EMERGING DIABETES TREATMENTS

BACKGROUND

As of 2020, diabetes effects one in ten or 34.2 million Americans. One in three or 88 million Americans are on their way to developing diabetes and are classified as having pre-diabetes (CDC)[1]. There are three types of diabetes: type 1, type 1, and gestational diabetes. Type 1 diabetes results when a person's body does not make insulin. Insulin, molecule released from beta cells in the pancreas, decreases glucose in the blood after a meal. Type 1 diabetes is like an autoimmune disease, and people develop it at a young age and will require insulin their entire lives. Type 2 diabetes results when a person's body does not make enough insulin or there is something wrong with the insulin, leading to pancreatic cells that do not respond to insulin, and this is called insulin resistance. Gestational diabetes is the newly found presence of diabetes during pregnancy.

Management of diabetes involves lifestyle changes and medication[6]. Currently there are several classes of injectable and oral medications that treat diabetes. They include:

Injectables	**Non-injectables**
Insulin	Biguanides • Metformin
Glucagon-like-peptide-1 receptor (GLP-1) agonists: Exenatide • Exenatide extended release • Dulaglutide • Semaglutide • Liraglutide • Lixisenatide	Sulfonylureas • Glipizide • Glimepiride • Glyburide
Amylin mimetic • Pramlintide	DPP4 inhibitors • Alogliptin • Saxagliptin • Linagliptin • Sitagliptin
	SGLT inhibitors • Ertugliflozin • Dapagliflozin • Empagliflozin • Canagliflozin
	TZDs • Pioglitazone • Rosiglitazone
	Bile acid sequestrant • Colesevelam
	Alpha glucosidase inhibitors • Acarbose • Miglitol

Rather than discussing medications that are already incorporated into the Standards of Care (guidelines), this review is about emerging therapies for the treatment of diabetes.

INCEPTOR

Scientists at the German Research Center for Environmental Health, Helmholtz Zentrum München, discovered a molecule that blocks insulin receptors. They call this molecule Inceptor which blocks the insulin receptors on pancreatic beta cells and results in insulin sensitivity and an increase in pancreatic beta cell mass[2].

The function of inceptor in mice is to block beta cells in the pancreas from receiving insulin and initiating the insulin pathway that leads to decreased blood glucose levels after eating. People with diabetes produce more inceptor and inceptor contributes to insulin resistance. When scientists knocked out the inceptor genes in mice, they found these mice to have higher activation of the insulin and insulin growth factor receptor. Therefore, higher activation of the insulin pathways resulted in an increase of larger pancreatic beta cells and improved glucose tolerance[3].

With the discovery of inceptor and what happens because of blocking it in pancreatic beta cells, the research team is looking to further study and develop drugs for beta-cell regeneration that would be useful for people living with type one and type two diabetes[3].

IMMUNOTHERAPY

Type one diabetes is an autoimmune disease and occurs when autoantibodies destroy beta cells in the pancreas, leading to the requirement for exogenous insulin. Immune therapy seeks to modulate the immune system and therefore shows promise as a therapeutic option for people with type one diabetes. An abbreviated list of non-antigen specific drugs includes cyclosporine, mycophenolate and rituximab. Some non-antigen specific treatments include glutamic acid decarboxylase and heat shock protein[4].

Cyclosporine

Cyclosporine blocks signal transduction via T cell receptors leading to interference with T cell activation and the release on interleukin two by helper T cells. Concerns with cyclosporine include toxicity and high cost[4].

Mycophenolate

Mycophenolate minimizes the increase of both T and B cell, thereby lowering the number of antibodies and cell-mediated responses. Unfortunately, in a multicenter trial in North America and Europe designed to see if mycophenolate would slow down the destruction of beta cells, neither mycophenolate nor another immune therapy called daclizumab lowered C peptide (a component of insulin) significantly over placebo[4].

Rituximab

Rituximab is a monoclonal antibody that targets an antigen (CD20) found on B cells. Rituximab was used in a phase 2 trial in 87 patients with newly diagnosed type one diabetes to preserve pancreatic beta cell function. The results showed an increase in C peptide with rituximab versus placebo, however the response did not last long[4].

Glutamic acid decarboxylation

In non-obese diabetic mice, clinical studies showed that glutamic acid decarboxylase (GAD) 65 can bring about immunotolerance and slow down the progression of pre-diabetes. GAD 65 blocks the T-helper cells that contribute to the development of type 1 diabetes. Additionally, GAD 65 brought about high levels of immunoglobulin 1 (IG1) antibodies. As well as slowing the progression type 1 diabetes, GAD 65 was also successful at lowering insulitis[4]

Heat shock protein

Heat shock protein resides in mitochondria and helps with the folding of various proteins. Its levels are increased under mitochondrial stress and in type one diabetes. In response to heat shock protein, the body makes antibodies, which cause hyperglycemia and insulitis in new onset diabetic mice. DiaPep 277 is a peptide derived from heat shock protein. In a phase two trial, 35 participants with high levels of C-peptide were treated with DiaPep 277 versus placebo and after 18 months, they found sustained high levels of C-peptide in the DiaPep 277-treated group versus lower levels in the placebo group. Unfortunately, these results were not able to be sustained[4].

ISLET CELL REGENEARTION

Found in the pancreas, islet cells secrete insulin. Current research is using stem cells to produce pancreatic islet cells that respond to glucose in vitro. By comparing stem cell induced differentiated islets to human islets, researchers are gaining insight into new signaling pathways and molecules contributing to pancreatic differentiation and maturation. Researchers have successfully transplanted these stem cell derived islet cells into mice, resulting in normalizing their pre-existing high blood sugar. In the future, researchers hope to replicate this in humans to further investigate the safety and efficacy of stem cell derived islet cells[5].

CONCLUSION

Diabetes is an increasing public health concern that is managed effectively by lifestyle changes and medications. Since the advent of insulin, many medications have been developed that work by different mechanisms and target different molecules and processes in the body that leads to diabetes. Emerging therapies are developing using new mechanisms and targeting new molecules in the process of developing diabetes. The challenge with emerging therapies is to create effective treatments while also minimizing safety and cost.

REFERENCES

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Updated February 11, 2020. https://www.cdc.gov/diabetes/library/features/diabetes-stat-report.html. Accessed August 24, 2021.
2. Ansarullah, Jain, C., Far, F.F. *et al.* Inceptor counteracts insulin signalling in β-cells to control glycaemia. *Nature* 590, 326–331 (2021). https://doi.org/10.1038/s41586-021-03225-8.
3. Helmholtz Zentrum München - German Research Center for Environmental Health. "Scientists discover a new promising target for diabetes treatment." ScienceDaily. ScienceDaily, 27 January 2021. <www.sciencedaily.com/releases/2021/01/210127122356.htm>.
4. Xin GLL, Khee YP, Ying TY, et al. Current Status on Immunological Therapies for Type 1 Diabetes Mellitus. Curr Diab Rep. 2019 Mar 23;19(5):22.
5. Sim EZ, Shiraki N, Kume S. Recent progress in pancreatic islet cell therapy. *Inflamm Regen*. 2021;41(1):1. Published 2021 Jan 5. doi:10.1186/s41232-020-00152-5.
6. American Diabetes Association. Diabetes Care 2021. Jan; 44 (Supplement 1): S111-S124. https://doi.org/10.2337/dc21-S009. Accessed August 24, 2021.