 1999).

There are other methods of activating the B cells as well. Rorsman & Ashcroft, (2018) explains how the smell of food is one of the primary sources for the activation of B cells. They explain that when they increased blood glucose levels by 2.5 mm, there was only a 30% increase in insulin production of isolated B cells, but when doing that same process in a test subject, the result was 16 to 17 times the previous (Rorsman & Ashcroft, 2018).

Type 1 Diabetes Progression

There are multiple factors that could increase the risk of onset of the disease including environmental and genetic factors, yet how this process starts is still unknown, but there are multiple hypotheses that are available that provide some insight into how Type 1 onsets. Type 1 diabetes is divided into three main stages, beginning from being exposed to the risk factors, to facing presymptoms, finally ending with the symptoms.

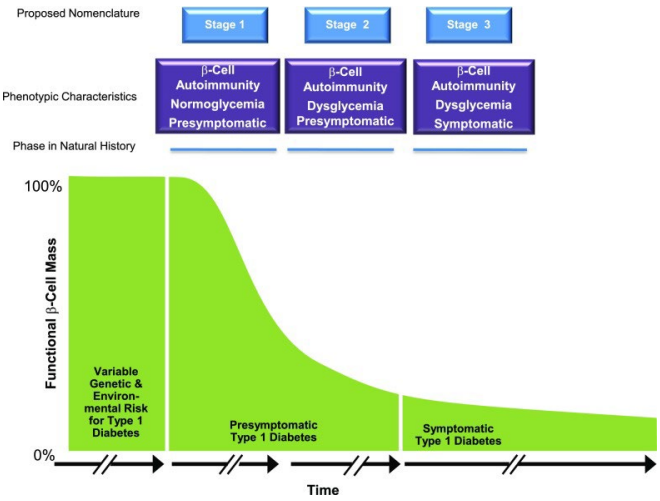

Figure 1. Source Insel et al. 2015. This graph shows the amount of B cell mass that is left as diabetic conditions progress. The B cells are responsible for the production of insulin. The graph shows that the amount of insulin producing cells decreases as the condition progresses, with less than 50% of beta cells remaining as the condition moves into stage 3.

The first stage represents the appearance of autoantibodies, but normal blood sugar levels and B cell mass (Insel et al., 2015). Autoantibodies may form from inflation in a specific organ and are proteins that attack certain cells, usually ones that are seen as a threat (Elkon & Casali, 2008). These can be produced by the body naturally to fight an infection, but can result in increased inflammation by impacting FcyR cells, and releasing cytokines (Elkon & Casali, 2008). FcyR cells are cells that are involved with the immune response and have multiple different functions in regulating how the body reacts to different antibodies (Takai, 2002). Cytokines are protein signals in the immune system that signal the body to initiate an immune response against something that is considered to be a threat (Cleveland Clinic, 2023a).

As Elkon & Casali, (2008) had discussed, this can result in a positive feedback loop. Autoantibodies mistakenly attack cells in an organ, potentially impacting FcyR cells. Cytokines are released, increasing inflammation and calling a stronger immune response, resulting in a continuous cycle. In the pancreas, this could be a potential reason for the reduction of B cells, especially the rapid reduction in the cells after the formation of the first autoantibodies, and also why the reduction of B cells stabilize as the number of B cells decrease. Since there are fewer B cells, this feedback loop is not going to persist as much anymore.

The second stage is where these autoantibodies then cause the reduction of B cells (Insel et al., 2015). The authors continue to describe how stage 2 may be associated with an increase in HbA1C levels over one to one and a half years (Insel et al., 2015). HbA1C, called Hemoglobin A1C is a test that is used to determine the amount of sugar found in one's body over a certain period of time, usually for over the past 2 to 3 months (MedlinePlus, 2022). Hemoglobin is a protein found in red blood cells that serve multiple functions such as carrying oxygen. An increase in one's HbA1C levels would mean that one's glucose levels may have been higher compared to the previous 2 to 3 month period. Insel

et al., (2015) explains that those who have a HbA1C level less than 6.5% and see an increase may begin to develop the symptomatic disease(stage 3) over the next 1 to 1 and a 1/2 years.

Type 2 Diabetes Progression

In one of the studies done by Galicia-Garcia et al., (2020) they had provided a slightly better understanding of the factors that could onset type 2. Obesity and lifestyle choices mixed with genetic risk factors are some of the potential causes for this disease. Type 2 diabetes usually begins its onset once B cells in the pancreas dysfunction and the body develops insulin resistance, resulting in a cycle of B cells being pushed to the extremes to keep up with insulin demands, while they are still unable to work at full capacity (Galicia-Garcia et al., 2020). Both type 1 and type 2 diabetes display a positive feedback loop during the onset of the disease. Potentially since the loop in type 1 diabetes results in inflammation, type 2 could also result in inflammation in some part of the body after a long period of time. This is supported by Galicia-Garcia et al., (2020) who explain that inflammation impacts B cells and that inflammation exists with other forms of stress that are exerted onto these cells such as amyloid stress, and metabolic and oxidative stress. This provides an interesting view into type 2 diabetes, signaling that there is a relation between the disease and amyloid proteins. In short, amyloids are irregular tangles of proteins that are usually insoluble and can build up inside of organs (Liu et al, n.d.; Mayo Clinic, 2023b) These types of stress can occur for multiple reasons such as through the presence of free fatty acids during a hyperglycemic condition (Galicia-Garcia et al., 2020). These FFAs(free fatty acids) can be found in substances such as triglycerides(lipids like oils) and can form when these substances break down (Creative Proteomics, n.d.). These FFAs are checked for by the CD36/FATP-1 transporter (Sears & Perry, 2015). CD36 is a fatty acid uptake and potentially a component in the endocytosis of fatty acids into cells (Hao et al., 2020). Endocytosis is essentially the intake of a substance from one cell to another. Depending upon some of the properties of the fatty acids that are being uptaken by CD36, specifically looking at whether the palmitic acid is contained in the fatty acid, it could release cortisol to increase insulin resistance (Sears & Perry, 2015). Palmitic acid increases the amount of a hormone called resistin, that binds to TLR4 receptors on SH-SY5Y cells, and impairs insulin activity on Akt phosphorylation (Amine et al., 2021). Resistin is released when FFAs bind to FFA Receptor 1(FFAR1) (Hernández-Cáceres et al., 2019). SH-SY5Y cells are model cells used by scientists to model neurodegenerative disorders (Kaya et al., 2024). TLR4 is a receptor that binds to lipopolysaccharides(LPS) and then causes an immune response (Moraes et al., 2014). In addition, it is worth to note that LPS binding to TLR4 is one method, along with insulin, for Akt phosphorylation to begin (Laird et al., 2009). Resistin is an insulin antagonist (Gimeno et al., n.d.). An antagonist is a substance that inhibits a compound's function. In this case resistin is inhibiting insulin from performing its task. When Akt receives insulin, it begins the process of metabolizing substances such as proteins and glucose (Huang et al., 2018). This works through the activation of AS160 and PFKFB2 receptors (*PI3K Akt Pathway,* 2016). AS160 regulates GLUT4 (Mîinea et al., 2005), which transports glucose under insulin regulation (Stöckli et al., 2011). PFKFB2 is responsible for the regulation of glycolysis(breakdown of sugar) through its control of F2,6BP (Raben D. M., et al., n.d.). Higher levels of F2,6BP molecule signal for glycolysis (Wu et al., 2006). With resistin binding to TLR4, there are less openings for LPS to bind to the receptor. In addition, when one eats food that contains fatty acids with palmitic acid content, it then correlates to higher levels of resistin, preventing glucose metabolism.

