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Abstract

Type 1 Diabetes Mellitus is a highly dangerous autoimmune disease. Type 1 diabetes is most commonly seen in children and young adults as pancreatic Beta (B) cell destruction is highest at this age. Patients with Type 1 Diabetes are required to take insulin injections to compensate for their lack of insulin, but many patients still have episodes of hyperglycemia. This paper analyzes and compares the effectiveness of different treatment options. The standard approach is to prescribe insulin injections, but this analysis finds insulin injections in conjunction with oral medications such as Metformin and Sodium-glucose co-transporter (SGLT) inhibitors has a positive effect on patient health. Metformin in addition to insulin therapy decreased metabolic syndrome. SGLT inhibitors decreased blood glucose levels in patients and have an increased efficacy to prevent hyperglycemia. If a patient were unable to take oral medications, rapid acting insulin aspart decreases blood glucose levels effectively compared to human insulin. Additionally, long acting insulin proved more efficient in reducing blood glucose levels than intermediate acting insulin. Extensive research is being conducted by different pharmaceutical companies for a potential cure. The first clinical trial using stem cells has shown positive results for the patients as they could now go days without taking insulin. More research is needed; however, insulin therapies can be adjusted to each patient to provide the most beneficial results, and insulin therapy alone no longer is needed to be the first and only choice as the other options appear to provide beneficial results.

Introduction

Diabetes Mellitus is a chronic health condition that occurs when blood glucose is too high. There are various subclasses of Diabetes Mellitus. The chronic conditions are Type 1, an autoimmune disease, and Type 2, in which insulin receptors don't recognize insulin. Potential reversible conditions are Gestational Diabetes which happens during pregnancy and Prediabetes.

Type 1 diabetes is a T cell autoimmune disease, characterized by the destruction of pancreatic Beta cells. Consequently, the body does not produce enough insulin, leading to hyperglycemia, an increase in levels of blood glucose. Hyperglycemia dramatically increases the risk of various cardiovascular diseases such as atherosclerosis, angina and high blood pressure. Type 1 Diabetes is usually present in infants and children because the rate of β cell destruction tends to be more aggressive at this age. (Kelly et al., 2003). There is no known way to prevent Type 1 Diabetes. As many as 37.3 million people have Diabetes and in adults Type 1 accounts for 5-10% of all cases. The rate of new cases within youth increased by 1.9% per year in the United States between 2002 and 2015 (Center for Disease Control and Prevention, 2020).

Autoimmune diseases have a complex genetic basis. For Type 1 diabetics, two gene regions of importance have been identified that are associated with the disease's genetic component: The Human Leukocyte Antigen Locus (HLA) and the insulin gene. The HLA region is the major genetic determinant of disease risk, accounting for 42% of the familial inheritance of Type 1 Diabetes. The insulin gene region contributes a further 10% of genetic susceptibility (Kelly et al., 2003).

While there is no known way to prevent Type 1 Diabetes, there are different treatment options that exist or are in the process of being developed. This paper will analyze different treatment options available for Type 1 diabetes and seek to determine which is the most effective option.

Methods

This comprehensive review of treatment options for Type 1 Diabetes Mellitus was based on the critical analysis of data collected from PubMed and other databases accessed through Touro College and University System's library including ProQuest and EBSCO. Among the keywords and phrases used to retrieve data included "Type 1 Diabetes treatment options," "Therapy for Type 1 Diabetes," "Type 1 Diabetes age correlation" and, "stem cells and Type 1 Diabetes."

Genetic Component of Type 1 Diabetes

The first diabetes susceptibility genes to be identified were the human leucocyte antigen (HLA) genes, located on chromosome 6p21 within the major histocompatibility complex, as well as the insulin gene region on chromosome 11p. A study in which genome screens were conducted confirmed that the IDDM1 locus (the HLA gene region) is the major genetic determinant of disease risk. It accounts for 42% of the familial inheritance of type 1 Diabetes. The IDDM2 locus (the insulin gene region) contributes a further 10% of genetic susceptibility (Davies et al., 1994).

