PharmaVOICE

THERAPEUTIC DIGEST

DIABETES

ADVANCES AND CHALLENGES IN DIABETES MANAGEMENT

IN COLLABORATION WITH thinkgen

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Advances and Challenges in Diabetes Management

Diabetes is the major cause of blindness, kidney failure, heart attack, and stroke. The number of people affected by all types of diabetic disorders is now over four times higher than just 40 years ago. This has led the World Health Organization to consider diabetes an epidemic[1], predicting it will soon be the seventh biggest cause of death worldwide, sentencing over 422 million people to lifelong medication.

Despite its huge impact, there is still no cure for any type of diabetes. Most treatments help patients manage the symptoms to a certain extent, but diabetics still face multiple long-term health complications. Diabetes affects the regulation of insulin, a hormone required for glucose uptake in cells, resulting in high levels of blood sugar. While there are some similarities in symptoms, the two main types of diabetes develop in different ways. Type 1 diabetes is an autoimmune disease that destroys insulin-producing beta-pancreatic cells. In contrast, patients with type 2 diabetes develop insulin resistance, meaning that it has less and less effect on reducing blood sugar.

The biotech industry recognizes the need to develop new diabetes treatments. Currently, there are 15 big pharma companies working on diabetes treatments. Additionally, there are 51 startups that are developing diabetes management tools from digital therapeutics to nutrition management. Here are a few advances in the world of diabetes management.

Estimated number of adults (>18 y/o) with diagnosed, undiagnosed, and total diabetes in the United States in 2018

Characteristics	Diagnosed diabetes (n= millions) *95% CI*	Undiagnosed diabetes (n= millions) *95% CI*	Total diabetes (n= millions) *95% CI*
Total	26.8	7.3	34.1
Ages in Years			
14-44	3.6	1.4	4.9
45-64	11.7	3.1	14.8
≥65	11.5	2.9	14.3
Sex			
Men	14.0	3.9	17.9
Women	12.8	3.4	16.2
Race/ethnicity			
White, non-hispanic	15.4	4.1	19.5
Black, non-hispanic	4.2	0.9	5.2
Asian, non-hispanic	1.6	0.7	2.3
Hispanic	4.9	1.5	6.4

Source: Centers for Disease Control and Prevention and 2018 US Census Bureau Data
Notes: CI: confidence interval; Diagnosed diabetes: self-reported; Undiagnosed diabetes: based on fasting plasma glucose A1C levels among people self-reporting 'no diabetes,'

TYPE 1 DIABETES

Replacing missing cells with cell therapy

Although still in the very early stages of development, cell therapy is one of the biggest hopes towards developing a cure for diabetes, especially for type 1 diabetes (T1D). Replacing the missing insulin-producing cells could potentially recover normal insulin production and cure patients. However, early attempts to transplant pancreatic cells have largely failed, mostly due to immune reactions that reject and destroy the implanted cells. The lack of donors is also a limitation.

One of the most advanced alternatives comes from the Diabetes Research Institute (DRI) in the US, which is developing a bioengineered mini-organ where insulin-producing cells are encapsulated within a protective barrier. In 2016, the DRI announced that the first patient in Europe treated with this approach in an ongoing phase I/II trial no longer requires insulin therapy[2]. They dubbed this artificial organ, the "BioHub." Prior to their destruction by the immune system in T1D, healthy islets thrive inside the pancreas, where they have sufficient oxygen, adequate space, and all the nutrients needed to perform the demanding job of normalizing blood sugar levels. The BioHub attempts to closely replicate the cells' natural environment and allows scientists to fine tune these cellular needs within the transplant site as never before. "The progress in islet transplantation has been incremental and has allowed us to get to this important juncture," says project directors Dr. Camillio Ricordi and Dr. Stacy Joy Goodman of the Diabetes Research Institute in a 2016 press release[3]. "I am confident that this approach could move cellular therapies and biological replacement strategies for the cure of diabetes to our final goal."

A similar device[4] is being developed by the US company Viacyte, in collaboration with JDRF, the leading global organization funding T1D research. In preclinical models, implants of PEC-Direct (also known as VC-02) are capable of forming a functional beta cell mass that controls blood glucose levels. This work complements clinical evaluation of PEC-Direct that is underway in North America. During the first phase of the European trial, implants will be evaluated for their ability to form beta cells; The second phase will examine their capacity to produce systemic levels of insulin that establish glucose control. The implantation in these first European patients is a major step in the development of a cell therapy for T1D[5].