Increasing Prevalence of Diabetes

Diabetes is a relatively common disease around the world. The projected number of diabetic cases in only America by around 2030 is around 55 million cases (Rowley et al., 2017). This is supported by data from the CDC who describe that as of 2020, around 37 million Americans potentially have this condition (CDC, 2020). In the entire world, there are approximately 415 million diabetic cases (Zimmet, 2017). With such a large number of cases, some seem to hint

at diabetes potentially being one of the largest epidemics of this century (Zimmet, 2017) while another perspective suggests that diabetes is more similar to a pandemic (Unnikrishnan et al., 2017).

The accuracy of the following data may not be infallible. Some of the methods in the following studies relied on the fasting glucose levels of patients in order to determine the prevalence of diabetes. Riley, who wrote an article for the WHO states that fasting glucose levels are measured by patients not eating for at least 8 hours before glucose levels in the blood are measured. 70-100 mg/dl is considered the normal glucose level. Up until 125 mg/dl, it is recommended to watch for any changes. Any level above 126 mg/dl is classified as diabetes (Riley, n.d.). The reason that people should be cautious when looking at data using this method is that studies have found that the fasting glucose method underestimates diabetes by 20-25% (Zimmet, 2017). The actual values may in fact be considerably more than what is shown in the data.

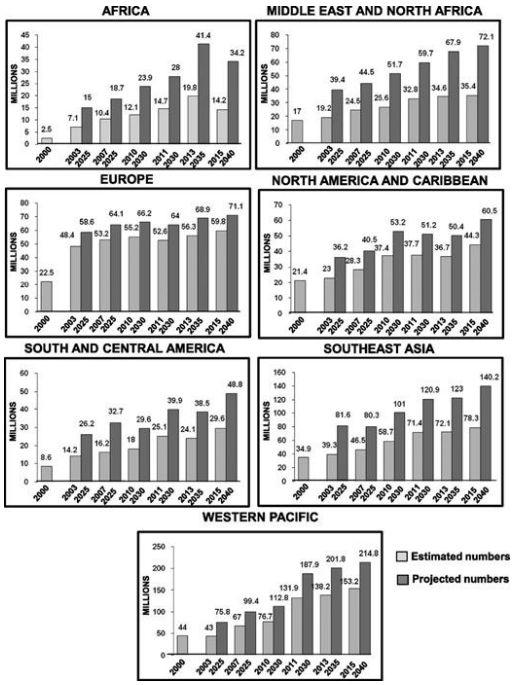

Figure 2. Source Unnikrishnan et al., 2017. The graphs show the estimated number of cases and the projected number of cases of diabetes. Estimated numbers are light gray while the projected numbers are dark gray. The graph shows multiple locations from around the world, and helps to give a scale of the problem, and the potential escalation that could be seen in the future.

There are some studies that suggest that diabetes is not increasing as much as suspected, with two studies, one conducted in 2008 and another conducted in 2012 which show a similar number of diabetes cases, 8-9 in 2008 and 7-8 in 2012 (Rowley et al., 2017). The researcher cautions, though, that this may be subject to change as obesity has shown to have increased by 3% from 2011 to 2012 (Rowley et al., 2017).

Many different people are impacted by diabetes, some being more impacted than others. It seems that more men than women have diabetes. A study found out of 2787 participants, 51% of the male subjects were type 1 diabetic while 49% of women were (Soedamah-Muthu et al., 2008). This is supported by data from the CDC who report that, in adults older than 18, as of 2018, it is estimated that there are 17.9 million cases of males with diabetes, compared to 16.2 millions cases of females (CDC, 2020).

In addition, different countries, races, and ethnic backgrounds have different rates of diabetic cases. So far, it seems that China experiences the most cases with 140 million patients, with India, the country with the second most

number of diabetic cases, lagging far behind with 74 million (Elflein, 2024). This may be due to air pollution. Type 2 diabetes has been connected to environmental pollution, especially chemicals such as BPA and phthalates (Unnikrishnan et al., 2017). BPA is a chemical found in many plastics and in large amounts can negatively impact parts of the body such as the brain (Bauer, 2023). Phthalates are another type of chemical that is used in plastic production, usually to give plastic flexibility (EPA, 2017). This chemical, as currently understood, is a potential endocrine disruptor that interferes with the functioning of the endocrine system (EPA, 2017). This may be a potential reason that China has such a large number of diabetic cases since studies have found high levels of BPA in the environment that people may be inhaling (Graziani et al., 2019).

According to the study conducted by the CDC, in 2018 it seems that White Americans have the most cases of diabetes and Asian Americans have the least cases of diabetes (CDC, 2020). This data does not seem to be totally accurate, or it could be reflecting a change in diabetic cases, as a study by the CDC from 2013 to 2016 showed White Americans with the least number of diabetic cases and Black Americans with the most (CDC, 2020). The idea that White Americans have fewer cases of diabetes is supported by other data, such as data from a study looking at immigrants in Canada, which found that people from areas such as Asia and Latin America had more cases of diabetes than American immigrants (Unnikrishnan et al., 2017).

Diabetic annual death rates have been going down over there years, probably due to advancements in technology, healthcare, and medicine, and potentially also due to an increased awareness of this disease. Diabetic cases resulting in death are still extremely high though, with around 100,000 cases of death due to diabetes in America alone (ADA, 2023). Annually, according to a 10 year study from 1999 to 2009 by Rowley et al, there is a 65% decrease in amputations due to diabetes. Projections indicate that by 2030, there will be a 25% decrease in annual death rates due to diabetes, and in fact, it is also projected that the life expectancy for diabetics has increased by 1-2 years from 1990 to 2011, in both men and women. The researcher reports, though, that overall, diabetic death cases are going to increase by around 100,000, and currently it seems that the number of cases is growing faster than the diabetic population is growing (Rowley et al., 2017).

Diabetic neuropathy, one of the main topics that is going to be discussed later in this paper, is projected to impact approximately 50% of diabetics in their lifetime (Hicks & Selvin, 2019). This is especially a problem since studies report that within 5-10 years of the formation of diabetic neuropathy, up to half of those with the condition are projected to succumb to the condition (Vinik, 2003). With such high rates of diabetes and complications, research should be conducted in order to better understand these conditions, and potentially find cures to help those impacted.

