Congress Review

Review of the 57th Annual European Association for the Study of Diabetes (EASD) Congress

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THE EUROPEAN Association for the Study of Diabetes (EASD) Annual Meeting is the largest international annual conference on diabetes research worldwide. Founded in 1965, the EASD's main goals are to encourage and support research in the field of diabetes, to quickly share acquired knowledge, and to facilitate the application of these new advancements. With the success of last year's virtual congress and the ongoing uncertainty of the COVID-19 pandemic, the EASD decided, once again, to hold their Annual Meeting virtually. The digital format of EASD 2020 saw many positives, including a further outreach to a wider audience, most notably in Brazil and Mexico, and a significant increase in the use of their eLearning platform, which attracted over 260,000 on-demand views during the congress period.

Stefano Del Prato, EASD President, kicked off EASD 2021 with the opening ceremony prior to the commencement of the scientific sessions. He noted that this year's "programme covers all interests in diabetes, from clinical developments to breaking research," all of which were presented by over 850 expert speakers. The continued virtual format as a consequence of the ongoing pandemic allowed for innovative changes to be made to the scientific programme, with a focus on interactivity. Del Prato summed up this year's programme reshaping, stating: "We have learned a lot and we have done our best to take advantage of that lesson to develop a new, improved, virtual EASD Annual Meeting 2021 platform to offer state-of-the-art diabetes science." Traditional poster presentations were replaced by informative short oral presentations that included an engaging question and answer session with the audience, allowing for a more personalised experience. The success of previous eLearning sessions saw expansion of the content on offer as well as a reform of the session structure to facilitate interactivity.

Del Prato went on to shine the spotlight on an exciting anniversary in the diabetes world:

100 years of insulin. Several sessions were focused on the celebration of this life-saving treatment and its modernisation in recent years as well as the announcement of two new insulin-focused award programmes, born from the collaboration of the European Foundation for the Study of Diabetes (EFSD) and the pharmaceutical industry. A range of exciting research presentations were on offer at EASD 2021, covering topics including precision medicine in diabetes, diabetes and COVID-19, and the use of novel glucose-lowering agents.

The awards ceremony saw a number of scientists receive esteemed prizes for their contributions to the field of diabetes. Juleen Zierath, Research Group Leader for Integrative Physiology, Department of Physiology and Pharmacology and the Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden, received the 53rd Claude Bernard Medal and Lecture, the highest recognition of the EASD for her work on exercise and metabolism. Hiddo Lambers Heerspink, Professor of Clinical Trials and Personalized Medicine, University Medical Center Groningen (UMCG), the Netherlands, received the 36th Camillo Golgi award for his lecture on treatment personalisation for patients with Type 2 diabetes. The 56th Minkowski Prize was awarded to Amélie Bonnefond, Researcher, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France, for her lecture delving into the genetics of diabetes. The 7th EASD–Novo Nordisk Foundation Prize for Excellence Lecture was awarded to John A Todd, Professor of Precision Medicine, University of Oxford, UK, for outstanding achievement in diabetes research following his lecture 'From HLA-DQ position 57 and back again'.

Highlights from the hot topics presented at EASD 2021 can be found within this issue, including the use of artificial intelligence in diabetic retinopathy screening, the role of β cells in the pathogenesis of Type I diabetes, and the personalisation of insulin therapy. These late-breaking stories contain some of the most up-to-date research and advancements in the field of diabetes.

Here at EMJ, we look forward to joining you all in Stockholm, Sweden in 2022, for next year's event, bringing together experts in diabetes care and research from across the globe. Until then, find our selection of key scientific discoveries from EASD 2021 in the following pages.