The Belgian company Orgenesis is pursuing an approach where cells from the patient's liver are transformed into insulin-producing cells or Autologous Insulin Producing (AIP) cell production, to

avoid the issues of sourcing cells from donors. ”We believe that this key study, our first human trial, will allow us to better understand the autologous immune response following AIP cell implantation in different patient populations (autoimmune or not),” says Prof. Sarah Ferber, Orgenesis chief scientific officer in a 2019 press release[6].

Islexa, in the UK, is developing a similar procedure sourcing cells from the pancreas. “The technology essentially takes the exocrine tissue from donated pancreas, once the islets have been removed from it, reprograms it and differentiates it from a kind of mesenchymal stem cell state,” explains CGT CEO and Islexa director Keith Thompson in a press release in 2016[7]. “That makes functional islets.” Islets are organoids found in the pancreas. Insulin-producing beta cells make up around 70% of the content of an islet. The remaining 30% is largely made up of alpha and delta cells, which respectively, produce the peptide hormones glucagon and somastatin. Both of these hormones are involved in the feedback system that regulates blood sugar levels.

Big pharma are still in earlier stages of developing their own cell therapy approaches for diabetes. Novo Nordisk, one of the largest providers of diabetes treatments, is bidding for stem cells and an encapsulation device. In December 2020, Procyon Technologies announced that it has entered into an exclusive research collaboration and license agreement with Novo Nordisk to develop an implantable cell encapsulation device to be used in Novo Nordisk’s development of a novel therapy in Type 1 diabetes. The collaboration brings together Procyon’s expertise with development of oxygen enabled implantable cell encapsulation devices and Novo Nordisk’s expertise in stem cell-derived insulin-secreting cells[8].

Sanofi, also a big name in diabetes, is working with the German Evotec in a beta cell replacement therapy for diabetics. “Evotec and Sanofi have developed the beta cell replacement therapy program since 2015 in a highly productive partnership,” comments Dr. Cord Dohrmann, chief scientific officer of Evotec in a 2020 press release last April[9]. “An off-the-shelf beta cell therapy product has the potential to revolutionize the treatment of insulin-dependent diabetic patients and therefore could represents a major therapeutic opportunity.”

Although the promises are big, these technologies are still far from the market. First, clinical trials have to show they do work. In addition, the price could be steep, as cell therapies for other applications, such as oncology, come with six-figure price tags and are finding it difficult to get reimbursement from health insurance companies. Considering that compared to cancer, diabetes is, for the most part, not an immediately life-threatening disease, health insurers in some countries might be reluctant to cover the treatment.

Attacking the origin with immunotherapy

In T1D, insulin-producing cells are progressively destroyed by the immune system. Stopping this process early enough could preserve the cells and provide a cure[10]. That is the goal of Imcyse, a Belgian company running a clinical trial with an immunotherapy designed to stop T1D by specifically killing the immune cells that destroy the pancreas.

ActoBio Therapeutics, a company in Belgium, is now running a phase I/II clinical trial with an unusual approach to stop the progression of T1D. The company uses cheese-producing bacteria to deliver two drugs that stimulate regulatory T cells to instruct the immune system not to attack insulin-producing cells. In August 2020, they announced that they have met the primary endpoint of their ongoing Phase 1b/2a clinical study demonstrating safety and tolerability. "Though preliminary, C-peptide data for Phase 1b AG019 monotherapy is encouraging in this limited data set," says Dr. Kevan Herold principal investigator for the AG019 Phase 1b/2a clinical study in a press release last year[11]. "The positive topline data from the Phase 1b monotherapy portion of study provides compelling rationale for continued clinical development of this promising investigational therapeutic candidate."

In France, the company Neovacs is developing a vaccine for T1D that stimulates the immune system to lower the levels of an inflammatory protein that is thought to be involved in multiple autoimmune diseases[12]. The vaccine can immunize patients with lupus for five years, and the next step is to test whether this effect is also achieved in people with T1D.