Stress: A Potential Factor

There are multiple explanations and theories out there that attempt to provide an explanation for the increase in diabetic cases. One potential avenue of research is into stress. Stress is a response of the body to some condition, and at certain amounts, stress can be natural and even healthy, yet overstress can lead to negative health consequences (Cleveland Clinic, 2024). Cortisol is a "stress hormone" that is produced in the adrenal glands (Cleveland Clinic, 2021). The regulation of cortisol is controlled by the Hypothalamus, which releases corticotropin releasing hormone to stimulate the anterior pituitary gland, which then releases adrenocorticotropic hormone which stimulates the adrenal glands and consequently resulting in the release of cortisol (Thau et al., 2023). The levels of cortisol in the body vary depending upon the time of day, but usually there are higher levels of cortisol during the morning than there are during the evening (Cleveland Clinic, 2021). Usually it should be around 10-20 mcg/dl early in the morning from 6-8 a.m. while towards the later parts of the day it should decrease to 3-10 mcg/dl (Cleveland Clinic, 2021). One study suggests that as age increases, so does the level of cortisol (Moffat et al., 2019). The study looked at the UFC/Cr levels, or the urinary free cortisol to creatinine ratio, and the results found from the age of 60 and onwards, the UFC/Cr rate of change is approximately 0.46 (Moffat et al., 2019). The study also shows that as one gets older, the amount of cortisol generally increases (Moffat et al., 2019). The current aging population is approximately 1.4 billion individuals who are currently over 60 years old, and this value is expected to almost double by 2050 (World Health Organization,

2022). In addition, stress has been increasing amongst the population in general. A poll found that out of around 4,600 participants, 74% felt severe stress that led them to feel overwhelmed (Mental Health Foundation, 2018). With both high levels of stress and a large aging population, this could be a potential cause for the increase in diabetic cases. Yet, does cortisol play any significant role in diabetes? If so, what is it?

First off, cortisol does play at least some role in diabetes. Cortisol is used for multiple functions other than the stress response, such as for glucose homeostasis, for example, cortisol can act on the liver to result in gluconeogenesis, resulting in the formation of glucose (Thau et al., 2023). Gluconeogenesis reverses glycolysis(breakdown of glucose, which results in pyruvate), and forms glucose (Melkonian et al., 2019).

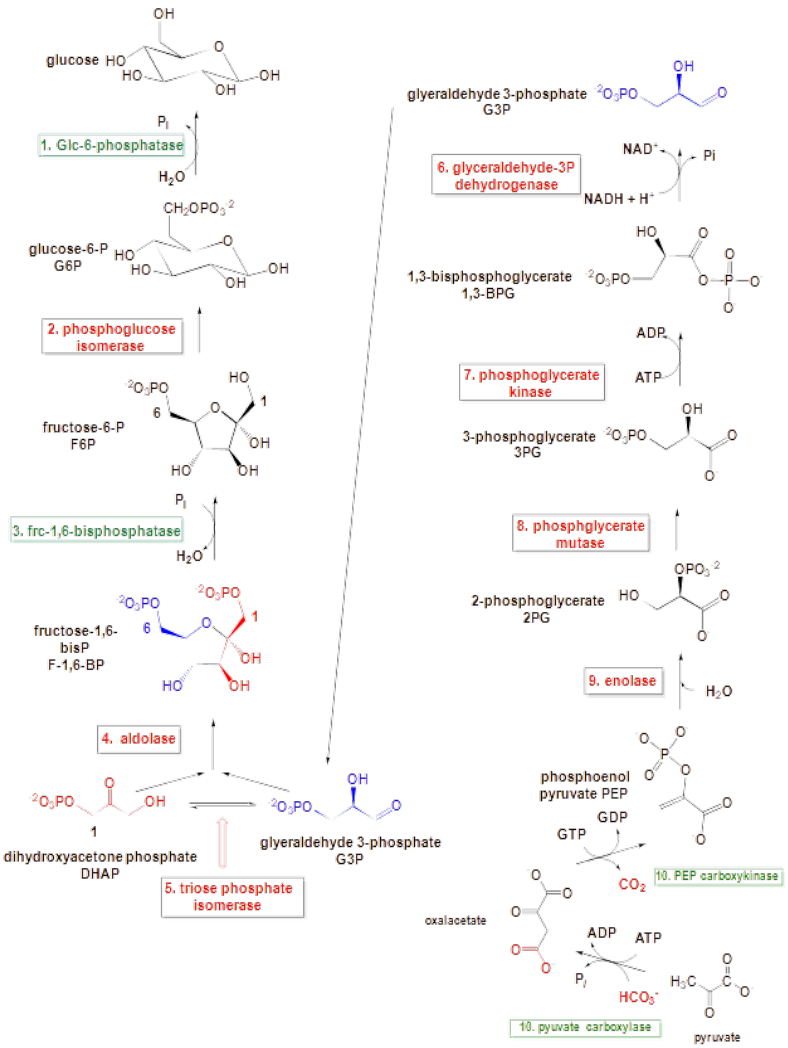

Figure 3. Source Jakubowski & Flatt, 2018. The image shows the general path to convert pyruvate into glucose through gluconeogenesis. It begins with pyruvate(bottom left) and the utilization of multiple enzymes(pyruvate carboxylase, PEP carboxykinase, enolase, phosphoglycerate mutase, phosphoglycerate kinase, G3P dehydrogenase), resulting in the formation of G3P. G3P is a molecule that forms from glucose, and can be seen in plants through photosynthesis. The graph shows that G3P is in an equilibrium reaction(essentially a back and forth reaction forming one product, then breaking down and forming another one continuously) with DHAP by using the enzyme triose phosphate isomerase. Next after the formation of G3P other enzymes are used to produce glucose from this

molecule(aldolase, frc1,6-bisphosphatase, phosphoglucose isomerase, Glc-6-phosphatase). After the use of these enzymes, it results in the formation of glucose which the body can then use.

Within the process of gluconeogenesis, glucose forms from amino acids, so, during a stress response, cortisol signals to muscles to decrease uptake of glucose and instead degenerate to provide the liver with more amino acids for glucose production, resulting in higher blood sugar levels (Thau et al., 2023). Not only does cortisol result in increased blood sugars, it also contributes to insulin resistance. Cortisol is an antagonist to insulin, and can cause a decrease in GLP-1 (Schernthaner-Reiter et al., 2021). GLP-1 is a hormone that signals insulin secretion and could potentially increase B-cell response to glucose (Kjems et al., 2003). With a decrease in GLP-1, B-cells would exhibit less of a response to glucose, and insulin secretion would decrease. At the same time, cortisol is causing gluconeogenesis, so cortisol is both raising blood sugars and preventing glucose metabolism.

Hypoglycemia

Hypoglycemia is the term for low blood sugars. As was defined earlier by an article in InformedHealth.org, hypoglycemia can usually be defined as blood sugars that are below 60 mg/dl (2023). Usually this condition can occur due to medication overdose (Mayo Clinic, 2023c). Hypoglycemia has multiple symptoms, such as shakiness, anxiety, or dizziness, to comas or seizures (Mayo Clinic, 2023c). These severe symptoms can develop when the brain does not receive enough glucose to function (Cryer, 2007).

