11-2018

Stem Cell Generated β-Cells: A Possible Solution to the Growing Problem of Type 1 Diabetes

Danielle Rae Steffen
Augustana College, Rock Island Illinois

Stem Cell Generated β-Cells: A Possible Solution to the Growing Problem of Type 1 Diabetes

Introduction

When people hear the word diabetes, they usually imagine someone who is inactive, overweight, and all around an unhealthy person. While this is the case for some people with diabetes, those characteristics typically apply to those with type 2 diabetes. Although type 2 diabetes is an ever increasing worry, it is not the only type of diabetes that is becoming a steadily growing problem throughout the world. According to the Juvenile Diabetes Research Foundation, approximately 1.25 million people in the United States are living with type 1 diabetes, 200,000 of which are under the age of 20 (JDRF 2018). Considering there are about 300 million people residing in this country, 1.25 million may not seem like a big enough number to cause concern. However, JDRF also states that the prevalence of type 1 diabetes in people under the age of 20 increased by 21% between the years 2001 and 2009 (JDRF 2018). Clearly this is a significant jump over a period of only eight years, and if the number of new cases continues to increase at its current rate, the incidence of type 1 diabetes is expected to double worldwide within the next ten years (Atkinson et al. 2014). Based on these statistics, it is obvious that something needs to be done to address the growing problem of type 1 diabetes throughout the world. Some people still may not be convinced that type 1 diabetes is an issue that demands attention; after all, most people with diabetes today are able to live a fairly normal life. Over the course of a lifetime, though, type 1 diabetes can lead to some dangerous, even deadly, complications such as retinopathy, neuropathy, amputation, and kidney failure (Rapoza 2017). At this time, there is no real solution to type 1 diabetes. The best diabetics can hope to do is keep their blood glucose levels fairly well controlled through the use of extraneous insulin in the form of daily injections or insulin pumps. However, in recent history, increasing time and money has

been focused on type 1 diabetes research, resulting in several new and innovative techniques. These new techniques include the bionic pancreas, pancreas transplants, islet cell transplants, and β-cells generated from stem cells. All of these options hold great potential for the future treatment of type 1 diabetes, but at this time, stem cell generated β-cells seem to be the most promising choice. Nevertheless, this literature review will delve into the ethics, economics, and mechanisms of each technique, with the ultimate goal of determining whether or not stem cell generated β-cells really are the most promising course of action in the treatment of type 1 diabetes.

History of Type 1 Diabetes

Although today diabetes is a fairly prevalent disease, this was not always the case. Despite this, it has been acknowledged in some form for most of history. According to Swartout-Corbeil and Cataldo, in their Credo Reference entry on diabetes mellitus, it was first recognized by the Egyptians who described its symptoms on papyri in 1550 B.C.E. Five hundred years late, the first mention of diabetic's sweetened urine was made by Hindu physicians after noticing that it attracted insects, and in 230 B.C.E., Apollonius of Memphis officially named the condition after the Greek word *diabainein*, which means to pass through, due to the excessive thirst and urine production of those with diabetes (Swartout-Corbeil and Cataldo 2013). The next step in the evolution of diabetes was the addition of the word "mellitus" in 1675 because diabetic urine had a sweet taste which was confirmed to be caused by the presence of excess sugar in 1776 (Wu 2017).

Clearly diabetes has a very long and interesting history, dating back to the time of the Egyptians. However, the real advancements did not begin until the end of the seventeenth century. The first significant development in the history of diabetes came when scientists

realized that the cause of diabetes was rooted in the pancreas. In 1889, Joseph von Mering and Oskar Minkowski, decided to remove the pancreas from a dog to see what effects this would have on the animal. To their surprise, it was not long before the dog began to exhibit the classic symptoms of diabetes mellitus, providing the first evidence of the cause of diabetes, and opening the door to new diabetes research throughout the world (Ehrenberger 2011). Up until this time, there was no treatment for diabetes. A diagnosis of the condition was viewed as a death sentence with a life expectancy of less than three years for children under the age of ten (Gale 2014). Attempts were made to prevent such an outcome, usually through the implementation of fad diets such as the oat cure which meant eating eight ounces of oatmeal mixed with eight ounces of butter every two hours. Other commonly used options included opium and overfeeding in an attempt to make up for the weight loss and dehydration (Wu 2017). The most frequent form of treatment, though, was the starvation diet which required diabetics to eat very little carbohydrates and around 750 calories a day. While this diet did serve to extend life expectancy, it also caused people to drop dangerously in weight, and eventually resulted in most people starving to death (Ehrenberger 2011).