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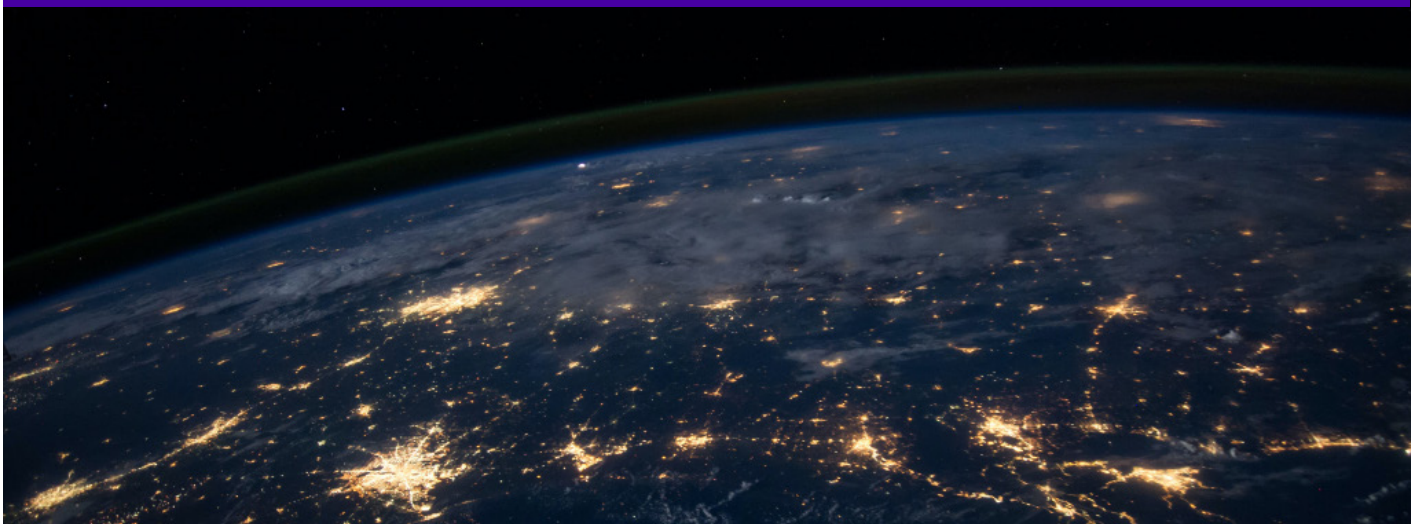

EASD 2021 REVIEWED →

Can Precision Medicine Improve Diabetes Control?

PRECISION medicine could be used when treating patients with Type 2 diabetes mellitus (T2DM). New research aimed at improving diabetes control and reducing medication side effects was presented at EASD 2021 on 29th September by John Dennis from the University of Exeter, UK.

Currently, metformin is the first-line treatment for individuals with T2DM; however, many patients eventually need additional drug treatments to lower their blood sugar levels. While doctors make prescription decisions on these additional drug options, they have limited guidance on the matter, which means prescriptions vary enormously.

Big data on millions of patients have been used to develop precision medicine in patients with T2DM. This approach shows how precision medicine is more useful to doctors and patients. At the meeting, Dennis shared how precision medicine can use simple patient characteristics that are available to any doctor to optimise T2DM treatment.

Routine blood tests, used to measure patients' blood sugar levels, are a low-cost method of determining a patient's clinical or biomarker characteristics, which can help doctors to determine the right drug for an individual. This would lead to improved blood sugar control and avoid side effects from certain medications in patients. Dennis also noted that factoring the patient's BMI and kidney function into prescription decisions can also help determine the right treatment for patients.

Dennis believes that precision medicine has a future in determining treatment options for patients with T2DM. "Using a person's specific characteristics to match them to their most effective medication for them will be a major advance in [T2DM] care," he stated. "Recent progress in precision medicine means there is now clear potential to move away from the current one-size-fits-all approach to [T2DM] treatment in the near future." ■

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Role of Artificial Intelligence in Diabetic Retinopathy Screening

DIABETES is a common condition that is predicted to affect 642 million people around the globe by 2040. One of the most common microvascular complications of diabetes is loss of eyesight, ultimately resulting in blindness if left untreated. Globally, diabetic retinopathy (DR) is prevalent in 34.6% of patients with diabetes. For this reason, it is important to be able to detect DR early so that the patient can receive treatment as soon as possible. This is where artificial intelligence (AI) comes in, an emerging technique in diagnosing and screening for DR, as shared in a presentation at EASD 2021.

