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# Treatments, Islet Transplantation and Beta Cell Research

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# Treatments, Islet Transplantation and $\beta$ -

## Cell Research for Diabetes

**Maria Estrada**

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**Abstract:** Diabetes is a disease that affects millions of people in the United States, but also all around the world. With different types of diabetes that exist, it has been hard for researchers to find a cure for diabetes. Current diabetes treatments are expensive, and not always available for

patients around the world. Researchers have tried to understand how insulin, Islets of Langerhans and diabetes functions in order to try to find more efficient treatments and possibly a cure in the future. Islet  $\beta$ -cells are found in the pancreas and produce the hormone insulin. In patients with Type 1 diabetes, islet  $\beta$ -cells don't function correctly, leading to very little or no insulin being produced. This is obviously an issue, if  $\beta$ -cells don't produce insulin, glucose cannot be. With this knowledge, researchers have explored a way to possibly use transplanted  $\beta$ -cell islets from donor cadavers to help type 1 diabetic patients whom are typically insulin dependent, become insulin independent. Islet transplantation has been explored in many countries. Being a new, experimental procedure many doctors are skeptical about this new treatment. Some patients seeing good results, gives hope that with future research and more trials performed that this can be an effective treatment for diabetes. Although this new treatment seems exciting and ground breaking for type 1 diabetic patients, it still hasn't been found to work as well as insulin. There's a fair chance that with further research there will be treatments that work as effective or even more than insulin, but for now, insulin dependent patients will have to continue to use insulin as their main treatments.

**Keywords:** Insulin, Glucose, Diabetes, Islet  $\beta$ -cells, Islet transplantation, diabetes research

## **Introduction**

Today, 336 million people around the world struggle with diabetes, while 4.1 million people die from diabetes every year (Ashcroft, 2012). Diabetes is a disease in which the body has a high level of blood glucose. Type 1 diabetes is when the body does not make insulin. This

happens due to diminished functions of  $\beta$ -cells in the pancreas, which leads to no production of insulin. Type 2 diabetes is when the body does not make insulin correctly. Insulin is a protein that lowers blood glucose in the body and is produced by  $\beta$ -cells. Current treatments for diabetes are very expensive and not many people around the world are able to afford these treatments. According to (Ashcroft, 2012) the cost of diabetes in the United States per day is around \$612M. Improved and cost-effective treatments need to be developed to target how our body produces insulin. Finding a way to improve treatments and lower costs could potentially save the lives of many people with this disease. Since being insulin dependent can be very expensive, researchers have tried to find a way to make these patients no longer need insulin to survive. Islet transplantations need a lot more research, clinical trials and decrease in flaws overall to be more accepted by doctors around the world. Future treatments might be more effective than current treatments for diabetes, but it will take a lot more work to make this happen. This review will analyze types of diabetes, traditional treatments, and describe new Islet  $\beta$ -cell research to develop improved treatments for diabetes. This review will also state whether current treatments or newer treatments are more effective at managing diabetes type 1 and type 2.

### **What is insulin?**

The most effective treatment for diabetes today is insulin. Insulin is a hormone that lowers blood glucose and is produced by the pancreas. Insulin is used to control glucose after a meal, this is done in several different ways. (Aronoff, 2004). Insulin sends signals to the cells in the body to increase their consumption of glucose. Insulin also helps the liver stimulate glycogenesis- which is the formation of glycogen from sugar. The body uses glucose as a form