HLA class 1 is expressed in all cells, class 2 expression is restricted to B lymphocytes, dendritic cells, macrophages and activated T lymphocytes. Class 1 and 2 express cell surface glycoproteins which are involved in the presentation of antigens to T cells. Cytotoxic T cells (CD8+) recognize antigen in the context of class I, whereas helper T cells (CD4+) recognize antigen in the context of the class II molecules. The class 2 HLA-DR, HLA-DQ, and molecules are involved in the activation of helper T cells.

The risk of these molecules for type 1 diabetes is most likely related to their role in antigen presentation and the activation of a helper T cell mediated immune response. This function is determined by the binding clefts of the molecules. In a study using x-ray crystallography, HLA molecules associated with type 1 diabetes share similar chemical

properties in their binding antigen domain. The characteristics of protective HLA molecules were different from the predisposing molecule structure. (Cucca et al., 2001).

The structural differences between the predisposing and protective surface molecules is seen in the peptide selectivity and binding affinity of the antigen binding cleft pockets 1,4 and 9.

P1 in the predisposing diabetes molecules contains a glycine residue at position 86 of the β chain which prefers to bind large aromatic side chains. The valine residue encoded at position β86 in the protective molecule prefers small hydrophobic residues.

P4 is important for the binding selectivity of the HLA DR molecule. In predisposing diabetes molecules, the alanine residue at β74 is selective for acidic residues, but for the protective molecules it cannot bind to acidic residues (Cucca et al., 2001).

P9 in the protection molecules carry an aspartate residue at position β57, whereas predisposing molecules carry an uncharged amino acid residue at this position. This alters the shape of P9 and alters the preference of the molecule for particular anchor residues in the bound peptide (Kelly et al., 2003) In summary, the structural differences between the predisposing and protective HLA molecules may result in differences in their ability to bind to diabetic antigens.

Treatments Options

Insulin Therapy

Type 1 Diabetics are insulin deficient and thus require an insulin supplement. The goal of exogenous insulin therapy is to mimic normal endogenous insulin secretion of the pancreas. Type 1 diabetics use insulin injections as their supplement as opposed to oral insulin because the acidity in the stomach would break it down (Gradel et al., 2018). Therefore, insulin needs to be injected subcutaneously to be released in the body. There are four different types of insulin injections. Rapid-acting begins to work within a few minutes and lasts a couple of hours. Regular or short-acting, which takes about 30 minutes to work fully and lasts 3 to 6 hours. Intermediate-acting, which takes 2 to 4 hours to work fully and lasts up to 18 hours. Finally, Long-acting, which can work for an entire day (Center for Disease Control and prevention, 2021).

Insulin Aspart vs Human Insulin

A study showed the difference in glycemic control of insulin aspart, an analogue of human insulin, and human insulin. The study included 423 basal-bolus treated patients with Type 1 diabetes, who take long acting and rapid acting insulin together. The researchers gave the patients an algorithm-driven dose optimization over 3 months. Glycated hemoglobin levels (HbA1c) were significantly lower in insulin aspart treated patients compared to the human insulin treated subjects by 0.17 with a P value less than 0.05. Additionally, blood glucose profiles showed lower levels with insulin aspart after breakfast, with a mean of 8.4 vs 10.1 mmol/l ($P<0.0001$), and dinner, 8.2 vs 9.3 mmol/l; ($P<0.01$), compared with human insulin. (Tamas et al., 2001). This study indicates the higher absorption rate of the insulin analogue and is why many patients have switched over for some time now. There may be other factors that lead to a higher absorption.

Short Acting vs Rapid Acting

A systemic review was done to determine the efficacy of taking rapid acting insulin aspart compared with short acting human insulin. In 13 randomized controlled trials it was shown that insulin aspart resulted in a significant decrease of .11% in glycated hemoglobin levels compared with regular human insulin. But there was an increased risk of a hypoglycemic episode with insulin aspart as was shown in six of the randomized controlled trials (Rys et al., 2011). This large review demonstrates the positive effect of taking rapid acting insulin compared with regular insulin. But, hypoglycemia is a risk factor and one must be careful in how they use rapid acting insulin to prevent hypoglycemia episodes.

Rapid Acting vs. Different Timings

Rapid acting insulin is usually taken before a meal when there will be a rise in glucose level. One study compared and analyzed the impact of three pre-meal timings of rapid-acting insulin on postprandial glucose excursions in type 1 diabetes. Ten subjects were used in the study and all were treated with insulin aspart. The subjects were randomly assigned to administer the insulin either 30, 15, or 0 minutes before the meal using a cross over design, each patient received different treatments during the different time periods.