Automated treatment in an artificial pancreas

For people that have already lost their insulin-producing cells, a shorter-term solution could be the "artificial pancreas" — a fully automated system that can measure glucose levels and inject the right amount into the bloodstream, just like a healthy pancreas would. Replacing human organs with computers could help patients better control their sugar levels and suffer less complications in the long term. However, in order to fully automate insulin therapy, there are several challenges yet to be addressed[13]. First of all, faster forms of insulin are needed to react quickly enough to changes in sugar blood. In addition, current algorithms need to significantly improve to be able to make accurate predictions.

TYPE 2 DIABETES

Stimulating insulin production

One of the biggest hits in type 2 diabetes (T2D) treatment is glucagon-like peptide (GLP)-1 receptor agonists, which induce insulin production in beta-pancreatic cells while suppressing the secretion of glucagon, a hormone with the opposite effect to insulin. All big pharma have GLP-1 drugs on the market or their pipelines, including Sanofi's Soliqua, Eli Lilly's tirzepatide, Roche's taspoglutide, AstraZeneca's exenatide, and Boehringer Ingelheim's BI 456906. But Novo Nordisk is going a step further with the first oral version of a GLP-1 drug, Rybelsus, which is now on the market since it's approval in 2019. While this oral semaglutide needs to be given daily instead of once a week, patients will be able to take the medication without the discomfort of an injection. "Patients want effective treatment options for diabetes that are as minimally intrusive on their lives as possible, and the FDA welcomes the advancement of new therapeutic options that can make it easier for patients to control their conditions," says Lisa Yanoff, acting director of the Division of Metabolism and Endocrinology Products in the FDA in a 2019 press release[14].

The French company Poxel is going after a different approach with a drug that simultaneously targets the pancreas, the liver and the muscles to reduce blood sugar. Poxel's candidate, Imeglimin, is an oral first-in-class drug that targets the mitochondria. The drug has proved this effect in a phase III trial in Japan, where Poxel was approved before Europe and US[15]. In Sweden, Betagenon and Baltic Bio are working on a first-class drug with the potential to simultaneously control sugar levels and reduce blood pressure, a big risk factor in patients with type 2 diabetes who are also obese[16].

Tackling the obesity component of T2D is also the German company, MorphoSys's, goal with their candidate bimagrumab. The Phase II trials with an antibody designed to reduce fat, prevent insulin resistance, and control excessive eating concluded in 2019 on a positive note[17].The double-blinded, placebo-controlled study showed that bimagrumab reduced body fat and weight while increasing lean body mass over the 48 week trial period and was safe and well tolerated. Dr. Markus Enzelberger, chief scientific officer of MorphoSys AG says in a 2019 press release, "We are very pleased to see these data from this clinical study in type 2 diabetes."

Targeting the microbiome

Just in the past decade, scientists have realized the big role that the microbes living inside and on us play in our health. The human microbiome, and especially the gut microbiome, has been linked to multiple chronic diseases, including diabetes[18].

An unbalanced microbiome composition has been found in patients with diabetes, who tend to have a less diverse gut microbiome as compared to healthy people. Researchers from the University of Amsterdam recently showed that fecal transplants, used to transfer the microbiome of a healthy person to the gut of one with diabetes, can result in a short-term improvement of insulin resistance in obese patients with T2D[19].

Some companies are developing diabetes treatments targeting the microbiome. The French company, Valviotis, is currently conducting preclinical testing of a drug aimed at increasing the microbiome diversity as a treatment for T2D[20]. Although promising, the microbiome field is very young and its complexity makes it difficult to establish causation after finding correlation. Until more diabetes treatments are tested in the clinic, it will be difficult to determine the real potential of the microbiome in this space.

THE NEEDLE-FREE REVOLUTION

"In a perfect world, blood sugar testing would be quick and painless," said Avner Gal, CEO of Integrity Applications in a 2013 interview for MedGadget[21]. That world may not be so far away, as many companies are developing non-invasive methods to substitute finger pricking. Integrity Applications has developed a device called GlucoTrack that can measure glucose using electromagnetic waves and is already available in Europe. Similar technologies are popping up, with GlucoSense in London using laser light to measure sugar levels and MediWise making use of radio waves.

Patches are also becoming a popular form of measuring blood glucose without needles, such as FreeStyle Libre, an inch-wide patch that can be worn for up to 2 weeks. At the University of Bath, researchers are developing a graphene patch that could provide greater accuracy by measuring sugar levels individually in multiple hair follicles[22].

