EMJ DIABETES

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Virtual EASD Annual Meeting 2021

EDITOR'S PICK

Disorders of Gastrointestinal Motility in Diabetes Mellitus: An Unattended Borderline Between Diabetologists and Gastroenterologists

INTERVIEWS

EMJ spoke with Chantal Mathieu and Bart Torbeyns, who shared insights into their work with the EASD and EUDF, and the future of the field.

Contents

"Expertly written articles explore screening for heart failure in diabetes, identifying the socio-demographic determinants of attendance at diabetes education centres, and the progression of diabetic retinopathy in patients with COVID-19..."

Spencer Gore, CEO

Editorial Board

VIEW IN FULL ←

Aims and Scope

EMJ is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

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EMJ Diabetes 9.1

Welcome

Dear Readers,

Welcome to this year's issue of *EMJ Diabetes*. The latest insights and research included in this eJournal come from peer-reviewed authors, key opinion leaders and experts in the field. *EMJ Diabetes* contains highlights, features and abstract summaries presented at the 2021 European Association for the Study of Diabetes (EASD) annual meeting. Moreover, this eJournal also contains novel articles, interviews, and reviews in diabetic research.

For the second year in a row, the EASD annual meeting took place virtually due to the ongoing COVID-19 pandemic. Nonetheless, researchers persevered on, and this is reflected in the numerous ground-breaking discoveries and innovative research shared in this year's *EMJ Diabetes* journal, spanning the use of artificial intelligence in diabetic retinopathy screening to discovering novel rare genetic variants in diabetes.

Other stand-out topics from this year's annual meeting include a riveting guidelines session on diabetes management, sharing the latest data from clinical trials. Alongside this feature, there are ten exciting highlights shared in this eJournal in topics including insulin therapy, precision medicine, direct cell reprogramming, muscle fat storage and much more.

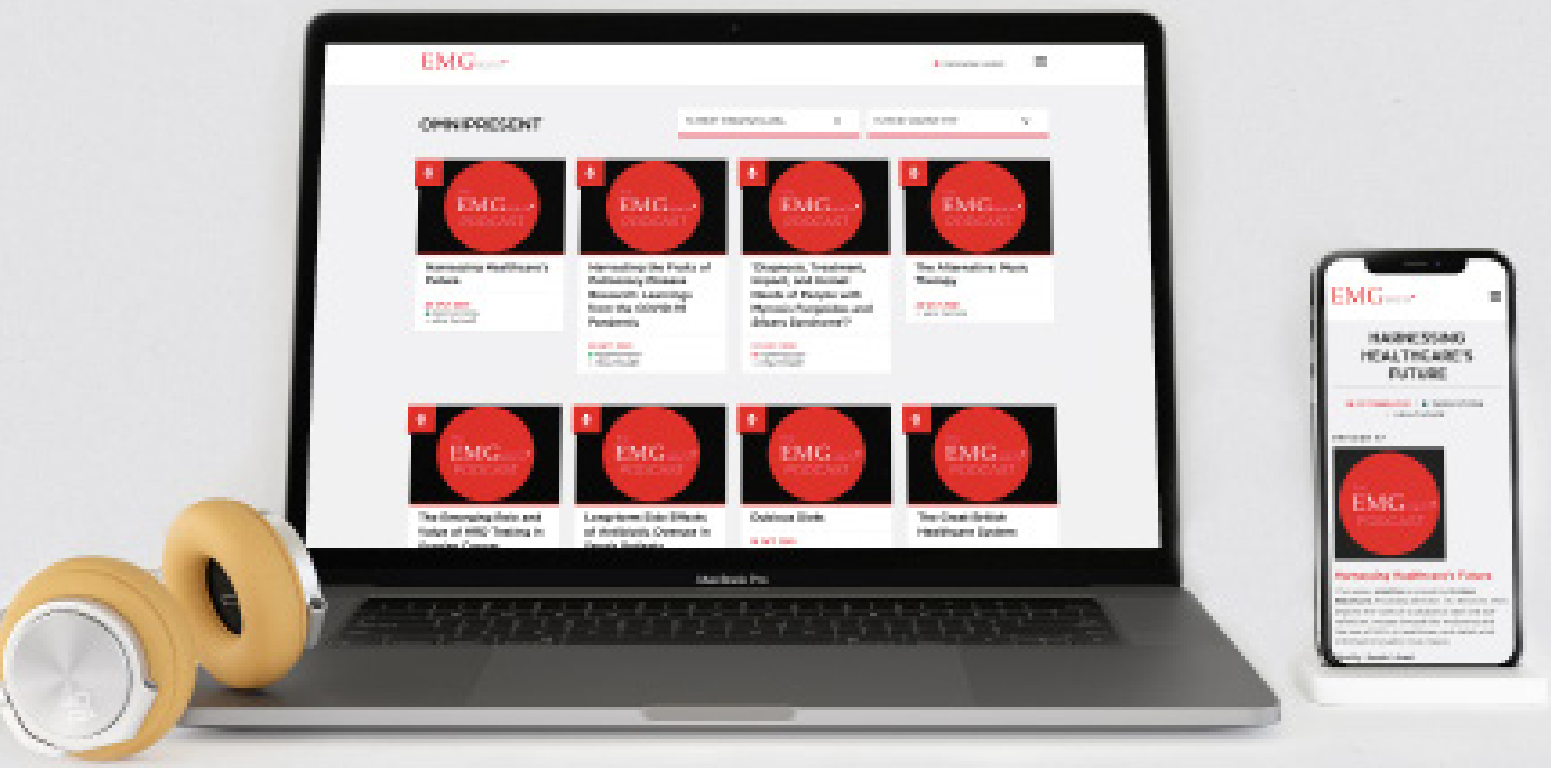
In addition to reporting on the EASD annual meeting, there are several interesting peer-reviewed articles within this journal, the editor's pick about disorders of gastrointestinal motility in diabetes is one not to miss. Other expertly written articles explore screening for heart failure in diabetes, identifying the socio-demographic determinants of attendance at diabetes education centres, and the progression of diabetic retinopathy in patients with COVID-19.

We are grateful for the inspiring interviewees, Awadhesh Kumar Singh and Alison McNeilly, who kindly shared their insights in diabetes treatment, personal accomplishments and current research. Additionally, we are also grateful for interviewing Bart Torbeyns and Chantal Mathieu who participated in this year's EASD annual meeting and shared their objectives, priorities, and personal achievements.

Finally, I would like to thank the Editorial Board, authors, and you, the readers, for your loyalty, as we continue to be the go-to place for healthcare professionals. We hope you enjoy reading our latest issue of *EMJ Diabetes*.

Spencer Gore

Chief Executive Officer, EMG-Health



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Foreword

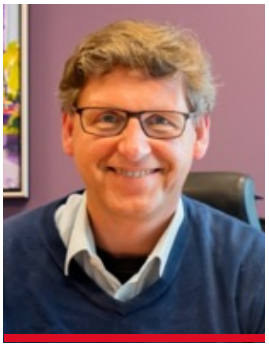
Dear Colleagues,

It is my pleasure to welcome you to *EMJ Diabetes 9.1*, which is dedicated to the 57th European Association for the Study of Diabetes (EASD) Virtual Meeting 2021. The continuing COVID-19 pandemic necessitated, as in 2020, a virtual meeting, but hopefully next year's meeting will take place in a hybrid format. Nevertheless, the organisers did a great job in presenting the latest news in diabetes. Impressive scientific progress was reported.

Among the wealth of science presented, I was particularly impressed by the EMPEROR-Preserved trial, which reported on the effectiveness of empagliflozin, a sodium-glucose co-transporter-2 inhibitor, in people with heart failure with preserved ejection fraction, regardless of the presence of diabetes. The data accumulated showed that glucagon-like pepitde-1 agonists and so-called twincretins (dual agonists of glucagon-like pepitde-1 and gastric inhibitory polypeptide receptors) are effective not only in reducing hyperglycaemia but also in enhancing weight loss.

Precision medicine in diabetes is gaining ground. In regard to diagnosis, distinguishing monogenic diabetes (e.g., the different types of maturity onset diabetes of the young) from 'common' Type 1 or Type 2 diabetes mellitus is now well-established. Precision treatment is less advanced, but the TriMaster trial reported that responses to a dipeptidyl peptidase-4 inhibitor, a sodium-glucose co-transporter-1 agonist, or a thiazolidinedione in patients who have suboptimal glycaemic control on dual therapy with metformin and a sulphonylurea can, to some extent, be predicted by routinely available variables such as age, sex, BMI, and estimated glomerular filtration rate.

I hope you enjoy this issue of *EMJ Diabetes*, and I wish you continuing strength and endurance in these difficult times.



Coen Stehouwer

Professor and Chair, Department of Internal Medicine, Maastricht University Medical Centre+, The Netherlands

Congress Review

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

Location: EASD 2021 Congress

Date: 27th September–1st October 2021

Citation: EMJ Diabet. 2021;9[1]:11-22. Congress Review.

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:

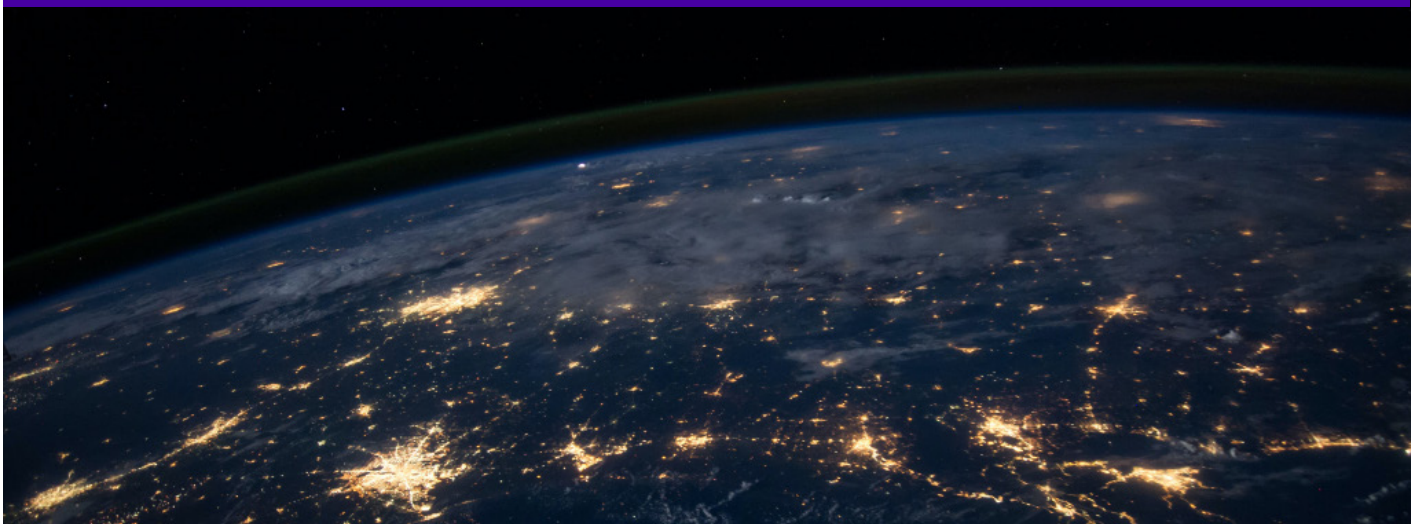
100 years of insulin. Several sessions were focused on the celebration of this life-saving treatment and its modernisation in recent years as well as the announcement of two new insulin-focused award programmes, born from the collaboration of the European Foundation for the Study of Diabetes (EFSD) and 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.

"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."



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." ■

"Big data on millions of patients have been used to develop precision medicine in patients with T2DM."

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. ■

"AI is just as accurate at detecting DR in fundus images as humans, which makes it an extremely beneficial tool for clinical use."

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.

"...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."

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.

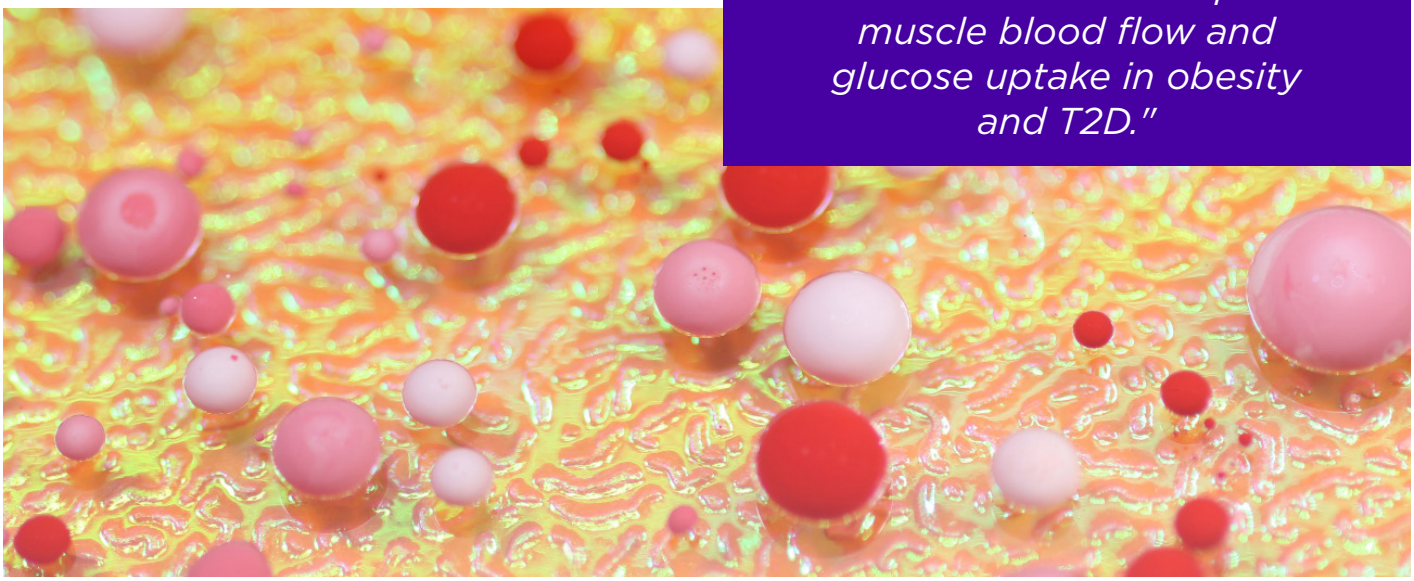
When the body is healthy, the vasodilatory actions of PVAT are mediated by the hormone adiponectin and the exercise-activated protein AMP-activated protein kinase. Obesity causes the vascular functions of PVAT to change from vasodilation to vasoconstriction. Obesity results in an accumulation of PVAT,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

"The data provide proof of concept that inflammation of PVAT in muscle impairs muscle blood flow and glucose uptake in obesity and T2D."



"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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"Rare variants... are a goldmine for Type 2 diabetes pathophysiology and precision medicine."

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." ■

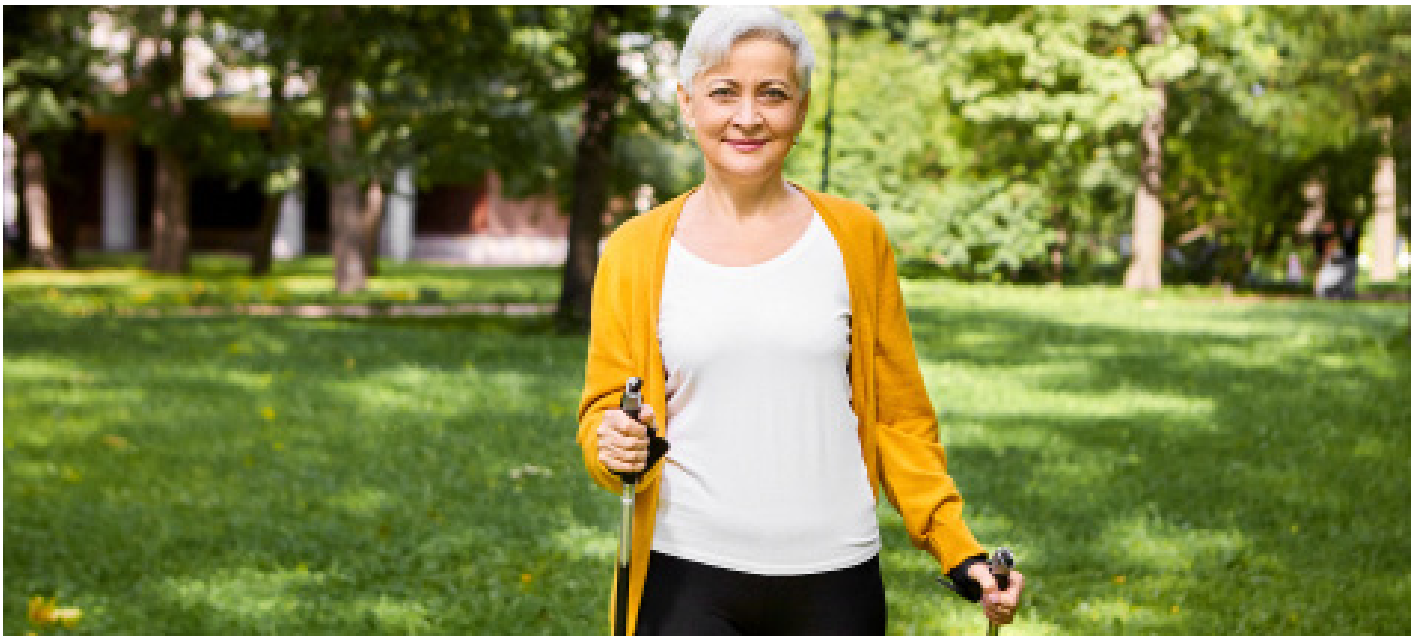
Advances to the Understanding of Non-coding RNA and Skeletal Muscle Metabolism

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. ■

"There are currently no drugs available that directly target skeletal muscle insulin sensitivity," identifying the gap in treatment avenues.



"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. ■

"JAK1 inhibitors have shown promising results in Type 1 diabetic mouse models and TYK2 inhibitors are being tested in mouse and in vitro models."

Current Guidelines on Type 2 Diabetes Management

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IN A SESSION at the 2021 European Association for the Study of Diabetes (EASD) congress, speakers discussed the current guidelines on Type 2 diabetes management. The Kidney Disease: Improving Global Outcomes (KDIGO) and European Society of Cardiology (ESC)/EASD guidelines were closely compared and analysed by the first speaker. The second speaker shared new clinical studies and how they may shape guidelines in the future.

COMPARING CURRENT GUIDELINES

Diabetes is predicted to affect 5.5 million individuals by 2030 in the UK alone. There is no known cure for this increasingly common condition and current treatment includes medication, weight loss surgery, and lifestyle changes. Guidelines put in place by societies and organisations help healthcare professionals make informed decisions on appropriate management plans. In the 57th EASD Congress this year, speakers discussed the current guidelines on Type 2 diabetes management and shared the latest clinical trials, explaining how they might shape guidelines in the future.

Christoph Wanner, Division of Nephrology, University Clinic Wurzburg, Germany, opened the session by reviewing the current guidelines on diabetes management, particularly the KDIGO and ESC/EASD guidelines. Guideline recommendations are classified based on the level of evidence behind them. Grading ranges from Class I to Class III, where Class I corresponds to recommended guidelines based on evidence from randomised clinical trials or meta-analyses, and Class III corresponds to not recommended guidelines, which are based on evidence from consensus of opinion or small studies. The recommendation for each class has been carefully worded to indicate how strongly the advice should be taken. Wanner compared these different guidelines to see if they were consistent and to identify any discrepancies.

The speaker shared some specific examples of guidelines that have been widely adopted, notably the recommendation that patients with diabetes should be screened annually for kidney disease by assessing the estimated glomerular filtration rate (eGFR) and urinary albumin to creatinine ratio. This recommendation is universal across all three sets of guidelines, and all physicians adopt this recommendation.

The most important components of the KDIGO guidelines include comprehensive care, glycaemic monitoring and targets, lifestyle interventions, antihyperglycaemic therapies, and approaches to

management. Comprehensive care can be divided into three sections: fundamental standard of care for all patients, most prescribed medication, and finally, antiplatelet therapies. The first section includes smoking cessation, nutrition, exercise, lipid management, glycaemic control, and blood pressure control. This fundamental standard of care is universally accepted in all guidelines. Overall, the guidelines concerning comprehensive care agree with each other. However, there are instances where the guidelines do not unanimously agree. This discrepancy occurs regarding another component of the KDIGO guidelines: glycaemic monitoring and targets.

"Wanner emphasised how the guidelines need to be more consistent and expressed his enthusiasm for the new guidelines expected in October."

The EASD guidelines state that targeting HbA1C (<7% OR <53 mmol/mol) is recommended to decrease microvascular complications in patients with diabetes as Class IA. However, interestingly, there is a slight deviation in the KDIGO guidelines, as they class this recommendation as IC. The KDIGO guidelines state that they recommend an individualised HbA1C target ranging from <6.5% to <8.0% in patients with diabetes and non-dialysis-dependent chronic kidney disease (CKD). So, not only does this KDIGO guideline have a different class compared to the EASD guideline, but they also have a marginally different HbA1C range.

Additionally, Wanner discussed lifestyle interventions for Type 2 diabetes management and the importance of measuring protein intake, salt intake, and physical activity in patients. However, this is not solidly recommended across all guidelines and has a low grading in class. Wanner implied that this may be because related trials are old and not as controlled as they are today. Lastly, another example where the guidelines vary is regarding anti-glycaemic therapies in patients with diabetes and CKD. The KDIGO guidelines recommend that metformin should be used as a first-line treatment for hyperglycaemia in Type 2 diabetes where the eGFR is >30 mL. In comparison, other guidelines recommend including sodium–glucose co-transporter-2 (SGLT2) inhibitors in the treatment regimen. This is another example of how recommendations vary between different guidelines.

Wanner explained that treatment is determined by patient preferences, comorbidities, eGFR, and cost. He described how different organisations class guidelines differently due to varying evidence. In a closing statement, Wanner emphasised how the guidelines need to be more consistent and expressed his enthusiasm for the new guidelines expected in October.

UPDATED EVIDENCE IN SGLT2 INHIBITORS AND MINERALOCORTICOID RECEPTOR ANTAGONISTS SHAPING FUTURE GUIDELINES

Hiddo Heerspink, University Medical Centre Groningen, Netherlands, shared the latest data from clinical trials on SGLT2 inhibitors and mineralocorticoid receptor antagonists (MRA). Heerspink expressed his belief that guidelines need to be fluid and will continue to change in the future especially as new clinical trials take place.