Hypoglycemia, Glutamate, and NeuroDegeneration

The brain is almost entirely dependent upon blood glucose to function (Cryer, 2007). This lack of glucose results in the release of glutamate, activating glutamate receptors (Cryer, 2007). Glutamate is a neurotransmitter that provides a multitude of functions through the brain and spinal cord (National Academy of Sciences, 2011). Glutamate is responsible for memory, mood, and other functions in the brain (Pal, 2021). Excess levels of this neurotransmitter usually lead to neuronal damage, and even death (Pal, 2021). Glutamate may be released as a result of severe hypoglycemia due to neuronal depolarization (De Angelis et al., 2021). There is some conflicting information with some studies stating that glutamate decreases during hypoglycemia (Terpstra et al., 2014). Further research could be conducted on this to understand if there are different pathways that could lead to the release of glutamate, and what conditions are needed for these pathways to activate. Glutamate can stimulate the autonomic nervous system, and thus might be a reason why glutamate is released during a hypoglycemic event (Discovery and Innovation at University of Utah Health, 2017). The autonomic nervous system may be activated to promote the release of stored energy in the body to help return the body to normal blood sugar levels (Taborsky & Mundinger, 2012). In a study utilizing mice, an increase of 8mM of glutamate resulted in 2 times the amount of cell death (Zhang & Bhavnani, 2006). Zhang & Bhavnani, (2006) describes that glutamate results in the production of a neurotoxin that may lead to apoptosis. Apoptosis is the process of cell death due to some normal cause (National Cancer Institute, 2019). To simplify, increase in the amounts of glutamate form a neurotoxin that signals cells to die. This is a possible reason why neurodegeneration occurs due to hypoglycemia. Glutamate is considered an excitatory transmitter and excess amounts of glutamate lead to excitotoxicity (Turski & Ikonomidou, 2014). Excitotoxicity is where prolonged activation of receptors, in this case glutamate, results in oxidative stress and other dysfunctions (Armada-Moreira et al., 2020).

The process begins as glutamate receptors called IGluR receive glutamate (Armada-Moreira et al., 2020).These IGluR receptors are ionotropic glutamate receptors, and they form a part of ion channels (Hansen et al., 2021). There are multiple different versions of these receptors and when they are hyperactivated it leads to large influxes of ions (Armada-Moreira et al., 2020). To dilute this influx of ions, water consumption is increased within a cell (Armada-Moreira et al., 2020). Large influxes of water could result in cell lysis, or ‘popping’ due to extreme

swelling. The cell can no longer hold any more fluid within it so the pressure causes the cell to burst. The researchers describe how not only do the cells begin to swell, but they also experience mitochondrial dysfunction (Armada-Moreira et al., 2020). As described earlier in the paper, severe hypoglycemic cases seemed to have doubled the prevalence of neurodegeneration biomarkers, specifically the FJB+ cells (Bree et al., 2009). These Fluoro Jade B cells are damaged NeuN + neurons (Gajavelli et al., 2012). NeuN is a protein that is found in the nucleus of neurons (Gusel'nikova & Korzhevskiy, 2015). Glutamate increases due to hypoglycemia may have resulted in the production of the FJB+ cells through the death of cells that have the NeuN protein. Yet this does not explain why diabetic rats in the study by Bree et al had approximately double the amount of neurodegeneration. They explain that some potential causes for this may have been due to changes in the brain that are caused by diabetes, or due to the impacts of uncontrolled diabetes on the body, such as greater drops of blood sugar, since glucose built up in the blood over time, or even due to insulin deficiency (Bree et al., 2009). Insulin deficiency could potentially be one pathway that leads to increased neurodegeneration in the brain. Again it needs to be reiterated that there could potentially be multiple pathways that could be taken, not just one specific pathway. Insulin deficiency could be one pathway since the brain is an insulin sensitive organ, as Milstein & Ferris, (2021) describes. Insulin receptors have been seen in large quantities within the brain along with IGF1(insulin like growth factor 1), and while they are not used by the brain for the uptake of glucose, they serve other purposes such as for cognition (Milstein & Ferris, 2021).

IGF-1 is a growth hormone that is used by the body, and this hormone works with GH to help promote growth in the body (Laron, 2001). A lack of GH leads to a lack of IGF1, while a lack of IGF1 but normal amounts of GH result in lower levels of development (Laron, 2001). The importance of insulin receptors, insulin, and IGF1 is shown when a lack of insulin receptors and IGF1R(IGF1 receptor) are found in patients who have Alzheimer's disease (Milstein & Ferris, 2021). Alzheimer's disease is associated with the presence of amyloid beta plaques (Milstein & Ferris, 2021). These plaques are formed from the breakdown of larger proteins, specifically APP (Chen et al., 2017). APP is the amyloid precursor protein (Chen et al., 2017). When APP is proteolyzed with BACE1 and Y secretase, it results in the formation of A-Beta (Chen et al., 2017). Proteolysis is the process of breaking down a protein by a protease (Misset et al, 2013). BACE1 and Y secretase are proteases that cut APP to eventually form A beta proteins (Vassar et al., 2009). There are two main parts that are used for this, the first is the forming of N terminus from APP being cut by BACE 1 and the second is the maturation of A beta through N terminus being cut by Y secretase (Vassar et al., 2009). N terminus may play a role in both the process of the forming of A beta proteins, but also may be a component of the intertangled fibrils that make up A beta (Söldner et al., 2017). A secretase is another protease that is utilized in the formation of A beta, yet other enzymes such as BACE 1 and Y secretase form plaques while A secretase does not. (MacLeod et al., 2015). After the production of A beta, overtime, oligomers form fibrils that then form into protein plaques (MacLeod et al., 2015). Oligomers are polymers(multiple units) that consist of multiple monomers(single units) (Negoro et al., n.d.). As more oligomers are produced, they may combine to form larger units, such as the fibrils then plaques. At the moment, there is not much information on how exactly A beta can result in brain damage, and there is only some evidence that suggests that A beta plays a major role in neurodegeneration and Alzheimer's disease (Jagust, 2016). Milsten and Ferris' study reports that either insulin or IGF1 treatment can help to control the production of A-Beta in the brain (Milstein & Ferris, 2021). With the lack of insulin production and/or insulin resistance in diabetic patients, it may become harder to control or prevent the formation of A beta in the brain, leading to further damage, especially when combined with the excitotoxic effects of glutamate.

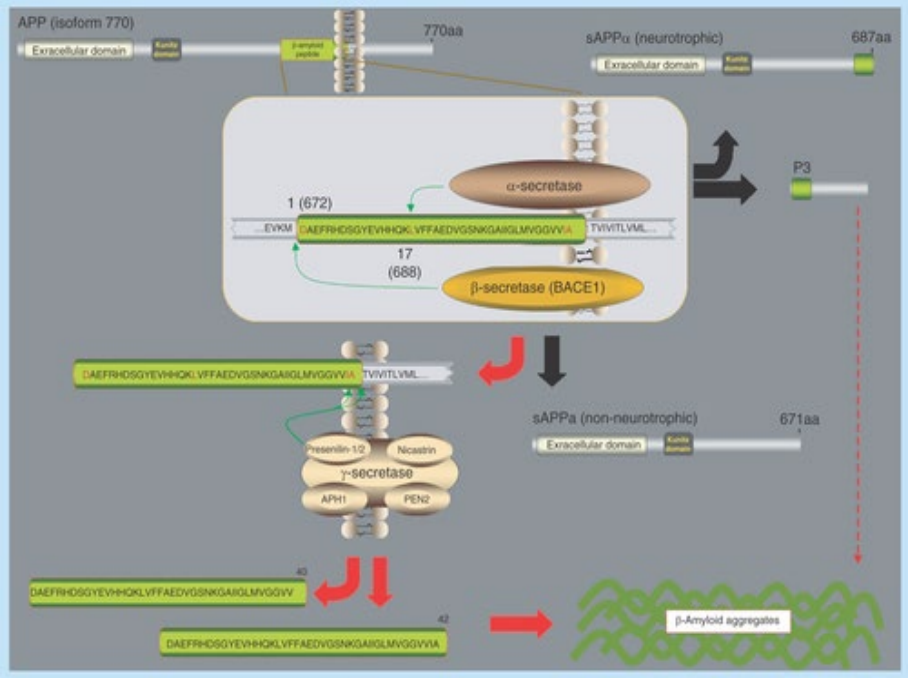

Figure 4. Source MacLeod et al., 2015. The figure displays the pathway that leads to the formation of Amyloid aggregates, and also displays some alternative pathways that do not lead to the production of A beta. The figure shows A secretase, BACE 1, and Y secretase and what parts of the APP genome that they cut in order to result in the formation of A beta.