These fad diets were clearly not sufficient in the treatment of diabetes, and scientists continued to search for more successful options. Due to the new, focused research that came from the discovery of the link between the pancreas and diabetes onset, it did not take long before insulin was discovered and realized to be the best way to treat this condition. According to the American Diabetes Association, in 1921, Frederick Banting and Charles Best successfully extracted insulin from a healthy dog's pancreas and injected it into diabetic dogs. They then watched as the dogs' blood glucose levels proceeded to return to normal levels. This success was a breakthrough in the treatment of diabetes. After Banting and Best's successful experiment,

scientists immediately got to work extracting and purifying animal insulin for use in humans (ADA 2013). For the first time, people were given hope that a life, living with diabetes would be possible. This is seen in a *New York Times* article published shortly after the beginning of insulin use on humans. “A boy of 12 in extreme illness from diabetes became free from sugar after twenty four hours of treatment with insulin has remained free although his diet has increased to practically normal. This boy is gaining weight at the rate of half a pound a day and is leading the type of life any normal, active child would lead” (Serum...1922). Clearly, the discovery and implementation of insulin in humans was a massive breakthrough, and by 1923, insulin became commercially available for the first time (ADA 2013).

Since the initial utilization of insulin in 1921, advancements have continued to be made in the understanding and management of diabetes mellitus. The next big development in the evolution of diabetes came in 1959 when two scientists used radioimmunoassay technology to measure the amount of insulin in the blood (ADA 2013). This was another important key in allowing researchers to understand diabetes because for the first time, it was possible to differentiate between type 1 diabetes, in which patients do not produce any insulin and therefore would have no insulin in their systems, and type 2 diabetes which allows for the production of insulin but prevents usage by the body’s cells (Swartout-Corbeil and Cataldo 2013). In addition to improvements in understanding the physiology of diabetes, progress was also made in the technology used to treat diabetes. In 1970, the first blood glucose meter was produced which allowed diabetics to test their blood sugars at home, and therefore have some idea as to their health on a day-to-day basis (ADA 2013). Next came the development of the Hemoglobin A1C test in 1978 which measured the amount of sugar binding to the hemoglobin molecule over a period of several months which provided doctors with insight into their patients’ level of control

over a longer period of time (JDRF 2018). Another significant breakthrough in the treatment of diabetes came in 1982 when scientists were able to successfully engineer insulin in a lab, making it the first human protein to ever be cloned, and ensuring an unlimited supply of the drug that was vital for the survival of an ever increasing number of people throughout the world (JDRF 2018).

What is Type 1 Diabetes

The ability to produce unlimited quantities of insulin was a significant accomplishment because insulin production is the key to successfully treating type 1 diabetes. Type 1 diabetes is an autoimmune disorder in which autoantibodies form in the body, and begin destroying the insulin producing cells, known as β-cells, of the pancreas (Atkinson et al. 2014). Although researchers are currently unsure of what exactly causes an individual to develop type 1 diabetes, a consensus has been reached that it is likely due to genetic factors. These genetic factors can range from having a family member with diabetes, to expressing a certain combination of alleles that make some people more vulnerable to the condition, to a mutation on one of the loci associated with the development of type 1 diabetes (Robertson and Rich 2018). However, according to DiMeglio et al. (2018), even though someone is born with a genetic disposition, they are not necessarily born with the disease; in fact it is possible that the person in question will live several years of their life with a completely normal amount of β-cells. Eventually though, something will trigger the decline in β-cell mass to begin, resulting in the gradual decline in the number of β-cells in a person's body and, by extension, the amount of insulin they are producing. Once enough β-cells have been destroyed, the body is no longer able to produce enough insulin to keep blood glucose levels within a normal range, forcing the individual to rely on extraneous sources of insulin to survive (DiMeglio et al. 2018). Because of this, finding a way

to restore the insulin producing capabilities of the body will be the key to the creation of a cure for diabetes.

Although it is well known that diabetics are forced to rely on insulin injections to control their blood sugars, it may not be immediately clear why that is. When people eat, they typically ingest a significant amount of carbohydrates. These carbohydrates are subsequently broken down by the digestive system into simple sugars. The most common form of simple sugar is glucose which acts as the main source of energy for the cells of the body. Once carbohydrates have been broken down into glucose, the glucose leaves the digestive system and enters the bloodstream, raising blood glucose levels. In someone without type 1 diabetes, when blood glucose levels become high enough, the β-cells of the pancreas release insulin which then binds to cells in need of energy, and acts like a key, causing the cells to allow glucose to enter. Once this occurs, blood glucose levels return to normal range. However, in a person with type 1 diabetes, there are no β-cells, and therefore no insulin to act as a key to allow cells to take up glucose. This lack of insulin results in cells starving for energy and continuously elevated blood glucose levels (Rapoza 2017).