Currently, the KDIGO guidelines recommend the use of metformin and SGLT2 inhibitors in the treatment of Type 2 diabetes in CKD. From clinical trials, it is now well-known that SGLT2 inhibitors can improve cardiovascular and kidney outcomes, although this was not always thought to be the case. Initially, SGLT2 inhibitors were not recommended due to their low efficacy. However, evidence from the CREDENCE trial[1] showed that these drugs are effective, even in individuals with a low eGFR. The trial demonstrated that the SGLT2 inhibitor canagliflozin reduced the risk of the primary outcome by 30%. Comparing the efficacy of SGLT2 inhibitors with a placebo, renal outcomes were improved at every dose. However, despite reducing the relative risk, there are still numerous patients who progress to end-stage kidney disease after 2.9 years and the primary endpoint remains the same, emphasising the importance of additional treatments.

Since the results of the CREDENCE trial, many scientists have been interested in the mechanism behind canagliflozin. SGLT2 is overexpressed

in patients with Type 2 diabetes, resulting in glucose reabsorption. However, with more glucose reabsorption in the nephrons, there is also more sodium ion reabsorption. As a result, fewer sodium ions are delivered to the macular densa and, consequently, this reduces the release of adenosine, promotes vasodilation of the afferent arteriole, leading to intraglomerular pressure and hyperfiltration seen in early diabetes. Inhibiting SGLT2 to restore the tubuloglomerular feedback would reduce glomerular hyperfiltration and preserve kidney function.

Heerspink shared another study, the DAPA-CKD trial,[2] that tested the effect of dapagliflozin on CKD in patients. The results had a similar positive outcome to the CREDENCE trial, and dapagliflozin reduced the primary and secondary outcomes such as cardiovascular disease. Following this, the speaker evaluated the safety profile of dapagliflozin compared to the placebo. Results showed that more patients with diabetes experienced adverse events and were more likely to discontinue treatment. Surprisingly, dapagliflozin had a greater effect on females than males, but Heerspink cautioned that this could be a chance finding and larger studies need to be performed.

Moving on, Heerspink reviewed MRAs in Type 2 diabetes, specifically finerenone, which is a novel non-steroidal receptor antagonist. Various factors such as a high-salt diet or oxidative stress can cause activation of receptors, which leads to activation of inflammatory and fibrotic factors leading to renal damage. Blocking the receptors to prevent the binding of the ligand to the receptor would prevent these damaging outcomes. Two large clinical trials, FIDELIO DKD and DIGARD DKD, developed receptor antagonists for blocking this cell signalling pathway. The combined data sets results of 13,000 patients, named FIDELITY, showed that finerenone significantly reduced the risk of the kidney composite outcome by 23% and reduced cardiovascular risk by 14%.

"SGLT2 and MRA are effective therapies to reduce renal failure in patients with Type 2 diabetes"

In his concluding remarks, Heerspink shared his suggestion that finerenone and SGLT2 could be combined as one treatment in the future due to their varying benefits. Finally, he concluded that SGLT2 and MRA are effective therapies to reduce renal failure in patients with Type 2 diabetes and expressed his belief that it is important to implement these new findings into future guidelines and clinical practice.

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Postprandial Glycaemic Excursions: Implications for Health and Effects of Non-pharmacological Interventions

This symposium took place on 30th September 2021, as part of the virtual European Association for the Study of Diabetes (EASD) Annual Meeting 2021

Chairperson: Bo Ahrén[1]

Speakers: Louis Monnier,[2] Bo Ahrén

1. Lund University, Sweden
2. University of Montpellier, France

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Meeting Summary

'The Ominous Quartet' represents four glycaemic disorders at the centre of cardiovascular diseases in diabetes, including ambient hyperglycaemia, glycaemic variability (GV), postprandial glucose (PPG) excursions, and hypoglycaemic episodes. It is important to understand the interrelationship between these disorders, targets and thresholds for monitoring purposes, and impact on cardiovascular outcomes. Louis Monnier's talk focused on PPG and GV. There is evidence that PPG excursions are responsible for adverse outcomes. GV could be responsible for adverse outcomes as short-term GV is strongly associated with the occurrence of hypoglycaemic episodes, which in turn leads to adverse outcomes. Therefore, both PPG excursions and GV should be targeted by therapeutic interventions. Pharmacological treatment can reduce PPG excursions by delaying gastric emptying, diminishing hepatic glucose output through reducing glucagon, and reducing glucose absorption from the gut. However, as it is important to reduce both the duration and magnitude of PPG excursions, non-pharmacological interventions are also required to achieve recommended targets. Bo Ahrén focused on non-pharmaceutical interventions for PPG management, particularly the use of whey protein (WP).

Health Risks Associated with Elevated Postprandial Glucose or Increased Glycaemic Variability

Louis Monnier

Monnier, University of Montpellier, France, opened his talk by mentioning 'The Ominous Quartet': four glycaemic disorders at the centre of cardiovascular diseases in diabetes. These include chronic/ambient hyperglycaemia, GV, PPG excursions, and hypoglycaemic episodes. Ambient hyperglycaemia and hypoglycaemia have a proven negative impact on cardiovascular outcomes.[1-4] A 1% reduction in haemoglobin A1c (HbA1c), a marker of sustained glucose exposure, results in a 20% reduction in cardiovascular disease risk. Hypoglycaemia enhances platelet aggregation and has pro-arrhythmic effects. However, whether PPG excursions and GV result in adverse outcomes requires further discussion. Monnier also emphasised the importance of defining thresholds and targets in these glycaemic disorders for monitoring and control purposes. For ambient hyperglycaemia, HbA1c should be <7% and time in range >70%. The alert threshold for hypoglycaemia has been defined at 70 mg/dL by the International Hypoglycaemia Study Group (IHSG), with significant hypoglycaemia recorded at <54 mg/dL.[5,6] Threshold and targets for GV and PPG excursions are less clear.

Postprandial Hyperglycaemic Excursions

In healthy individuals, the absorption of carbohydrates following a meal results in an increase in blood glucose, which is tightly controlled by the insulin response and reduction in glucagon secretion. This period, termed the postprandial state, lasts 4–5 hours, followed by the post-absorptive period, which lasts for 6–8 hours, during which blood glucose levels are maintained at a near-normal level by the hydrolysis of glycogen stored in the liver. In the fasting state, defined as 10 hours after meal consumption, the liver produces glucose from lactate and alanine through gluconeogenesis to maintain glucose levels. Monnier noted that an individual spends "half of the time in the postprandial state and only 2 hours in the fasting state at the end of the nocturnal period, emphasising the importance of the postprandial state."[7]

The degree of insulin secretion, insulin sensitivity, and metabolic consequences differ between individuals with normoglycaemia, impaired glucose tolerance (IGT), and Type 2 diabetes. In healthy individuals, relative insulin secretion is 80–100% compared with 50–80% and <50% in those with impaired glucose tolerance and Type 2 diabetes, respectively. Consequently, insulin sensitivity decreases while insulin resistance increases, both in the liver and peripherally, causing a diminished hepatic insulin sensitivity and sustained overproduction of glucose that ultimately presents as fasting and postprandial hyperglycaemia and Type 2 diabetes. It has been demonstrated that in normoglycaemia, peak glucose concentration occurs 30 minutes after a meal compared with 60–120 minutes in Type 2 diabetes.[8] Furthermore, evidence indicates that peak postprandial glucose usually occurs after breakfast as hepatic glucose production is governed by the circadian rhythm and is at its maximum at the time of breakfast.[9,10] Thus, the ideal timepoint to check postprandial glycaemia in patients with diabetes is 1–2 hours post-breakfast.

The threshold for defining PPG excursions is important. A strong correlation is evident between HbA1c and peak post-breakfast glucose, where an HbA1c of 7% corresponds to a peak post-breakfast glucose value of approximately 160 mg/dL.[9] Thus, maintaining an HbA1c <7% can help reduce the peak post-breakfast glucose to <160 mg/dL, the threshold recommended by the International Diabetes Federation (IDF). Reducing the peak post-breakfast glucose to <180 mg/dL, the threshold recommended by the American Diabetes Association (ADA), only ensures HbA1c levels <7.5%. Monnier noted that "the IDF recommendation may be preferable as it ensures an HbA1c below 7%."

PPG excursions may be responsible for adverse outcomes; Ceriello et al.[11] demonstrated a direct correlation between postprandial hyperglycaemia and production of nitrotyrosine, a marker of oxidative stress and contributor to the development of complications in Type 2 diabetes. Additionally, the absolute impact of postprandial glucose to HbA1c remained constant at approximately 1% across all

non-insulin-treated subjects with Type 2 diabetes and an HbA1c ≥6.8.[12] Thus, highlighting that PPG is the main contributor to overall hyperglycaemia in well-controlled subjects with Type 2 diabetes, whereas fasting hyperglycaemia is the primary contributor in individuals with advanced and poorly controlled Type 2 diabetes.[13]

Also under debate is the relationship between PPG excursions and GV. A strong positive correlation has been demonstrated between changes in PPG excursions (areas above pre-prandial glucose values [AUC_{PP}]) and changes in GV (mean amplitude of glycaemic excursion [MAGE]) from baseline to after 8 weeks of treatment with gliptins in patients with Type 2 diabetes (R^2=0.48; p<0.001), implicating that approximately 50% of GV is due to the PPG.[13]

Glycaemic Variability

Monnier discussed two main types of GV: short- and long-term variability. Short-term variability can be divided into two components: within-day and between-day glucose variability. The %GV (standard deviation of glucose/mean glucose) represents the best metric for evaluating GV. A %GV of 36% is the most suitable threshold to distinguish between stable and unstable glycaemia in diabetes.[14] Other metrics exist for estimating GV; however, Monnier noted that "most other metrics are too complex for clinical practice."

Whether GV has a role in adverse outcomes remains questionable. A strong correlation is evident between MAGE and the urinary excretion rate of isoprostanes, a marker of the activation of oxidative stress.[15] This implies that, at minimum, GV is associated with the activation of oxidative stress, a key player in diabetes complications. This was confirmed by Ceriello et al.,[16] who determined that fluctuations in blood glucose correlate to fluctuations in nitrotyrosine, another indicator of oxidative stress. Despite these indications, Monnier stated that "we have no strong evidence that GV is responsible for adverse outcomes." Numerous studies have, however, indicated that high GV is associated with risk of hypoglycaemic episodes.[14,17] Thus, there is an indirect relationship between GV and adverse outcomes, as hypoglycaemic episodes are responsible for adverse outcomes.

Therapeutic Implications

Monnier went on to discuss the therapeutic implications and emphasised that both PPG excursions and GV are equally important to reduce HbA1c, MAGE, and AUC_{PP}, as evidenced when individuals with Type 2 diabetes were treated with a combination of dipeptidyl peptidase-4 (DPP-4) inhibitor and metformin.[13] However, there are limitations with pharmacological agents. For example, the implementation of a basal insulin regimen in Type 2 diabetes results in a downward shift in the 24-hour glycaemic profile without any improvement in GV. Monnier noted the importance of reducing both the duration and magnitude of PPG excursions, which would also require non-pharmacological interventions.

In summary, while numerous conclusions can be made regarding the interrelationship between optimum blood glucose targets and impact on outcomes of the ominous quartet of glycaemic disorders, the IDF recommends PPG excursions be <160 mg/dL and measured after breakfast. With respect to short-term GV, Monnier et al.[18] demonstrated that %GV should be <36% and that 50% of GV is explained by PPG excursions. There is evidence that PPG excursions are responsible for adverse outcomes, but it is predominantly short-term GV that has been strongly associated with the occurrence of hypoglycaemic episodes and in turn leads to adverse outcomes. Non-pharmacological interventions are the first-line measures for controlling excessively high PPG excursions and GV. Pharmacological interventions can be further implemented when non-pharmacological interventions are insufficient. Non-pharmacological interventions must be added when pharmacological therapies have been used first and failed to achieve the recommended PPG excursions and GV targets.

Nonpharmacological Interventions for Postprandial Glucose Management

Bo Ahrén

Importance of Managing Postprandial Glucose in Type 2 Diabetes

Ahrén, Lund University, Sweden, opened his talk by highlighting the clinical importance of PPG and the subsequent need to develop therapeutic interventions to target this problem. He underscored the findings by Monnier et al.[18] demonstrating that in individuals with Type 2 diabetes treated with oral anti-hyperglycaemic agents alone and with an HbA1c <7.3%, the relative contributions of PPG and fasting plasma glucose (FPG) to HbA1c were >60% and <40%, respectively.[18] This emphasises the importance of targeting PPG with therapy to reduce HbA1c.[18] Furthermore, a prospective intervention trial found that only 64% of patients with FPG <5.5 mmol/L had an HbA1c <7%.[19] In contrast, 94% of patients with PPG <7.8 mmol/L had an HbA1c <7%. Decreases in PPG accounted for nearly twice as much of the reduction in HbA1c as did decreases in FPG. Thus, control of fasting hyperglycaemia is not sufficient for good glycaemic control, with control of postprandial hyperglycaemia essential for achieving recommended HbA1c goals.

Pharmacological Management of High Postprandial Glucose

Ahrén reiterated the importance of targeting both peak PPG after meal ingestion and duration of elevated PPG. PPG excursions can be managed by reducing overall glycaemia, specifically by delayed gastric emptying, reduced hepatic glucagon secretion, and decreased glucose absorption from the gut. Current medications target all the aforementioned approaches.

Glucagon-like peptide 1 (GLP-1) is a gut hormone that stimulates insulin secretion, inhibits glucagon secretion, delays gastric emptying, and reduces appetite. These effects together result in a reduction in FPG, PPG, and body weight. The reduction in PPG is achieved by reducing hepatic glucose outputs through inhibition of glucagon secretion together with a delay in gastric emptying.[20] GLP-1 forms the basis for incretin therapy (i.e., GLP-1 receptor agonists and DPP-4 inhibitors). The latter prevents the inactivation of GLP-1, thereby increasing endogenous levels of GLP-1.

A strong association is evident between gastric emptying time and PPG (r^2=0.4889; p=0.0018), emphasising the importance of delaying gastric emptying to lower PPG by a GLP-1 receptor agonist.[21] Shah et al.[22] showed that glucagon reduction is another mechanism to reduce PPG, which was confirmed by Ahrén et al.[23] who demonstrated that a reduction in glucagon by DPP-4 inhibition after 4 weeks of therapy correlated to improved glycaemia in subjects with Type 2 diabetes. This supports the role and importance of DPP-4 inhibitors as an intervention to reduce hepatic glucose output and reduce glucagon production. Another factor to target in intervention for PPG is to reduce glucose absorption; e.g., by inhibiting the enzyme α-glucosidase. The latter results in diminished glucose formation, leading to a delayed carbohydrate digestion, reduced rate of glucose absorption, and lower PPG; Hücking et al.[25] showed that acarbose, an α-glucosidase inhibitor, reduces PPG by 64% in Type 2 diabetes.[24,25] Finally, insulin lowers PPG by inhibiting glucagon and hepatic glucose output and enhancing glucose utilisation.

Non-pharmacological Management of High Postprandial Glucose

Ahrén noted that "pharmacological approaches, however, are not sufficient; non-pharmacological tools are also needed for the management of high PPG." Several nutraceuticals (i.e., food products that are non-specific biological therapies) have been developed and tested.[26] These are generally accessible and affordable; however, nutraceuticals have not been studied in as much detail as pharmaceuticals in Type 2 diabetes. Most studies have focused on insulin resistance and few studies on PPG.[27] There have been several clinical trials on the use of cinnamon; however, only with regards to HbA1c, fasting blood sugar, and body weight.[28] A Cochrane report concluded that there is insufficient evidence to support the use of cinnamon for diabetes.[29] A small number of studies on the use of blueberries also exist but no effect on PPG has been demonstrated.[30] Ahrén highlighted that the most convincing

effects have been seen with WP and mulberry leaf extracts.

Whey, the liquid remaining after milk has been curdled and strained, contains WP, which may be useful in diabetes. Animal studies have found marked suppression of PPG when WP was used in conjunction with glucose through the mechanisms of increased insulin and GLP-1, and inhibition of DPP-4.[31] These encouraging results led to a translational study in humans that also showed a reduction in PPG and increase in insulin and GLP-1 when WP was given before a meal, demonstrating the potential of a WP preload to manage PPG in Type 2 diabetes.[32] A similar conclusion was reached by Wu et al.[33] who showed that DPP-4 inhibition with vildagliptin augments the beneficial effects (reduction in PPG and increase in GLP-1) of WP. Further clinical studies have been conducted on WP given in different doses and at varying times ahead of a meal, and most have shown a reduction in PPG in Type 2 diabetes.[34-36] In addition, encouraging long-term effects of WP have been demonstrated, with a sustained reduction in PPG at 12 weeks.[37] The exact mechanism of action is not fully understood; however, leucine and isoleucine, but not valine branched-chain amino acids, contained in whey have been shown to reduce PPG.[38] Ahrén stated that what is known at present is that "WP, which is rich in branched-chain amino acids and bioactive peptides, stimulates the release of GLP-1 and other gut hormones, inhibits gut DPP-4, delays gastric emptying, stimulates insulin secretion, and reduces appetite, all of which contribute to a reduction in PPG, highlighting its potential benefit for the treatment of Type 2 diabetes."[39] However, limitations exist with traditional WP formulas to regulate PPG. These include the pre-meal timing as most studies have presented WP before a test meal challenge, which is less representative of free-living behaviours (i.e., compliance, forgetfulness, and the burden of planning ahead) and dosing, as evidence to date has primarily used large doses (20–50 g) of WP, entailing a significant caloric load. A novel formulation of WP, in the form of a microgel, has been developed, which allows for the use of highly concentrated WP to be given in small doses. A study that investigated the effects of very-low-dose pre-meal WP microgels in Type 2 diabetes showed a significant reduction in PPG, increased insulin levels, and increased GLP-1 levels compared to placebo.[40] These results support the use of WP microgel as a convenient pre-meal shot to improve the postprandial metabolic profile in Type 2 diabetes; however, longer-term studies are needed to understand the full translational metabolic impact of this novel WP microgel formulation.

Mulberry leaf extracts have a long history of use as traditional medicine and one component, 1-deoxynojirimycin (i.e., moranolin), has been shown to competitively inhibit α-glucosidase activity.[41-43] A double-blind, randomised, placebo-controlled crossover study showed that mulberry leaf extract (Reducose®; Phynova, Banbury, UK) significantly reduced PPG in healthy subjects compared to placebo.[44] A further study described a dose–response relationship such that the highest dose (500 mg) reduced PPG by 22%, whereas 250 mg only reduced PPG by 14%. At the lowest dose of 125 mg, no significant difference was observed with mulberry leaf extract compared to placebo.[45] A meta-analysis of the effects of general mulberry leaf extract on PPG showed a significant reduction by approximately 1 mmol/L in a pooled analysis of 114 subjects, and a sole study on mulberry leaf use in Type 2 diabetes showed a significant reduction in glucose levels.[46,47]

Ahrén concluded that PPG is an important target to achieve near or absolute normoglycaemia in Type 2 diabetes, with several pharmacological and non-pharmacological interventions for consideration: including insulin, GLP-1 receptor agonists, DPP-4 inhibitors, and α-glucosidase inhibitors; and nutraceuticals, WP, and mulberry leaf extracts, respectively, to reduce PPG. In particular, WP has shown clear benefits on PPG and a novel microgel formulation has the potential to allow for smaller loads to be taken.

Questions and Answers

Are data available regarding the effects of WP on patients with gestational diabetes?

A recent study from China published in August 2021 found a significant reduction in glycaemia in 60 patients with gestational diabetes given 25g WP 30 min prior to a meal.[48]

Is adherence an issue in terms of the need to take WP prior to a meal?

Adherence could be an issue if long-term administration prior to a meal is required. The microgel formulation could be an exciting new solution to avoid the adherence problem, as it can be given much closer in time to the meal with the same effect and a lower amount of whey is required. However, it has not yet been tested in a randomised manner.

Are there any recent studies regarding WP with updated conclusions on the effect on FPG, PPG, as well as HbA1c?

There are no recent data, but it will be important to conduct such studies.

Glycosylated plasma protein after breakfast has the same importance whatever the type of diet. Does it matter if a diet is, for example, higher in protein and lower in carbohydrates? Are there non-pharmacological interventions available for individuals with Type 1 diabetes?

The content of breakfast is different in various countries, but the amount of carbohydrate given at breakfast is similar (30g). With a low glycaemic index or the addition of supplements in the diet, it is important to add these especially at breakfast, particularly in Type 2, and maybe Type 1, diabetes. There are no studies using non-pharmacological treatments in Type 1 diabetes.

Is there potential to use Nestlé's WP microgel in different populations (i.e., pre-diabetes, Type 2, etc.)?

There is the option to use this product in different populations (e.g., gestational diabetes) as it has such a broad mechanism of action.

What impact does exercise have?

There have been no studies to assess this; however, exercise increases insulin sensitivity. Thus, adding a mechanism to reduce PPG following exercise would be extra beneficial.

"All disease begins in the gut" (Hippocrates). Is this true for glucose metabolism and disorders?

Incretins and the gut are important in Type 2 diabetes; however, the β cell (in the pancreas) is the centre stage.

What is the impact of WP on the gut microbiota?

There are ongoing studies to address this, but no conclusions have yet been reached.

How much WP does the microgel formulation contain compared to whey given in a different formulation?

Parallel studies have not been conducted, but whey from the microgel better reaches the site of action and thus has a better effect. The microgel is formulated by Nestlé.

Why do we consider PPG excursions have a direct deleterious effect on cardiovascular risk while the majority of data have demonstrated glycaemic control has an indirect effect on cardiovascular risk?

There is no direct evidence that PPG affects cardiovascular outcome; all evidence is indirect. A controlled randomised trial to demonstrate that postprandial or GV affects cardiovascular outcome would be very difficult to conduct.

To what degree does an elevated PPG level impact the microbiota?

It is unknown whether PPG excursions are deleterious for microvascular circulation or the microvascular system. A challenging study with a difficult design will be required to elucidate this.

Is the PPG limit of 180 mg/dL recommended by the ADA too high?

Yes, as this limit has been set for capillary blood glucose, which is slightly lower than plasma venous blood glucose. A capillary blood glucose of 180 mg/dL corresponds to a plasma venous blood glucose of 200 mg/dL. The IDF recommendation of 160 mg/dL is preferable.

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Abstract Reviews

Sharing late-breaking advancements from abstracts presented by key experts in the field of diabetes healthcare at the European Association for the Study of Diabetes (EASD) Congress 2021.