Dutch firm NovioSense is going for a tiny device that is placed under the eyelid and would be more affordable than current continuous glucose monitors[23]. Meanwhile, Senseonic and Roche are working on a device that is implanted under the skin.

Still, non-invasive options to measure blood sugar often face issues regarding accuracy. The famous glucose-measuring contact lens that Google announced in 2014 was dismissed as "technically infeasible" and further developments will be needed to reach the degree of accuracy of finger-pricking methods[24].

CONCLUSION

The diabetes market is expected to reach a massively big $105 billion by 2025 combining both type 1 and type 2, and we can expect all sorts of revolutionary technologies to come forward and claim their market share. Researchers are already speculating about microchips[25] that can diagnose diabetes type 1 before the symptoms appear or nanorobots[26] traveling in the bloodstream while they measure glucose and deliver insulin. Whatever the future brings, it will undoubtedly make a huge difference in the lives of millions of people worldwide.

NOTES

[1] Diabetes. World Health Organization. Accessed: January 2, 2021.

[2] "Novel tissue-engineered islet transplant achieves insulin independence in type 1 diabetes." Science News. May 11, 2017.

[3] "Diabetes Research Institute's first patient in BioHub trial no longer requires insulin therapy." Diabetes Research Institute Foundatio. September 2015.

[4] "ViaCyte does it again: insulin production in people with T1D." JDRF. October 3, 2019.

[5] "Center for beta cell therapy in diabetes and ViaCyte announce start of European clinical trial of human stem cell-derived implants in type 1 diabates patients." ViaCyte. January 21, 2019.

[6] "Orgenesis announces planned study to confirm suitability of liver cells as a source for personalized cell replacement therapy for insulin-dependent diabetic patients." Orgenesis. April 30, 2019.

[7] Taylor N. "Islexa fires up to develop cell therapy for type 1 diabetes." FierceBiotech. May 19 2016.

[8] "Procyon Technologies LLS and Novo Nordisk A/S to collaborate on the development of a stem-cell based therapy for type 1 diabates." Procyon Technologies. December 8, 2020.

[9] "Evotec regains global rights to beta cell replacement therapy." PharmiWeb. April 4, 2020.

[10] "The type 1 diabetes immunotherapy consortium." Diabetes. Accessed: January 2, 2021.

[11] "Precigen ActoBio announces positive topline results from phase 1b study of AG019 ActoBiotics, a novel therapy designed to address the underlying cause of type 1 diabetes." Precigen. August 10, 2020.

[12] "Neovacs to present the pre-clinical results of its IFNalpha Kinoid to treat type 1 diabetes – American Diabetes Association's 79th scientific sessions. Global News Wire. June 5, 2020.

[13] Bequette BW. "Challenges and recent progress in the development of a closed-loop artificial pancreas." Annual Reviews in Control. 2013.

[14] Smith J. "FDA greenlights first oral version of Novo Nordisk's type 2 diabetes drug." Labiotech. September 9 2019.

[15] Mast J. "Poxel passes 3rd straight phase III diabetes trial in Japan, but what's going on with US/EY partner Roivant?" Endpoints News. December 20, 2019.

[16] "Betagenon and Baltic bio announces positive results from a 28-day phase IIa trial of the first in-class AMPK activator 0304 in type 2 diabetes." BioSpace. November 2, 2017.

[17] "Results for bimagrumab in obesity and type 2 diabetes presented by MorphoSys's partner." Bloomberg. November 11, 2019.

[18] Sharma S, Tripathi P. "Gut microbiome and type.2 diabetes: where we are and where to go?" The Journal of Nutritional Biochemistry. January 2019.

[19] Harstra A, et al. "Insights into the role of the microbiome in obesity and type 2 diabetes." Diabetes Care. January 2015.

[20] Fernandez C. "The future of diabetes treatment: is a cure possible?" Labiotech. July 15, 2019.

[21] Krisnamurthy G. "Non-invasive measurement of blood glucose levels using GlucoTrack: interview with CEO Avner Gal." MedGadget. October 15, 2013.

[22] "Bloodless revolution in diabetes monitoring." University of Bath. April 9, 2018.

[23] Waltz E. "Why Noviosense's in-eye glucose monitor might work better than Alphabet's." Spectrum. November 15, 2018.