Their glucose levels were measured before and after the meals. The time spent in euglycemia, normal concentration of blood glucose 3.5-10 mmol/l, was highest when the insulin was given 15 minutes before the meal. Another finding from the study indicates that when insulin is administered 15 min before, the patients' blood glucose declines slightly before mealtime. This finding shows that administering the insulin must be only when the patient's pre-prandial glucose levels are greater than 5.0 mmol/l (Luijf et al., 2010). The small sample size as well the resulting decrease in blood glucose suggests a need for further investigation.

Intermediate Acting vs Long Acting

A meta-analysis of twenty-six randomized control studies and 6,776 patients was done to show the effect of using intermediate acting vs long acting insulin on HbA1c levels. The results showed that compared to Neutral Protamine Hagedorn, (NPH) an intermediate acting insulin, Glargine and Detemir, long acting insulin, significantly reduced HbA1c levels in the body (Tricco et al., 2014).

A sub-group analysis of hemoglobin A1c was done using 12 randomized controlled trials which included 4,002 patients who had poorly controlled hemoglobin A1c (>8%). When given once daily, Glargine significantly improved blood glucose levels compared to NPH, with a mean difference of –0.65%, –0.96% to –0.35% and Detemir once daily –0.41%, –0.74% to –0.08% for the three different trials.

The analysis also sought to compare the cost effectiveness of taking long acting insulin compared to intermediate acting. Fourteen studies were found on the cost effectiveness: five of which compared Detemir to NPH. The results reported that Detemir costs less and is more effective. Another eight studies compared Glargine to NPH. The former was less costly and more effective in two of these analyses, while six studies found that Glargine was costlier and more effective than NPH (Tricco et al., 2014). Intermediate acting is taken twice daily compared to long acting which is daily. This meta-analysis demonstrates the effective use of long acting insulin and thus creates a possible opportunity for diabetic patients to feel comfortable taking less injections each day.

Attempts were made to try to create a more practical and easier therapy for patients. A study was done to try and show the effects of mixing rapid acting insulin analogues with insulin Glargine in children. The study was done using 55 children whose mean age was 13.4 years old. The children mixed the two types of insulin in the same syringe and were injected by their medical care provider. A group of 55 similar children served as the control. Data was collected 6 months prior and post the mixing of insulin began. HbA1c values were collected after the six months and were 8.54% vs 8.61% with a P value of 1.00 indicating there is no statistical significance in the difference. (Fiallo-Scharer et al., 2005). These findings suggest that there is no issue with mixing the two insulins in one syringe. Additionally, the results are especially encouraging for those patients who wish to minimize the number of total daily injections because of needle fear or forgetting injections.

Oral Medications in Conjunction with Insulin Therapy: Metformin

Metformin is an oral anti-hyperglycemic medication and it is commonly used to treat type 2 diabetes. This drug increases both hepatic and peripheral insulin sensitivity by inhibiting the amount of glucose the liver produces and by increasing glucose uptake in cells. People with type 2 Diabetes can control their blood glucose level by using metformin and insulin therapy. One study shows the effect of including metformin as an add-on therapy to insulin in overweight adolescents with type 1 Diabetes Mellitus. The results show that at the end of the experiment there was no improvement in glycemic control (Libman et al., 2015).

A different study was done to investigate the effects of metformin on type 1 diabetics. Twenty-nine patients with type 1 Diabetes included metformin as an adjunct to their insulin therapy for 12 months. Their glycated hemoglobin levels (HbA1c) were quite high while only using insulin therapy. They were compared to a placebo control group whose weight; blood pressure and other factors did not differ from the experimental group. The results of the experiment show that there was an increase in insulin dosage by 0.11 IU/kg/d in the control group, whereas in the test group dosage decreased by 0.03 IU/kg/d. Metabolic syndrome prevalence in the control group was 44.8% compared to 41.4%, in the test group. The resulting p value was higher than 0.05 indicating that there was no statistically significant difference in their metabolic syndrome prevalence. But, after treatment with metformin, metabolic syndrome was decreased in the metformin-insulin group by about 8.9% after treatment compared to the insulin alone group which decreased by 2.5% ($p = 0.028$). However, HbA1c did not differ between the groups ($p > 0.05$) (Beysel et al., 2018). These results show a positive effect on the inclusion of metformin in treatment as it reduced metabolic syndrome which is a factor that greatly influences a diabetics probability of developing cardiovascular diseases. But, blood glucose levels were not reduced indicating a need for better adjunct therapy for patients whose blood sugar remains very high.