Both Gestational Diabetes Exposure and Maternal Methylome Interaction Impact Offspring Epigenetic Signature

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Keywords: Epigenetics, gestational diabetes, methylation.

Citation: EMJ Diabet. 2021;9[1]:34-36. Abstract Review No. AR1.

BACKGROUND AND AIMS

Gestational diabetes mellitus (GDM), defined as hyperglycaemia during pregnancy, is associated with an increased future offspring risk of insulin resistance and obesity later in life,[1] suggesting that hyperglycaemia exposure during pregnancy could have an adverse effect on the offspring. This could be explained by an epigenetic mechanism in response to GDM, however, this link remains inconclusive. Therefore, the authors sought to perform the largest epigenome-wide association study

(EWAS) using the Finnish Gestational Diabetes (FinnGeDi) prospective multicentre cohort[2] to investigate epigenetic changes associated with GDM exposure during pregnancy in both mothers and offspring.

MATERIALS AND METHODS

The authors designed a case-control study using a total of 536 offspring–mother pairs, of which 55% were exposed to GDM. DNA extracted from whole blood for the mothers and from cord blood for the offspring was subjected to methylation analysis using the Infinium MethylationEPIC (850K) arrays (Illumina, San Diego, California, USA). The authors performed three EWAS, adjusted for age, BMI, maternal weight gain, and cellular composition (blood) for mothers, and adjusted for sex, gestational weight, gestational week, and cellular composition (cord blood) for the offspring. EWAS was performed to identify differentially methylated sites associated with mothers and offspring, separately; shared methylation sites between mothers and offspring; and offspring-specific effects, adjusted for maternal methylation, to account for maternal methylation status.

RESULTS

The present study did not identify any false discovery rate (FDR) significant sites associated with mothers or offspring, separately, nor shared sites between mothers and offspring. For the offspring-specific effects, the authors adjusted for the maternal methylome to account for the impact of the maternal environment. The authors identified a single FDR-significant site associated with GDM exposure: a hypomethylation at the cg22790973 probe, located upstream of the transcription start site of the *TFCP2* gene.

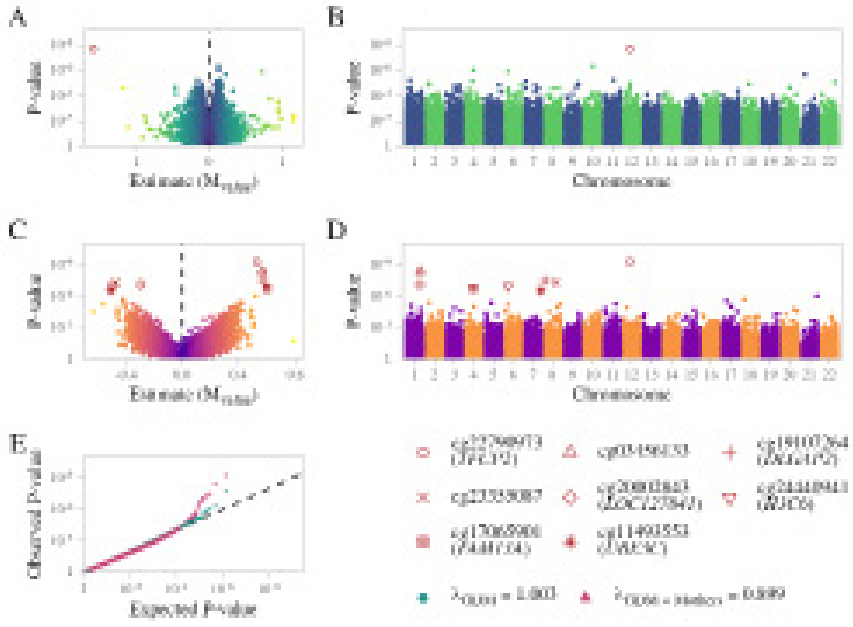

Figure 1: Summary results for EWAS associations.

A) Volcano plot and **B)** Manhattan plot for offspring differentially methylated sites associated with GDM exposure. **C)** Volcano plot and **D)** Manhattan plot of the GDM exposure interaction effect. **E)** Probability–probability plot of the GDM exposure main effect (green) and interaction term (red) on the methylation of the offspring. The black line illustrates the expected distribution.

GDM: gestational diabetes mellitus.

Furthermore, the study also included an interaction term in the model between GDM exposure and maternal methylation (i.e., GDM exposure in the context of the maternal methylation status) and identified a further seven CpG sites, of which the most significant was the same cg22790973 probe (*TFCP2*), in addition to cg03456133, cg24440941 (*H3C6*), cg20002843 (LOC127841), cg19107264, cg11493553 (*UBE3C*) and cg17065901 (*FAM13A*), and cg23355087 (*DLGAP2*) (Figure 1). Of relevance, *UBE3C* and *FAM13A* are reported susceptibility genes for Type 2 diabetes and BMI,[3,4] whereas the *DLGAP2* gene was associated with insulin sensitivity during pregnancy.[5]

CONCLUSION

In conclusion, the authors present a comprehensive study investigating the epigenetic associations in response to GDM exposure in mother–offspring pairs. The study data do not support robust epigenetic associations for mothers and offspring exposed to GDM during pregnancy; however, in terms of offspring-specific effects, the maternal environment may have a moderating effect. Therefore, the authors identified a novel perspective in maternal transmission, determined by not only GDM exposure, but also other factors, such as maternal epigenetic status, that establish epigenetic signatures in offspring. ■

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Continuous Glucose Monitoring with Multiple Daily Insulin Injections Improves Perinatal Outcomes in Females with Type 1 Diabetes Mellitus

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Keywords: Caesarean section, continuous glucose monitoring (CGM), continuous subcutaneous insulin infusion (CSII), hypoxia, large for gestational age (LGA), multiple daily insulin (MDI) injections, operative delivery, perinatal outcomes, self-monitoring of blood glucose (SMBG), Type 1 diabetes mellitus (T1DM).

Citation: EMJ Diabet. 2021;9[1]:37-39. Abstract Review No: AR2.

BACKGROUND AND AIMS

Females with Type 1 diabetes mellitus (T1DM) are at increased risk of adverse pregnancy outcomes.[1] Compared to the general population, there is a higher prevalence of congenital malformations, caesarean delivery, fetal macrosomia, large for gestational age (LGA) infants, pre-eclampsia, preterm delivery, and neonatal mortality.[2-4] Insulin regimens in pregnancy include multiple daily insulin (MDI) injections and continuous subcutaneous insulin infusion (CSII) via insulin pumps.[5-7] With advancing technologies, continuous glucose monitoring (CGM) is increasingly used in antenatal care at the expense of self-monitoring of blood glucose (SMBG).[8-10] The aim of the authors' study was to evaluate the effectiveness of different management options on perinatal and neonatal health outcomes.

MATERIALS AND METHODS

The authors performed a retrospective cohort study of 232 pregnant females with T1DM from a single university-affiliated perinatal centre in the Czech Republic. Females were divided into four groups, according to the mode of glucose monitoring and treatment: SMBG with MDI injections (SMBG+MDI), SMBG with CSII (SMBG+CSII), CGM with MDI injections (CGM+MDI), CGM with CSII (CGM+CSII). Data were retrieved from the electronic medical records.

RESULTS

Overall, 35.3% of females attended preconception counselling, with more females in CGM+CSII and less in the SMBG+MDI group (52.7% versus 18.2%; p=0.002). The authors observed lower mean HbA1c concentrations prior to conception in CGM+MDI and CGM+CSII groups (55.1±15.3 and 54.3±12.4, respectively; p=0.005). On univariate analysis, a higher rate of liveborn infants (97.0%; p=0.031) was observed in the CGM+MDI group. There was a higher incidence of operative delivery (caesarean section or instrumental vaginal delivery) in the SMBG+CSII (81.3%; p=0.048) group and fewer cases of LGA infants among females with CGM+MDI, but more in the CGM+CSII group (18.8% versus 48.1%; p=0.039). There were no cases of umbilical artery pH <7.15 in the CGM+MDI group (0; p=0.006). Perinatal results are summarised in Table 1. Logistic regression showed that CGM+MDI decreases the odds of operative delivery (odds ratio [OR]: 0.29; 95% confidence interval [CI]: 0.116–0.707; p=0.007), LGA (OR: 0.34; 95% CI: 0.124–0.923; p=0.034), and umbilical artery pH <7.15 (OR: 0.04; 95% CI: 0.002–0.790; p=0.034). The results did not reach statistical significance after adjusting for maternal age, BMI, diabetes compensation, and morbidity.

Table 1: Perinatal results for operative delivery, caesarean section, or instrumental vaginal delivery.

Outcome	SMBG+MDI	SMBG+CSII	CGM+MDI	CGM+CSII	Total	p
	n=47	n=75	n=32	n=54	n=208	
Liveborn infants (% of total)	47 (85.5%)	74 (83.1%)	32 (97.0%)	53 (96.4%)	206 (88.8%)	0.031
Pre-eclampsia/HELLP	5 (10.6%)	4 (5.3%)	3 (9.4%)	3 (5.6%)	14 (6.7%)	0.645
Intrahepatic cholestasis of pregnancy	1 (2.1%)	1 (1.3%)	2 (6.3%)	2 (3.7%)	6 (2.9%)	0.539
Gestational age at delivery (weeks, days)	38w1d±1w4d	38w0d±1w3d	38w0d±2w3d	38w1d±1w0d	38w1d±1w5d	0.949
Preterm birth <34 weeks	1 (2.1%)	3 (4.0%)	2 (6.3%)	1 (1.9%)	7 (3.4%)	0.679
Onset of delivery						
Spontaneous onset	20 (42.6%)	21 (28.0%)	13 (40.6%)	20 (37.0%)	74 (35.6%)	0.359
Labour induction	8 (17.0%)	15 (20.0%)	9 (28.1%)	8 (14.8%)	40 (19.2%)	
Elective C-section	19 (40.4%)	39 (52.0%)	10 (31.3%)	19 (35.2%)	87 (41.8%)	
Operative delivery	29 (61.7%)	61 (81.3%)	19 (59.4%)	38 (70.4%)	147 (70.7%)	0.048
Birthweight (g)	3,338±101	3,356±81	3,355±123	3,675±95	3,528±697	0.135
LGA infant	17 (36.2%)	29 (38.7%)	6 (18.8%)	26 (48.1%)	79 (38.0%)	0.039
SGA infant	1 (2.1%)	3 (4.0%)	2 (6.3%)	3 (5.6%)	9 (4.3%)	0.789
Respiratory distress	9 (19.1%)	10 (13.3%)	8 (25.0%)	14 (25.9%)	41 (19.7%)	0.241
Umbilical artery pH <7.15	10 (21.3%)	7 (9.3%)	0	11 (20.4%)	28 (13.5%)	0.006
Umbilical artery pH	7.22±0.02	7.26±0.01	7.27±0.02	7.22±0.01	7.25±0.09	0.056
Neonatal hypoglycaemia	22 (46.8%)	42 (56.0%)	18 (56.3%)	30 (55.6%)	112 (53.8%)	0.622
Phototherapy for neonatal jaundice	13 (27.7%)	17 (22.7%)	8 (25.9%)	14 (25.9%)	52 (25.0%)	0.945
Congenital malformations	4 (8.5%)	4 (5.3%)	2 (6.3%)	3 (5.6%)	13 (6.3%)	0.916
Diabetic fetopathy	2 (4.3%)	9 (12.0%)	1 (3.1%)	6 (11.1%)	18 (8.7%)	0.264
NICU admission	9 (19.1%)	12 (16.0%)	6 (18.8%)	8 (14.8%)	35 (16.8%)	0.942
Hospitalisation length after delivery (days)	5.5±2.3	6.9±4.3	8.1±12.5	7.2±9.2	6.9±7.3	0.469

CGM: continuous glucose monitoring; C-section: caesarean section; CSII: continuous subcutaneous insulin infusion; d: days; HELLP: haemolysis, elevated liver enzymes, and low platelet count syndrome; LGA: large for gestational age; MDI: multiple daily insulin; NICU: neonatal intensive care unit; SGA: small for gestational age; SMBG: self-monitoring of blood glucose; w: weeks.

CONCLUSION

The authors' study suggests that perinatal outcomes of females with T1DM are affected by the modality of glucose monitoring and insulin regimen. CGM together with MDI injections are associated with lower rates of operative delivery, LGA infants, and fetal hypoxia. ■

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Congress Interviews

This selection of interviews delves into the careers of Prof Chantal Mathieu and Bart Torbeyns, who spoke to EMJ of their roles in the EASD and EUDF, as well as providing key insights into the field of diabetes.

Chantal Mathieu

Professor of Medicine, Katholieke Universiteit Leuven, Belgium; Chair of Endocrinology, University Hospital Gasthuisberg Leuven, Belgium

Q1 What are the most exciting changes that have been made to the programme for the European Association for the Study of Diabetes (EASD) 2021 compared to last year's Congress?

The most exciting changes have actually been to the changes in format. The EASD this year is, again, a virtual meeting only. There's a couple of interesting changes in format. First of all, we are starting not at 8 a.m. in the morning, Central European Summer Time, but 10 a.m.; and it goes on until 5:30 p.m. or 6 p.m. This is so that people in different time zones don't have to get up at 3 in the morning or stay up until 3 at night at the end of each day.

There will be a wrap up by members of the Programme Committee, reviewing the highlights of the day. So, that's also an interesting format change. And we will have the Congress over the full 4 days. So, Tuesday until Friday.

We will have a whole interactive Congress track on e-Learning, so that individuals who participated in making e-Learning modules are available to take part in a discussion with the audience. There will be 11 of these interactive sessions, where speakers of these e-Learning modules will be open for questions from the audience. There will be a very short introduction by the speaker of a module, just setting the scene, and then 60–90 minutes of questions fired by the audience. That is very nice, too. It will be very interactive, very dynamic.

Lastly, and probably the biggest change, we do not have posters sessions. Instead of posters, we will have short, oral discussions. The whole mantra of the EASD virtual conference is interaction. So instead of having posters, everybody will have this short oral discussion where they will have 4–5 minutes for the introduction of their topic and

"the key word for this EASD Congress will be interactivity."

then be open for discussion. So, the key word for this EASD Congress will be interactivity. We have now 1.5 years of virtual meetings behind us and, honestly, I like virtual meetings because you can jump and skip and go if you know the session, But, the negative thing is that some of these meetings are very sterile and very, you know, flat, very one-dimensional, where the speaker gives us an often pre-recorded talk. So, in the EASD, we hope that most people will be live and then we build in a lot of interactivity. We hope people will appreciate that.

Q2 How much of an impact do you believe that the EASD Congress has both directly on endocrinologists and indirectly on patients?

We are the EASD but we realised, especially last year, with over 20,000 participants and looking at the geography of attendance, it is clear that we are more than the European Association. We had people from every continent from every country in the world, with the number one countries being Brazil and Mexico. There are endocrinologists but there's also physicians, you know, general medicine physicians. There's also quite a bit of primary care and we see cardiologists and nephrologists appearing. We have nurses and dietitians. So, the impact for people living with diabetes is not to be underestimated because, first of all, we are reaching the world and, also, we're not only reaching the niche endocrinologist. We're reaching all doctors who treat people with diabetes (endocrinologists but in some countries, they're called diabetologists and in others, physicians) with an interest in diabetes. It is global in geography but also global in the profile of doctors and we also have non-doctors.

Let's not forget that we also have a community of patients, or rather people living with diabetes, attending through a community called #dedoc°. As experts themselves in the disease, they're very, very active. They also attend the conference and have a booth in the meeting area. So, we're very conscious about our reach to people living with diabetes.

Normally, in a face-to-face meeting, we have about between 10,000–15,000 attendees. However, for 5 years before COVID-19 we already streamed our conference and, because of our charity status, 30 days after the end of the conference all materials that are in the virtual space are open and free for everybody, as is our EASD e-Learning website. You just have to register. Even without registering, you have a lot of material there for you. So, the global reach and, again, it's a choice. That way, our meeting and the e-Learning reaches tens of thousands of people worldwide.

Also, this year, we kept our registration fees very low, and 30 days after the end of the conference it is open for everybody. So, what we saw before COVID-19, when we had 10,000–15,000 attend our meeting live, we had many people attending virtually, and so we were not surprised about the 20,000 present last year. We wanted a very democratic registration rate and if you now go to the EASD website, you will see the number of people going. We are at 60,000 people visiting and looking at this material, and that's actually a choice. This year, we kept our registration fees very low and so we hope next year, even if the situation allows for us to go again face-to-face, but immediately design it as a hybrid meeting. Not just streaming what is happening face-to-face, but also having some virtual only tracks, so that people in the virtual space also feel very appreciated.

We're playing around with novel concepts. Whether we will have posters next year is unclear. It all depends on the success of the short oral presentations this year, whether people appreciate it or whether they don't like it. We'll see.

Q3 In your interview with *EMJ* last year, you mentioned your mission for the INNODIA project. What developments have been made in the last year regarding this project and its mission?

So, the years 2020 and 2021 were, because of COVID-19, not nice because we couldn't go to the labs, and we had to halt our recruitment of the newly diagnosed. People had to stop recruitment of first-degree relatives of people with Type 1 diabetes mellitus (T1DM), so it was

very bad. Fortunately, the stop on recruitment only lasted about 2 months, so by October 2020 we were back on the recruitment rates that we were before. So, if you ask me, the last year or so between my last interview and now, it has been an enormous year for INNODIA. First of all, due to the success of recruitment, we're now above predicted targets after 7 years. So, we're done actually; we could stop recruitment. We're not stopping. Secondly, all the labs are open again and all the basic research has also restarted.

The most important thing is that we have four clinical trials running. The first clinical trial started recruitment in November 2020, and now we have over 100 people screened in clinical trials running in INNODIA, and the sister project INNODIA Harvest. Over 45 people are now being treated in clinical trials in INNODIA and INNODIA Harvest. It's an amazing time. It has been very hard work for all the teams all over Europe and the UK. But it's just so exciting. We're very proud and, on the Thursday of the EASD Congress, we had a whole, dedicated symposium to INNODIA. First of all, our biological analysis of all the biomarkers that we have in INNODIA was showcased; second, we discussed the clinical trials.

Q4 You also briefly spoke about how there are key gaps in the literature in identifying individuals who are at risk of developing T1DM through biomarkers. Have any advancements has been made in this aspect of the field since your last interview?

Yes, and we presented some of our data at the EASD meeting this year, on higher-level analyses of data in INNODIA and we can come to new signatures for understanding T1DM. However, more and more we are moving to the screening of the general population. Many initiatives are happening throughout Europe, and also in the UK, and in INNODIA we've now just agreed to accept people with antibodies who come from general population screening because once you have antibodies for T1DM and all the other

"So, if you are a bright woman, please do not say: "I cannot have children, because I want a professional career with seven science papers."

biomarkers happening, it seems to be quite comparable whether you are a family member of a person with T1DM or not.

Q5

How do you think that sufferers of diabetes have been affected by the COVID-19 pandemic?

That's another very interesting question. We have discovered many people with T2DM when infected with COVID-19 who did not know they had diabetes. People with T2DM were sicker because of COVID-19. They were people who were more obese, had hypertension, etc., and also had T2DM. Whether COVID-19 precipitates T1DM is not clear at the moment. Most registries have not seen an epidemic of Type 1. Also, COVID-19 itself does not seem to be worse in people with T1DM; however, we see that people with T1DM are coming to hospitals and are also dying more, not because of COVID-19 but because of diabetic ketoacidosis and because of the not having the appropriate care for their diabetes.

Q6

There is an ever-growing interest in the use of artificial intelligence (AI) in many aspects of healthcare. Do you feel that there is room for AI in the field of diabetes?

Oh, yes. So, if you had asked me 'What is the biggest jump you have made in diabetes care in the last year?', I would have said AI, and specifically in T1DM. Since last year, we have actually seen a boom in the use of what we call smart pumps. These are sensor augmented pumps that are like hybrid closed loop systems, where sensors talk to the pumps and make the pumps adapt the basal rate and give corrections. That has proven to be an enormous success. Unfortunately, they are quite expensive but an enormous success in people with T1DM, and I'm sure that AI would also enter into T2DM. There is an initiative of the American Diabetes Association (ADA), which is also supported by EASD, looking at precision medicine in diabetes, and not only in the therapy but also in diagnosis, so I'm sure that AI and algorithms will enter to advise on therapy in T2DM.

Q7

Do you think that there are any other noteworthy innovations on the horizon that could positively impact the field other than AI?

Interestingly, there's a new product still being made to give you a once-weekly insulin injection. So, basically, it's insulin that only has to be injected once a week. There are several companies working on that, with two already in Phase III studies. Then there's the double incretin agonists which are combinations of a glucagon-like pepitde-1 receptor agonist and glucose-dependent insulinotropic polypeptide. So, tirzepatide, for instance is a very interesting product. So, a lot of new stuff is coming.

Q8

Earlier this year, INNODIA published an article earlier for the International Day of Women and Girls in Science. What advice you would give to women and girls who are striving for a career in the science Industry?

I think what is most important is that we are gender blind, and I never care if somebody is male or female when I hire them, but we also have to acknowledge the choices that people make. If people choose to take time off to spend with their children and work part-time, etc., we need to respect it. And, unfortunately, there's the biological reality that females do not have a choice when they can have their children, and so girls and boys need to choose a career. What I mean by 'career' isn't only a professional career, but also personal career, where, if they feel happy having four children and want to spend time with these four children, I respect that. It may mean you will have to spread your professional career in a different way, but it doesn't make it less interesting.

So, if you are a bright female, please don't say: "I cannot have children, because I want a professional career with seven science papers." When you're 50, and you look back, you cannot change your mind. That's a biological reality and I don't like it when some of my peers, male or female, say: "You know girls need to go for science papers." Yes, but if the girl, or boy, chooses to have kids, it's not worth less. Unfortunately, you can only have them a certain time when and also,

not seeing your children grow up is not very nice. You cannot turn back the clock.

So, my advice to girls and boys is to choose what makes you happy. I respect everybody's choices, but girls shouldn't stop and say: "I cannot be a good scientist." Everybody can be a good scientist if you have the brains and the energy. And there is the possibility that you will spend all of your wage, like I did, on a cleaner, gardener, and babysitter, etc.

Q9 What has been your proudest achievement in your career?