of energy. Insulin is a highly regulated process, where getting disrupted can cause serious issues. Insulin was isolated and used for treatments by Frederick Banting and medical student Charles Best. Together they experimented on dogs, soon after they began to experiment on humans. These scientists experimented on a 14-year-old boy, his symptoms, which today would be called diabetes, were diminished by their treatments. Banting alongside of professor McLeod won a Noble Prize in 1923. (Wilcox, 2005) The structure of insulin is very complex, it consists of two chains- A and B. (Wilcox, 2005) These two chains are linked together by disulfide bonds. (Fu, 2013) Chain A consists of 21 amino acids, and chain B consists of 30 amino acids. Together Insulin consists of 51 amino acids, which was discovered in 1952. (Wilcox, 2005) Insulin encodes and is synthesized as Proinsulin. Proinsulin is made up of a signal peptide, B chain, C peptide and A chain. When the signal peptide gets removed this is then converted to proinsulin. Proinsulin is then converted to insulin. Insulin alongside of C-peptide are stored in granules- where they wait until they are needed. (Fu, 2013) Insulin is an important hormone and when it is defective it can lead to Diabetes. The most common insulin related problem is Diabetes.

### **Traditional Treatments for Type 1 and 2 Diabetes**

Type 1 diabetes is when the body does not produce insulin, this type of diabetes is the least common type of diabetes. (CDC) Type 1 diabetes is sometimes described as an “autoimmune disease” because it causes the body to attack itself harming  $\beta$ -cells that produce insulin. This type of diabetes is not known to be caused by environmental factors, such as lifestyle and diet. (CDC) Type 1 diabetes treatments are not the best, since the pancreas produces little to no insulin. Treatments consist of managing blood sugar, and living a healthy life style and insulin injections. Insulin is required for type 1 diabetic patients because without insulin,

glucose cannot be moved into the cells to be used for energy. Insulin pumps are commonly used for treatment and are being used more than daily multiple insulin injections (Atkinson, 2013). A study showed that insulin pumps actually lower HbA<sub>1c</sub> concentrations more than daily multiple insulin injections. (Atkinson, 2013) HbA<sub>1c</sub> is glycated hemoglobin, this is created when hemoglobin joins with glucose making it glycated. (Diabetes.co.uk). There are several different types of insulin. Rapid acting, regular, intermediate acting, long acting, and premix. Rapid acting insulin starts working in 15 minutes, this is generally taken right before a meal. Regular insulin starts working within 30 minutes, this is also taken right before a meal, but it lasts longer than rapid acting insulin. Intermediate insulin lasts about 10-16 hours and is taken twice a day. Long acting insulin lasts for about 20-24 hours, so it is taken once a day. Lastly, premixed insulin is the combination of two or more types of insulin (Smith-Marsh). Glucose monitoring is also used as a treatment for type 1 diabetes. This is pretty simple, patients with diabetes monitor their glucose levels throughout the day. Patients then adjust their diet accordingly to the levels that were read on the monitor. If levels were found higher than normal, patients will decrease their consumption of carbohydrates and added sugars, and will increase insulin intake to help stabilize glucose.

Type 2 diabetes is when the body doesn't produce insulin in the right way. Type 2 diabetic patients do produce the hormone insulin on their own, but it isn't effective and produced correctly. Since type 2 diabetic patients already produce insulin, they do not need insulin injections like type 1 diabetic patients do. Although most type 2 diabetic patients are not insulin dependent, some patients of type 2 diabetes can become insulin dependent later on in their lifetime as their condition worsens. (add cite.) Type 2 diabetes is known to be caused by

obesity. As said by author Olokoba, obesity contributes to about 55% of type 2 diabetes. Genetics play a major role in the connection to type 2 diabetes. A study showed that if a family member has diabetes, there is 25% connection between developing diabetes yourself. (Olokoba, 2012) Treatments for type 2 diabetes are not the best either. Treatments consist of healthy diet and lifestyle. (Olokoba, 2012) Diet and exercise are important for managing type 2 diabetes, since type 2 is linked to obesity, losing weight and eating healthy can help control type 2 diabetes. Although diabetes is not yet cured, type 2 diabetes can be prevented with a healthy diet and lifestyle.