Diabetic Neuropathy

Diabetic neuropathy is a condition where high blood sugar levels damage nerves (Mayo Clinic, 2022b). This damage could have negative impacts on sensations, movement, and other bodily functions (National Institute of Diabetes and Digestive and Kidney Diseases, 2018). This can pose a detriment to everyday life since in severe cases people could potentially have irreparable damage preventing them from fully moving any limbs. This condition is common in diabetic patients. Feldman et al., (2019) states that it is predicted that by 2050, that approximately 1.62 billion diabetic patients are going to experience this condition. (Feldman et al., 2019) This conditions comes in multiple forms the four main types of are:

Table 1. Information from (Mayo Clinic, 2022b).

Type	Details
Peripheral	Mainly feet, legs, arms, and hands. Tingling, weakness, or sensitivity in those parts.
Autonomic	Impact on organs. Problems in multiple areas around the body such as swallowing and digestion.
Focal	Damage to a certain nerve somewhere in the body. Sensitivity, pain, difficulty using a muscle.

Proximal	From the legs to the chest. Pain when moving.

Pathway of Progression

Diabetic neuropathy has multiple ways in which it could onset. Through hyperglycemia, there are four potential pathways in which the disease occurs: the sorbitol pathway, hexosamine pathway, DAG pathway, and the AGE pathway (Dahiya et al., 2022). Due to many pathways this disease could take, and all of the potential ways through which the disease could progress, a general review of the progression of neuropathy is going to be described without going into deep detail on one specific pathway.

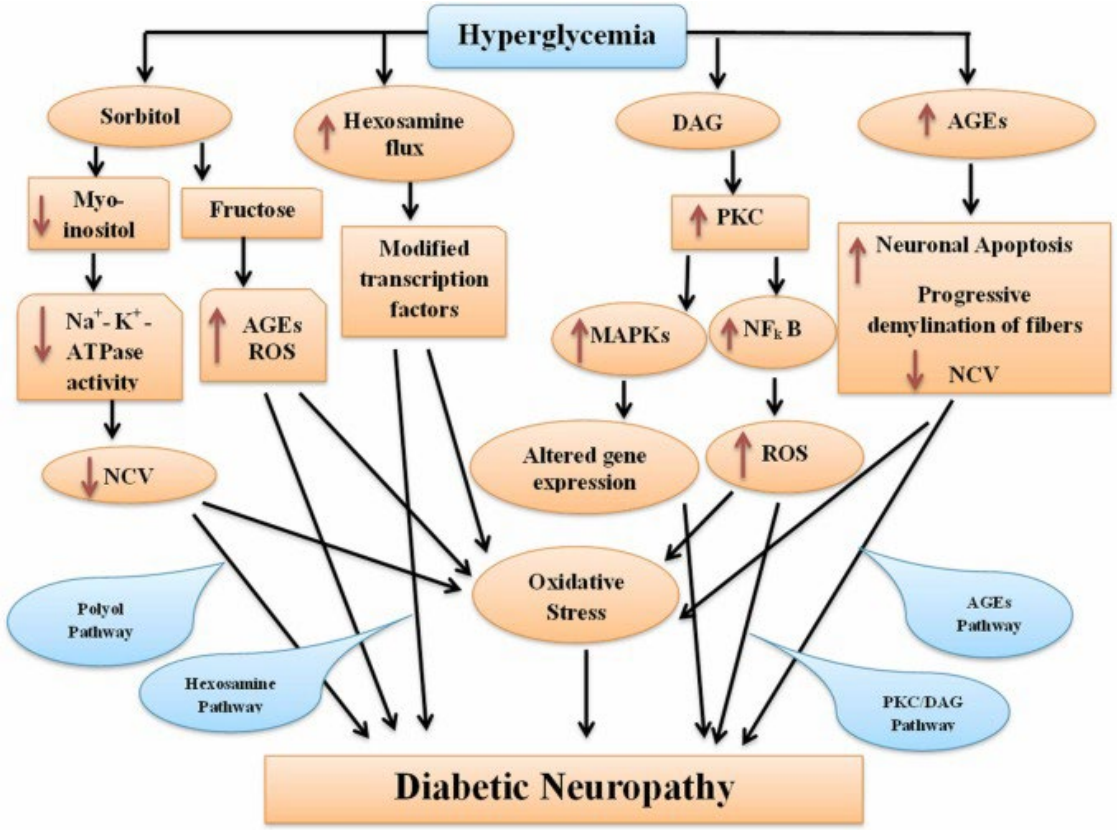

Figure 5. Source Dahiya et al., 2022. The image describes the pathways of diabetic neuropathy progression that results from hyperglycemia. There are a few things to make a note of. First of all , each pathway can have subpaths through which the disease can progress. Secondly, at least one of the subpathways results in oxidative stress, leading to neuropathy.

High blood sugar levels can negatively impact schwann cells in neurons (Yagihashi et al., 2011). Schwann cells are the cells that make up the myelin sheath around neurons (Lee et al, n.d.). The myelin sheath is a structure that helps to speed up the transmission across an axon, or the part of the neuron that is sending the signal. Damage to these cells results in slower transmission of signals and can result in multiple sclerosis. Through glycation, the schwann cells develop deposits of AGE, or advanced glycation end products (Yagihashi et al., 2011). Glycation is the reaction between sugars and proteins or lipids in the body forming AGE (Rahbar et al, n.d.). With larger amounts of sugar in the bloodstream, the glycation process may increase, forming more AGE. Exposure to large amounts of AGE and

other inflammatory chemicals such as cytokines, there were degenerative results in the axon, and also inhibition of repair (Yagihashi et al., 2011). AGE is accepted by RAGE(receptors for AGE) cells, cells that are responsible for inflammation (Sessa et al., 2014). In addition, these cells accept the S100 proteins which are produced during cell damage (Sessa et al., 2014). S100 proteins are released as a signal to the body during a dangerous situation and are used for immune homeostasis and inflammation (Xia et al., 2018).