In my whole career, my proudest achievement is the career of my junior collaborators. The fact that all of them now have bigger careers than I have means I trained them well. All of my PhD students, postdocs, and collaborators have got very nice careers in the government, with companies, or universities. I'm very proud of them. And, also, my clinical co-workers are now leaders in the field. That's my biggest achievement. And perhaps, also being able to make clinical and basic researchers in Europe, singing in harmony in INNODIA. That's not a small feat. So, I'm happy about that, too. ■

Bart Torbeyns

Executive Director, European Diabetes Forum (EUDF)

Q1 What initially sparked your interest in pursuing a career in medical affairs, and how did this lead you to the field of diabetes?

In my previous role, I worked in the Pharma and was in the industry for about 20 years, but I felt that by working in medical affairs, I was also working closely with people. By with people, I mean people with diabetes first of all, and also with disease experts. So, in a role such as this, I would say that it involves working both for the company, with commercial interests, and for the real world, which is the world of patients and physicians. Being a bit in between, testing what disease experts and patients think about your solutions, and bringing that back internally to the company was really interesting for me.

I was also involved in a lot of internal training. In the beginning of that role, I was working more with people with diabetes and physicians. Over time, I have also started to work more and more with payers, sick funds, and politicians. That was a natural evolution in my career.

Where I am now, I'm working more in what we call public affairs or lobbying. Still, today, I would say that in the European Diabetes Forum (EUDF), it is really important to actually be the catalyst, or the linking person between politicians and academics and researchers. And that's a lot of the work that I'm doing now; making sure that for instance, at the EASD conference, we successfully put three politicians and decision-makers in touch with researchers and clinicians. So, that's the evolution from medical affairs to where I am now.

Q2 Having been founded in 2018, what led to the formation of EUDF?

There are basically two reasons. The first one is that there are a lot of diabetes associations in Europe; associations with patients, primary care providers, researchers, diabetologists, and companies. The idea was to bring all of these associations together into one forum, which is, today, the EUDF. This brings value because you can exchange a lot of information in a structured way. There is the low hanging fruit that you can align on very practical things, like making sure we do not end up hosting symposia on the same date. But, more importantly, the EUDF unifies voices regarding some strategic topics that are common to all stakeholders. Once we agree on these strategic topics, we then define clear, common objectives.

Secondly, there is a real belief that, despite a lot of innovative advances in the medical field, whether it's medicines, solutions, or a way of treating people with diabetes, a lot of these advances do not translate to better outcomes for people with diabetes. So, if you look at mortality rates for people with diabetes today, it's not going down, which is frustrating.

On a more positive side, we have the understanding that we need to talk to policymakers and governments of countries much more so they can make the necessary changes that must take place.

So, the first reason for the setting up of the EUDF was for the unification of voices. Secondly, to ensure that research solutions and innovation all translate into policy actions. Overall, the EUDF aims to provide better outcomes for people with diabetes.

Q3 The mission of the EUDF is to improve the care for diabetes at a national level. Can you talk about the steps the EUDF are taking to achieve this?

I see different layers to this. First of all, most of the time we are working with European or

global institutions such as the World Health Organization (WHO), European Commission, European Parliament, and European Council. These European institutions have an impact at a national level, so when we are able to impact people working in these institutions, we can influence, inspire, and help different countries through, for example, sharing the best practices.

Another layer is, that we are an umbrella organisation, and many of our members have activities at country level. Of course, we inspire and motivate all members to be active at a country level.

The third layer is that we often involve national policymakers in our activities. From France, Belgium, Germany, or any other European country, we involve speakers.

The fourth layer is that we observe, with great interest, that some of the countries in Europe already have a national forum. This helps the implementation of topics at country level. The EUDF inspired countries like Belgium and Romania to set up their own country forum, which is quite effective as our role as the EUDF is limited in these countries. We are not responsible for organising these forums locally, but we try to demonstrate that working in a very inclusive matter and involving people with diabetes, primary care providers, specialty care providers, the diabetes industry, and research brings value to a country, in whatever format that they want to organise this. You can see that these countries are also very efficient, so I see different levels of impacting countries, from European inspiration to fostering more a national implementation in inclusive forums.

Q4 What changes have you brought into effect since being appointed Executive Director of the EUDF?

For the first few years, the EUDF was mainly run by volunteers, who were usually academic professors with very busy schedules, and supported by part-time consultancy. I was the first full-time professional employee in that respect. I was the first person brought in to organise things in a more professional or structured

"the first reason for the setting up of the EUDF would be for the unification of voices. Secondly, to ensure that research solutions and innovation all translate into policy actions."

way, even very basic things like establishing an agenda and ensuring effective internal and external communication.

We also developed membership proposals, both for non-governmental organisations and companies. So, the membership has grown from the founding four members to where we are now, with a total of 10 members and supporting collaborators. We have all of the relevant diabetes associations in Europe around the table, so, in a way, we feel like the family really is complete.

Recently, we formed three strategic forums that allows each of our members to delegate one or two experts to work on a specific topic. This has been the first time that we have really focused on content. We brought together subject matter experts in professionally facilitated meetings to work together towards common objectives and recommendations. This has been a key positive change.

The fourth pillar is the external engagement side, because often we speak to people with diabetes or specialists who are already convinced that diabetes is important and crucial. So, we developed an outreach programme to engage beyond the diabetes community. We are specifically targeting decision makers, politicians, and the media to ensure diabetes moves to the top of their agenda.

Overall, a big part of my job is about mobilising volunteers because everybody that works alongside me is a volunteer. As I already mentioned, the 45 experts across the three forums have busy careers in diabetes, and so they spend quite some time with me, sometimes in the evening, to work on this common goal. I have a lot of respect for them, and it is an important part of my job to make sure that these people are willing to contribute and to spend their time on the EUDF mission.

Q5 In what ways did the COVID-19 pandemic impact the EUDF and their mission?

The first way is probably a bit more dramatic than the second one. Recently, I saw a WHO report that clearly stated that 95% of people dying from COVID-19 have a non-communicable disease such as diabetes or a cardiovascular disease. Diabetes has been in the news a lot, but not necessarily in a positive light. A lot of patients who are affected by these non-communicable diseases were heavily and disproportionately affected by COVID-19, which shows that we need to work on non-communicable diseases and, more specifically, on diabetes. In a way, this shows that if we think about future threats, the people that have been hit today might be hit in the next pandemic. I'm referring to people who are more vulnerable with diseases like diabetes.

If you look at the three topics that we are prioritising, they are even more relevant than ever. To give an example: integrated care and the role of primary care. Now that we are nearly two years into the pandemic, it is clear that continuity of care is crucial for any patient. For patients with diabetes, it is crucial that they have a good general practitioner and nurse to ensure that their condition is well controlled.

Regarding our work on digitalisation, we work a lot on medical applications at the moment as well as telemonitoring in healthcare. Everybody knows that digitalisation has become more important, from online shopping to contacting friends; however, for patients with diabetes in many countries, the only way of getting in touch with their general practitioner or nurse was, for quite some time, through digital services. Patients with a sufficient level of digital literacy were able to keep their condition under control more effectively. The digitalisation of services was a solution in this period, which will certainly remain an integral part in the future provision of care.

Lastly, when you look at data and registries, everyone knows the daily rates of COVID-19 cases and hospitalisations, which was unseen before. We also have a good example with COVID-19 that having data, and a clear and updated registry at country level, allows us to adapt the behaviour of people, the treatment of patients, and informs and directs decision making of politicians . For example, in Belgium, the protocol is to vaccinate certain populations who are a high priority, including patients with diabetes. Without registries, we wouldn't know where to go. I think that the emergence of solid data, which we have seen in the pandemic, has allowed us to treat patients more effectively. Let's ensure that we also create solid diabetes registries in those countries that don't already have these data. And for those countries that have the data, let's ensure they use these to act and improve the outcomes.

Q6 The recent EUDF Symposium presented at the 2021 EASD Congress on the topic of data usage to raise awareness in diabetes care. Could you tell us a bit about what areas are currently lacking in diabetes care?

We talked about raising awareness first, followed by initiating action. Some countries do not have good diabetes registries and so do not have good data. You cannot raise awareness in a country if you don't have the appropriate figures about the disease. You need to know your enemy. So, raising awareness, I would say, is a call to action for countries that do not have access to these registries; however, it's also about making sure that once you have the data, you really use it and let it speak for itself. Currently, 11% of the population has diabetes, but not everybody is convinced of the problem that diabetes is and will be in the future. Unfortunately, this is only going to increase over time. Having data available and making sure that policymakers have a clear idea about the size of the problem in their country is crucial for raising awareness.

"Currently, 11% of the population has diabetes, but not everybody is convinced of the problem that diabetes is and will be in the future. Unfortunately, this is only going to increase over time"

In the session, we gave recommendations on how to set up good registries and ensure that the data is used effectively. This might seem obvious but we know that in many, many countries this is not happening, and the European Commission is also working on this issue. This session projected ideas of what we want to achieve, which is improvement in diabetes care. If you have data and you're able to detect, for instance, uncontrolled patients and high-risk patients, it seems obvious. However, we can do a better job in making sure that we use this level of granularity to also work to improve outcomes for these patients with diabetes. So, there was a call to action to evolve from a description of the situation to a real intervention.

Using data to improve clinical care is often referred to as primary use of the data. The secondary use of data by policy makers would be to make decisions on what is needed in a specific country based on solid facts and figures.

Overall, I would say that raising awareness and ensuring that the data we have available is put to good use are the two main areas currently lacking in diabetes care.

Q7 One of the EUDF's objectives is to "continuously improve and innovate diabetes care." How can we expect to see the field of diabetes progress in regard to innovative technology and digital care?

I believe that there is already a lot on the market in regard to digital care; however, in one way or another, healthcare still has a lot of room for further uptake of digital solutions compared to other areas where digitalisation is more advanced. I think that, in the coming years, it is important to ensure that there is an uptake of digital health solutions.

A lot of the solutions are probably still standalone and tackle a specific issue, so more integration may be seen as well. So not a standalone app but an app that can integrate into the electronic health record of physicians, which will be better connected to medicines, treatments, and management schemes.

I also expect that further integration of digital tools will allow people with diabetes to have more of an influence and open up more possibilities. Patients will have more influence over the way the care is delivered to them, for example, in regard to their appointments, as to their preference of digital or face-to-face appointments. Digitalisation will also be an enabler towards more personalised healthcare. Let's hope that these innovations will also benefit in the near future from more accessible reimbursement schemes, thereby improving the quality of patient care and increasing accessibility to a range of available treatment options.

Q8 Could you give us an overview of the EUDF strategic forums and how they impact both diabetes patients and diabetologists?

We have three forums, the first being data and registries. As I alluded to previously, with better use of data, patients can expect better treatment outcomes and improved self-management. Having good data is not only useful for physicians to make decisions, but also is valuable to inform patients with diabetes how to optimally manage their condition, which will increase quality of care.

Our second forum is focused on integrated care. Currently, there is still quite a lot of fragmentation between primary and secondary care, as well as with social care, so we work a lot on the concept of care continuity. This allows patients with diabetes to know exactly what they can expect from the whole team and process, being clear about shared goals and have access to all information. Hopefully, this will improve decision making and the overall management, so that physicians can really use their medical expertise at the right moment. Too often we hear of patients being referred too late or not at all, so I hope that this will also lead to a more proactive and co-ordinated approach, with advantages to both patients and physicians.

The third forum is about digitalisation and self-care. After certification and regulatory approval, we also focus on reimbursement as an incentive, which will allow patients to access certain treatments that may not usually be available to them. Both patients and healthcare professionals have expressed a need for better education on digital solutions, and this improvement in education will also increase the quality of care and lead to better outcomes for patients.

Q9 What are the key priorities for the EUDF in the coming years?

First of all, we are working with the three strategic forums to ensure that adequate policy recommendations are made for the diabetes community. One of our main priorities is to go further with what we are already doing, namely by evolving from description and recommendation to action and implementation. So first, ensuring that our members are on board with the recommendations that we are making, and that they are also thinking about what they can do to extend the impact of our goal. Second, I also wanted to mention the importance of going beyond the diabetes community to decision makers and politicians. Next year, we will further increase our efforts towards policy and decision makers, which will contribute to the implementation of our recommendations reaching a wider population. So, it's all about implementing and ensuring that we have the right partnerships. Let's work together and join forces! ■

Interviews

Awadhesh Kumar Singh and Alison McNeilly spoke to *EMJ* about what made them pursue careers in diabetes and how COVID-19 has impacted their work.

Featuring: Awadhesh Kumar Singh and Alison McNeilly.

Awadhesh Kumar Singh

Senior Consultant Endocrinologist and Diabetologist, GD Hospital and Diabetes Institute, Kolkata, West Bengal, India; Sun Valley Hospital and Diabetes Research Center, Guwahati, Assam, India

Q1

What initially sparked your interest in the field of diabetes?

More than two decades ago, during the 3-year course as a post-graduate trainee of internal medicine and working in the largest medical college of Asia, that too under a renowned diabetologist, I was exposed to handling an extremely busy diabetes clinic catering several hundred patients a day, with a limited backup supporting staff. I think this was the trigger for my keen interest in pursuing post-doctoral course in diabetes and endocrinology. Even during my undergraduate days, there was a notion that if you do not fully know how to treat diabetes and tuberculosis in India, you have not learnt anything about internal medicine. The field of diabetology was set to hold a great promise since a lot was left to be learnt about the complex pathophysiology including the management of Type 2 diabetes mellitus (T2DM).

Q2

Diabetes is an increasingly prevalent disease amongst the population. Have you seen much improvement in its management and treatment over the last few years?

India had the dubious distinction of diabetes capital of the world earlier and is still in race to remain as such, as projected in recent International Diabetes Federation (IDF) Diabetes Atlas.[1] Fortunately, modern pharmacotherapy has changed the entire landscape of T2DM management today. The last two decades have witnessed several newer classes of antihyperglycaemic agents (AHA) that has helped us in a great way to manage T2DM today. Besides being effective glucose lowering agents, some of these newer AHAs have shown a consistent beneficial effect on preventing long-term diabetes complications such as heart and kidney diseases, including prolonged survival in

people with T2DM. These convincing evidence with newer AHA has forced all major guidelines in the world to change the choice of using pharmacotherapy in T2DM in last couple of years, especially in a background cardiovascular and kidney diseases.

Q3

With over 100 publications to your name for research in diabetes and its treatment, what do you believe to be the current gap in the literature that merits greater attention?

While we have progressed substantially in the field of T2DM including its management over past two decades, as mentioned earlier, we still have miles to go. Several knowledge gaps exist in current literature. One of them that merits greater attention include risk stratification in Asians. We still lack a proper validated tool to risk stratify people with T2DM in Asia, despite knowing the heightened risk of cardiovascular and kidney diseases including premature death at younger age. This gets even more complicated by generalising the term 'Asians', which encompasses several distinct ethnic identities including East Asians, South Asians, migrant Asians, etc., who have a typically distinct genotypic, phenotypic, and psycho-socio-cultural differences. Second, while we all follow international diabetes guidelines that gets modified from time to time, based on the outcomes from the multinational studies, notably the representation of some ethnic groups is disproportionately low. Therefore, guidelines may not be generalisable. In my opinion, regional groups should modify guidelines based on their country-specific available evidence.

Q4

You have also co-authored numerous publications on the topic of COVID-19. How do you feel the field of diabetes has been impacted by the pandemic?

Widespread lockdown and forced closure of non-emergency outpatient departments during the COVID-19 pandemic gave me the opportunity to learn, research, revisit, write, and publish quite a few papers in relation to COVID-19. So much so that our initial few papers on COVID-19, written during the earlier part of pandemic, become one of the top cited papers in the world. Needless to say, each and every sector including research

in the field of diabetes got immensely effected. Several ongoing clinical trials in diabetes had to be prematurely stopped.

Q5 How did you acquire the leadership skills to carry out your role as Chairman of the World Congress of Diabetes, India, in 2018?

I have always been a keen learner, since my undergraduate days, and have closely followed my seniors in organising meetings and conferences. I have been immensely enthusiastic to organise and participate in all these conferences, given the opportunity. I have been a part of several academic organisations throughout my journey including our regional Integrated Diabetes and Endocrine Academy (IDEA) and national organisations such as the Research Society of Diabetes in India (RSSDI) and Endocrine Society of India (ESI), and each passing year of learning and experience has helped me to learn and acquire leadership and organisational skills. I am extremely overwhelmed to conduct the arguably largest physical diabetes meeting of the World Congress of Diabetes, India, 2018, conducted during pre-Covid era.

Q6 You have been involved in many Phase III and IV clinical trials for diabetes treatments. Are there currently any innovations on the horizon in the field of diabetes that you think are particularly noteworthy?

As I mentioned earlier, research in the field of diabetes has always been exceptionally ahead over other streams of medical science. There have always been something waiting in pipeline in the field of diabetes that needs a closer watch. Amongst many, the most-exciting and new kid on the block is a novel dual glucose-dependent insulinotropic polypeptide and glucagon-like pepitde-1 receptor agonist tirzepatide and once-weekly basal insulin icodec. As we all are celebrating 100 years since the discovery of insulin in 2021, we are still waiting for oral insulin for a long time. Glucose responsive insulin or smart insulin is what future holds as breakthrough in insulin segment.

Q7 In your recent publication 'Diabetes Monotherapies versus Metformin-Based Combination Therapy for the Treatment of Type 2 Diabetes', what were the main points that you were trying to deliver?

In this review, we analysed the evidence available from all randomised, head-to-head trials that reported the efficacy and safety outcomes with diabetes monotherapy versus metformin-based combination therapies. From the available evidence, it is apparent that a metformin-based combination therapy reduces HbA1c better than monotherapy with AHA. Amongst the metformin-based oral combinations, metformin plus sodium-glucose co-transporter-2 inhibitor (SGLT-2I) therapy appears to have the best HbA1c reduction, with a longer durability of glycaemic control without any apparent increase in hypoglycaemia or other adverse events other than genital tract infection (GTI). Interestingly, GTI was significantly less associated with metformin-SGLT-2I combination compared to the SGLT-2I monotherapy and this finding was quite new for me. We had some evidence earlier suggesting that combination of SGLT-2I with dipeptidyl peptidase-4 inhibitors had less GTI compared to SGLT-2I monotherapy.

Q8 What has been your proudest achievement throughout your career as an endocrinologist?

The opportunity and power to save lives in itself is the greatest honour for any medical professional. On the professional front, the delight and contentment after treating my patients, and to contribute to improving medical care in my country, is something that makes me immensely satisfied and proud each day. On the academic front, the delight of having contributed to science and research to high impacting, esteemed journals and to be included amongst the group of editors of the bible of endocrinology, the *Williams Textbook of Endocrinology* (2020), South Asian Edition, during the peak of the ragging COVID-19 pandemic, makes me immensely humbled. To know that I have played at least some role in encouraging and guiding budding diabetologist and lighting up a passion in them toward the subject makes me feel truly overwhelmed and satisfied.

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Alison McNeilly

Principle Investigator, Division of Systems Medicine, University of Dundee School of Medicine, UK

Q1

What initially interested you about diabetes that led you to pursue a career specialising in this therapeutic area?

I have always been interested in physiology and how the body works, and, during my PhD, I had the opportunity to work with models of glucose dysregulation. Many of us take the ability to control our blood glucose within a 'healthy euglycaemic' range for granted. It is only when things go wrong that we appreciate how complex this process is. My recent work has focused on Type 1 diabetes mellitus (T1DM), where individuals cannot produce their own insulin and rely on insulin replacement therapy. Although insulin therapy has revolutionised Type 1 and long duration Type 2 diabetes mellitus (T2DM) management, it is not without complications, with low blood glucose (hypoglycaemia) being a major barrier to glycaemic control. When most people think of diabetes, they think of the impact of high blood glucose (hyperglycaemia) on the body. However, individuals on insulin therapy often experience periods of very low blood glucose and fluctuations between high and low glucose can be very damaging to many organs such as the brain, heart, and vascular system. In my research, I am focusing on what causes this damage and how we can treat this.

Q2

You are a widely published researcher on the topic of diabetes. Do you think there are any common misconceptions held by both the general public and the research community about diabetes and diabetes treatment?

Yes, I think most people view diabetes as a single disease, but there are many different forms of diabetes, the most well-known being T1DM and T2DM. Historically, T1DM was a disease of the young, whereas T2DM was more common in middle age; however, this is not the case. For example, Theresa May, former Prime Minister of the UK, was diagnosed with T1DM in her 50s and, conversely, children are being diagnosed with T2DM, predominantly due to the link with obesity. Likewise, treatment differs between T1DM and T2DM. T2DM can be managed with changes in lifestyle and insulin sensitising drugs, and even reversed by weight loss. In contrast, there is no cure for T1DM, and individuals must rely on exogenous insulin therapy.

Q3

As a researcher specialising in the impact of hypoglycaemia on cognitive and vascular function, where can we expect to see the focus of your publications lie over the coming years?

Up until now, I have been focused on the impact of recurrent hypoglycaemia on cognition and peripheral vascular function, but now I want to combine the two fields. The brain is one of the most highly perfused organs in the body and relies on glucose carried in the bloodstream to function. Disruption of this vascular system supplying the brain can have catastrophic effects; for example, when someone has a stroke, the blood supply to the brain is cut off and part of the brain dies. I am investigating whether the cognitive complications that we see in those experiencing hypoglycaemia occur to changes in blood supply to particular parts of the brain or damage to the vessels within the brain. I am also keen to explore the inflammatory profile of the brain and have some interesting studies looking at the link between neuroinflammation and cognitive function.

Q4

Where do you perceive the gaps in the literature for diabetes and hypoglycaemia to lie, and what areas do you believe merit greater attention?

T1DM research is much less well researched than T2DM, primarily because only around 5–10% of the population diagnosed with diabetes have Type 1. However, hypoglycaemia is common in those with long-duration T2DM reliant on insulin therapy, and we see hypoglycaemia with sulfonylureas, especially in the elderly. The data generated from continuous glucose monitors will be highly informative and suggest that individuals are experiencing far more hypoglycaemic episodes than they thought. The long-term implications of repeated exposure to hypoglycaemia are of particular interest to our group.

Q5

What has been your proudest or most memorable moment as a member of the Hypo-RESOLVE consortium?

Hypo-RSEOLVE has been an amazing opportunity. Meeting and working with world experts in the field of hypoglycaemia research has given me a greater appreciation of the impact of hypoglycaemia on everyday life for those living with T1DM. Collaboration between research groups from all around Europe and the bi-directional communication between basic researchers and clinicians has enabled us to perform experiments that would not be possible working alone.

Q6

How do you believe the contemporary climate of the COVID-19 pandemic has impacted the field of diabetes research and treatment?