While it is possible to live with extremely high blood sugars for a while, spending too much time outside of healthy blood glucose range quickly becomes very dangerous. Individuals living with type 1 diabetes have an increased risk for many complications and diseases compared to other members of the populations. For example, the risk of developing some sort of heart disease is ten times higher in people with type 1 diabetes, making diabetes one of the leading causes of heart disease (Atkinson et al. 2014). Prolonged high blood glucose levels can also cause damage to nerves and blood vessels along with poor circulation of blood throughout the body which can lead to neuropathy, retinopathy, and even amputation (Rapoza 2017). In addition

to the long term complications caused by high blood sugars, type 1 diabetics also face the more immediate risk of ketoacidosis and hypoglycemia. In a comprehensive review from *The Lancet*, DiMeglio et al. (2018) outline these additional risks. While it is possible to live with prolonged high blood sugars for a significant period of time, if they are allowed to rise high enough, the individual will eventually enter a state of ketoacidosis which occurs when the body is forced to break down stored forms of energy for fuel resulting in the formation of acidic compounds called ketones. While ketoacidosis is not considered dangerous in non-diabetics, and is sometimes even induced purposely as a dieting tool, in diabetics ketoacidosis is extremely dangerous and accounts for 13-19% of type 1 diabetes related deaths. On the other end of the spectrum, low blood sugars, or hypoglycemia, can become a life-threatening condition even more rapidly. If left untreated, hypoglycemia can lead to seizures, loss of consciousness, and eventually death, all within a period of hours (DiMeglio et al. 2018). Between the long term consequences associated with uncontrolled type 1 diabetes, and the immediately life-threatening conditions of ketoacidosis and hypoglycemia, it is clear that diabetes is a significant problem in desperate need of a cure.

Current Treatment

While a fully functional cure for type 1 diabetes has not yet been developed, there are a wide range of tools available to help ensure that diabetics can do the best possible job of managing their condition and living a normal life. The oldest and most traditional method of doing this involves the injection of insulin through multiple shots daily. The amount of insulin a person injects is dependent on the number of carbohydrates they are ingesting at a given meal as well as their body's personal sensitivity to insulin (Swartout-Corbeil and Cataldo 2013). When using this method, the person in question is responsible for all insulin delivery. If they skip a

shot, they will receive no insulin and are likely to experience high blood glucose levels as a result.

While missing a dosage of insulin will likely always result in hyperglycemia, there is another method of insulin delivery which ensures the user receives at least a small quantity of insulin. Insulin pumps, small devices that connect to the body using a small tube which attaches to an infusion site on the stomach or leg and inject insulin without the use of shots, can be programed to deliver pre-determined, miniscule doses of insulin every five minutes without input from the user (Swartout-Corbeil and Cataldo 2013). This is an improvement over relying exclusively on insulin shots because, even if the user forgets to deliver insulin, they will still receive a baseline amount of insulin which serves to keep blood glucose levels from rising completely out of control due to the fact that these pumps are worn at all times. Despite this improvement over shots, the person must still inform the insulin pump when they are eating and how many carbohydrates they will be consuming before the pump will deliver insulin for the meal (Swartout-Corbeil and Cataldo 2013). Because of this, forgetting to communicate a meal to the pump will still result in the person's high blood glucose until a correction dosage of insulin is delivered.

As can be expected, if someone experiences hyperglycemia due to a missed dosage of insulin, they may not realize their blood glucose is high until several hours have passed. However, an article in Scientific American introduces readers to another form of technology called continuous glucose monitoring, in which users can realize that their blood sugar is too high almost immediately. Continuous glucose monitors are another device that diabetics can wear attached externally to their bodies, with a sensor under the skin that can determine the person's blood glucose level. This sensor then instantly sends blood glucose levels to a

transmitter or cell phone app, allowing the user to know their blood sugar values at all times without physically testing their blood (Sheng 2016). This is an extremely useful tool because it allows for more timely correction of high blood sugars and more effective prevention of low blood sugars.

The newest and most advanced form of diabetes technology utilizes a combination of continuous glucose monitoring and an insulin pump. This option, known as the artificial pancreas, involves a diabetic person wearing both devices. As the continuous glucose monitor senses the user's blood sugar, it transmits that number to the insulin pump which is then able to make automatic adjustments to the amount of baseline insulin being delivered, independent of user input. This system, which was approved by the FDA in September of 2016, still requires the person to enter carbohydrate intake for meals, but is a big step in the right direction of diabetes care (Sheng 2016). The artificial pancreas is the first form of technology that can act autonomously, thereby granting the user a sense of freedom from constantly thinking about their blood sugars, and comfort that the device will prevent blood sugars from reaching dangerous levels.