The healthcare system is continuously under pressure and resources are often limited; using AI would help not only to screen for DR early but create one less step for healthcare professionals to worry about, especially as AI is just as accurate at detecting DR in fundus images as humans, which makes it an extremely beneficial tool for clinical use. Clinical trials have already proved the efficacy of AI and it has already been implemented into practice. A few years ago, an AI diagnostic system for DR was developed and approved for DR screening by the U.S. Food and Drug Administration (FDA). Due to the efficacy of AI systems, the American Diabetes Association has now recognised the use of AI for DR screening as a standard of care.

Ways to improve the AI system for DR include the ability of AI to categorise the stage of disease, make it inclusive for multiple ethnicities, and expand the screening so that it covers other diabetic eye conditions, namely glaucoma. Another system called Medios AI is moving toward this direction, in hope that AI can be used for other eye conditions in diabetes in the future.

The speaker of the presentation, Sosale Aravind, Bangalore, India, shared his thoughts: "The management of diabetes-related eye complications is primarily preventative. Regular eye examinations and appropriate ophthalmologist referral remain important strategies to reduce the impact of diabetes-related vision loss." Using AI in DR could help streamline the screening process and benefit everyone, but most importantly, the patients. ■

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Insulin Therapy Verses GLP-1 Receptor Agonists

INSULIN extraction from animal pancreas occurred a century ago in 1921; shortly after, insulin therapy was used to treat diabetes in humans. Typically, insulin is injected into the fat under a patient's skin using a syringe. Back to 2021, at the virtual EASD Annual Meeting, Michael Nauck compared insulin therapy with a newer treatment, glucose-lowering medications such as GLP-1 receptor agonists, which have been offered since 2005.

GLP-1 receptor agonists are a type of non-insulin medication that are usually prescribed along with lifestyle changes for Type 2 diabetes and obesity. GLP-1 receptors can increase insulin secretion from the pancreas; however, only when the plasma glucose is at high levels. This is a complete contrast to insulin therapy, which does not rely on glucose levels.

GLP-1 receptor agonists usually lead to weight loss in patients, which is why they are particularly useful for both these conditions as a high BMI exacerbates these conditions. Nauck shared the difference between GLP-1 receptor agonists and insulin therapy regarding weight: "GLP-1 receptor agonists reduce body weight in typically obese subjects developing Type 2 diabetes, while insulin treatment is often accompanied by weight gain."

Another difference between glucose-lowering medication, in this case, SGLT-2 inhibitors, and insulin therapy is their secondary benefits. SGLT-2 inhibitors have proven to have cardiovascular and renal benefits. Nonetheless, the effects of SGLT-2 inhibitors on lowering glucose and body weight are not as effective as GLP-1 receptor agonist treatment.

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The speaker concluded that although the development of insulin therapy was a major scientific breakthrough at the time, there are better medications available now for Type 2 diabetes and current guidelines recommend considering GLP-1 receptor agonists for many patients with Type 2 diabetes. Nauck shared his final remarks: "We will see further significant improvements in effectiveness concerning medications belonging to the GLP-1 receptor agonists' class, e.g., by addressing other gut hormone receptors with dual or triple agonists." ■

The Role of Perivascular Fat in Obesity and Diabetes-Related Pathology

MAJOR threats to global health are presented by obesity and Type 2 diabetes (T2D). Both strongly increase the risk of both organ failure and cardiovascular disease (CVD). Recent research investigating the role perivascular adipose tissue (PVAT) plays in contributing to insulin resistance and CVD was presented at EASD 2021.