The COVID-19 pandemic has significantly impacted my work as our labs are based in a hospital and we could not come to work for nearly 4 months. All our teaching was held online, and it was hard not being with work colleagues that you usually see on a day-to-day basis. I am

"T1DM research is much less well researched than T2DM, primarily because only around 5–10% of the population diagnosed with diabetes have Type 1. "

relatively early on in my career, so having nearly 1.5 years where I could not start any long-term experiments for fear of another lockdown has been difficult. Grant funding for work that is non-COVID-19 related is also scarce as many charitable organisations do not have the funds available. It means more people are applying for fewer grants, so it is not a great time to be in science.

Q7

Your proposed concept, 'habituation to hypoglycaemia', has been explored as a potential treatment through dishabituation in rodent and clinical trials. Can you tell us about the current stage of research into this concept and whether this might be something we can expect to see used clinically?

This is an exciting area of research, and we have several studies on the go to look at the potential mechanisms that may contribute to the phenomenon of dishabituation. Although we demonstrated improvements in the counter-regulatory response to hypoglycaemia in rodents and the clinic and, crucially, improvements in symptom awareness in those with impaired awareness of hypoglycaemia, we do not know how long this effect will last. Furthermore, we would anticipate that you would habituate to the dishabituating stimulus if exposed to it repeatedly. We are currently performing rodent studies to look at both of these aspects, and our clinical fellow has some exciting news that we hope to publish shortly, so watch this space!

Q8

What are the most important shifts in focus that you have seen in the time you have spent within the field of diabetes research?

One of the first diabetes conferences I went to was almost entirely focused on the β-cell. I spoke in a session called 'Outside the Islet' as very few of us presented data on other aspects of the disease. There are now more groups looking at the complications of diabetes such as cardiovascular disease, cognition, and renal damage. Even within the Hypo-RESOLVE consortium, eight or nine work packages focus on different aspects of the disease, such as how hypoglycaemia impacts quality of life and the use of smart technology to improve glycaemic control. There seems to be a more holistic approach to treatment, with individuals being more involved in their care packages as it is clear that what works for one person may not work for another.

Q9

Are there any innovations on the horizon of diabetes research that you think are particularly exciting or noteworthy?

I think everyone will be focusing on generating an artificial pancreas using stem cell therapy as a potential 'cure' for diabetes. The closed-loop systems where the insulin pump and continuous glucose monitor communicate are becoming more common, and it will be interesting to follow these individuals and see if this system improves glycaemic control. If we can improve glycaemic control, the long-term complications associated with hypoglycaemia will hopefully be minimised. Finally, glucagon administration for recovery from severe hypoglycaemia is an area that is often overlooked. Many see glucagon as a last resort or find it challenging to administer, so the ability to inhale glucagon via the nasal passage would be a game-changer and would hopefully limit the complications associated with severe hypoglycaemia.

Q10

What advice would you have for an individual keen to pursue a career similar to your own?

I still love my job and would not want to do anything else. I have been lucky in that I found a great mentor who has always looked out for me. I've also had the opportunity to work with many amazing people and travel to many different countries. However, it is not an easy career, and you have to accept frequent knockbacks as paper and grant rejection. If you can cope with this, however, it makes the positives even better!

Metformin: Arguments for Maintaining its Position as First-Line Pharmacological Treatment in Type 2 Diabetes Mellitus

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CASE

A 62-year-old female was referred to her primary care physician for newly diagnosed Type 2 diabetes mellitus (T2DM). She was overweight (BMI: 29.1 kg/m^2) and had well-controlled hypertension and dyslipidaemia. She stopped smoking 5 months previously, after she had suffered a myocardial infarction. Her history was otherwise unremarkable. Glycated haemoglobin was 8.4% (68 mmol/mol); her estimated glomerular filtration rate was normal and there was no albuminuria. She was moderately physically active and tried to adhere to a healthy diet. She was not motivated to enter a weight-loss programme at this point. Her physician considered pharmacological treatment of her diabetes, especially as intensification of lifestyle changes in this patient would be difficult. How should this patient be advised?

'Good' versus 'less good' glycaemic control has been shown to reduce the incidence and progression of classic microvascular complications of diabetes (i.e., retinopathy, kidney disease, and polyneuropathy). These effects are widely held to be mostly independent of the way good glycaemic control is achieved, although this has not been formally demonstrated. However, good glycaemic control, at most, modestly reduces the incidence of macrovascular disease. Additionally, good glycaemic control has not convincingly been shown to reduce the incidence or progression of other complications of diabetes such as heart failure, late-life depression, and cognitive impairment, which may have mixed microvascular, macrovascular, and metabolic origins.

In this context, recent large cardiovascular and renal outcome trials have clearly shown that, in T2DM, sodium-glucose co-transporter-2 inhibitors (SGLT2i), and glucagon-like peptide-1 receptor agonists (GLP-1RA) reduce the incidence of cardiovascular events, heart failure, and kidney disease progression, especially in people at high cardiovascular risk. Additionally, such findings have been reported for multiple members of each drug class, notably for the SGLT2i empagliflozin, dapagliflozin, and canagliflozin; and for the GLP-1RA liraglutide, semaglutide, albiglutide, and dulaglutide.[1-3] It should be noted that the outcomes of these trials, even within one drug class, cannot be considered truly identical. The difficulty of deciding whether there is a 'class effect' is well illustrated by the VERTIS CV trial. This trial, which used ertugliflozin, did not show a reduction in major adverse cardiovascular outcomes, even

though the participants in this trial were at high cardiovascular risk.[4] Nevertheless, the fact that beneficial effects have been demonstrated for more than one drug in each class greatly increases confidence in the overall results.

Appropriately, the American Diabetes Association (ADA), together with the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC), have responded to these developments by issuing strong recommendations for the use of SGLT2i and GLP-1RA in people with T2DM at high cardiovascular risk.[1-3] Both guidelines recommend the use of these agents in people with T2DM and established atherosclerotic cardiovascular disease (CVD) or without established atherosclerotic CVD but deemed at high cardiovascular risk because of the presence of multiple other risk factors. Importantly, both guidelines recommend use of these agents regardless of the level of glycaemic control because these outcome trials did not target glycaemic control *per se*; because effects were by and large consistent across levels of glycaemia; and because effects appeared to be largely independent of the improvement of glycaemic control that is achieved by these agents.

However, a key difference between the recommendations by the ADA and the EASD on the one hand and the ESC on the other concerns the role of metformin. Briefly, the ADA and EASD continue to recommend metformin as first-line pharmacological treatment in people with T2DM, regardless of level of cardiovascular risk, whereas the ESC limits first-line use of metformin to people with T2DM with diabetes duration of up to 10 years and without other risk factors.[1-3] This paper will discuss the pros and cons of these diverging points of view.

In the trials on which the recommendations are based, metformin was usually prescribed as baseline therapy.[1-3] Therefore, a strict interpretation of these trials would argue in favour of continuing using metformin as baseline therapy. Against this, trial results appeared similar in users and non-users of metformin,[5] although this has not been evaluated in an appropriately designed (i.e., individual participant-level) meta-analysis. Non-users of metformin are a heterogeneous group[6] as non-use may be related to intolerance (probably a major factor), as well as to (perceived) contraindications such as a history of heart failure or reduced glomerular filtration rate. Therefore, and especially with regard to metformin intolerance, the conclusion that, in people with T2DM, SGLT2i, and GLP-1RA have effects that are in general independent of the background use of metformin rests on the assumption that people who are prescribed metformin but cannot tolerate it will not differ importantly from other people with respect to the effects SGLT2i and GLP-1RA. As the biological basis of metformin intolerance is not well understood, this assumption is difficult to test outside a cardiovascular outcome trial.

Against maintaining metformin as a first-line therapy is the argument that the evidence base for metformin, insofar as it is derived from randomised controlled trials, is not very strong. Some trials did find that metformin reduced the incidence of cardiovascular events,[7,8] but a meta-analysis of randomised controlled trials found 13 trials reporting on just 2,079 individuals with T2DM allocated to metformin and a similar number to comparison groups. Participants were mainly white, aged 65 years or less, overweight or obese, and with poor glycaemic control. All outcomes, with the exception of stroke, favoured metformin, but none achieved statistical significance.[9] The authors concluded that there remains uncertainty about whether metformin reduces risk of CVD in T2DM, and that this is mainly due to absence of evidence,[9] which, of course, should not be equated with evidence of absence.

In contrast, observational data overwhelmingly support the use of metformin. For example, a systematic review found that metformin users with T2DM had significantly lower all-cause mortality compared with people without diabetes (hazard ratio [HR]: 0.93; 95% confidence interval [CI]: 0.88–0.99) or people with diabetes receiving non-metformin therapies (HR: 0.72; 95% CI: 0.65–0.80), insulin (HR: 0.68; 95% CI: 0.63–0.75), or sulfonylurea (HR: 0.80; 95% CI: 0.66–0.97). Metformin users with T2DM also had a reduced incidence of cancer compared to people without diabetes (rate ratio: 0.94; 95% CI: 0.92–0.97) and of CVD compared with people with diabetes receiving non-metformin therapies (HR: 0.76; 95% CI: 0.66–0.87) or insulin (HR: 0.78; 95% CI: 0.73–0.83).[10]

The findings on cancer may be especially important.[11,12] Although cancer is not traditionally considered a complication of diabetes, people with diabetes are more likely to develop liver, pancreatic, endometrial, gallbladder, kidney, colorectal, bladder, and breast cancer.[12] A recent investigation using a nationally representative primary care database found that, in 2018, cancer had overtaken CVD as the leading cause of excess death associated with diabetes.[11] Thus, any anti-cancer effect of metformin may be of considerable importance. Indeed, a Phase III randomised placebo-controlled trial showed that 1 year of treatment with metformin reduced the recurrence of colorectal cancer precursors in 151 individuals without diabetes,[13] suggesting that metformin might have chemopreventive effects against cancer. Metformin might influence tumourigenesis, both indirectly, through the systemic reduction of insulin levels, and directly, via induction of the adenosine monophosphate-activated protein kinase (AMPK) pathway and inhibition of the mechanistic target of rapamycin (mTOR) pathway.[14,15] These effects obviously require further investigation, and a number of trials to test the anti-cancer effects of metformin are ongoing.[15]

In an ageing population, a further important consideration is metformin's potential preventive effects on cognitive impairment. Compared with normal glucose metabolism, T2DM is associated with a subtly but measurably worse cognitive performance and additionally with a 1·5-times increased risk of dementia.[16,17] Observational studies have quite consistently shown that use of metformin is associated with reduced risk of cognitive impairment and dementia.[15] These effects may again be related to adenosine monophosphate-activated protein kinase activation, through which metformin mimics the imbalance between energy supply and demand seen in fasting and exercise, thus activating pathways that reduce cellular stress.[15]

So how should the patient in the vignette above be advised? Metformin is a time-honoured option that may reduce CVD, cancer, and cognitive impairment. However, the cardiovascular effects of metformin remain a matter of controversy, and additional effects of metformin must be considered unproven. Additionally, starting with metformin monotherapy would deny the patient the cardiovascular benefits of a GLP-1RA or an SGLT2i for an undefined period of time. Conversely, starting treatment with a GLP-1RA or an SGLT2i would deny the patient any beneficial effects of metformin and, additionally, expose her to the unproven assumption that the effects of a GLP-1RA or an SGLT2i in T2DM are similar regardless of the use of metformin. Paradoxically, if this patient had presented with a glycated haemoglobin of 7.4% (57 mmol/mol), while having been treated with metformin for 3 months, further treatment advice (i.e., continue metformin and add a GLP-1RA or an SGLT2i) would not be controversial. Further treatment advice would also not be controversial if, in this scenario, the patient had presented with a glycated haemoglobin of 6.8% (51 mmol/mol), because, as mentioned before, the guidelines recommend use of a GLP-1RA or an SGLT2i regardless of level of glycaemic control.

Therefore, this patient should be advised to start combination treatment with metformin and a GLP-1RA or an SGLT2i. This recommendation is fully in line with the way GLP-1RA and SGLT2i were used in the trials on which the guidelines are based. Additionally, there is the possibility that such combination treatment will provide greater and more durable long-term benefit with respect to glycaemic control, as demonstrated for the combination of metformin and a dipeptidyl peptidase-4 inhibitor as compared with metformin monotherapy.[18] Finally, metformin may have anti-cancer effects and slow down cognitive impairment, which are exciting potential additional benefits.

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How to Manage Type 2 Diabetes Mellitus During the COVID-19 Pandemic: Let's Hear the Patient's Voice

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Abstract

Diabetes is one of the most significant comorbidities associated with COVID-19 susceptibility and severity, and recent statistics have identified that up to half of all individuals with COVID-19 have had diabetes. Over 90% of people with Type 2 diabetes mellitus are overweight or obese, and obesity itself increases the severity of COVID-19 and the risk of needing intensive care and ventilation. Careful glycaemic control improves outcomes for individuals with diabetes and also significantly reduces risks if they become infected with COVID-19. It is, therefore, essential that research focuses on effective ways in which to manage Type 2 diabetes mellitus during this global pandemic. What healthcare professionals focus their attention and resources on is also crucial to its niftiness and, considering that patient self-management is key to effective glycaemic control, it makes sense that healthcare practitioners call on the patient for some advice.

COMMENTARY

Diabetes is one of the most significant comorbidities associated with COVID-19 susceptibility and severity,[1] and recent statistics have identified that up to half of all individuals with COVID-19 have had diabetes.[2] Furthermore, over 90% of people with Type 2 diabetes mellitus (T2DM) are overweight or obese[3] and obesity itself increases the severity of COVID-19 and the risk of needing intensive care and ventilation.[4,5] Moreover, COVID-19 can potentially predispose individuals to severe illness and poorer disease outcomes as hyperglycaemia modulates immune and inflammatory responses.[6] Careful glycaemic control improves outcomes for individuals with diabetes and also significantly reduces risks if they become infected with COVID-19.[7] It is, therefore, essential that research focuses on effective ways in which to manage T2DM during this global pandemic. Current guidance for managing diabetes during COVID-19 recommends tight control of glucose levels with frequent monitoring,[8] alongside eating well, staying connected, and remaining active.[9] Although insulin and dipeptidyl peptidase 4 inhibitors are reported as safe for patients with diabetes and COVID-19, the evidence points to personalised adjustment to medication.[8] What healthcare professionals focus their attention and resources on is crucial to its niftiness and, considering that patient self-management is key to effective glycaemic control,[10] it makes sense that we call on the patient for some advice.

It is assumed that medical staff would be implicitly interested in the patient as a whole person living with a chronic disease. Moreover, patients with chronic illness tend to generate self-management strategies automatically as they learn to live with their illness.[11-13] This can be communicated to medical staff, which, in turn, can empower the patient and encourage a collaborative patient–staff relationship.[13] While it is clear that recent years have witnessed a slight shift in thinking within the field of medicine and healthcare, moving toward a more patient-centred approach to care,[14] the extent to which this shift has translated into practice remains questionable.

Indeed, on reviewing current literature on diabetes management, the weight still leans heavily toward what the physician is doing to manage the illness during COVID-19, with negligible reference to the voice of the patient. Patient-led pathways have been a topic for debate since the last millennium;[14,15] however, there is yet to be any real paradigm shift in the practical management of diabetes.

Moreover, supporting diabetes self-management to reduce the risk of complications is central to national policy.[16] However, the reality of managing this condition is complex and challenging in normal times, with individuals often not conforming to recommended self-management practices.[17,18] We therefore need to understand how the COVID-19 pandemic has affected self-management of T2DM, changes in illness and risk perceptions, and any links with coping strategies and outcomes, e.g., glycaemic control.

This information would provide understanding of changes in stress, wellbeing, resilience, and coping at this time and identify barriers and facilitators to effective self-management. In turn, enhancing known difficulties would provide understanding for key clinicians to use and adapt their approaches to assist the patient with self-managing their condition. Novel research using this fresh approach will provide a body of evidence and vital understanding of the specific needs of patients that can be used to develop support mechanisms and new management strategies for this vulnerable group during the current crisis and for future waves of the pandemic.[5,19]

It is vital that the effect of COVID-19 restrictions on self-management in T2DM is understood because this group generally experience poor health outcomes.[20,21] Moreover, up to half of those who test positive for COVID-19 have diabetes and are more vulnerable to critical effects and mortality compared with the general population.[22] Diabetes can often be difficult to self-manage but careful management and control significantly improves health outcomes,[2,18] not only when individuals have COVID-19 but also during more normal times. Now there is a unique opportunity to generate essential knowledge of how this patient group have self-managed their condition during a period of stress, isolation, and uncertainty. What can be learnt now will generate a core understanding of approaches to managing a condition that is doubling in prevalence every 20 years in the Western world.[22] These are lessons that can be applied nationally and internationally.

RESEARCH INTO THE PATIENT PERSPECTIVE

A multi-method research approach would be necessary to tackle this and fully appreciate how individuals self-manage and cope with T2DM during a global pandemic and the aftermath, as well as the influence that illness and risk perceptions play on their actions.

The authors propose that future research adopts a longitudinal approach to the collection of routine data from established clinical diabetes information systems to explore the effects of living with diabetes during a pandemic on glycaemic control. This way, key lessons can be learned from the patients themselves about how people with T2DM are supported to optimally self-manage their condition.

Furthermore, gaining a full appreciation of the difficulties, complexities, and effects of T2DM self-management during a pandemic from patients' perspectives would provide vital insight and understanding into how people self-manage. Comparing and contrasting those who have found self-management most challenging with those who appear the most resilient would generate information used to underpin support strategies and new approaches for key clinicians to assist with diabetes self-management for those most vulnerable to poorer health outcomes.

To gain a rich and insightful understanding about how the COVID-19 pandemic has affected

individuals with T2DM in terms of illness and risk perceptions, self-management, and glycaemic control, researchers should be asking patients to express their experiences with the following qualitative questions:

1. What were your perceptions of risk (of both COVID-19 and T2DM) during the COVID-19 pandemic?
2. How do these perceptions appear to have been affected by the pandemic?
3. How did you experience illness self-management during the COVID-19 pandemic?
4. How did you perceive the effects on your health and/or glycaemic control?
5. What improvements and/or deteriorations in your glycaemic control became apparent during the COVID-19 pandemic?
6. What factors do you consider to be most important in managing diabetes during a pandemic?
7. What decisions and/or changes did you make to your self-management routine during the COVID-19 pandemic?
8. What might healthcare providers do better to support patients and their families during a pandemic?
9. What strategies worked best for you in managing your diabetes during COVID-19?

It is important to explore influences on individual responses during the health crisis and identify sources of individual and collective resilience when listening to a patient. This would ascertain support needs during this and future waves of the pandemic (short-, medium-, and long-term). It will also determine what can be done now to equip societies and vulnerable groups for health emergencies in the future, which can then also be applied to those individuals who experience difficulties in normal times. A narrative approach to interviews would allow the individual experiences, which are the most significant, to emerge. Alongside narrative interviews, introspective methods can also be used to encourage self-examination and analysis to ensure that patients can tell their own story and explore how they have coped under pandemic-related stress. In turn, this can identify problems, actions, and motives. Quantitative methods can be utilised for analysing routine data relating to blood glucose control prior to and during the COVID-19 pandemic. This method would provide immediate and necessary information relating to the effects of the pandemic on glycaemic control and how this differs across population groups. Analysis of these available healthcare data would offer an objective portrayal of the consequences of the pandemic for people self-managing T2DM.

CONCLUDING REMARKS

Overall, the authors' opinion is one that hears the patient voice and speaks directly to patient-centred care. In many ways, the recent COVID-19 pandemic has permitted the patient to take ownership over their condition to a greater extent than may have been the case pre-COVID-19. However, it is certainly time that healthcare professionals fully engage with patients to learn the best ways to support them in managing their T2DM. Placing the patients and their families at the forefront when it comes to deciding on what might be the optimal strategies for diabetes self-management is the way forward, and the COVID-19 pandemic might have just prompted healthcare professionals in reaching this sure-fire end-goal for medicine with more haste.

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Disorders of Gastrointestinal Motility in Diabetes Mellitus: An Unattended Borderline Between Diabetologists and Gastroenterologists

EDITOR'S PICK

This issue's Editor's Pick by Pal et al. is a compelling paper that focuses on a review of disorders of gastrointestinal motility in diabetes. Such disorders are often mild but, in some cases, have the potential to become quite severe, difficult to treat, and extremely distressing for patients. While existing therapeutic choices for the management of diabetic gastroenteropathy are suboptimal, many potential novel agents are in development. This review highlights the importance of collaboration between endocrinologists and gastroenterologists to facilitate the optimal screening and treatment of diabetic patients with gastrointestinal dysmotility.

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Abstract

Gastrointestinal (GI) symptoms represent an important and often poorly appreciated reason of morbidity in diabetes mellitus. Diabetes can affect nearly all parts of the GI tract; however, data on the prevalence of 'diabetic gastroenteropathy' are inconsistent. The significance of disturbed GI motility in diabetes across the patient spectrum and pathophysiological basis also remain inadequately defined. Fluctuating glucose levels, altered drug pharmacokinetics, variable absorption of nutrients, and impaired quality of life are important consequences of GI dysfunction. Diabetic gastroparesis is the best characterised manifestation of GI motility disorder in diabetes. Since there is a poor correlation between subjective GI symptoms and objective motility findings, a diagnosis of delayed emptying in diabetes requires a proper measurement of gastric emptying. There are fewer studies on

intestinal motility in diabetes than those on the stomach. Several established modalities exist for the assessment of gastroenteropathy but the lack of standardisation, exposure to radiation, advanced data interpretation, and high cost limit their widespread use. While existing therapeutic choices for the management of diabetic gastroenteropathy are suboptimal, many potential novel agents are in progress. Both endocrinology and gastroenterology specialties working together will facilitate screening and treating patients with diabetes and GI dysmotility.

INTRODUCTION

People with Type 1 and Type 2 diabetes mellitus (T1 and T2DM) can present with a diverse range of symptoms in all levels of the gastrointestinal (GI) tract. However, there are inconsistent data on the prevalence of GI symptoms, and the frequency of symptoms is much higher when data are reported by a gastroenterologist than reported by a diabetologist.[1] The picture is further confounded by the dissociation between GI symptoms and the transit profile. Although motility disorders in DM are pan-enteric, perhaps the best-known diabetic GI complication is gastroparesis (Gp), or abnormally delayed gastric emptying (GE).[2] GI dysfunctions in diabetes not only have a detrimental effect on the quality of life, but also significant medical consequences. In recent years, the data in regard to the underlying pathophysiology of diabetic gastroenteropathy is expanding.[3] The importance of the evaluation of the entire GI tract in patients with diabetes and motility impairment is also being increasingly recognised. In this context, this review aims to explore the GI motility disorders in diabetes, focusing on the pathophysiology, effects on glycaemia, limitations of assessment methods, unmet needs in the treatment, and an outlook on future research.