Sodium-glucose cotransporter (SGLT) inhibitors:

Sodium-glucose cotransporter (SGLT) inhibitors, a new class of oral hypoglycemic agents, lowers serum blood glucose levels. There are two classes of the inhibitors SGLT2 and SGLT1.

SGLT-1 is responsible for glucose absorption in the small intestine, and for the reabsorption of nearly 10% of the filtered glucose load in the renal proximal tubule. SGLT-2 is primarily expressed in the renal proximal tubule and is responsible for the reabsorption of 90% of the filtered glucose load. Most patients with type 1 diabetes do not have adequate glycemic control with just insulin therapy. The currently available SGLT-2 inhibitors, canagliflozin, dapagliflozin, and empagliflozin, have similar

characteristics and have similar effects on glycemic control. However, sotagliflozin acts on both sodium–glucose cotransporters 1 and 2.

In a study done to observe the efficacy of canagliflozin, the goal was to reach a decrease in HbA1c of more than .4%. Three hundred and fifty-one patients were included in the 18-week study. At the end of the study, 36.9% of patients with insulin and canagliflozin 100 mg, 41.4% with insulin and canagliflozin 300 mg, and 14.5% with insulin and placebo reached a reduction in blood glucose level greater than .4%. (Henry et al., 2015).

Another study was done to test the efficacy of empagliflozin as an adjunct to insulin treatment. A total of 75 patients with high HbA1c levels were randomized to receive once-daily empagliflozin 2.5 mg, 10mg, 25mg, or placebo for 4 weeks. The goal of the study was to increase urinary glucose excretion (UGE). The results show that there was an increase in UGE and a statistically significant ($p < 0.05$) decrease in HbA1c of 0.49% was noted for the empagliflozin group after 28 days in comparison with the placebo group (Pieber et al., 2015).

Compared with the previous two studies, a much larger randomized, placebo-controlled study was done to evaluate the safety and efficacy of sotagliflozin in combination with insulin therapy. The study was conducted at 133 sites in 19 countries and included 1,402 patients with type 1 diabetes. Eligible patients were randomly assigned, in a 1:1 ratio, to receive either sotagliflozin (400 mg per day) or placebo for 24 weeks. The patients that received the medication took it before the first meal of the day. The primary goal of the study was to reach a glycated hemoglobin level (HbA1c) lower than 7.0% at week 24, without episodes of severe hypoglycemia or diabetic ketoacidosis. The secondary goal of the study was a possible reduction from the baseline to week 21, body weight and blood pressure. A significantly larger proportion of patients in the sotagliflozin group than in the placebo group 200 of 699 patients [28.6%] vs. 107 of 703 [15.2%], ($P<0.001$) reached the primary endpoint goal of a blood glucose level less than 7 percent. There was a greater reduction in the glycated hemoglobin level from baseline in the sotagliflozin group than in the placebo group, the difference was −0.46 percentage points ($P < 0.001$) (Garg et al., 2017).

A glycated hemoglobin level lower than 7.0% was achieved with no weight gain in 171 patients in the sotagliflozin group and 51 patients in the placebo group. The reduction in body weight was significantly greater in the sotagliflozin group than in the placebo group with a difference of -2.98 kg ($P<0.001$). Among patients with a systolic blood pressure of 130 mm Hg or higher at the start of the experiment, reduction in blood pressure from start to week 16 was significantly greater in the sotagliflozin group than in the placebo group with a difference of, -3.5 mm Hg. The rate of diabetic ketoacidosis was higher in the sotagliflozin group than in the placebo group (3.0% [21 patients] and 0.6% [4], respectively) (Garg et al., 2017). It appears from this study that patients using sotagliflozin in adjunct with insulin showed increased improvement reducing their blood glucose level and overall health and there is greater benefit to using this medication compared to other SGLT-2 inhibitors. Yet, there is still a chance of ketoacidosis and further research might need to be done to perfect the drug.