Impaired function of the microcirculation within organs contributes to insulin resistance, T2D, and heart failure. When placed in co-culture, microvascular endothelial cells enhance the contraction and relaxation of heart muscles, a process mediated by nitric oxide and impaired by inflammation. PVAT influences a variety of vascular functions including endothelial function and infiltration of inflammatory cells; it also regulates vascular diameter. Researchers therefore theorised that PVAT may play a role in the development of insulin resistance and cardiovascular disease.

When the body is healthy, the vasodilatory actions of PVAT are mediated by the hormone adiponectin and the exercise-activated protein AMP-activated protein kinase. Obesity causes the vascular functions of PVAT to change from vasodilation to vasoconstriction. Obesity results in an accumulation of PVAT, which can become inflamed and impair vasodilatory functions.

Researchers removed healthy PVAT from mice using microsurgery to model local loss of PVAT function. By subsequently measuring local vasodilation, muscle flow, and glucose uptake, they were able to show that local PVAT regulates insulin-stimulated muscle blood flow and glucose uptake *in vivo*. The removal of intramuscular PVAT also altered protein clusters, causing upregulation of clusters that feature Hsp90ab1 and Hsp70 and downregulation of a cluster of mitochondrial protein components.

"We discovered distinct small blood vessels between PVAT and the adjacent muscle, or adipomuscular arterioles, which mediate PVAT regulation of local blood flow," explained Etto Eringa, Department of Physiology, Maastricht University and Amsterdam University Medical Centres, Maastricht and Amsterdam, the Netherlands. The data provide proof of concept that inflammation of PVAT in muscle impairs muscle blood flow and glucose uptake in obesity and T2D.

Looking to the future, Eringa concluded: "This previously overlooked fat tissue provides a new target for preventing heart failure in obesity and diabetes." ■

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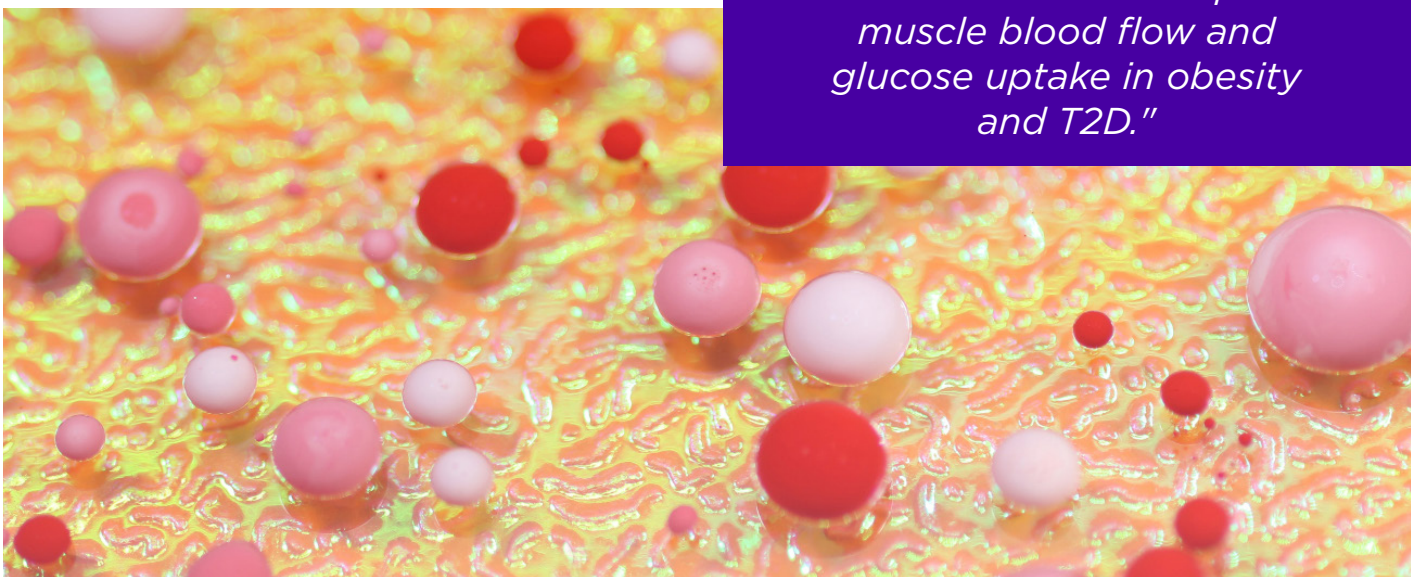