PATHOPHYSIOLOGY

Understanding the pathophysiology of DM-induced GI dysmotility is important to develop therapies to correct or prevent the underlying mechanism of this widely prevalent disorder. DM-induced GI dysmotility is multifactorial and not completely elucidated. It can affect any part of the GI tract via a composite of several dysfunctional factors.[4] Autonomic neuropathy and hyperglycaemia are the two main factors implicated in the pathogenesis of DM-induced GI dysmotility.[5] Parasympathetic nerve dysfunction, known as autovagotomy, in DM leads to gastric stasis and rapid small bowel transit. Sympathetic nervous system dysfunction due to loss of α2 adrenergic tone causes small bowel dysmotility, abnormal fluid transport, and nocturnal faecal incontinence due to the loss of internal anal sphincter tone.[6] Prolonged hyperglycaemia alters GE, myoelectrical activity, and gastrocolic reflex.[6]

Although studies have shown an association between poor glycaemic control or autonomic neuropathy and GI symptoms in DM, these symptoms can develop before the onset of autonomic neuropathy or have a poor correlation with neuropathy. Hence, other pathophysiological mechanisms are likely to be present (Figure 1). These mechanisms have been studied in human and experimental models of DM, which include enteric myopathy and neuropathy.[7] Atrophy of smooth muscles and apoptosis of neurons have been observed in experimental models of DM as a result of autoimmunity and metabolic derangements leading to alteration of critical cellular pathways (e.g., phosphatidylinositol 3-kinase pathway) and signalling of trophic factors. Reduction of insulin or insulin-like growth factor 1 signalling in DM results in atrophy of intestinal smooth muscles. This leads to the decreased production of trophic factors such as stem cell factor, which results in loss of pacemaker interstitial cells of Cajal (ICC) or trans-differentiation into a smooth muscle phenotype.[8] Trans-differentiation also leads to an imbalance in number of excitatory and inhibitory enteric neurons and neuropeptides (e.g., vasoactive intestinal peptide, nitric oxide, calcitonin gene-related peptide, substance P).[9] Loss of ICC in myenteric plexus leads to obliteration of slow-phase peristaltic movements and gastric dysmotility. ICC located in the muscle layer impair neurotransmission in the enteric and autonomic nervous system, as well as to smooth muscle.[3] Moreover, abnormal central processing of visceral pain has been reported in DM.

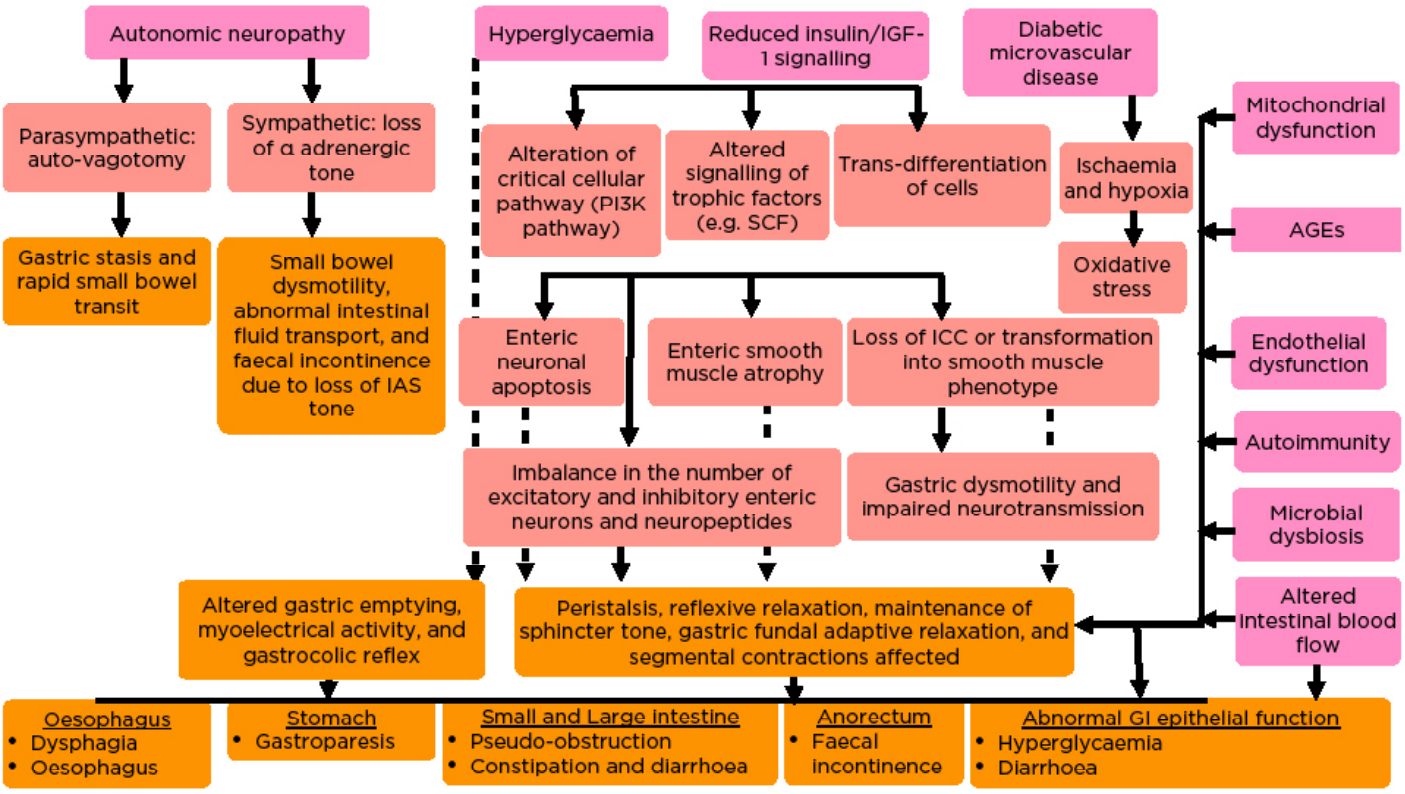

Figure 1: Pathogenesis of diabetes mellitus-associated gastrointestinal dysmotility.

Key pathogenetic factors and their effects are shown in pink and blush red-coloured boxes, respectively. Consequent clinical effects on various parts of the GI tract are depicted in dark yellow boxes.

AGE: advanced glycation end product; GI: gastrointestinal; IAS: internal anal sphincter; ICC: interstitial cells of Cajal; IGF-1: insulin-like growth factor 1; PI3K: phosphatidylinositol 3-kinase; SCF: stem cell factor.

Diabetic microvascular disease causing ischaemia and hypoxia, leading to oxidative stress; mitochondrial dysfunction; advanced glycation end products; and endothelial dysfunction mediated by peroxynitrite are other mechanisms for DM-induced dysmotility.[3]

Complex intestinal motor functions such as peristalsis, reflexive relaxation, maintenance of sphincter tone, gastric fundal adaptive relaxation, segmental contractions, and also intestinal blood flow are altered in DM due to the collective effect of various defective factors, discussed above, such as autonomic neuropathy, loss of ICC, and imbalance of enteric neurotransmission.[3] These altered GI motor functions lead to dysphagia and reflux oesophagitis, Gp, intestinal pseudo-obstruction, alternating constipation and diarrhoea, and faecal incontinence due to anal sphincter dysfunction. Abnormal GI epithelial function due to defective signalling of trophic factors and enteric neuropathy lead to enhanced nutrient transport and consequent hyperglycaemia, whereas abnormal intestinal transport of salt and water leads to diabetic diarrhoea. Compromised intestinal vascular flow in DM can lead to intestinal mucosal dysfunction, which can indirectly affect motility.[4]

EPIDEMIOLOGY

The prevalence of GI motility disorders in diabetes varies depending on the place of study (tertiary centre versus community-based), the definition employed (self-report versus validated questionnaire versus ecological momentary assessment), and the specialty involved (gastroenterology versus diabetology).[10] The risk factors include older age and longer duration of diabetes, female sex, higher HbA1c level, lower socio-economic status, greater prevalence of microvascular complications (particularly neuropathy), anti-diabetic medication use

(metformin and acarbose), and associated depression.[11] Among oesophageal symptoms, reflux is seen in up to 24% of patients with T1DM and 60% of patients with T2DM, but dysphagia is less common (4–13% in different studies).[10] Recent analysis from the follow-up cohort of Diabetes Control and Complications Trial (DCCT) showed that 47% of patients with T1DM have delayed GE of a solid meal.[12] If diabetes is long-standing and poorly controlled, the prevalence of Gp in T1 and T2DM is likely comparable. The data from Mayo Clinic, Scottsdale, Arizona, USA, provided the cumulative incidence of Gp (defined by a scintigraphic study and/or symptoms suggestive of Gp). Over the course of 10 years, 5% of people with T1DM and 1% of those with T2DM developed Gp.[13] The upper abdominal symptoms (nausea, bloating, early satiety, or upper abdominal pain) range between 10% and 40% in different studies.[10] However, the GE data with T2DM is scarce. Furthermore, symptoms often do not correlate with GE. Interestingly, some scintigraphy data are demonstrating GE is relatively more rapid in people with well-controlled T2DM.[14] The prevalence of diarrhoea is seen in up to 41% of patients with T1DM and 35% of patients with T2DM, while constipation is seen in up to 33% of patients with T1DM and up to 28% of patients with T2DM in different trials.[10] In the National Health and Nutrition Examination Survey (NHANES) dataset, which evaluated the prevalence of GI disturbances through the Bowel Health Questionnaire, after adjusting the covariates, chronic diarrhoea was more prevalent in patients with diabetes than in those who do not have diabetes, whereas chronic constipation (CC) was not.[15]

CLINICAL PRESENTATIONS

The prevalence of GI symptoms in patients with diabetes is higher than in the general population. Clinical manifestations of GI motility disorders can be classified into three sections according to the site of involvement.

Oesophagus

Gastro-oesophageal reflux and dysphagia are two common oesophageal motility disorders. Reflux disorders are more prevalent and mostly asymptomatic but can present with heartburn or cough.[16]

Stomach

Gastric symptoms are mostly related to slow GE called Gp. Post-prandial fullness, early satiety, bloating, nausea, vomiting, and upper abdominal pain are the common presentations.[17] Vomiting and early satiety are more frequent in diabetic gastroparesis (DGp), whereas abdominal pain is more frequent in idiopathic Gp.[18] Symptoms are more common in women, patients who are obese, and those with coexistent depression.[19] Interestingly, new symptoms sometimes appear and old symptoms disappear, with total prevalence remaining constant. This symptom 'turnover' may be as high as 15–25% over 2 years.[20] Sometimes Gp may present with poor nutritional status or unusual changes in post-prandial glycaemic patterns, such as erratic peaks and troughs in glucose concentrations.

Intestine

Symptoms at the intestinal level are constipation, diarrhoea, pain, and bloating. Among these, CC is the most commonly reported. DD is painless, chronic (>6 weeks), watery diarrhoea.[21] Nocturnal diarrhoea and faecal incontinence are two of the most typical findings of DD. Slow intestinal transit may predispose to small intestinal bacterial overgrowth, which can also lead to diarrhoea.[22]

DIAGNOSTIC APPROACH FOR GASTROINTESTINAL MOTILITY DISORDERS IN DIABETES

The symptoms of DM-induced intestinal dysmotility can be diverse as it can affect any part of the GI tract as outlined above. None of the symptoms are specific for DM-induced dysmotility. Organic diseases such as gallstone disease, gastro-oesophageal reflux disease, GI malignancies, and autoimmune conditions like coeliac disease can be associated with DM (commonly with T1DM) and mimic symptoms of DM-induced GI dysmotility. Among neuroendocrine tumours, glucagonoma can present with glucose intolerance, diarrhoea, and abdominal pain. Hence, it is important to distinguish GI motility disorders in diabetes from other organic diseases.[23] A review of anti-diabetic medications is also important since agents like metformin and acarbose can cause nausea, vomiting, flatulence, and diarrhoea, mimicking symptoms of GI dysmotility.

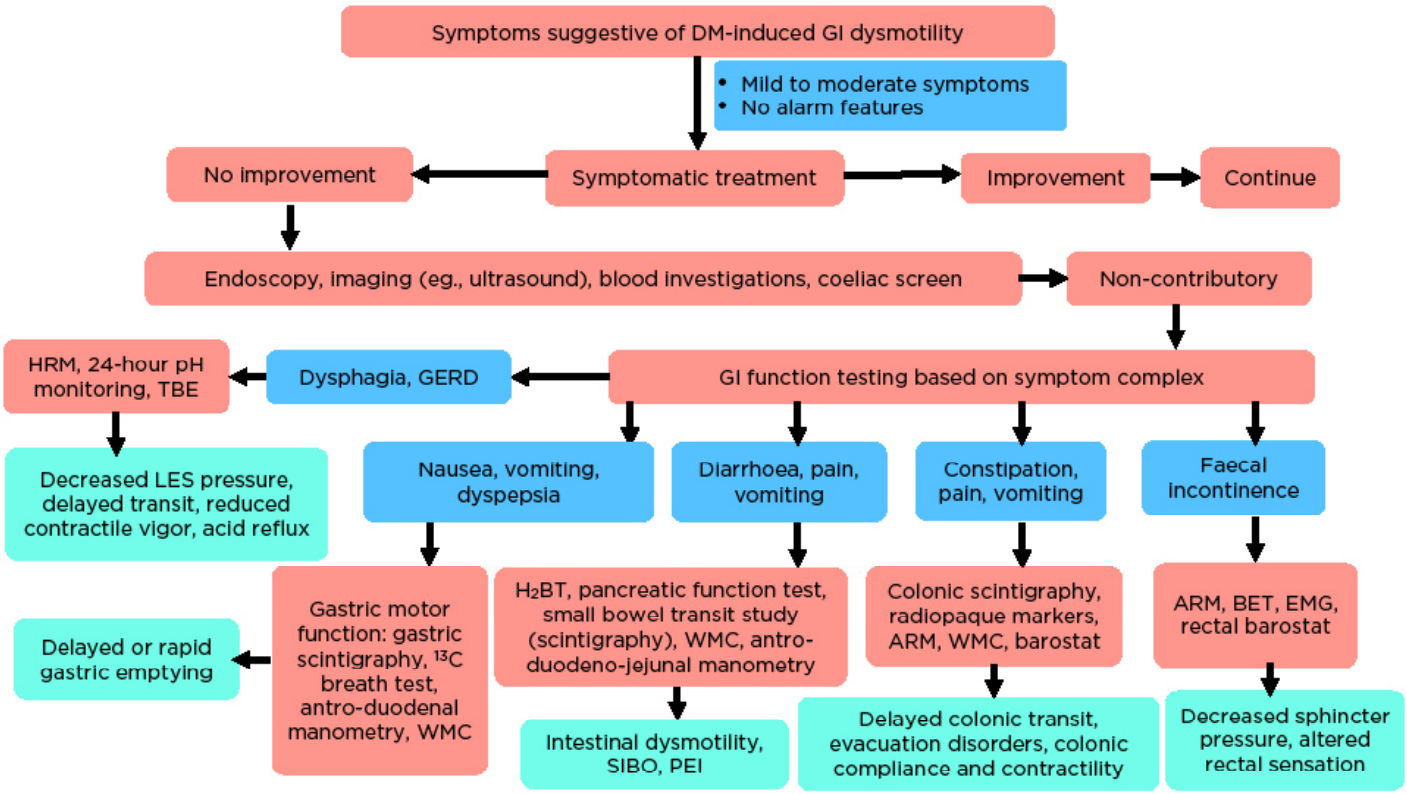

Figure 2: Clinical approach in suspected diabetes mellitus-associated gastrointestinal dysmotility.

ARM: anorectal manometry; BET: balloon expulsions test; EMG: electromyography; GERD: gastroesophageal reflux disease; HRM: high-resolution manometry; H^2BT: hydrogen breath test; LES: lower oesophageal sphincter; PEI: pancreatic exocrine insufficiency; SIBO: small intestinal bacterial overgrowth; TBE: timed barium oesophagogram; WMC: wireless motility capsule.

The first step to evaluate symptoms of GI dysmotility in patients with DM is to perform basic laboratory investigations, imaging, and an endoscopy to rule out other organic diseases (Figure 2). GI function testing is recommended if these investigations are non-contributory and symptoms do not respond to symptomatic treatment such as laxatives for constipation. However, the most readily available GI motility tests cannot prove causation by DM-induced dysmotility or gauge the relative contribution of DM in the case of multifactorial causation of dysmotility.[23]

Investigations that are specific for DM-induced gastroenteropathy like pancreatic polypeptide (a reduction in pancreatic polypeptide is specific) and antro-duodenal motility testing (Phase II and post-prandial hypomotility and increased Phase III motility, specific for DGp) are not readily available.[24,25] Other organ involvement (e.g., cardiac autonomic neuropathy) increases the probability of DM-induced GI changes. Commonly available tests like high-resolution manometry showing oesophageal hypomotility and GE studies show that Gp cannot differentiate DM-induced dysmotility from other causes. However, the GE study is important and should be done in patients with poorly controlled diabetes early as it has important implications in glycaemic control.[25] Both impaired gastric motility and rapid GE (in up to 20% with impaired GE) can occur, leading to dumping syndrome, which can cause similar symptoms (e.g., unexplained nausea, vomiting) to be differentiated based on GE.[26] A detailed approach to DM-induced GI dysmotility is illustrated in Figure 2.

Newer emerging diagnostic modalities include ^{13}C-breath test (for GE test based on hepatic metabolism after intestinal absorption, good correlation with scintigraphy), wireless motility capsule (to assess the entire gut and measure regional transit time in a single test without any

radiation), and electromagnetic capsules (Motilis 3D-Transit system [Molitis Medica SA, Lausanne, Switzerland] to reflect gut contractility and regional transit time).[25,27,28]

CLINICAL MANAGEMENT

Management of Diabetic Gastroparesis

Advances in dietary recommendations

The first step in the management of Gp is dietary modification. Patients with DGp tend to have a lower than recommended caloric intake as well as a significant deficiency of micronutrients.[29] Multiple small meals (≥6 /day) are preferable than fewer, large ones. It appears logical to avoid hard-to-digest solids and fats, consume larger calorie proportions as a liquid rather than solid, and take solids of small particle size, but this has a limited evidence base.[30] Intake of small-particle, low-fat, and low-fibre diets with sufficient hydration may improve GE. Solid foods that are high in fat are probably the offenders. In practice, it has been observed that fat-containing liquids are mostly well-tolerated.[31] Smoking and alcohol consumption should be avoided. For individuals who fail to meet their nutritional requirements consistently or regain the lost weight, enteral nutrition is recommended to bypass the dysfunctional stomach.[31] In patients with Gp, using parenteral nutrition should be the exception.

Glycaemic control and gastric emptying

The connection between glycaemic control and Gp is not completely understood and may be bi-directional. Hyperglycaemia can delay GE, whereas disturbances of GE affects glycaemic control.[32] Data regarding the long-term effect of glycaemic control on GE are conflicting, with several earlier studies finding no correlation in T1DM and T2DM patients.[33-35] However, in an evaluation of a subset of the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC) cohort, GE weakly related to both HbA1c at the entry into DCCT and the mean HbA1c over the intervening years.[12] Another recent retrospective review of patients (both T1 and T2DM) who underwent GE scintigraphy found a significant association of higher HbA1c levels with higher gastric retention at 4 hours.[36]

There is evidence, although inconclusive, that improvement of glycaemic control can correct abnormally delayed GE in DM, but that an exact threshold of good control may be required. An abnormally slow GE may predispose to hypoglycaemia. The unexplained hypoglycaemic episodes, mainly early in the post-prandial period, may be the sole presenting feature of DGp and warrant prompt evaluation of GE.[37]

Optimising glycaemia in patients with gastroparesis

Optimisation of glycaemic control is essential to reduce the acute symptoms of Gp, improve nutrient utilisation, and prevent catabolism.[38] A survey of patients with DGp revealed an observation that blood glucose control had become more difficult since the diagnosis of stomach dysfunction, with recurrent episodes of both hypo- and hyperglycaemia.[39] Delayed GE affects the pharmacokinetics of oral antidiabetics; hence, these agents do not appear to be suitable for effective glycaemic control in patients with T2DM and clinically significant Gp. Patients with T1DM and most of the patients with T2DM and DGp will require insulin for glycaemic control. Compared to basal insulin, the challenges are more complex for the bolus insulin. There are two practical recommendations regarding the bolus insulin for patients with Gp: the use of regular insulin (rather than insulin analogues) and insulin administration after a meal. It is advocated to use continuous subcutaneous insulin infusion (CSII) together with continuous glucose monitoring to improve glycaemic control in patients with Gp.[40] Administering of a second wave of prandial insulin through the dual wave CSII could be especially helpful when the carbohydrate emptying is delayed.[41] Nevertheless, there is a lack of randomised clinical trials of CSII in DGp. Glucagon-like peptide-1 receptor agonists can exacerbate symptoms of delayed GE and should be avoided.[42] Dipeptidyl peptidase-4 inhibitors, contrary to glucagon-like peptide-1 receptor agonists, are unlikely to have a considerable impact on GE.

Current medications: unmet needs

Theoretically, the symptoms of Gp should best be treated with promotility agents that accelerate GE, which should improve symptoms. Nevertheless, there is a poor correlation of

symptoms with GE, and enhancement of GE may not provide improvements in symptoms. For DGp, studies with prokinetic drugs have reported improvement in GE, without consistent effects on symptoms or glucose control.[43] A recent systematic review demonstrated a relationship if studies using 'suboptimal' techniques for assessing GE were removed, but this analysis excluded the motilin receptor agonists. This is further confounded by the fact that certain prokinetic agents have antiemetic properties as well.[44]

Prokinetics currently in clinical use are metoclopramide and erythromycin. Though each has been shown to improve GE and reduce symptoms, there are problems with these agents (Table 1).[45] Consequently, there continues to be a considerable unmet need for patients with Gp. Newer agents including dopamine receptor antagonists and ghrelin, motilin, and 5-HT4 receptor agonists are being investigated, which demonstrate efficacy and have fewer adverse effects (Table 1).