Stem Cell Generated □-Cells

Despite the vast improvements in technology available to help treat and manage type 1 diabetes that have come over the past several decades, there is still no functional cure for this dangerous condition. However, the increasing amount of research into a cure for diabetes has produced some innovative results, the most promising of which seems to be a transplantation of the β-cells that the patient is missing. These β-cells would come in the form of stem cells, cells that can be differentiated into other types of body cells and are capable of self-renewal, that have been induced to become cells capable of producing insulin. At this time, there are a wide variety

of stem cell types that have been successfully differentiated into insulin producing β-cells in mice and are moving to trials in primates (Intagliata 2016). Some of the most promising of these include induced pluripotent stem cells, adult stem cells such as those found in adipose tissue, and mesenchymal stem cells found in bone marrow (Pan et al. 2018).

While research into the use of stem cells as a potential source of treatment is fairly new, there have already been some promising results. A study conducted at Washington University School of Medicine examined the ability of induced pluripotent stem cells to differentiate into functional β-cells capable of producing insulin in response to fluctuating levels of glucose in the system. In this study, researchers extracted stem cells from skin fibroblasts of type 1 diabetic patients and induced them to become β-cells. These β-cells were then tested *in vitro* to determine their response to glucose, and it was found that the stem cell derived β-cells responded to varying glucose levels in a way similar to that of β-cells derived from stem cells of non-diabetics. After this was confirmed, researchers turned to non-diabetic mice to test these results *in vivo.* β-cells were implanted under the kidney capsule of these mice. One group received β-cells derived from stem cells of type 1 diabetic patients, one group received β-cells derived from non-diabetics, and one group was given no β-cells in order to act as the control. The mice were observed for three months, with serum insulin levels being measured both before and thirty minutes after glucose injections. Throughout this time, the amount of human insulin found in the mice who had undergone β-cell transplants increased in response to the varying quantity of glucose they received. After a period of about three months, some of the mice were injected with alloxan which served to kill off mice β-cells, but not human β-cells. This allowed researchers to determine whether the insulin being secreted from the derived β-cells alone could lead to controlled blood glucose levels in mice. The mice were then observed for an additional 80 days

during which time it was found that the blood glucose levels of mice injected with β-cells derived from both type 1 diabetics patients and non-diabetics were consistent with those of the control group containing only their own function β-cells. This was true of both fasting and post-glucose injection situations. However, when exposed to chemicals thought to be involved in the onset of type 1 diabetes, many of the induced β-cells lost their function. Despite this loss of function, the study was able to prove the functional ability of β-cells derived from the induced pluripotent stem cells of type 1 diabetic donors for a period of approximately six months before they were deliberately damaged or the mice were killed for tissue examination (Millman et al. 2016).

In addition to the promising results in the usage of induced pluripotent stem cells, other types of stem cells have also been successfully derived to become insulin producing cells. One of these options was examined in a study conducted by Mona Amer et al. in which adult stem cells extracted from the adipose tissue of type 1 diabetics were successfully driven to become insulin producing cells. This study was performed *in vivo* on 30 male rats divided into three groups. Ten of the rats were placed in Group 1, a control group and were injected only with phosphate buffered saline. The other 20 rats were injected with streptozotocin to induce type 1 diabetes, and were then subdivided into Group 2, which received no diabetes treatment, and Group 3 which were given β-cells differentiated from adipose tissue-derived stem cells taken from their own abdomens. Prior to transplantation, the differentiated cells were determined to be phenotypically identical to the β-cells of non-diabetic rats. After β-cell insertion, the blood glucose and insulin levels of the rats were observed for two months in response to glucose delivery. Group 2, the untreated diabetics, displayed consistently elevated blood glucose levels and a low level of insulin in their systems. However, researchers found no significant difference between the blood

glucose and insulin levels of Group 1 and Group 3. Additionally, the number of islet cells present in Group 3 was found to be significantly higher than both Group 1 and Group 2, leading researchers to the conclusion that, not only do adipose tissue-derived stem cells successfully differentiate into fully functional β-cells, but they are also capable of inducing islet cell regeneration. The rats were killed for tissue examination after two months, but throughout this time, the transplanted cells were becoming increasingly successful at regulating blood glucose levels. Despite this, longer studies will be needed before β-cells derived from adipose tissue stem cells can move into clinical research (Amer et al. 2018).

In addition to induced pluripotent stem cells and adipose tissue-derived stem cells, a study recently published in *The International Journal of Biochemistry and Cell Biology* has shown that mesenchymal stem cells taken from the bone marrow of type 1 diabetic patients are also a promising option in the usage of stem cells to treat type 1 diabetes. This study was performed on 40 rats, 30 of which received an injection of streptozotocin to induce diabetes. Mesenchymal stem cells were extracted from rat bone marrow and induced to become insulin producing cells. The rats were subdivided into four groups, each containing 10 rats. Group 1 served as the control group and consisted of the non-diabetic rats, Group 2 rats received no diabetes treatment, rats in Group 3 were given injections of undifferentiated mesenchymal stem cells, and rats in Group 4 received injections of insulin producing cells differentiated from mesenchymal adult stem cells. Serum insulin and blood glucose levels were measured for two weeks. It was determined that the blood glucose levels of the rats containing both the undifferentiated mesenchymal stem cells and those who had received insulin producing cells were significantly lower than the untreated diabetic group, and on day 15, the insulin producing cells group displayed blood glucose levels almost identical to the non-diabetic group.