Going back to the schwann cells, during hyperglycemic conditions, the cells are going to be saturated with glucose and fatty acids (Feldman et al., 2019). Acetyl-CoA is produced in the schwann cells for ATP synthesis in the mitochondria (Feldman et al., 2019). With excess glucose and FAs, ATP synthesis would be occurring much more frequently. This is supported by research from Félix-Martínez et al., (2014), who state that as the amount of glucose increases, GLUT 1 and 3 will become more active in the transport of glucose, which results in increased metabolism. This will send an electrical signal to stimulate insulin production that impacts B cells in the pancreas (Li et al., 2022).

There are some receptors that can have inhibitory effects on insulin production when going through this process, but one receptor, P2Y1 has been seen to release CA2+ due to ATP (Li et al., 2022). ATP works in autocrine signaling, to activate the P2Y1 receptor (Khan et al., 2014). Autocrine signaling is essentially where a cell produces a signal which it releases and accepts itself. The other receptors however, had some detrimental effects. The researchers found that activation of ATP-P2X7 led to cell death and DNA breakage, and other receptors such as P2X3 had negative effects on the production of B cells in the pancreas (Li et al., 2022). Both of these receptors are activated by extracellular ATP content (Li et al., 2019; Shokoples et al., 2021) When the formation of Acetyl-CoA in the schwann cells is saturated, excess acetyl CoA are converted to toxic acylcarnitines, which produce axonal degeneration (Feldman et al., 2019). Acetyl-CoA is converted to acylcarnitines by CPT1(carnitine palmitoyltransferase 1) which replaces the CoA with a carnitine (Schooneman et al., 2013). Carnitines are essential nutrients that are used to transfer FAs for oxidation in the mitochondria (National Institutes of Health, 2023).

Essential nutrients are nutrients that the body needs but cannot produce itself. While carnitines are produced by the body, it is still considered an essential nutrient since the need for carnitines usually exceeds the amount the body can produce (National Institutes of Health, 2023). As acylcarnitines build up inside of schwann cells, it results in toxicity that can lead to axonal degeneration, potentially through mitochondrial damage (Feldman et al., 2019). Inflammation from the production of AGE, along with damage caused by increased levels of acylcarnitines, neurons could be damaged by high blood sugars, due to the stress that results from the production of these substances.

Basic Treatments for Diabetes

The treatments suggested in this article should not be taken as medical advice. It is always recommended to check with a medical professional before utilizing certain medications or treatments.

There are a multitude of treatments available for both type 1 and type 2 diabetes. Most of these are different medications that can be taken in order to help manage glucose levels and for type 2 diabetes, even help control weight. The NIDDK lists some of these treatments. For type 1 diabetes, the main medication is insulin that is provided externally. This could be through a syringe, insulin pen, or insulin pump. There are multiple forms of insulin that one may need to take, ranging from ultra rapid acting to ultra long acting. These vary in the amount of time it takes for the hormone to take effect, and also how long the hormone will last inside of the body. This is especially used in type 1 diabetes since the pancreas cannot produce insulin. Those with type 2 diabetes may occasionally need insulin depending upon other health circumstances (National Institute of Diabetes and Digestive and Kidney Diseases, 2019). Type 2 diabetes usually may also require oral drugs that need to be taken occasionally (*Diabetes - Diagnosis and Treatment - Mayo Clinic*, n.d.). One such drug is Metformin (*Diabetes - Diagnosis and Treatment - Mayo Clinic*, n.d.) which can be used for glucose regulation and increasing sensitivity to insulin (*Metformin: MedlinePlus Drug Information*, 2024). In extreme cases, surgical procedures may also be used to help with the condition. For type 1 diabetes, a pancreas transplant could be an option, even though there could be numerous life-threatening side effects (*Diabetes - Diagnosis and Treatment - Mayo Clinic*, n.d.). Type 2 diabetes has some forms of bariatric surgery that

one could undergo (*Diabetes - Diagnosis and Treatment - Mayo Clinic*, n.d.). Most of these surgeries affect parts of the stomach and the small intestine (Mayo Clinic, 2024). For example, sleeve gastrectomy is where surgeons remove about 80% of the stomach, limiting the amount of food that it could hold (Mayo Clinic, 2024). While bariatric surgery could be beneficial, it could lead to infection, malnutrition, or other side effects (Mayo Clinic, 2024). For both type 1 and type 2 diabetes, exercise and diet can be ways to help manage blood sugar levels and other conditions, and help to prevent any complications from arising (*Diabetes - Diagnosis and Treatment - Mayo Clinic*, n.d.). Medical professionals can provide different exercise and dietary plans for patients and these recommendations are ever changing and improving as new research is conducted. For example, a study was looking at the potential benefits of a dietary supplement, and the study found that beans are a potential way to help manage blood sugar levels. They had found that participants that had 10% bean supplemented diet had overall lower blood sugar levels (Calderón Guzmán et al., 2020).

Further Treatment Options

There are multiple newer options that are being researched that could be used to cure diabetes, and there are even options to help manage some of the complications that may have arisen due to diabetes, such as neuropathy. Two solutions are going to be looked at in this paper, stem cell therapy and TMS. Stem cell therapy is going to be looked into as a potential cure for diabetes and TMS is going to be looked into as a solution for diabetic neuropathy.

Stem Cell Therapy

NIH gives a brief explanation of stem cells in one of their articles. They describe that stem cells are types of cells that can reproduce quickly. These can be in the form of pluripotent stem cells, also called embryonic stem cells. These cells can be either derived from the embryo of a human or can be formed inside of a lab. These types of stem cells have the ability to divide into any type of cell in the body. There is another form of stem cell called adult stem cells that are specialized cells that are not derived from an embryo or are not similar to embryonic cells. These cells have specific functions in the body such as for repair. Stem cells are special since they replicate themselves, which is not seen in many other cells. In addition, since embryonic stem cells do not have any specialization, they can reform tissues (National Institutes of Health, 2016).

Stem cells can be harvested in multiple ways, such as from the blood, bone marrow, and umbilical cord (NHS , 2022). One type of stem cells that is used are the embryonic stem cells (ESCs). Developing cells form a circular mass called the blastocyst (Yang et al., 2022), inside of which is an inner fluid called the blastocoele (Bakkum B. A., et al, n.d.). The outer layer of cells that makes up the circular mass is the trophoblast (Bakkum B. A., et al, n.d.). Inside of this circular mass of cells is the inner cell mass(ICM) which are the embryonic stem cells (Bakkum B. A., et al, n.d.). These cells are able to be replicated in vitro and have the ability to form any tissue in the body (Yang et al., 2022).