Treatment for refractory gastroparesis

For resistant Gp, which is not responding to dietary modifications and pharmacotherapy, surgical options such as gastric electric stimulation (GES), pyloric surgery (PS) such as a pyloromyotomy or pyloroplasty, or a combination (GES+PS) may be considered. Recent studies have shown that combined GES+PS and GES improve nausea and vomiting better than PS alone, particularly in DGp compared with idiopathic Gp.[47] GES gastric pacing delivers high frequency (12 /minute) low-energy pulses via a pacemaker to gastric serosa along the greater curvature. GES is recommended for use in DGp by the U.S. Food and Drug Administration (FDA). Accelerated GE, improved gastric accommodation, and central effects (via the vagus nerve) mediate the beneficial effects of GES. Infection is the major limiting side effect (10%), requiring treatment discontinuation.[48]

Several relatively non-invasive endoscopic options are upcoming for refractory Gp. Intra-pyloric botulinum toxin injection can be used for Gp in uncontrolled studies. However, placebo-controlled studies have failed to show a benefit.[49] Data from a multicentre, non-randomised study of 30 patients with refractory Gp have shown efficacy and technical feasibility of gastric per-oral endoscopic myotomy (G-POEM) with pyloromyotomy (a natural orifice endoscopic transluminal endoscopic surgery; NOTES) leading to normalisation of GE time.[50] In a prospective matched cohort study comparing G-POEM and laparoscopic pyloroplasty, G-POEM had significantly lower post-operative morbidity with comparable improvement in GE and symptoms.[51] Hence, there is a current trend of shifting from surgical management of refractory Gp to less morbid endoscopic procedures.

Management of Diabetic Enteropathy

Diabetic diarrhoea

Initial treatment should be directed towards the correction of fluid and electrolyte imbalances, with implementation of measures to optimise glycaemic control. Two of the most frequently prescribed anti-diarrhoeals are loperamide and diphenoxylate. However, for DD their use is off-label.[21] Unlike diphenoxylate, loperamide is peripherally acting and, thus, is preferred. In DD, bile acid-binding resins may be of therapeutic value, and these agents also reduce HbA1c levels.[21] The supportive evidence for use in DD is limited to case reports only. One of the best-studied medications for DD is clonidine.[52] However, its use is limited largely by hypotension, mostly in patients with postural hypotension secondary to autonomic neuropathy. In refractory cases of DD, long-acting somatostatin analogues (e.g., parenteral octreotide) may be considered.[53] However, high cost, steatorrhoea, gallstones, and dysglycaemia are the limiting factors.

Eluxadoline is one promising future drug for the treatment of DD. Currently, it is a μ-opioid agonist, δ-opioid receptor antagonist, and κ-opioid receptor agonist approved for diarrhoea-predominant irritable bowel syndrome.[54] Mixed opioid receptor agents are associated with less constipation and have low potential for dependence or tolerance as compared to their counterparts (μ-receptor agonist). A combined Phase II/III study of eluxadoline for the treatment of DD is currently underway.

Table 1: Prokinetic agents for gastroparesis that are currently available and under study.

Available agents				
Class	**Drug**	**Effect on GI tract**	**Use in gastroparesis**	**Comments**
D2 receptor antagonist	Metoclopramide	Improves gastric emptying	Approved for up to 3 months	Side effects of concern (black box warning)
	Domperidone	Increases antral contraction and gastric emptying	Used under FDA Investigational new drug application	Advantage: less CNS effect than metoclopramide; Disadvantage: cardiac adverse effects, increased prolactin levels
Motilin receptor agonist	Erythromycin and azithromycin	Increases antral contractions and gastric emptying	Low dose for prokinetic effect	Advantage: no extrapyramidal side effects; Disadvantage: tachyphylaxis may occur after 4 weeks of use
5-HT4 receptor agonist	Prucalopride	Improves gastric emptying, SB transit, colonic transit	Improves symptoms and gastric emptying in patients with IGp; Potentially useful 'off-label' for gastroparesis	Results of a Phase II trial in DGp are awaited (NCT02031081)[46]
Agents being studied				
Class	**Drug**	**Effect on GI tract**	**Symptom improvement**	**Current status and comments**
D2/D3 antagonist	TAK-906	Increases antral contraction; Does not improve gastric emptying	Early results show improvement of selected symptoms of gastroparesis	Less cardiotoxic than domperidone
	Metopimazine (NG101)	Increases antral contraction	Results not yet available	Not associated with cardiac side effects
	Deuterated domperidone	Results not yet available	Results not yet available	To be studied
Motilin receptor agonist	Camicinal	Increases antral contraction	Improves gastric emptying and symptoms but at different doses	Not actively being studied
5-HT4 receptor agonist	Velusetrag	Improves gastric emptying and colonic transit	Preliminary results suggest improvement in symptoms of gastroparesis	Undergoing further studies
Ghrelin receptor agonist	Relamorelin	Increases migrating complex and vagal signalling	Improves nausea/vomiting, abdominal pain, bloating, early satiety	Undergoing Phase III studies

CNS: central nervous system; DGp: diabetic gastroparesis; D2: dopamine type 2 receptor; FDA: U.S. Food and Drug Administration; GI: gastrointestinal; IGp: idiopathic gastroparesis; SB: small bowel; 5-HT4: 5-hydroxy tryptamine receptor 4.

Diabetes-associated chronic constipation

Treatment intends to have an improvement of symptoms and restoration of bowel function by accelerating colonic transit and facilitating defecation.[55] Implementation of lifestyle and dietary modifications should be done prior to opting for prescription medications. A high-fibre diet, adequate water intake, and physical activity are regularly recommended. However, increasing dietary fibre appears to be useful in those with a deficiency in fibres and too much fibre intake can exacerbate bloating and flatulence.[56] High-fibre diets fail to improve bowel movements in people with slow transit or defecation problems.[57]

If satisfactory relief is not obtained with dietary modifications, the standard treatment is the use of laxatives. However, no studies have assessed a stepwise approach to laxative therapy. The Asian Neurogastroenterology and Motility Association (ANMA) recommends that treatment should start with bulk-forming laxatives, followed by an osmotic laxative and stimulant laxative in individuals who are not responding to bulking agents.[58] Lactulose appears to be a suitable and effective osmotic laxative for managing CC in patients with diabetes.[59] Nevertheless, well-designed, placebo-controlled clinical trials of available laxatives are limited.

Newer agents such as the 5-HT4 agonist and chloride channel activators can be considered for resistant cases. A novel 5-HT4 agonist, prucalopride, has been approved for CC.[60] Lubiprostone, a chloride channel activator, is found to be a safe and effective treatment option for diabetes-related CC.[61]

CONCLUSION AND FUTURE DIRECTIONS

DM-induced GI dysmotility is common and can affect any part of the GI tract, causing significant disability. However, treatment of diabetic patients with GI dysmotility is limited and currently includes tight glycaemic control and symptom-based management in close consultation with both endocrinologists and gastroenterologists. However, such therapy can be ineffective in a significant subset of patients due to irreversible or unidentified underlying disease mechanisms. The current understanding of mechanisms of DM-induced GI dysmotility is still inadequate, although it has been evolving rapidly in the last decade. Mechanisms other than autonomic neuropathy and hyperglycaemia help to explain why GI symptoms often precede or have a poor correlation with diabetic autonomic neuropathy. DM leads to an altered microenvironment of the enteric nervous system and ICC, leading to either apoptosis or trans-differentiation. Oxidative stress from diabetic microvascular disease, microbial dysbiosis, mitochondrial dysfunction, autoimmune mechanisms, reduction in trophic factor signalling (insulin or insulin-like growth factor 1 pathway), alteration of key cellular pathways, and post-transcriptional regulation of protein synthesis by micro-RNAs can lead to this altered microenvironment. Identification of reversible risk factors holds the key to newer treatment modalities. For example, restoring the trophic signals could restore trans-differentiated ICC and stem cell therapies can reverse ICC apoptosis, leading to resolutions of GI symptoms.

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Fast Progression of Diabetic Retinopathy with SARS-CoV-2 Infection

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Abstract

COVID-19 is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and has been shown to affect a multitude of organ systems. It is often associated with vasculitis or thromboembolic disease with resultant tissue hypoxia. This report presents a case of fast progression diabetic retinopathy in the case of a SARS-CoV-2 infection. The findings conclude that patients with diabetes should be more frequently monitored for emergence or progression of diabetic retinopathy if they present with COVID-19.

INTRODUCTION

COVID-19, which was originally identified in December 2019, has now spread across the globe and was declared a pandemic by the World Health Organization (WHO) in March 2020. COVID-19 is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and has been shown to affect a multitude of organ systems.[1] It is often associated with vasculitis or thromboembolic disease, and several forms of ocular involvement have also been reported.[2] Initial studies have shown that the virus can be isolated in eye secretions and may cause ocular surface problems such as conjunctivitis.[3,4] More recently, retinal involvement has been reported from SARS-CoV-2 infection. Viral RNA of SARS-CoV-2 has been confirmed in post mortem retinal biopsies of infected patients.[5] Retinal findings on funduscopic examination are mostly flame-shaped retinal haemorrhages and cotton wool spots.[6] Additionally, optical coherence tomography (OCT) has shown small hyperreflective lesions at the level of the ganglion cell and inner plexiform layers.[7] Marinho et al.[8] suggested that these lesions may be correlated with central nervous system (CNS) findings in SARS-CoV-2 infections as OCT angiography scans were normal in all patients. However, after further investigation and correspondence, the authors discovered that these hyperreflective lesions were found to have an absence of blood flow.[9] Both of the previously described funduscopic and OCT findings in patients with COVID-19 may be explained by viral invasion and subsequent immune-mediated inflammation. This results in wide spread microvascular ischaemia that affects many organs including the retina. The effect of COVID-19 on the microvasculature could preferentially affect patients with pre-existing microvascular diseases, such as diabetes. This

case represents an acute, severe progression of diabetic retinopathy in the setting of COVID-19.

CASE REPORT

This case reports a 49-year-old African-American male who has had poorly controlled Type 2 diabetes mellitus for 10 years, presenting with blurry vision following COVID-19 contraction and hospitalisation. He was being treated with metformin and dulaglutide. His HbA1c was 9%. The patient did not have any history of micro- or macrovascular complications. The primary care physician reported no neuropathy.

During hospitalisation between 16th May and 6th June 2020, the patient's vision in both eyes became blurry. While hospitalised his blood sugar levels were well managed within normal limits. He had moderate COVID-19 symptoms as defined by the U.S. Food and Drug Administration (FDA).[10] He needed supplemental oxygen with continuous positive airway pressure therapy. He was monitored and did not need a ventilator. He reported being screened in previous years for diabetic retinopathy because he had been diabetic since 2010. He stated no previous eye problems or diabetic retinopathy from his previous eye exams, which were screened by an optometrist. No images were available to compare.

When the patient was first examined in the clinic on 16th June 2020, his best-corrected visual acuity was 20/30 in the right eye and 20/25 in the left eye. There was no sign of ischaemic optic neuropathy or any specific visual field defect that could have come from optic nerve inflammation. Anterior segment and vitreous examination showed only mild cataracts in each eye and no inflammation. Fundus examination revealed prepapillary and peripapillary subhyaloid vitreous haemorrhages; additionally, it showed intraretinal flame-shaped and dot blot haemorrhages in both eyes. There were hard exudates in the macula in both eyes (Figure 1). The view of most of the optic disc was obscured by the prepapillary haemorrhage in the right eye and there was disc neovascularisation in the left eye. Fluorescein angiography showed late staining of the optic disc mostly blocked by the preretinal haemorrhage in the right eye, and the left fluorescein angiography showed disc neovascularisation (Figure 2). The rest of the retina showed some microaneurysms and moderate peripheral ischaemia in both eyes. The diagnosis was proliferative diabetic retinopathy with diabetic macular oedema in both eyes. OCT showed mild perifoveal focal macular thickening representative of clinically-significant diabetic macular oedema (Figure 3). Other than the thickening of the temporal macula in the OCT, the structural architecture of the retina was preserved.

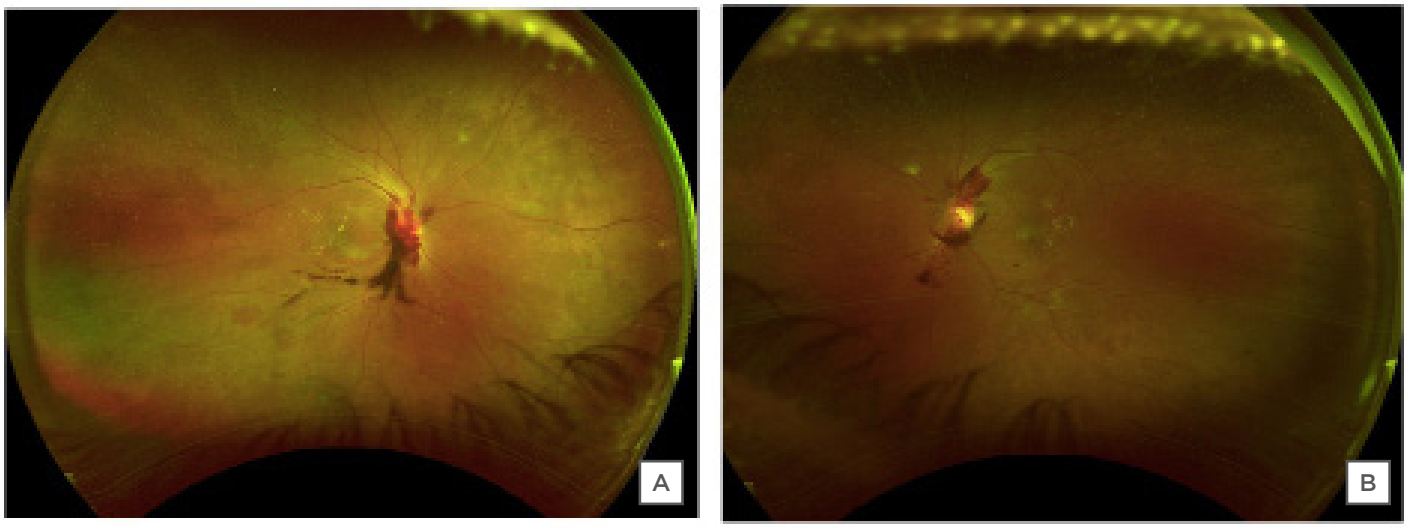

Figure 1: Wide-angle colour fundus photograph of the right (A) and the left (B) eyes.

The images of both eyes reveal preretinal and prepapillary vitreous haemorrhages, flame-shaped, and dot blot retinal haemorrhages, and hard exudates in the macula.

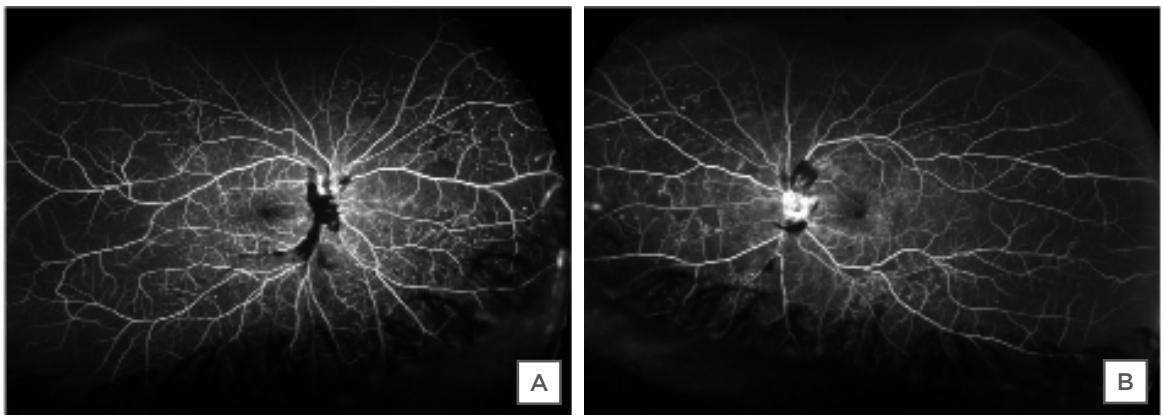

Figure 2: Fluorescein angiography showing the blockage from preretinal haemorrhage, staining of the visible part of the optic disc in the right eye (A), and leaking disc neovascularisation in the left eye (B).

The rest of the retina shows peripheral retinal ischaemia and diffuse microaneurysms.

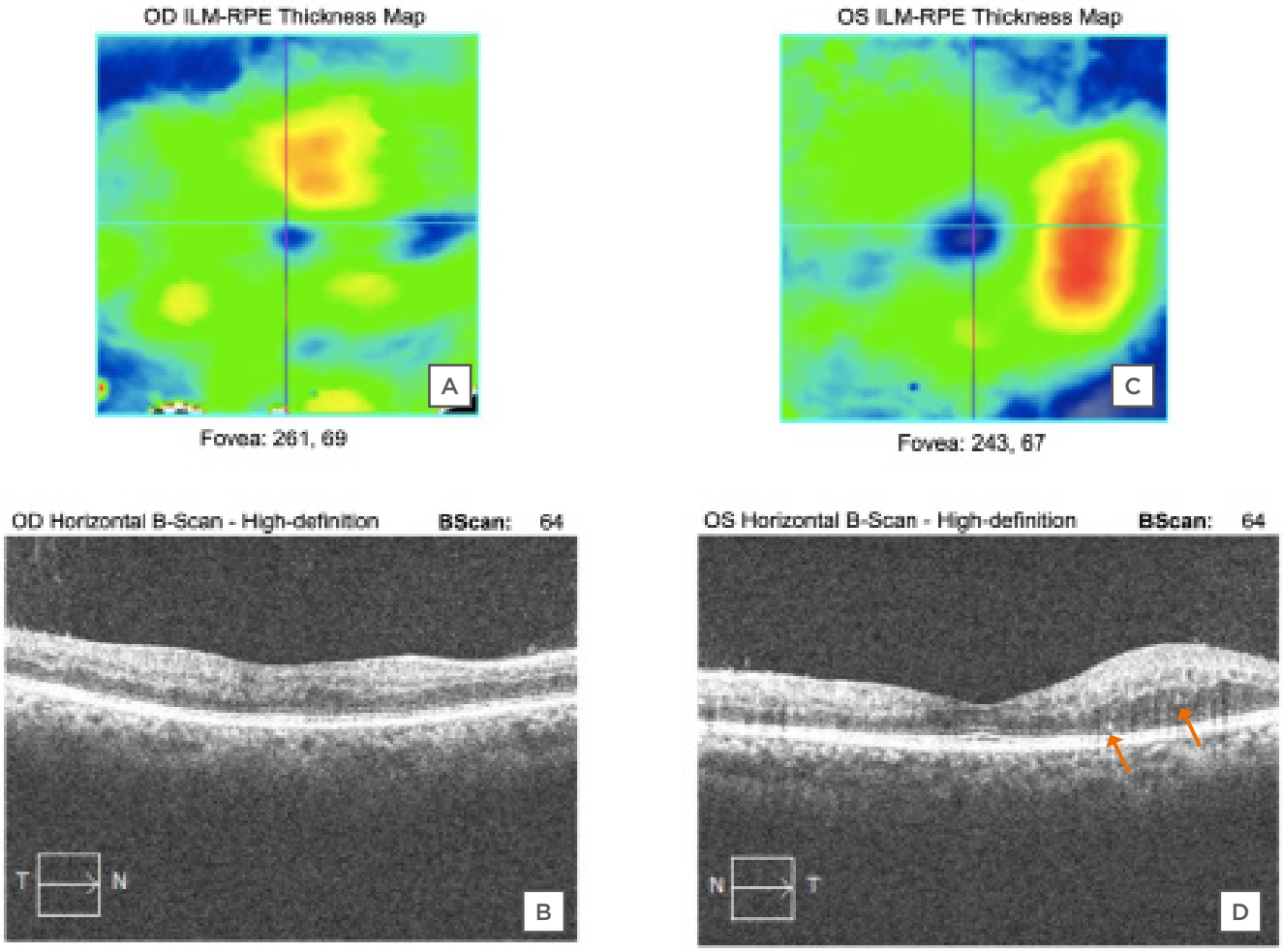

Figure 3: Perifoveal macula is thickened in the right (A and B) and left (C and D) eyes with fairly well-preserved structural integrity, indicating recent onset macular oedema. Several hyperreflective spots (arrows) are identified as well.

These are similar to those previously described by Pereira et al.,[6] however, hyperreflective spots are non-specific findings that are also commonly seen in diabetic macular oedema alone. They do not necessarily indicate association with COVID-19.

In the following 3 months, the patient was treated with monthly injections of bevacizumab, focal macular laser in each eye, and peripheral panretinal photocoagulation. This was done for the sake of caution in case the vitreous haemorrhage may have happened from a disc neovascularisation covered by the overlying haemorrhage. On the last examination on 3rd September 2020, his visual acuity was 20/20 in both eyes with near total resolution of macular oedema and partial resolution of the prepapillary haemorrhage.

CONCLUSION

Previously reported retinal findings in patients with COVID-19 include haemorrhages, cotton wool spots, and hyperreflective ischaemic lesions on OCT. In the largest cohort study of 18 patients, one-half of whom had diabetes, ischaemic retinal findings were present in nearly 50% of participants. This report describes a patient with diabetes whose retinopathy progressed significantly with COVID-19; the condition progressed from no reported retinopathy or visual symptoms 1 month prior, to high-risk proliferative diabetic retinopathy with vitreous haemorrhage. Existing diabetic vascular compromise may have made his eyes more vulnerable to presumed COVID-19-related vasculitis or venous occlusion. It is thought that this patient's retinopathy may have progressed because of a combined vasculitis and resistance to venous blood flow in the central retinal vein. This may have been because of the SARS-CoV-2 infection or the associated secondary effects such as cytokine storm or thrombotic tendency. Similar to previously reported patients, this patient had not received any other known concomitant vasoactive medication that could have further progressed retinal findings. It seems reasonable to suggest that concomitant SARS-CoV-2 infection contributed to developing this clinical picture in an eye that had no previously noticeable diabetic retinopathy.