Stem Cells

A curative treatment for Type 1 diabetes mellitus involves pancreas transplantation, but due to the incidence of transplant rejection and complications associated with immunosuppression, alternatives are being explored. One such alterative is the use of stem cells. This treatment revolves around the idea of pluripotency, the ability of a stem cell to differentiate into multiple lines of cells. There are four different types of stem cells: human Embryoinc stem cells (hESC), induced pluripotent stem cells (iPSCs), and adult stem cells that are being tested to generate functional islet cells. There is another class of cells that is being testing called progenitor cells which are descendants of stem cells that then further differentiate to create specialized cell type that belong to the same tissue or organ. Stem cell differentiation can be manipulated by controlling the cells environment when placed in a medium.

Human embryonic stem cells compared to Induced Pluripotent stem cells.

Induced pluripotent stem cells are created by essentially reverse engineering of an already differentiated cell. This method can be done using the CRISPR-Cas9 system. HESC are made when inner mass cells are taken from the fertilized blastocyst egg.

A study showed the efficacy of hESC compared to pancreatic progenitor iPSC that were made from pancreatic progenitors. Using key markers at the mRNA and protein level they were able to assess beta cell development of the stem cells i.e. MAFA and G6PC2. This study was done in seven stages, each with a new cell line. In the thirteenth day of the stage (S) 7, hEBSC cells injected into the mouse models showed transcript levels of key markers, INS, MAFA and G6PC2 that were indistinguishable from human islet preparations. S7 also included an iPSC line that produced key markers for beta cells, although not as efficiently as with the hESC line used. The embryo-developed S7 reversed diabetes in mice approximately four times faster than iPSCs from pancreatic progenitors.

The iPSC line also produced less insulin producing cells compared to the hESC. Although the data showed that hESC-derived S7 cells did not rapidly secrete insulin in response to high glucose, a statistically significant ($P < 0.0001$) accumulation of human C-peptide, a peptide that is measured to tell the difference between insulin the body produces and insulin that is injected into the body, was seen in incubation of the cells in vitro (Rezania et al., 2014). This study showed the reversal of diabetes with the S7 cells when injected in the mouse models.

In another study, researchers successfully generated billions of functioning beta cells using iPSC and hESC together. In vitro the cells exhibited glucose sensitive insulin secretion just as human pancreatic B cells. When injected into mice, the cells from both hEBSC and iPSC cell lines secreted insulin directly into the bloodstream and showed increased human insulin secretion. (Pagliuca et al., 2014)

Vertex Pharmaceuticals initiated a 17-person phase I clinical trial that would be the first test in people of islet cells derived from stem cells, VX-880 is an investigational allogeneic stem cell-derived, fully differentiated, insulin-producing islet cell therapy manufactured using proprietary technology (Nature, 2021).

On October 18, 2021 the company announced positive Day 90 data for the first patient from the clinical trial of VX-880. Prior to treatment with VX-880, the patient's insulin dose was 34 units per day. Fasting and stimulated C-peptide levels were undetectable, which indicated that the patient was not making their own insulin. The patient received half the target dose of VX-880 through a hepatic portal vein infusion with a combination of immunosuppressive agents. At Day 90, fasting C-peptide was 280 pmol/L, reflecting restored basal insulin production and increased to a peak of 560 pmol/L. This shows restored glucose-responsive insulin production. Also, at Day 90, HbA1c improved from 8.6% at baseline to 7.2%, and daily insulin dose decreased from 34 units per day prior to treatment with VX-880 to an average dose of 2.9 units per day over a 7-day period at the Day 90 visit, reflecting a 91% decrease in daily exogenous insulin use. (Vertex Pharmaceuticals Incorporated, 2021)

The patient mentioned above is Brian Shelton, a 64-year-old male who has been living with Type 1 diabetes for over 50 years. On June 29, he got an infusion of VX-880 together with an immunosuppressant to prevent his body from attacking the newly engineered cells. Mr. Shelton said in an interview that the suppressants "cause him no side effects" and he finds them far less onerous or risky than constantly monitoring his blood sugar and taking insulin (Kolata, 2021). In an additional interview he explained that he can go days now without having to take insulin and the treatment has given him a new-found freedom on life (Vollmayer, 2021).