Additionally, at the end of the study, researchers identified no significant difference between the serum insulin levels of the control group and the group that had received a transplant of insulin producing cells. The transplantation of undifferentiated mesenchymal stem cells also resulted in increased serum insulin when compared to the untreated diabetic group, but it was still significantly lower than that of the non-diabetic group. Tissue examination also displayed increased presence of islet and β-cells in both the mesenchymal stem cell and insulin producing cell groups when compared to the untreated diabetic group. It was also observed that positive immunoreactions between β-cells and anti-insulin antibodies had returned to normal in the group receiving the insulin producing cell transplant group implying that these cells are not targeted by the immune system (Domouky et al. 2017).

Between induced pluripotent stem cells, adult stem cells derived from adipose tissue, and mesenchymal stem cells extracted from bone marrow, it is clear that there is plenty of research supporting the possibility of stem cell use in producing functional β-cells for transplant in the treatment of type 1 diabetes. This is further proven by the FDA's recent approval for clinical trials involving the use of human induced pluripotent stem cells, bone marrow derived mesenchymal stem cells, and embryonic stem cells taken from umbilical cords (Sordi et al. 2017). While these clinical studies have not yet produced any significant results, the fact that they are even happening is a testament to the promise that stem cells hold in the future treatment of type 1 diabetes.

Other Treatment Options

While replenishing the lost β-cell mass with new insulin producing cells created from stem cells seems to be an encouraging option, there are other treatment options for type 1 diabetes that are also being researched. One example of this is the bionic pancreas which has the

potential to allow for much better blood sugar control, with much less work on the part of the user. The bionic pancreas is an externally worn device very similar to the artificial pancreas currently on the market. However, in addition to insulin, the bionic pancreas can also deliver glucagon, another hormone produced by the islet cells of the pancreas that is responsible for increasing blood glucose when levels drop too low. This would provide a means of correcting for dropping blood sugars without being forced to consume extra carbohydrates. Another, even more impressive, feature of the bionic pancreas is the fact that it is completely self-sufficient. The device is able to make all adjustments to insulin and glucagon delivery without input from the user, including compensation for meals (Gower 2018). Theoretically, this would mean that the person would not need to do anything other than wear the device in order to achieve optimal blood glucose levels. A study recently published in *The Lancet* involved 39 patients who wore the bionic pancreas for a period of 11 days, and were told to go about their normal lives. The data supplied by the continuous glucose monitor aspect of the device was then compared to data from a period of 11 days during which the person was not using the bionic pancreas. Overall, the study showed that average blood glucose levels were significantly improved during the time in which the participants were wearing the device. However, because the bionic pancreas does not involve replenishing lost β-cells, there was still a substantial amount of time spent out of target range (El-Khatib et al. 2017). When insulin is produced by the pancreas, it begins working immediately; however, when it is delivered extraneously, it can take 20 to 30 minutes before it reaches the bloodstream and allows glucose to enter the body's cells. No matter how advanced a device like this may become, it will never be quite as effective as a functioning pancreas (Gower 2018). This means that, although the bionic pancreas may be a good option in the future

management of type 1 diabetes, it is not a cure and would not prevent all complications associated with diabetes.

While the bionic pancreas would not be a functional cure, pancreas transplants do result in replenished β-cells and insulin independence. According to a review conducted by the University of Oxford, the first pancreas transplant was performed in 1966. Since then, these transplants have been a successful method for curing type 1 diabetes. However, pancreas transplants are fairly risky as far as surgeries go, and they are typically only performed in people with end-stage renal failure or other life-threatening complications. In order for someone to be considered to receive a pancreas transplant, it must be determined that the potential risks of the surgery are worth the consequences that would result if the transplant were not performed (Knight et al. 2017). When it is decided that the surgery is necessary, it is also performed in conjunction with a kidney transplant, resulting in an 80% chance of insulin independence post-operation (Pellegrini et al. 2018). Despite these promising results, there are several other drawbacks to pancreas transplants. In order to prevent the recipient from rejecting the new pancreas, it is necessary to suppress their immune system for the rest of their life, leaving them vulnerable to many other diseases. Additionally, pancreas transplants have a higher rate of complications than most other surgeries, and about 25% of pancreas recipients require additional surgery after transplantation. Lastly, there are a shortage of donors for functioning pancreases, and even with immunosuppressive drugs, about 15-25% of them are rejected (Knight et al. 2017). Therefore, although pancreas transplants are usually effective and are often used in life-threatening situations, they are not a realistic solution for everyone with type 1 diabetes.