[24] "What happened to the plans for a smart contact lens for diabetes?" Labiotech. January 1, 2018.

[25] "Microchip can speedily diagnose type 1 diabetes." Medical Design Briefs. September 1, 2014.

[26] Cavalcanti A, et al. "Medical nanorobotics for diabetes control." Nanomedicine: Nanotechnology, Biology, and Medicine. June 2008.

RESOURCES

Bequette BW. "Challenges and recent progress in the development of a closed-loop artificial pancreas." Annual Reviews in Control. 2013.

"Betagenon and Baltic bio announces positive results from a 28-day phase IIa trial of the first in-class AMPK activator 0304 in type 2 diabetes." BioSpace. November 2, 2017.

"Bloodless revolution in diabetes monitoring." University of Bath. April 9, 2018.

Cavalcanti A, et al. "Medical nanorobotics for diabetes control." Nanomedicine: Nanotechnology, Biology, and Medicine. June 2008.

"Center for beta cell therapy in diabetes and ViaCyte announce start of European clinical trial of human stem cell-derived implants in type 1 diabates patients." ViaCyte. January 21, 2019.

"Diabetes Research Institute's first patient in BioHub trial no longer requires insulin therapy." Diabetes Research Institute Foundatio. September 2015.

Digitale E. "Researchers invent nanotech microchip to diagnose type-1 diabetes." Stanford. 2014.

"Evotec regains global rights to beta cell replacement therapy." PharmiWeb. April 4, 2020.

Fernandez C. "The future of diabetes treatment: is a cure possible?" Labiotech. July 15, 2019.

Harstra A, et al. "Insights into the role of the microbiome in obesity and type 2 diabetes." Diabetes Care. January 2015.

Krisnamurthy G. "Non-invasive measurement of blood glucose levels using GlucoTrack: interview with CEO Avner Gal." MedGadget. October 15, 2013.

Mast J. "Poxel passes 3rd straight phase III diabetes trial in Japan, but what's going on with US/EY partner Roivant?" Endpoints News. December 20, 2019.

"Microchip can speedily diagnose type 1 diabetes." Medical Design Briefs. September 1, 2014.

"Orgenesis announces planned study to confirm suitability of liver cells as a source for personalized cell replacement therapy for insulin-dependent diabetic patients." Orgenesis. April 30, 2019.

"Precigen ActoBio announces positive topline results from phase 1b study of AG019 ActoBiotics, a novel therapy designed to address the underlying cause of type 1 diabetes." Precigen. August 10, 2020.

"Procyon Technologies LLS and Novo Nordisk A/S to collaborate on the development of a stem-cell based therapy for type 1 diabates." Procyon Technologies. December 8, 2020.

"Results for bimagrumab in obesity and type 2 diabetes presented by MorphoSys's partner." Bloomberg. November 11, 2019.

Sharma S, Tripathi P. "Gut microbiome and type.2 diabetes: where we are and where to go?" The Journal of Nutritional Biochemistry. January 2019.

Sinclair A, Abdelhafiz A. "Challenges and strategies for diabetes management in community-living older adults." American Diabetes Association. 2020.

Skoler E, et al. " The biggest news in diabetes technology, drugs, and nutrition: highlights from ADA 2020." DiaTribe Learn. June 22, 2020.

"National Diabetes Statistics report 2020; Estimates of diabetes and its burden in the United States." CDC. 2020.

"Neovacs to present the pre-clinical results of its IFNalpha Kinoid to treat type 1 diabetes – American Diabetes Association's 79th scientific sessions. Global News Wire. June 5, 2020.

"Novel tissue-engineered islet transplant achieves insulin independence in type 1 diabetes." Science News. May 11, 2017.

Vasilevskis E. "The challenges of diabetes medication management at hospital discharge in older adults." JAMA. March 24, 2020.

"ViaCyte does it again: insulin production in people with T1D." JDRF. October 3, 2019.

Waltz E. "Why Noviosense's in-eye glucose monitor might work better than Alphabet's." Spectrum. November 15, 2018.

"What happened to the plans for a smart contact lens for diabetes?" Labiotech. January 1, 2018.

Zierath J. "Major advances and discoveries in diabetes – 2019 in review." Current Diebetes Reports. 2019.

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