"This personalised treatment strategy is a step closer to achieving the ultimate goal of calculating the optimal insulin dose to meet each individual patient's needs."

Insulin: 100 Years On

ONE HUNDRED YEARS now marks the life-changing scientific development that saw the successful subcutaneous administration of insulin. Since this discovery, it is surprising to think that little has changed regarding the process of insulin administration and absorption, so how has this area advanced in the last century? This revolutionary topic was the focus of a session presented on 29th September at the EASD 2021 Virtual Congress.

Both upon its discovery and today, the pharmacodynamics of insulin remains unchanged. Insulin is injected subcutaneously and, following absorption, is transported via the bloodstream to insulin receptors present on specific cells where it binds and triggers a biological response. Alterations to the physical properties of insulin leads to different rates of absorption through varied action profiles. The real advancement to the treatment in recent years lies in the progressive potential of these action profiles in allowing an individualised approach to insulin therapy. This personalised treatment strategy is a step closer to achieving the ultimate goal of calculating the optimal insulin dose to meet each individual patient's needs.

Cees Tack, Professor in Department of Medicine, Radboud University Medical Center, Nijmegen, Netherlands, explained: "An individualised approach in insulin treatment means in fact finding the right combination of insulin(s), glucose monitoring approaches, and the right dose adjustment system." It was reiterated throughout the session that the success of insulin treatment is dependent on glucose monitoring, and how fluctuations trigger changes in the algorithm and to subsequent insulin dose.

Despite current and looming advances, insulin therapy still has its physiological challenges. A notable issue lies with the resorption of the hormone from the subcutaneous space into the systemic circulation, which results in a significant increase in circulating insulin and a subsequent drop in systemic concentration. It is speculated that this may be a contributing factor to patients' tendency to gain weight during insulin therapy. The patient demographic of those receiving insulin has also shifted over the century. Individuals receiving treatment are now more likely to be obese, which merits higher insulin doses and subsequently puts patients at risk of peripheral hyperinsulinaemia.

Future advancements to insulin therapy will likely lie with a form of fully automated insulin infusion that is based on continuous glucose monitoring. Given the development of other glucose-lowering drugs, we should also expect to see insulin administered at a later stage of the treatment algorithm for patients with Type 2 diabetes, in order to reduce the risk of weight gain and hyperinsulinaemia. Tack added: "Insulin, 100 years old, is the best we have but still not perfect and dependent on important partners in treatment: monitoring and adjustment algorithms." ■

Muscle Fat Storage and Insulin Sensitivity

LIPID droplet dynamics could potentially act as a target to improve insulin sensitivity according to a talk presented at EASD 2021 on 29th September by Anne Gemmink, Maastricht University, the Netherlands. Research shows that people with Type 2 diabetes have higher levels of fat storage within their muscles compared to those without Type 2 diabetes. Additionally, athletes who are endurance trained store a large amount of fat within their muscles and are insulin sensitive. Muscle fat is stored in lipid droplets, which are observed as dynamic organelles and are not necessarily harmful for insulin sensitivity.

Studies using different microscopic techniques have shown that the lipid droplets stored within the skeletal muscle vary in size, location, number, and protein decoration. As stated by Gemmink, the lipid droplets stored within athletes' muscles are smaller compared to patients with Type 2 diabetes who have fewer but larger lipid droplets. Additionally, patients with Type 2 diabetes can enhance their insulin sensitivity with an exercise training program and this could transform their muscle storage similar to that of an endurance athlete. Unfortunately, approximately 20% of patients with Type 2 diabetes are not able to exercise and thus do not improve their insulin sensitivity.