The final option for the cure of type 1 diabetes is another type of transplantation in the form of pancreatic islet cells. A review article published by faculty at the Oxford Center for

Diabetes, Endocrinology, and Metabolism tells readers that replacing the lost islet cells is a good possibility in the treatment of diabetes because, similarly to pancreas transplants, it replaces the cells that produce both insulin and glucagon in the patient. Unlike pancreas transplants, however, islet cell transplantation is minimally invasive and quite safe. The procedure is performed by infusing islets into the portal vein of the liver which is very low-risk. Unfortunately, islet cell transplants only result in about 50% of recipients achieving insulin independence, and that number drops significantly within the first two years after receiving the transplant (Spiliotis and Johnson 2017). Additionally, as is the case with pancreas transplants, there is a shortage of available donors, and constant suppression of the immune system is required in order to prevent the islet cells from being rejected. Because of this, islet cell transplants are currently only used in adults who are unable to feel when they are becoming hypoglycemic, and only after the risks of immunosuppression have been weighed against those of hypoglycemic events (Pellegrini et al. 2018). While islet cell transplants may be a viable option for diabetes treatment in the future, at this time the inability to produce complete, long-lasting insulin independence, the lack of donors, and the required immune system suppression make it an unreliable cure.

Evaluation of Stem Cell Generated β-Cells

When considering all of the options for the treatment, and eventual cure, of type 1 diabetes, it seems that stem cell generated β-cells are the most promising option. However, every possible course of action has its drawbacks, including the use of stem cells. In order to determine whether or not they are really the best and most viable option for the cure of type 1 diabetes, it is necessary to consider things such as the ethics behind the usage of stem cells, the economics involved in their research, and the future improvements that must be made before this research can reach the next step.

The first issue that must be evaluated is the ethics behind the usage of stem cells. Stem cells have been a very politically controversial subject ever since their discovery. For the most part, though, this is because people do not really understand the different types of stem cells and the ways in which they have the potential to help our society. According to Karen Weintraub in an article published by *National Geographic*, most people are opposed to stem cells because they believe that using them results in the death of an embryo. While this is often true of embryonic stem cells, there are many other kinds of stem cells that have nothing to do with embryos. For example, the stem cell options discussed in this review focus on the use of induced pluripotent stem cells, adipose-tissue derived stem cells, and mesenchymal stem cells extracted from bone marrow, all of which are taken from adults, and typically from the patient on which they will be used (Weintraub 2014). Furthermore, even if embryonic stem cells are the best option for the creation of new insulin producing cells, as some studies have shown, these cells can be extracted from sources such as the umbilical cord or the placenta after a baby is born (Pan et al. 2018). Even if someone were convinced that the destruction of human embryos was not worth the potential benefits that may come from the use of stem cells, the wide variety of alternative sources makes this an irrelevant argument when it comes to the ethical aspects of stem cell use.

In addition to the question of whether or not stem cell usage is ethical, it is also necessary to evaluate the economics behind their utilization. At this time, stem cell research is very costly and demands a large economic commitment (Pellegrini et al. 2018). A *National Public Radio* article written by David Gorn tells readers that, despite the hope that came with the discovery of stem cells, the political controversy that quickly followed led to limitations on federal funding into stem cell research. Because of these limitations, most research in the field of stem cells must be state funded. Over the past 14 years, California alone has spent over $3 billion on stem cell

research, and the state is planning to ask voters for more money soon (Gorn 2018). Clearly this is a hefty price to pay for research into a field that has, so far, not yielded the promised results. However, in order to determine if it is worth the economic cost, it is necessary to evaluate how much money is currently being spent on type 1 diabetes, and whether or not that amount is something that people can be expected to live with. It is estimated that the amount of money spent on the management of type 1 diabetes annually in the United States is between $14.4 and $14.9 billion (Atkinson et al. 2014). A big portion of that money goes towards increasingly expensive insulin, the one thing that diabetics absolutely must have in order to survive. On average, type 1 diabetics go through about three vials of insulin each month, and each vial costs almost $100. This is leading to a rising problem in the US in which people are unable to afford their insulin, and are being forced to go without it until they have saved up enough money. In some cases, they are forced to choose between the drug they need to live, and feeding their family for a week (Sable-Smith 2018). Furthermore, access to insulin is a problem in other countries as well. However, while in the United States, cost is to blame, in some areas of Africa and South America, there simply is not any insulin, no matter how much money someone has. For example, in Mozambique, a child diagnosed with type 1 diabetes is only expected to live for about seven months (Atkinson et al. 2014). When viewing the economics of stem cell research in this light, it seems that a few billion dollars is a small price to pay when it has the potential to result in countless lives saved.