There have been multiple successes in utilizing the ICM cells in forming B-cells that function (Yang et al., 2022). The author describes how Lumelsky et al. had success in forming stem cells using a 5 stage differentiation protocol (Yang et al., 2022). Lumelsky et al. explains in their abstract that these cells self-assemble into clusters similar to pancreatic cells, and even maintained this formation when tested in mice (Lumelsky et al., 2001). Furthermore, Jiang J. et al had further success with human embryonic stem cells(hESCs), as they described in their abstract, in which they were able to make almost fully functioning pancreatic cells that could respond to glucose levels (Jiang et al., 2007). Bhonde et al describe in their abstract that there are potential ethical concerns with gathering embryonic stem cells since it can harm or destroy the embryo and when implanted into the body, can result in an immune response. They state that mesenchymal stromal cells(MSCs) may be a better option since they have less ethical concern and usually do not lead to an immune rejection (Bhonde et al., 2014). MSCs are multipotent cells,

compared to the pluripotent ESCs (E. Ambrosio et al., 2015). There is a difference between pluripotent, and multipotent cells. There are three main types of potency for cells, totipotent which can form embryonic cells including the placenta; pluripotent, which can form all body cells but not the placenta, and multipotent cells, which can only divide a certain number of times (MacDonald, 2023). How would MSCs work properly as stem cells then? This happens by transforming MSCs into iPSCs or induced pluripotent stem cells (Spitzhorn et al., 2019). These iPSCs work similar to normal ESCs yet do not have the same ethical concerns that would be seen in ESCs (E. Ambrosio et al., 2015). In addition, it is much easier to gather MSCs making iPSCs more available than ESCs (E. Ambrosio et al., 2015). MSCs themselves have some benefits, such as usually being void of immune rejection, and showing potential to be used in targeted therapy (Flamant et al., 2023). Targeted therapy is used in dealing with cancer and trying to inhibit tumor growth (Ferretti, n.d.). Despite the potential benefits that come with MSCs, and despite MSCs being more available than ESCs, MSCs are still expensive to obtain and require invasive techniques in order to harvest the cells from parts of the body such as bone marrow (Flamant et al., 2023). iPSCs could be a better option since it does not always require MSCs to be formed and can form from skin cells or other cells in the body (UCLA, n.d.). These cells form by genetic reprogramming, and converting cells back into an embryonic form (UCLA, n.d.). iPSCs also do not have any ethical concern, but there is one issue regarding iPSCs and that is the use of retroviruses in their formation (Surat, 2022). Retroviruses are RNA viruses that enter a cell, and utilize enzymes to change RNA into DNA. Following this, they can insert the DNA into the genome of a cell (Surat, 2022), forming something called a provirus. This can be dangerous since it could lead to potential mutations or over-expression of certain genes, some of which could be cancerous, such as c-Myc (Surat, 2022). MYC genes are genes that are usually involved in cell growth and some other cellular process, and its dysregulation has been connected to forms of cancer (National Cancer Institute, n.d.).

Despite all of the drawbacks, there have been multiple uses of stem cells on human patients in an attempt to manage diabetes. One major case is that in China. They had used stem cell therapy on a 50 year old type 2 diabetic patient (Wu et al., 2024). They had made use of E islet tissues that had been formed in vitro from autologous EnSCs (Wu et al., 2024). The E islet cells are pancreas endocrine cells that can either raise or lower glucose levels through the release of insulin or glucagon (National Cancer Institute, 2011b). EnSCs are a type of stem/progenitor cell (Cheng et al., 2017). Progenitor cells are similar to stem cells, but have less of an ability to replicate, and there are no pluripotent progenitor cells (Gleichmann, 2024). Autologous stem cells would be cells that were obtained from the patient (National Cancer Institute, 2011a). Over the course of 25-30 months, there were some short term side effects such as loss of appetite, which was relieved using medication. There were numerous benefits with regards to blood sugar control. The scientists noted that there were no cases of hyper or hypoglycemia during the entire period and by 11 weeks the patient was off of insulin and by 56 weeks the patient was off of most other medications (Wu et al., 2024). This trial seems like a promising result, yet the researchers should be cautious and continue to pay attention to how the cells will function in the long run. The patient was monitored for 116 weeks, about 2 and a half years. It could be possible that the cells would begin to degenerate over time. Ahmed et al., (2017) explains that stem cells deteriorate with age. A study by Cryo-Cell.com explains how in type 1 diabetics that had undergone stem cell therapy, the cells were viable for around 30 months, but nearing the 30 month mark, the cells became less active and eventually the patients had to go back on insulin (*Stem Cells in the Treatment of Diabetes | Cryo-Cell*, 2019).

TMS

A study that is going to be conducted by Nelson A. was looking at utilizing rTMS in treating diabetic neuropathy. They described rTMS as repeated transcranial magnetic stimulation. This process occurs by sending magnetic impulses into the brain by using an electromagnetic coil. They describe that TMS can be used to promote neuroplasticity in the brain, send inhibitory or excitatory signals, and potentially can be used in nerve regeneration. They explain that since diabetic neuropathy is associated with inflammation, TMS could be potentially used to help the inflammation caused by DN. They plan to test the impact of rTMS by utilizing a sham group that will seem to be

receiving TMS treatment, and an experimental group that is actually receiving stimulations from the device (Nelson, 2024).

There are multiple forms of TMS, rTMS being amongst the only forms that can produce lasting results in a patient (Xu & Xu, 2021). The authors explain that rTMS works by sending continuous patterns of pulses that act upon neurons. The authors also add that TMS can not only potentially be a good tool in managing symptoms and repairing the nervous system, it could potentially be used in diagnosing DN, though other tools such as fMRI may be needed (Xu & Xu, 2021). fMRI is a type of magnetic imaging(functional magnetic resonance imaging) that can be used to notice blood flow inside the brain (Cleveland Clinic, 2023b). Xu & Xu, (2021) describes that there have been multiple successes in the past in which forms of magnetic stimulation and TMS had been used to repair neuronal damage. They found that some treatments promoted myelin sheath regeneration and others activated certain pathways such as the brain-derived neurotrophic factor-tyrosine receptor kinase B N-methyl-D-aspartate receptor signaling pathway (Xu & Xu, 2021).

We will break down the pathway into smaller parts, and attempt to understand the progression. We will begin by looking at brain-derived neurotrophic factor(BDNF) which is a type of protein that plays a role in cell survival, growth, and can be neuroprotective in certain cases such as neurotoxicity (Bathina & Das, 2015). BDNF is a type of neurotrophin and neurotrophins are proteins that are used in the survival and regulation of neurons in both the central and peripheral nervous systems (Sahay et al., n.d.). Next, we will look at tyrosine receptor kinase B(TrKB), which is a receptor for BDNF and other neurotrophins (Gupta et al., 2013). Once it receives a neurotrophin, it undergoes an equilibrium cycle between monomerization and phosphorylated dimerization, which may play a role in regulating other neutrophils and receptors, with TrKB playing a role in the regulation of the Ras-PI3K-Akt pathway through which cell growth is controlled (Gupta et al., 2013). So far, we have covered BDNF-TrKB, but there is still one aspect left to cover, N-methyl-D-asparate. Jewett et al., explains that n-methyl-D-aspartate(NMDA) is a type of receptor that respond to glutamate. It has also been found to play a role in excitotoxicity. Jewett et al. describes that glutamate may bind to NMDA receptors, which can be used to activate calcium channels. They explain that this may not always occur and sometimes may require a second receptor, like an AMPA receptor to recieve glutamate to open the calcium channel. They describe how long periods of depolarization(in this case, which results in activation of the calcium channel), can lead to toxic levels of calcium to enter cells (Jewett & Thapa, 2022). In hypoglycemic conditions where there are high levels of glutamate in the body, it may over activate the calcium channels further leading to cell death.