### **Cost of Diabetic Treatments**

Managing diabetes 1 and 2 can be very expensive. Studies have shown that the cost of type 1 diabetes annually is around \$14.4- \$14.9 billion in the united states. (Atkinson, 2014) Since type 1 diabetic patients require insulin to survive, most are forced to pay the price for insulin, regardless if insurance covers it or not. A single vial of insulin costs \$100-\$500 dollars according to GoodRx, depending on brands. If you are an insulin diabetic you have no choice but to pay for insulin no matter the cost of insulin. Insulin prices have increased drastically throughout the years. It has been found that insulin prices have nearly doubled from 2012-2016 (nbcnews.com). This is only in the span of 4 years, so will insulin continue to increase in price? This is making it very hard for diabetic patients to afford insulin. Some patients often resort to using less than the prescribed amount to make insulin last longer (Hai Global). Serious complications can occur if patients that are insulin dependent, go without insulin for a long period of time. Diabetes can also be treated with a good lifestyle and exercise. On average, a gym membership ranges from \$30-50

a month, making it around \$800 dollars a year (cnbc). The cost of treatments for diabetes is very high, not only insulin but a healthy lifestyle also is involved with the treatment of diabetes. Finding new and improved ways that will lower cost of diabetic treatments need to be developed so diabetic patients are not left between choosing to pay for insulin or other things they might need.

### **Islet of Langerhans $\beta$ -cell research**

Although current, effective treatments exist today researchers are looking for ways to make managing diabetes less expensive and easier. Trying to understand how insulin is made in the body is important for understanding how to cure it. Islets of Langerhans are found in the pancreas, which consists of clusters of cells that function in many ways. These are important for glucose homeostasis. There are about 3.2 to 14.8 million islets in the pancreas. (Da Silva Xavier, 2018). Although there are many types of islets of Langerhans,  $\beta$ -cells are the most important to diabetes because they work to produce the hormone, insulin. There is a potential to be able to use these cells for diabetic treatments. Transplantation of islet cells is a highly researched topic at the moment. Taking healthy, islets from a donor, specifically  $\beta$ - cells, can help the pancreas produce insulin on its own.

### **Treatments being researched**

Transforming growth factor (TGFB) has been found (Jing, 2018) to play an important role in influencing pancreatic endocrine development and maturation. A study done by (Lei, 2014) in china, studied the role in TGFB signaling in  $\beta$ -cell proliferation and  $\beta$ -cell mass



adaption after they had performed a 50% partial pancreatectomy. This group of researchers used mutated mice as their chosen laboratory animal. The mice had their pancreas removed and studied the results over some period of time. 10 mice were analyzed in each condition. However, did not state the sex of the mice, so would this affect the results or would it be the same? The researchers performed islet isolation from the biliary pancreatic bile duct. The researchers then extracted genomic DNA from the isolated islets, they then stained the insulin to identify  $\beta$ -cells. The results from this experiment were found to be similar to other studies done, when you inhibit TGFB signaling in  $\beta$ -cells this resulted in higher  $\beta$ -cell production 1 week after they did the pancreatectomy. However, they also found that  $\beta$ -cell mass in the mutated mice decreased 12 weeks after they performed the pancreatectomy which then resulted in the increase of  $\beta$  cell death. Main conclusion found by the authors (Lei, 2014) was that TGFB signaling may be required for the prevention of  $\beta$ -cell death after proliferation.

### **Islet Transplantation**

Islet Transplantation is used with patients that have type 1 diabetes. Usually islet transplantation is done with patients that have severe hypoglycemia, and other treatments have failed. This is done when islet cells are separated from a donor pancreas and then transplanted into the patients. Islet transplantation is a simple procedure, that is done with patients being awake and typically takes an hour to be completed. The best part about this procedure is that it is non-surgical. A catheter is inserted into a portal vein, and into the liver. The islet cells then get transported into the patient and flow to the liver where they begin to produce insulin. (Bruni, 2014) This procedure sounds very effective, but it does have flaws just like other treatments, patients that undergo islet transplantation are required to be on immunosuppressive drugs. Immunosuppressive drugs do just that- they suppress the immune system, which leaves these