Finally, in order to determine whether or not stem cells are really the best choice in the future cure of type 1 diabetes, it is necessary to determine what must still be accomplished before they are a viable treatment option. The main issue with the current studies regarding the use of stem cell generated β-cells is the length of the studies. For the most part, these studies have

lasted no longer than a few months (Millman et al. 2016). Additionally, most of these studies have been performed on a small number of test subjects, all of which up to this point have been rodents (Amer et al. 2018). However, there has been recent movement into clinical trials, which shows that the use of functional insulin producing cells created from stem cells is being regarded as a serious potential solution (Guhr et al. 2018). This technique has already overcome several obstacles that other lines of research have encountered such as lack of donors and required immunosuppression due to the fact that stem cells can be taken from the patient in question. These stem cells are typically more easily and safely accessible than other treatment options, and are also capable of self-renewal, even leading to islet cell regeneration once transplanted (Amer et al. 2018). Because of this, although significantly more research is needed in the field, stem cell generated β-cells seem to be the most promising option for the future cure of type 1 diabetes.

Conclusion

Overall, type 1 diabetes is a dangerous disease that can lead to horrible, lifelong complications and even death if left uncontrolled for too long, and more and more people are being diagnosed every day. While it is possible to maintain fairly good control over blood glucose levels through the delivery of extraneous insulin, it is impossible to keep blood glucose levels consistently within target range using this method alone. Because of this, research geared towards possible treatments for type 1 diabetes have increased greatly in recent years, leading to a variety of innovative and promising options such as the bionic pancreas, pancreas transplants, islet cell transplants, and fully functional β-cells generated from human stem cells. Throughout this review, each of these methods has been carefully evaluated, and it has been determined that, while much research still needs to be done before this new therapy can be utilized in the diabetic

population, at this time, β-cells generated from the patient's own stem cells appear to be the most promising option for the future treatment, and ultimately the cure, of type 1 diabetes.

Works Cited

1922 Oct 8. Serum proves boon in fighting diabetes. New York Times (New York, NY). [Internet] [cited 2018 Oct 2]. In Historical New York Times database. Available from: search.proquest.com/hnpnewyorktimes/docview/100145283/56511349812C416BPQ/34

Amer M, Embaby A, Karam R, Amer M. Role of adipose tissue derived stem cells differentiated into insulin producing cells in the treatment of type I diabetes mellitus. Gene 2018 May 15;654:87-94. Available From: ScienceDirect

American Diabetes Association. History of Diabetes [Internet]; c2013 [cited 2018 Sep 29,]. Available from: http://www.diabetes.org/research-and-practice/student-resources/history-of-diabetes.html.

Atkinson M, Eisenbarth G, Michels A. Epidemiology of type 1 diabetes. The Lancet 2014 Jan 14,;383(9911):69-82. Available From: ScienceDirect

DiMeglio L, evans-molina c, Oram R. Type 1 diabetes. The Lancet 2018 June 16,;391:2449-62. Available From: ScienceDirect

Domouky A, Hegab A, Al-Shahat A, Raafat N. Mesenchymal stem cells and differentiated insulin producing cells are new horizons for pancreatic regeneration in type I diabetes mellitus. The International Journal of Biochemistry & Cell Biology 2017/06;87:77-85. Available From: ScienceDirect

Ehrenberger K. Insulin. In: World history encyclopedia. Santa Barbara, CA, USA: ABC-CLIO; 2011.

El-Khatib F, Balliro C, Hillard M, Magyar K, Ekhlaspour L, Sinha M, Mondesir D, Esmaeili A, Hartigan C, Thompson M, Malkani S, Lock J, Harlan D, Clinton P, Frank E, Wilson D, DeSalvo D, Norlander L, Ly T, Buckingham B, Diner J, Dezube M, Young L, Goley A, Kirkman M, Buse J, Zheng H, Selagamsetty R, Damiano E, Russell S. Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: A multicentre randomised crossover trial. Lancet, The 2016;389(10067):369-80. Available From: ScienceDirect

Gale E. Historical Aspects of Type 1 Diabetes [Internet]; c2014 [cited 2018 Oct 4,]. Available from: https://www.diapedia.org/type-1-diabetes-mellitus/2104085134/historical-aspects-of-type-1-diabetes.

Gorn D. Will State Voters Continue To Pour Money Into Stem Cell Research? National Public Radio [Internet]; c2018 [cited 2018 Oct 4,]. Available from: https://www.npr.org/sections/health-shots/2018/01/25/579727683/will-state-voters-continue-to-pour-money-into-stem-cell-research.