Conclusion

Treatment options for Type 1 Diabetes Mellitus are limited and require more research. Many doctors believe that since Type 1 diabetes is an autoimmune disease, the best course of action is to provide insulin injections to compensate for the lacking insulin. While as a first line of treatment this may be necessary to prevent hyperglycemia and diabetic ketoacidosis, it has been reported that most patients are not stable even with insulin. Other options including Sodium-glucose cotransporter (SGLT) inhibitors, Sotagliflozin, canagliflozin, and empagliflozin, have shown statistically significant benefits in reducing blood sugar levels when taken in conjunction with insulin therapy. Metformin has shown to benefit the patient metabolic syndrome. Stem cell research has had its first successful clinical trial and proves to have very effective outcomes. This suggests that Type 1 diabetic patients have a potential cure on the horizon. However, more research is needed to evaluate the effectiveness and efficiency of all currently available possibilities. https://pubmed.ncbi.nlm.nih.gov/25103565/

References

Beysel, S., Unsal, I.O., Kizilgul, M. et al. The effects of metformin in type 1 diabetes mellitus. BMC Endocr Disord 18, 1 (2018). https://doi.org/10.1186/s12902-017-0228-9

Center for Disease Control and Prevention (2021). Diabetes data and statistics

https://www.cdc.gov/diabetes/data/index.html

Center for Disease Control and Prevention (2021). What Is Type 1 Diabetes?

https://www.cdc.gov/diabetes/basics/what-is-type-1-diabetes.html

Cucca, Francesco, Rosannna Lampis, Mauro Congia, Efisio Angius, Sarah Nutland, Stephen C. Bain, Anthony H. Barnett, John A. Todd, A correlation between the relative predisposition of MHC class II alleles to type 1 diabetes and the structure of their proteins, Human Molecular Genetics, Volume 10, Issue 19, 15 September 2001, Pages 2025–2037, https://doi.org/10.1093/hmg/10.19.2025

Davies, J., Kawaguchi, Y., Bennett, S. et al. A genome-wide search for human type 1 diabetes susceptibility genes. Nature 371, 130–136 (1994). https://doi.org/10.1038/371130a0

Fiallo-Scharer R, Horner B, McFann K, Walravens P,

Chase HP. Mixing rapid-acting insulin analogues with insulin glargine in children with type 1 diabetes mellitus. J Pediatr. 2006 Apr;148(4):481-4. doi: 10.1016/j.jpeds.2005.11.036. PMID: 16647408.

Garg, S. K., M.D., Henry, R. R., M.D., Banks, P., M.S., Buse, John B,M.D., PhD., Davies, M. J., M.D., Fulcher, G. R., M.D., . . . Strumph, P., M.D. (2017). Effects of sotagliflozin added to insulin in patients with type 1 diabetes. The New England Journal of Medicine, 377(24), 2337-2348. doi:http://dx.doi.org/10.1056/NEJMoa1708337

Gradel AKJ, Porsgaard T, Lykkesfeldt J, Seested T, Gram-Nielsen S, Kristensen NR, Refsgaard HHF. Factors Affecting the Absorption of Subcutaneously Administered Insulin: Effect on Variability. J Diabetes Res. 2018 Jul 4;2018:1205121. doi: 10.1155/2018/1205121.

Henry, R. R., Thakkar, P., Tong, C., Polidori, D., & Alba, M. (2015). Efficacy and Safety of Canagliflozin, a Sodium-Glucose Cotransporter 2 Inhibitor, as Add-on to Insulin in Patients With Type 1 Diabetes. Diabetes care, 38(12), 2258–2265. https://doi.org/10.2337/dc15-1730

Kelly, M. A., Rayner, M. L., Mijovic, C. H., & Barnett, A. H. (2003). Molecular aspects of type 1 diabetes. Molecular pathology : MP, 56(1), 1–10. https://doi.org/10.1136/mp.56.1.1

Kolata, G. (2021, November 27). A Cure for Type 1 Diabetes? For One Man, It Seems to Have Worked. The New York Times. https://www.nytimes.com/2021/11/27/health/diabetes-cure-stem-cells.html