There are proteins present on the lipid droplet surface that have various roles in the storage and release of fat depending on energy demand. There is an observable difference in the abundance of certain proteins between athletes and patients with Type 2 diabetes. The contrast in protein abundance on the lipid surface of athletes and patients with Type 2 diabetes could be important in understanding the difference in lipid droplet formation between the two groups. Gemmink and team set up a live-cell microscopy approach to observe the formation of these lipid droplets over a period of time, which could allow further insight into targeted lipid droplet dynamics as a way to enhance insulin sensitivity.

Sharing these findings, Gemmink concluded: "Lipid droplet dynamics are a potential important target for improving insulin sensitivity, and we need to use a dynamic approach to gain a better understanding of these lipid droplet dynamics as a target to improve insulin sensitivity." ■

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Importance of Studying Rare Genetic Variants in Diabetes

DIABETES is the sixth leading cause of mortality in the world. This condition is becoming increasingly common, with 420 million people diagnosed with diabetes around the world. Type 2 diabetes is the most common type of diabetes and is largely heritable. Despite there being 74 approved drugs for this condition, only 50% of patients with Type 2 diabetes achieve adequate blood glucose control. Understanding the genetics behind a condition can result in novel drug targets and treatment. In this presentation at EASD 2021, speakers who had been awarded the 56th Minkowski Prize shared their genetic research in diabetes.

Genetic research largely focuses on common genetic variants linked to the risk of Type 2 diabetes. Although common variants have been discovered successfully, rarely do these common variants lead to novel drugs. However, rare genetic variants have been very useful in finding new drug targets for metabolic disorders. Next-generation sequencing of the genome has enabled scientists to discover rare mutations in genes associated with metabolic conditions. Amelie Bonneford, director of research at INSERM, Paris, France, believes that rare variants can be of more use than common variants for creating new drugs for diabetes.

Bonneford examined the medical mystery link between opioid use and metabolic disorders. Some studies have shown people who use opioids have lower BMIs compared to people who don't use opioids. In contrast, other studies have shown opioids could cause Type 2 diabetes. Using large-scale DNA sequencing and functional genetics, Bonneford found that loss of function of the *OPRD1* gene, which codes for the Δ opioid receptor (DOP), was linked with a higher risk of Type 2 diabetes. Interestingly, she also found that this gene was expressed at greater amounts in pancreatic β cells and that activation of the DOP reduced insulin secretion. The results imply that using DOP antagonists in the pancreas could help treat Type 2 diabetes. Overall, this discovery supports the research of rare mutations of Type 2 diabetes, which could be important in the treatment and care for patients with these rare mutations, in this case the loss of function of DOP.

The speaker concluded: "Rare variants play a common role in Type 2 diabetes and should be carefully considered as they are a goldmine for Type 2 diabetes pathophysiology and precision medicine." ■

Advances to the Understanding of Non-coding RNA and Skeletal Muscle Metabolism

INSTRUMENTAL to regulating blood sugar levels and metabolic balance, skeletal muscle is a hotspot for insulin action. Research into the influence of non-coding RNA (ncRNA) on glucose control in people with Type 2 diabetes (T2D) has been conducted and may provide new opportunities to treat metabolic disorders like T2D. Insights into the role of ncRNA in T2D were shared in a press release dated 28th September from EASD 2021.