Finally, the Ras-PI3K-Akt pathway needs to be discussed. Ras is a family of GTPases proteins that are used in cell regulation (Castellano & Downward, 2011). GTPases are guanosine triphosphatase proteins that are used as catalysts of the hydrolysis of GTP(guanosine triphosphate) (Zhou et al., n.d.). Ras can be used to activate or deactivate GTP(deactivated form is GDP, guanosine diphosphate) (Wang et al., n.d.). PI3K, or phosphatidylinositol 3-kinase is another molecule useful in bodily regulation, and Castellano & Downward, (2011) describe how knocking out PI3K subunits involved in regulation result in B cell defects, and embryonic death. PI3K are a type of enzyme that have three different types, but not too much is known about this family of enzymes (Castellano & Downward, 2011).

Castellano and Downward show multiple pathways through which PI3K can be activated, and the resulting consequences of such activation. The Ras signalling pathway has Ras GDP and Ras GTP in equilibrium utilizing GAPs. GAPs are GTPase activating proteins. Then the Ras pathway activates p110a, which is a form of PI3K. From there, it can signal Akt with support from PDK1, which supplies a phosphate for Akt phosphorylation, which consequently activates cellular activity such as through Cyclin 1 which is for cell cycle progression, or GSK-3 which is for glucose metabolism (Castellano & Downward, 2011).

In short, the Ras-PI3K-Akt pathway works as Ras is activated by GAP, which results in the equilibrium reaction between GDP and GTP, signaling PI3K, resulting in activation of Akt which is phosphorylated by PDK1, and consequently impacting cell growth and other cellular function. Overall, TMS may be a beneficial method for dealing with diabetic neuropathy due to research that supports this method and also examples that show such a process is viable.

Results and Discussion

The purpose of this article was to attempt to understand what the impact of diabetes was on neurodegeneration. There was specific focus on hypoglycemia and FJB+ cells along with diabetic neuropathy due to hyperglycemia. Especially with the projected number of diabetic cases in America to be in the 50-60 millions by 2030 (Rowley et al., 2017), gaining a deeper understanding of this topic, and looking into potential solutions, with emphasis on stem cell and TMS, would be crucial in helping the population. Excitotoxicity was found to be one potential cause for the result of neurodegeneration due to hypoglycemia. It was found that glutamate is released in hypoglycemic events (Discovery and Innovation at University of Utah Health, 2017), and activates IGluR receptors, resulting in ion release into cells (Armada-Moreira et al., 2020), and over release of ions causing swelling and cell apoptosis. Death of NeuN+ neurons results in the formation of Fluoro Jade B cells (Gajavelli et al., 2012), which are neurodegeneration biomarkers (Bree et al., 2009). This was further influenced by insulin deficiency through the production of Beta amyloid proteins could have been a potential factor in neurodegeneration. This shows how hypoglycemia can result in neurodegeneration and the formation of FJB+ cells which was one of the goals of the study.

Diabetic neuropathy can be the result of hyperglycemia, and there are multiple pathways that could be responsible for the condition. Schwann cells may be impacted by AGE that is formed from high blood sugars, and when RAGE accepts AGE it could result in inflammation. In addition, excess ATP synthesis due to high blood glucose levels results in the formation of acylcarnitines. As acylcarnitines build up in schwann cells, excess damage can occur and lead to degeneration (Feldman et al., 2019). This helps to show how high blood sugars can cause nerve damage, and why maintaining blood sugars within a reasonable range is important in maintaining the health of a diabetic.

Stem cell treatment, despite some drawbacks, seems to be a potential viable solution for diabetes. ESC cells are not as viable to use due to ethical concerns and costs of gathering these types of stem cells. MSC or iPSC cells seem to be a much better candidate of cell type since they do not have as much of an ethical concern. MSC are multipotent cells that can only form a specific type of cell for a certain amount of time (MacDonald, 2023). iPSCs are pluripotent stem cells that work similarly to ESC cells, but do not require gathering cells from the ICM of an embryo. The drawback is that they require retroviruses in their creation, which could lead to cancer (Surat, 2022). There have been multiple tests utilizing stem cells, one recent example being from China, where a type 2 diabetic patient had drastic improvements in blood sugar levels over the course of 116 weeks (Wu et al., 2024), yet it would be wise to be cautious and continue researching stem cells as stem cells are known to degenerate over time (Ahmed et al., 2017). This research shows that stem cells are a promising method that seems to have a lot of potential, yet further research needs to be conducted to better understand stem cells, and determine whether stem cells can fully cure diabetes in the long run.

TMS also seemed to be a promising method for dealing with diabetic neuropathy. Through multiple pathways such as through the activation of BDNF-TrKB-NMDA, which consequently activate Ras-PI3K-Akt pathway, neuronal growth is possible through the use of repetitive TMS(rTMS). This research on TMS sheds light onto a not so commonly discussed method of managing diabetic neuropathy. There is a lot of research on how this could be used to manage diabetes, and the current research seems to support that this could potentially be an excellent noninvasive technique to manage diabetic neuropathy.

Conclusion

Diabetes has been increasing drastically in the past few decades. With millions of cases around the world, and the projected number of cases only expected to grow. This puts more people at risk for neurodegeneration due to diabetes. High blood sugar, hyperglycemic conditions can result in diabetic neuropathy which can impact motor function and in severe cases cause total loss of function in limbs. Low blood sugar, hypoglycemic conditions can cause neuronal cells to die due to excitotoxicity, and the formation of beta amyloid plaques. There are multiple medications and

treatment options that are commonly available to diabetics such as insulin injections and metformin. Some more modern, potential treatment options are stem cell therapy, which has shown to be promising in a patient in China, yet it may be too early to tell if the treatment effectively cured diabetes or if the stem cells are going to degenerate. TMS, specifically rTMS has shown great promise in mitigating the impacts from diabetic neuropathy. Future research should further research stem cells to find better versions of stem cells that are more easily accessible, lack ethical concerns, less costly, and do not degenerate over time. Diabetic neuropathy could also benefit from further research since more detail on specific pathways could be beneficial in formulating potentially even better ways to manage DN compared to utilizing TMS.

Limitations

There are multiple limitations to this study. One limitation that was faced was in regards to time to complete the article and conduct research. This impacted the article by forcing me to limit my scope and not cover all of the details. Explanations provided are more generalized and do not cover all of the details of how a process works. Another limitation was with regards to having little to no experience with this topic. This played a role with the time limitation since with little experience in this topic, the scope had been set too broad. Over the course of the research the scope was decreased and became more specific, yet still may have been slightly broad, forcing a more generalized view on the issue. A third limitation is that the study only focuses on two of the ways that diabetes can result in neurodegeneration. There were two other topics that were planned to be discussed but were removed since they fell out of the scope. These topics were in regards to amyloid and prion proteins, and analyzing what role they played in diabetes and neurodegeneration. In addition, a discussion on type three diabetes, or insulin resistance in the brain, which results in Alzheimer's disease (Hobbs, 2023) was also planned to have its own section, but was not able to make it into the paper. A fourth limitation is that treatment for excitotoxicity was not covered in the paper, so future research would need to look deeper into this topic. Future studies should try to focus and go in depth on less topics to help better explain diabetes and neurodegeneration. For example, focusing on diabetic neuropathy and cures, or hypoglycemia and how to prevent excitotoxicity, rather than combining both into a single paper. This would help with any time constraints and allow for much more detail to be provided.

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