patients at risk for more infections and sicknesses. Studies have shown that islet transplantations have actually lowered HbA<sub>1C</sub> in diabetic patients better than insulin pumps and daily multiple insulin injections. (Bruni, 2014) Islet transplantations have also been found to lower risks of complications associated with diabetes. Studies have also found that patients that have undergone islet transplantation during 2007-2010 have a higher success rate than patients that underwent islet transplantation in 1999-2002. 44% of patients that had the procedure done in 2007-2010 were insulin independent 3 years post procedure. While, only 27% of patients that had the procedure done in 1999-2002 were insulin independent. (Bruni, 2014) So, the number of patients that are insulin independent following this procedure doubled in about 8 years. This suggests that with time and more research, islet transplantation has improved. Although many transplantation centers around the world are using this treatment, the United States practices few islet transplantations. Since this is an experimental treatment and the United States has more regulations, this leads to lack of funds for future research. This is only preformed under a FDA clinical trial. Not all type 1 diabetic patients are good candidates for islet transplantations. The outcomes do have to outweigh the risks in order to be considered for islet transplantation. There are some risks with having this procedure, just like most procedures performed. There is possibility of blood clots and bleeding out with islet transplantation. Rejection of the islets from the donor is also possible. The body can react to these foreign cells as if they are “bad” and can attack the islets. (USCF) This is why patients that do undergo an islet transplantation are required to be on immunosuppressive drugs to try to keep the body from attacking the healthy islets.

Another problem with islet transplantation is donor availability. Most patients need several transplantations done to get enough healthy islet cells in their system. (USCF) Islet cells are

taken from a deceased organ donor. Organ donation is a major topic, since organ donation is not commonly practiced, pancreas donors are hard to find. Only about 7,000 pancreases are donated each year, and some are not even healthy enough to be used for “whole organ pancreatic transplantations.” Since these organs are hard to find and sometimes hard to harvest, this leaves patients with diabetes type 1 very lost. Factors can also contribute to the success of islet transplantation. These include, the age of the donor, cause of death and body mass index. A system, created by O’Gorman has been developed to assess if a pancreas should be used for islet transplantation, but cannot predict the outcomes. (Bruni, 2014). Islet transplantations would be one of the best treatments for diabetes type 1, if it didn’t have so many flaws. Studies have shown that islet transplantations are sometimes more effective than insulin pumps and other treatments, but there are too many risks and flaws associated with it. Having enough pancreatic donors is a huge issue, since some patients require multiple islet transplantations there is simply not enough donors for these transplantations. Also, the risks of the body rejecting the healthy donor islets is high, and having to be on immunosuppressive drugs increase your potential of having infections and other disease. If more research is done on islet transplantation and more clinical trials are preformed, this could be a life changing treatment for type 1 diabetics.

### **Conclusion**

Current treatments for diabetes, although effective have flaws. Treatments can be very expensive for diabetic patients. Insulin, insulin pumps and proper diets can be a burden for some patients as well, especially without insurance. Insulin availability is also a problem. Patients in 3<sup>rd</sup> world

countries sometimes don't have the resources available to supply themselves with insulin. Average cost of insulin in the United States alone is 14 billion dollars. Patients with diabetes type 1 depend on insulin to live, so patients would have to go to extraordinary measures to be able to stay alive. Researchers have studied Islets of Langerhans to try to understand how  $\beta$ -cells are produced in the pancreas, since these cells are important for maintaining a balanced glucose level because they create insulin. Islet transplantation does have many flaws that can sometimes outweigh the positive results. Although not a fully accepted and practiced treatment, islet cell transplantation has been found to be effective in patients. However, from evidence found from many studies, insulin seems to still be the major diabetic treatment available now. This review found that although islet transplantation has potential to be one of the best treatments for diabetes, it is not quite there yet. Availability of donor pancreas's is low, and the risk of the body attacking the donor islets is high. This review found that although insulin is expensive and a burden for diabetic patients, it is still the most effective treatment for diabetes. There still has to be further research conducted in order to be able to find better treatments. Researchers are going in the right direction, but given the evidence of what has been presented, it is believed that there are no other major treatments for diabetes other than insulin.

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