Insulin resistance is an early symptom in the identification of T2D. This reduced ability of skeletal muscle to respond to insulin is partly under genetic control, but is also governed by physical activity levels and metabolic milieu. Recent evidence has uncovered that the expression of ncRNA alters with exercise in skeletal muscle; Ilke Sen, lead investigator in the current research, aimed to "understand the regulation of skeletal muscle ncRNA, and how changes in specific ncRNA species impact glucose control in people with Type 2 diabetes, with or without exercise." Whilst the term 'ncRNA' is usually used to refer to RNA that does not encode proteins, this does not mean that ncRNA carries information with no function. Sen highlighted this by stating the focus of his research: "There are currently no drugs available that directly target skeletal muscle insulin sensitivity," identifying the gap in treatment avenues. He went on to clarify the value of this work and to outline the future directions for exploration: "Thus, identification of key ncRNAs involved in regulating the skeletal muscle insulin sensitivity will give insights into the plasticity of skeletal muscle and provide avenues for novel therapeutic approaches for the treatment of Type 2 diabetes and related metabolic disorders."

The need for further study in this field is clear, emphasised by the growing number of individuals affected by T2D. The full presentation of this investigation, with results and conclusions, may accelerate progress by defining the role of ncRNA in skeletal muscle metabolism, growth, and insulin sensitivity. ■

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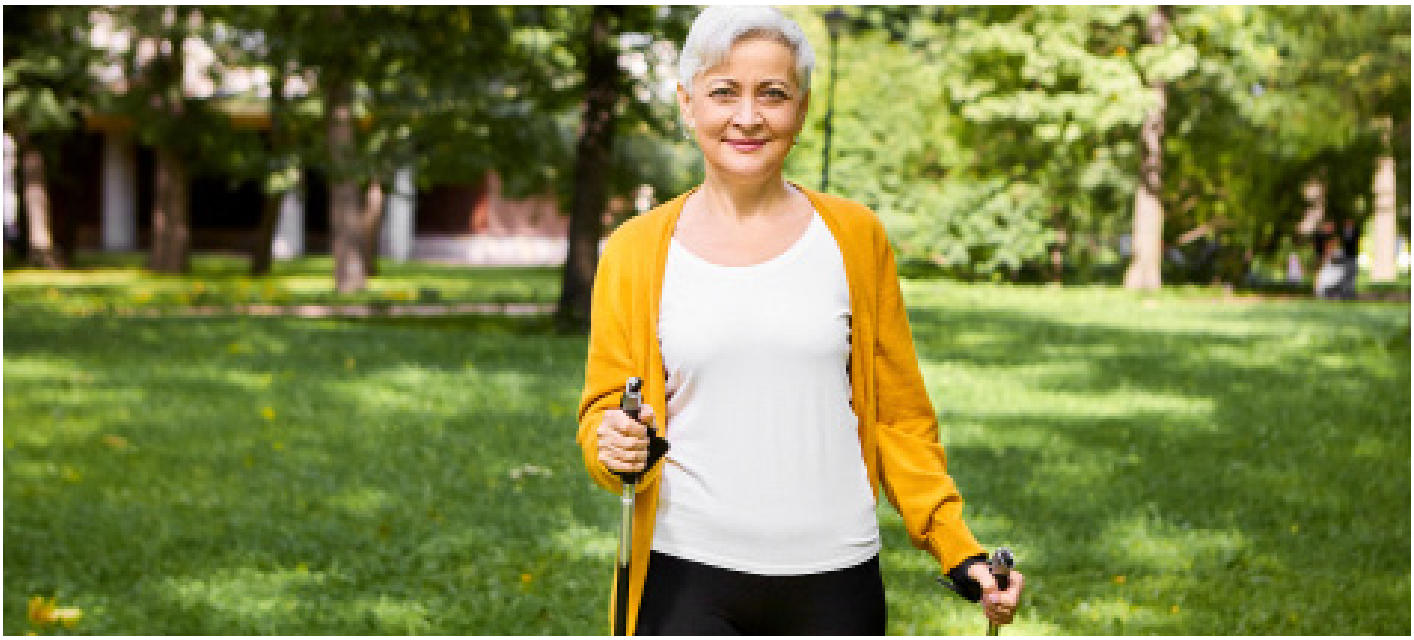

"Direct reprogramming has the potential to treat not only diabetes but a range of degenerative diseases."