Libman, I. M., Miller, K. M., DiMeglio, L. A., Bethin, K. E., Katz, M. L., Shah, A., Simmons, J. H., Haller, M. J., Raman, S., Tamborlane, W.V., Coffey, J. K., Saenz, A. M., Beck, R. W., Nadeau, K. J., & T1D Exchange Clinic Network Metformin RCT Study Group (2015). Effect of Metformin Added to Insulin on Glycemic Control Among Overweight/Obese Adolescents With Type 1 Diabetes: A Randomized Clinical Trial. JAMA, 314(21), 2241–2250. https://doi.org/10.1001/jama.2015.16174

Luijf, Y. M., M.D., van Bon, Arianne C, MD, Hoekstra, Joost B,M.D., P.H.D., & DeVries, J. H. (2010). Premeal injection of rapid-acting insulin reduces postprandial glycemic excursions in type 1 diabetes. Diabetes Care, 33(10), 2152-5. doi:http://dx.doi.org/10.2337/dc10-0692

Pagliuca, F.W., Millman, J. R., Gürtler, M., Segel, M., Van Dervort, A., Ryu, J. H., Peterson, Q. P., Greiner, D., & Melton, D. A. (2014). Generation of functional human pancreatic β cells in vitro. Cell, 159(2), 428–439. https://doi.org/10.1016/j.cell.2014.09.040

Pieber, T. R., Famulla, S., Eilbracht, J., Cescutti, J., Soleymanlou, N., Johansen, O. E., Woerle, H. J., Broedl, U. C., & Kaspers, S. (2015). Empagliflozin as adjunct to insulin in patients with type 1 diabetes: a 4-week, randomized, placebo-controlled trial (EASE-1). Diabetes, obesity & metabolism, 17(10), 928–935. https://doi.org/10.1111/dom.12494

Rezania A, Bruin JE, Arora P, Rubin A, Batushansky I, Asadi A, O'Dwyer S, Quiskamp N, Mojibian M, Albrecht T, Yang YH, Johnson JD, Kieffer TJ. Reversal of diabetes with insulin-producing cells derived in vitro from human pluripotent stem cells. Nat Biotechnol. 2014 Nov;32(11):1121-33. doi: 10.1038/nbt.3033. Epub 2014 Sep 11. PMID: 25211370.

Rys P, Pankiewicz O, Łach K, Kwaskowski A, Skrzekowska-Baran I, Malecki MT. Efficacy and safety comparison of rapid-acting insulin aspart and regular human insulin in the treatment of type 1 and type 2 diabetes mellitus: a systematic review. Diabetes Metab. 2011 Jun;37(3):190-200. doi: 10.1016/j.diabet.2010.12.003. Epub 2011 Feb 17. PMID: 21333580.

Tamás, G., Marre, M., Astorga, R., Dedov, I., Jacobsen, J., Lindholm, A., & Insulin Aspart Study Goup (2001). Glycaemic control in type 1 diabetic patients using optimised insulin aspart or human insulin in a randomised multinational study. Diabetes research and clinical practice, 54(2), 105–114. https://doi.org/10.1016/s0168-8227(01)00262-5

Tricco, A. C., Ashoor, H. M., Antony, J., Beyene, J., Veroniki, A. A., Isaranuwatchai, W.,

Straus, S. E. (2014). Safety, effectiveness, and cost effectiveness of long acting versus

intermediate acting insulin for patients with type 1 diabetes: Systematic review and network

meta-analysis. BMJ : British Medical Journal

(Online), 349 doi:http://dx.doi.org/10.1136/bmj.g5459

Vertex Pharmaceuticals Incorporated (2021) Vertex Announces Positive Day 90 Data for the First Patient in the Phase 1/2 Clinical Trial Dosed With VX-880, a Novel Investigational Stem Cell-Derived Therapy for the Treatment of Type 1 Diabetes https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-positive-day-90-data-first-patient-phase-12

Vollmayer, D. (2021, December 6). Man Says He Feels Cured after Living with Diabetes for Almost 50 Years. Good Morning America. https://www.goodmorningamerica.com/wellness/story/man-describes-receiving-potential-cure-type-diabetes-81576256