Gower T. The Dawn of the Bionic Pancreas. Proto Magazine [Internet]; c2018 [cited 2018 Oct 14,]. Available from: http://protomag.com/articles/dawn-bionic-pancreas.

Guhr A, Kobold S, Seltmann S, Seiler Wulczyn, Andrea E M, Kurtz A, Löser P. Recent trends in research with human pluripotent stem cells: Impact of research and use of cell lines in experimental research and clinical trials. Stem Cell Reports 2018 Aug 14;11(2):485-96. Available From: ScienceDirect

Intagliata C. Transforming Stem Cells into Diabetes Beaters. Scientific American [Internet]; c2016 [cited 2018 Oct 14,]. Available from: https://www.scientificamerican.com/podcast/episode/transforming-stem-cells-into-diabetes-beaters/.

Jeffrey R Millman, Chunhui Xie, Alana Van Dervort, Mads Gürtler, Felicia W Pagliuca, Douglas A Melton. Generation of stem cell-derived [beta]-cells from patients with type 1 diabetes. Nature Communications 2016 May 1,;7:11463. Available From: ScienceDirect

Juvenile Diabetes Research Foundation. Path to a Cure: An Interactive Timeline [Internet] [cited 2018 Sep 29,]. Available from: https://www.jdrf.org/timeline/.

Juvenile Diabetes Research Foundation. Type 1 Diabetes Facts [Internet] [cited 2018 Sep 24,]. Available from: https://www.jdrf.org/about/what-is-t1d/facts/.

Knight S, Vogel T, Friend P. Pancreas transplantation. Surgery (Oxford) 2017 /07/01;35(7):397-403. Available From: ScienceDirect

Millman J, Xie C, Van Dervort A, Gürtler M, Pagliuca F, Melton D. Generation of stem cell-derived [beta]-cells from patients with type 1 diabetes. Nature Communications 2016 May 1,;7:11463.

Ossola A. Hacking Diabetes At Home. Popular Science [Internet]; c2016 [cited 2018 Oct 4,]. Available from: https://www.popsci.com/diy-diabetes.

Pan G, Mu Y, Hou L, Liu J. Examining the therapeutic potential of various stem cell sources for differentiation into insulin-producing cells to treat diabetes. Annales D'Endocrinologie 2018 Jul 21. Available from: ScienceDirect

Pellegrini S, Piemonti L, Sordi V. Pluripotent stem cell replacement approaches to treat type 1 diabetes. Current Opinion in Pharmacology 2018 /12/01;43:20-6. Available From: ScienceDirect

Rapoza K. Type 1 diabetes mellitus. In: Harvard Medical School, editor. Harvard medical school health topics A-Z. Boston, MA, USA: Harvard Health Publications; 2017. Available From: Credo Reference

Robertson C, Rich S. Genetics of type 1 diabetes. Current Opinion in Genetics & Development 2018 Jun;50:7-16. Available From: ScienceDirect

Sable-Smith B. Insulin's High Cost Leads To Lethal Rationing. National Public Radio [Internet]; c2018 [cited 2018 Oct 4,]. Available from: https://www.npr.org/sections/health-shots/2018/09/01/641615877/insulins-high-cost-leads-to-lethal-rationing.

Sheng E. The Artificial Pancreas Is Here. Scientific American [Internet]; c2016 [cited 2018 Oct 4,]. Available from: https://www.scientificamerican.com/article/the-artificial-pancreas-is-here/.

Sordi V, Pellegrini S, Krampera M, Marchetti P, Pessina A, Ciardelli G, Fadini G, Pintu, C, Pantè G, Piemonti L. Stem cells to restore insulin production and cure diabetes. Nutrition, Metabolism and Cardiovascular Diseases 2017;27(7):583-600. Available From: ScienceDirect

Spiliotis I, Johnson P. Islet/stem cell transplantation – what's new? Paediatrics and Child Health 2017 /04;27(4):181-6. Available From: ScienceDirect

Swartout-Corbeil D, Cataldo LJ. Diabetes mellitus. In: Brigham Narins, editor. The gale encyclopedia of nursing and allied health. 3rd ed. ed. Detroit: Gale; 2013. COPYRIGHT 2013 Gale, Cengage Learning; 23. Available From: Credo Reference

Weintraub K. New Stem Cell Treatment, Successful in Mice, May Someday Cure Type 1 Diabetes. National Geographic [Internet]; c2014 [cited 2018 Oct 14,]. Available from: https://news. nationalgeographic.com/news/2014/10/141009-stem-cell-therapy-diabetes-science/.

Wu B. History of diabetes: Past treatments and new discoveries [Internet]; c2017 [cited 2018 Sep 29,]. Available from: https://www.medicalnewstoday.com/articles/317484.php.