Is Direct Cell Reprogramming the Future of Diabetes Therapy?

GROUND-BREAKING research has demonstrated that the adult pancreas has the ability to regenerate new, functional insulin-producing cells, with findings shared at EASD 2021. There are several endocrine cells in the pancreas that produce the hormones responsible for regulating blood sugar levels, grouped into the islets of Langerhans; diabetes occurs in the absence of functional β cells.

"I wanted to determine the exact origin of insulin-producing β-cells during pancreas development," stated Pedro Herrera, Faculty of Medicine, University of Geneva, Switzerland. Understanding this origin is crucial to the process of generating surrogate insulin-producing cells from pluripotent stem cells necessary for devising cell-replacement therapies to treat Type 1 diabetes.

Using a genetic tool, Herrera's team has demonstrated regeneration of new, functional insulin-producing cells within the adult pancreas in mouse models.

"We have provided direct evidence of how human islet cell plasticity can be exploited to reprogramme non β-cells into β-like cells," stated Herrera. "We showed the conversion of human α-cells and γ-cells into glucose-sensitive insulin-producing cells." This provides the additional advantage of promoting insulin production by non-β-cells, which, in turn, would also mean decreased glucagon production in autoimmune diabetes.

"Biology textbooks teach us that mature and fully differentiated adult cell types remain fixed in the identity they have acquired upon maturation and differentiation," explained Herrera. "By inducing non-insulin-producing human pancreatic cells to modify their function to produce and secrete insulin in response to glucose, we show the adaptive capacity of our cells is much greater than previously thought."

Looking to the future, Herrera's team are now investigating how to exploit this phenomenon of cellular reprogramming to propose entirely new therapeutic strategies for diabetes. Furthermore, the utilisation of human cell plasticity has applications far and beyond the pancreas. Direct reprogramming has the potential to treat not only diabetes but a range of degenerative diseases. ■

Potential New Inhibitor for Type 1 Diabetes Treatment

FASCINATING discovery has revealed a class of cytokine-signalling inhibitors with potential to treat Type 1 diabetes. In Type 1 diabetes, immune cells invade the islets of the pancreas and lead to the release of various cytokines, chemokines, and signals. An important cytokine family that is associated with early Type 1 diabetes is interferon-α (IFN-α). Researchers tested a new inhibitor called BMS-986202 in two Type 1 diabetic mouse models and human islets that had been treated with IFN-α. The research, led by Carmella Evans-Molina, Indiana University School of Medicine, Indianapolis, Indiana, USA, was presented at EASD 2021 on the 20th September.

IFN-α works by binding to its receptor, IFNAR1, and other tyrosine kinases such as JAK1 and TYK2. This cytokine family has been shown to stimulate the three hallmarks of Type 1 diabetes: chemokine production, endoplasmic reticulum stress, and overexpression of HLA class 1. JAK1 inhibitors have shown promising results in Type 1 diabetic mouse models and TYK2 inhibitors are being tested in mouse and *in vitro* models.

Novel research from pre-clinical studies was presented in the EASD 2021 symposium "Beta cell (dys)function in Type 1 diabetes." The main results showed that inhibiting TYK2 in human β cells treated with IFN-α had effects on mRNA induction, specifically on mRNAs that code for chemokines and endoplasmic reticulum stress signals. The TYK2 inhibitor has been found to delay diabetes in Type 1 diabetic mouse models. In addition, the TYK2 inhibitor resulted in a decrease in IFN-α response genes in mouse models. Other fascinating findings include an increase in Treg cells in mice treated with a TYKR inhibitor and a decrease in cytotoxic CR8+ T-cells.

Overall, this exciting discovery of inhibition of the receptors of IFN-α could potentially lead to new innovative drug targets and treatment for a condition that currently has no known cure. The results provide promise to patients with Type 1 diabetes as research is in favour of inhibition of TYK2 and JAK1. ■

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