COVID-19 appears to have unique forms of thrombotic and inflammatory processes; in nearly all tissues, thrombosis associated with COVID-19 could be either micro- or macrothrombosis.[11] This differs from previously described thrombotic and inflammatory processes such as macrophage activation syndrome, disseminated intravascular coagulation, and cytokine release syndrome.[12-14] Macrophage activation syndrome is rarely associated with thrombosis. Disseminated intravascular coagulation has more disseminated thrombosis associated with low fibrinogen levels. Cytokine release syndrome has different cytokine types and levels than COVID-19-related thrombosis and inflammation. In studies done by Ackermann et al.[15] and Piazza et al.,[16] pathologic examination of COVID-19-related thrombotic/necrotic tissue shows evidence of a much higher amount of microvascular injury and microthrombi.[15,16] Diabetic microvasculature already has compromised circulation and a high tendency for occlusion. This may make diabetic retinopathy more prone to occlusions when microthrombosis and microvascular injury happens as a result of COVID-19. Although this kind of injury has been reported in other tissues, it has not yet been directly observed pathologically in cases of diabetic retinopathy. In this report, some diabetic microvasculature may have already been compromised and easily occluded when the patient contracted COVID-19. Similar specific accelerated thrombotic processes have been recently shown to be particularly apparent in the lungs and CNS.[11] The retina is an extension of the CNS and therefore, the retinal and optic nerve vasculature may similarly be particularly susceptible to such a thrombotic event. The new nomenclature suggested by Bilgin et al.,[17] 'inflammatory thrombosis with immune endotheliitis-ITIE', may also apply to the case presented here as the contributory factor for the progression of diabetic retinopathy with SARS-CoV-2 infection. This case and the previously reported cases of retinal findings secondary to retinal ischaemia, even in the absence of diabetic retinopathy in patients with COVID-19, warns us that diabetic retinopathy may progress faster than expected in patients infected with SARS-CoV-2.[6,7] Patients with diabetes should be more frequently monitored if they get COVID-19 for emergence or progression of diabetic retinopathy.

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Screening for Heart Failure in Diabetes: A Way to Reduce Its Prevalence? A Proof of Concept of a Risk Assessment Tool

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Abstract

Background: Heart failure (HF) is underdiagnosed among patients with diabetes. Awareness is required to improve its management and to reduce its impact.

Objectives: To suggest a risk assessment tool that could facilitate the early diagnosis of HF and even reduce its incidence by facilitating individualised management plans.

Methods: Assess current medical literature, searching for parameters that indicate a higher risk of HF among the diabetic population.

Results: Twenty-four parameters were found that could be the potential basis for a risk stratification tool.

Conclusion: The concept of a risk stratification tool is presented. Work on validating will be required. It has the potential to affect the future management of patients with diabetes and to reduce the incidence and prevalence of HF in this population.

BACKGROUND

Patients with diabetes have a two-fold increase in the risk of heart failure (HF).[1] Unfortunately, many patients with diabetes remain undiagnosed for HF, even when screening tools like the brain natriuretic peptide (BNP) blood test have been around for some time.[2,3] This test remains underutilised.[4] Furthermore, it is not very specific; in consequence, one has to consider how to increase its predictive value and how the screening for HF could be improved. Looking at the literature for other parameters, combining their predictive value, and creating a potential tool to assess more specifically those at risk of developing HF could be possible before the need for a referral for tests like an echocardiogram to confirm the presence of HF; therefore, it could improve screening. Thinking proactively, it could also be used to determine a pre-HF status in the same way that patients are monitored when presenting with pre-diabetes to change its natural progression to established disease. Assessing a patient in more detail, assessing the risk of developing HF, and

managing those factors could be a way to reduce the prevalence of this condition. The authors, therefore, aim to provide a proof-of-concept for a risk stratification tool to be used in primary care.

METHODS

A non-systematic review of the literature was conducted, looking for "heart failure risk" AND "diabetes" in PubMed with a filter to limit results to the last 5 years. A total of 48 manuscripts were found and, among them, 16 articles were considered for further analysis. Additional papers from references were searched to sustain statements of risk factors already known and were also included in this review.

RESULTS

It can be summarised that a family physician, while reviewing a patient with diabetes, could calculate the risk this patient has of developing HF by taking into consideration particular parameters.

General factors:

- Age of the patient, as the risk of developing HF increases with increasing age[5-7]
- Sex, as the risk is significantly greater among women[8]
- The length of time the patient has had diabetes, which is associated with a higher risk of developing HF[5,6]

Lifestyle factors:

- Smoking is associated with an increased risk of HF[7]

Symptoms suggestive of heart failure:[2]

- Ankle swelling
- Dyspnoea
- Fatigue

Physical examination findings:

- Obesity, or elevated BMI and waist to hip ratio (WHR) increase the risk of HF[6,9]

Blood tests:

- Higher levels of HbA1c are associated with the development of HF[6,10]
- Raised BNP levels[3,6,9]
- Note that raised uric acid levels have been associated with the development of HF[11]

Medication:

- Some oral antidiabetics have a negative effect on HF, such as insulin, sulfonylureas (i.e., glibenclamide), dipeptidyl peptidase-4 inhibitors (i.e., sitagliptin), and thiazolidinediones (i.e., pioglitazone)
- Other oral antidiabetics have a positive effect on HF, such as sodium-glucose co-transporter-2 inhibitors (i.e., dapagliflozin) and metformin
- Some pharmaceutical agents seem to be more neutral, such as glucagon-like peptide-1 (i.e., liraglutide)[3,12]

Comorbidities:

- Cardiovascular disease increases the risk of HF, whether atrial fibrillation, hypertension, ischaemic heart disease, or peripheral vascular disease[2,5-7,9]
- Increased risk of HF linked to chronic kidney disease, dyslipidaemia, and obstructive sleep apnoea[5,6,13]

DISCUSSION

Several parameters are linked to developing HF or additional risk to be admitted with HF (Table 1).[2,3,5-12,14-16] Up to now, the focus on screening has been on the use of BNP and not on these other factors. It has to be argued that it should be possible to validate their combined risk as part of a new scoring tool that could provide a more valuable and accurate risk assessment of patients with HF.

In primary care, family physicians are probably screening patients with diabetes with BNP to diagnose early HF, but it is not enough. BNP alone is sensitive enough, but its use is probably not as widespread as required to make an impact on reducing the burden of undiagnosed HF. BNP is utilised too little to consider it as part of a wider assessment of the management of the patient that could, theoretically, reduce the incidence of HF by acting on those parameters that could be amenable to change (such as lifestyle changes, medication, or management of comorbidities).

Table 1: Suggested parameters for a risk assessment tool.

Parameter	Possible sliding groups
General factors	
How old is the patient?[5-7]	<50 years, 50–60 years, or >60 years
What is the sex of the patient?[8]	Female/male
How long has the patient had diabetes?[5,6]	<5 years, 5–10 years, or >10 years
Is the patient a smoker?[7]	Yes/no
What is the patient's BMI?[6,9]	<30, 30–40, or >40
Symptoms	
Does the patient have ankle swelling?[2]	Yes/no
Does the patient have dyspnoea?[2]	Yes/no
Does the patient have fatigue?[2]	Yes/no
Blood tests	
What is the patient's last HbA1c level?[6,10]	<58 mmol/mol, 58–68 mmol/mol, or >68 mmol/mol
What is the plasma BNP plasma level?[3,6,9]	<50 pg/mL, 50–125 pg/mL, or >250 pg/mL
What is the serum uric acid test level?[11]	< or >5.34 mg/dL
Medication	
Is the patient on insulin?[3,5,6]	Yes/no
Is the patient on DPP4 (i.e., sitagliptin) or similar?[3,6]	Yes/no
Is the patient on metformin?[10,12]	Yes/no
Is the patient on SGLT2 (i.e., dapagliflozin) or similar?[3,15]	Yes/no
Is the patient on sulfonylurea (i.e., glibenclamide) or similar?[3,6,12]	Yes/no
Is the patient on thiazolidinedione (i.e., pioglitazone) or similar?[3]	Yes/no
Is the patient on thiazide (i.e., indapamide) or similar?[3,6,12]	Yes/no
Comorbidity	
Does the patient have AF?[5,6]	Yes/no
Does the patient have CKD?[16,5]	Yes/no
Does the patient have hypertension?[5-7,9]	Yes/no
Does the patient have ischaemic heart disease?[5]	Yes/no
Does the patient have PAD?[2]	Yes/no
Does the patient have OSA?[6,13]	Yes/no

AF: atrial fibrillation; BNP: brain natriuretic peptide; CKD: chronic kidney disease; DPP4: dipeptidyl peptidase-4; OSA: obstructive sleep apnoea; PAD: peripheral artery disease; SFLT2: sodium-glucose co-transporter-2.

A more structured way to assess patients is needed to change the goal from early HF detection to reducing incidence by managing the risks better, allowing an informed patient to understand how to better their chances, and to engage them in the relevance of those changes that can significantly alter their future health.

HF risk stratification tools to understand the risk of patient hospitalisation and death after discharge from hospital have been developed.[5,17] Berg's tool was based on five independent parameters

(prior HF, history of atrial fibrillation, coronary artery disease, estimated glomerular filtration rate, and urine albumin-to-creatinine ratio), while the tool developed by Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) was based on 13 patient factors (age, gender, diabetes, chronic obstructive pulmonary disorder, HF diagnosed within the last 18 months, current smoker, New York Health Association [NYHA] classification, use of β-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, BMI, systolic blood pressure, creatinine, and left ventricular ejection fraction).[5,17] These tools were intended for different use in secondary care. Although Berg's tool could be the basis of a wider tool to assess the risk of developing HF, not just the risk for hospital admission, MAGGIC's tool is for use in patients already diagnosed with HF.[5,17] General practitioners are in need of a new instrument to be able to proactively manage patients with diabetes differently, similar to the concept of QRISK3, thus reducing the prevalence of HF.[18] Preventative treatment could be initiated before the potential diagnosis of HF is made; patients, understanding their risk of developing HF, could put more interest on lifestyle changes as improving diabetes alone does not seem to be enough to trigger these changes. Furthermore, the management of diabetes could be transformed by selecting different hypoglycaemic agents and with additional cardiovascular support in the way of renin–angiotensin–aldosterone inhibition therapy, for example.[9]

Finally, starting to use a risk calculator will have additional effects on improving and updating this type of tool, looking for more ways to understand the risk of developing HF as well as preventing it, promoting research in this subject.

CONCLUSION

Family physicians could reduce the burden of HF among patients with diabetes by using a risk calculator like the one suggested here. It is time to be more proactive and, thus, a tool to assess the risk of HF and, potentially, to reduce its prevalence in the population should be validated.

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Stroke in Patients with Diabetes: Is It Time to Expand Public Health Priority to Encompass High-Risk Patients with Increased Insulin Resistance?

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Abstract

Diabetes and stroke, with an interlinking aetiology, contribute to a growing cardiovascular disease burden and mortality around the world. Given the disproportionate prevalence and the burden of these conditions in the developing world, as well as the high risk of both Type 2 diabetes and cardiovascular disease carried by patients with metabolic syndrome, public health strategies are vital to mitigate the impact. Systematic approaches towards identifying undiagnosed patients in the community and building health systems around those targeted interventions have been implemented. However, growing evidence indicates potential for approaches to capture high-risk patients, such as those who suffer from pre-diabetes or increased insulin resistance, to provide early and optimal treatments, which could translate to population-level benefits, including reduced prevalence, disability, and disease burden.

INTRODUCTION

Cardiovascular disease (CVD), including stroke, is a leading cause of illness, death, and disability worldwide.[1] A predominant factor driving morbidity and mortality is diabetes, which is a major contributor to poor outcomes in acute ischaemic stroke.[2,3] Given the increasing prevalence of diabetes in the world and more specifically in Asia,[4,5] it is warranted that an approach directed towards understanding the trajectories of patients with diabetes experiencing a stroke or those at a high risk of diabetes needs to be addressed. In this article, the authors discuss the emerging burden and associated morbidity of stroke in patients with diabetes and provide insights on therapeutic management from a public health perspective. The authors also provide insights on shifting the public health message towards identifying patients in the community at high risk of developing diabetes or stroke or both.

STROKE IN PATIENTS WITH DIABETES

Diabetes puts patients at higher risk for cardiovascular events, including fatal stroke, non-fatal stroke, and transient ischaemic attack.[6] The clinical profile of diabetic stroke differs from a non-diabetic stroke.[7] A Cochrane review showed that concurrent metabolic syndrome and diabetes were associated with recurrent strokes in patients with minor stroke and transient ischaemic attack.[8,9] Furthermore, a diagnosis of diabetes is associated with an increased risk of lacunar strokes, which are associated with stroke recurrence.[13] There is also evidence to suggest an increased burden of post-stroke poor clinical outcomes, such as functional disability, in patients with diabetes relative to patients without diabetes, particularly those with admission hyperglycaemia.[11,12] Diabetes is associated with greater mortality, poorer neurological outcomes, poorer stroke rehabilitation outcomes, and futile recanalisation.[13-17] The overall disease, financial, and social burden of stroke and diabetes is provided in Table 1.

It has been suggested that HbA1c levels are associated with the development of cerebral white matter damage, as higher levels of white matter damage have been seen in patients with diabetic stroke.[10,28] There is conflicting evidence over whether a history of diabetes predisposes a patient to dementia, including Alzheimer's disease.[29,30] A 2016 large sample cohort study found a significant association between a history of diabetes and brain infarction, particularly lacunar strokes, with a lower mini-mental state examination (MMSE) score at the end of life, but not with Alzheimer's disease generally.[13] A novel 2021 mouse model of post-stroke cognitive impairment showed a new biomarker of brain and serum quinolinic acid concentrations and quinolinic acid-to-kynurenic acid ratios that was increased in diabetic mice.[14] It was associated with long-term memory impairment, leukoaraiosis, neuronal death, and microglial and macrophage infiltration. Given the increasing burden of diabetes and global ageing populations, the impact of diabetes on cognitive function is an area of concern.

There is a lack of defined treatment protocols targeted at patients with diabetes and stroke. Given the different clinical profiles of stroke in patients with diabetes relative to patients without diabetes, there is a necessity for collaborative management between primary healthcare physicians, endocrinologists, internal medicine physicians, and neurologists. Whilst some guidelines recommend against the use of tissue plasminogen activator in patients with diabetes and previous stroke, recent evidence has shown that tissue plasminogen activator is beneficial for use in such patients.[15-17] There is also a lack of consensus about the use of glucose control in stroke treatment for patients with diabetes. A 2020 meta-analysis recommended against the use of tight glucose control after ischaemic stroke because it does not improve neurological or functional outcomes but rather increases the risk of symptomatic intracranial haemorrhage and hypoglycaemia.[31]

Table 1: The burden of disease, prevalence, disability-adjusted life years, and financial burden due to diabetes, stroke, diabetic stroke, and pre-diabetes.

	Burden of disease	Prevalence	DALY	Financial burden
Diabetes	9.30% or 463 million people (global prevalence in 2019)[28]	N/R	2.8 (% of DALYs 2019)[19]	827 billion USD (direct medical costs) 1.7 trillion USD (Loss in GDP estimate from 2011–2013)[20]
Stroke	42.43 million (prevalence of cerebrovascular disease in 2015)[21] 13.70 million people (global incidence in 2016)[22]	N/R	5.7 (% of DALYs 2019)[19]	Global statistics couldn't be found In Australia: $32.2 billion lost (2020)[23]
Diabetic stroke	65% (proportion of deaths caused by diabetes that are attributable to CVD or stroke or both in the USA)[8]	3.84 million (prevalence of diabetes in stroke is estimated to be 28%.[24] Twenty-eight percent multiplied by 13.70 million in 2016)	32.48 million DALYs lost (28% multiplied by 116 million DALYs lost in 2016)[25]	The median annual costs per patient for stroke are approximately 322% higher compared with those for patients with T2DM but without CVD[26]
Pre-diabetes	352.1 million (7.3%) (prevalence of impaired glucose tolerance in 2017)[27]	N/R	N/R	$43.4 billion for pre-diabetes 2017 (the USA only)[9]

CVD: cardiovascular disease; DALY: disability-adjusted life years; GDP: gross domestic product; N/R: not reported; T2DM: Type 2 diabetes mellitus.

PRE-DIABETES

Early identification of patients with pre-diabetes is important to reduce the burden of comorbid diabetes and stroke. A 2017 prospective cohort study compared pre-diabetes definitions that used fasting glucose (American Diabetes Association [ADA] and World Health Organization [WHO]), HbA1c (ADA and International Expert Committee [IEC]), and the 2-hour glucose tolerance test (ADA and WHO). It found that HbA1c pre-diabetes definitions were more specific and provided a better indication of clinical complication risk.[32] However, there is concern that some patients classified as pre-diabetic from glucose testing may be determined to be normoglycaemic when HbA1c alone is used, particularly patients with impaired fasting glucose.[33] Furthermore, HbA1c is only an indirect measure of insulin resistance. There are also issues of availability of HbA1c testing at primary healthcare practices, particularly in certain Asian, African, and South American regions.[34] Capturing

at-risk individuals earlier would reduce the risk of complications associated with diabetes, and the homeostatic model assessment of insulin resistance (HOMA-IR) is a rarely used tool that can indicate insulin sensitivity and β-cell function prior to an increase in glucose levels.[35]

PUBLIC HEALTH APPROACHES AVAILABLE IN TARGETING THIS POPULATION

Public health approaches towards population-level screening and prevention of diabetes and stroke vary across countries. A list of public health strategies implemented in several nations is provided in Table 2.

Role of Primary Healthcare Networks

The role of primary healthcare networks is critical in the early capture and routine monitoring of at-risk patients. Patients should receive serial glucose monitoring and should be categorised into high, moderate, and low-risk groups to determine the necessity for prophylactic anti-diabetic medication and lifestyle management. In Australia, the National Association of Diabetes Centres (NADC) network membership allows primary, secondary, and tertiary level care facilities to collaborate towards better outcomes for patients with diabetes.[3] In the UK, the Diabetes UK Primary Care Network provides monthly newsletters, expert information, and resources to practitioners.[4] In India, the National Programme on Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS), which was launched in 2010, utilises opportunistic screening for hypertension and diabetes for persons above 30 years.[37] The programme functions at all four levels of healthcare: village, sub-centre, community health centres, and district hospitals.[44]

Table 2: Country-level public health strategies in diabetes screening and prevention

Country	Public health strategy
USA	The Centers for Disease Control and Prevention (CDC) prediabetes risk test.[36]
India	National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) focuses on screening of the common non-communicable diseases, at sub-centres, primary health centres, district, and above, through the setting up of non-communicable disease clinics.[37]
China	65% (proportion of deaths caused by diabetes that are attributable to CVD or stroke or both in the USA)[8]
Singapore	352.1 million (7.3%) (prevalence of impaired glucose tolerance in 2017)[27]
New Zealand	Pre-diabetes and self-management pilot projects.[40]
Australia	Reduce modifiable risk factors in the general population (physical activity, healthy eating, education and social media campaigns, healthy food availability, upskill primary healthcare physicians and public health workforce to support patients, especially Aboriginal and Torres Strait Islanders.[41] AUSDRISK tool.[42]
UK	National Health Services Diabetes Prevention Programme ([NHS DPP] identify high-risk individuals and refer them to a behaviour change programme).[43]

AUSDRISK: Australian Type 2 Diabetes Risk Assessment Tool.

Moreover, other community-led initiatives, such as a network of volunteer female community health workers, envisaged to link vulnerable individuals with the public health sector, government health initiatives, and national health programmes.[18] Limited funding and underutilisation are major concerns. Mexico's national Integrated Management of Diabetes in Stages programme at Mexico's Institute for Social Security and Services for State Workers clinics promoted patient empowerment and education nationwide through outpatient consultations with a multidisciplinary team from 2007–2014.[19] An analysis of the programme determined it to be a feasible and suitable programme to address this issue.[20]

Social Prescribing

Social prescribing (SP) is a method used by primary healthcare practitioners, initially implemented in the UK, that aims to connect patients with local and social services through prescription to improve patient wellbeing and health in a variety of areas.[45] A review of SP practices in Bristol, UK, described three different models: SP Light, SP Medium, and SP Holistic. SP Holistic projects aim to play a preventative role and work to improve long-term conditions.[46] They involve partnerships between general practitioners and tertiary care partners and sometimes evolve from SP Light and Medium models. SP Light projects aim to refer at-risk patients to specific programmes to improve outcomes, for example, prescribing exercise to a patient. In SP Medium, a health facilitator will see referred patients and provide advice on exercise, diet, programmes, and mental health support among other resources.[46]

An evaluation of the Community Connectors Social Prescribing Service in Bradford, UK, reported increasing coverage of the population and general practice clinics and found overall improvements of health, mental wellbeing, and social connectedness.[47] An evidence synthesis of available UK studies on SP, however, found that there is not enough evidence to support the effectiveness of such programmes given the lack of uniformity in how practices implement such programmes and the need for more large-scale studies on their impact.[48] SP is gaining attention internationally, and a joint report by the Royal Australian College of General Practitioners (RACGP) and the Consumers Health Forum (CHF) recommended the implementation within the Australian healthcare system to incorporate local, non-clinical services into primary care.[49] Despite emerging benefits, high quality and comparable evaluations of the efficacy and cost-effectiveness of SP as a public health intervention are warranted.[50]

Undiagnosed Diabetes

Undiagnosed diabetes is a major problem in the community, and methods to improve asymptomatic diagnosis are needed. Epidemiological studies have demonstrated the link between insulin resistance and CVD risk, including for stroke.[51,52] The landmark Insulin Resistance Intervention after Stroke (IRIS) trial showed that in insulin-resistant patients (n=3,876) without diabetes who had a recent ischaemic stroke or transient ischaemic attack, pioglitazone, a glucose-lowering drug (thiazolidinediones), reduced the risk of future vascular events, such as stroke or myocardial infarction, by 24%, and progression to diabetes by 52%, relative to those who received placebo.[53] This, along with secondary analyses of IRIS data,[54] highlighted the preferential use of pioglitazone in high-risk patients for stroke with Type 2 diabetes mellitus (T2DM) for primary and secondary stroke prevention.[54,55] More recently, during the COVID-19 pandemic, metformin use has been associated with reduced mortality and severity in patients with T2DM.[56] However, close monitoring for lactic acidosis and deterioration of kidney function is needed in patients with severe COVID-19. Moreover, population-based studies have also indicated association of increased insulin resistance, metabolic syndrome, and diabetes with increased levels of inflammatory markers, such as C-reactive protein, IL-6, and TNF-α.[57,58] Use of such inflammatory biomarkers could also be considered as a useful strategy in screening patients at high risk for CVD. This is especially a problem in under-resourced settings, due to lack of access to primary care physicians, appropriate tests, and immaturity of primary healthcare networks.[59,60] South Asian migrants to highly developed countries such as the UK are at a particularly high risk of CVD, due to a combination of systemic disparities and structural and innate factors. This group is a target group due to their higher risk of

developing T2DM.[61] Similarly, Canadian studies have shown that migrants from South Asia, Sub-Saharan Africa, Latin America, and the Caribbean have a higher burden of diabetes and CVD.[62] A recent study also showed that the prevalence of undiagnosed pre-diabetes in migrant workers in Singapore increased their risk of pneumonia and electrolyte abnormalities from COVID-19.[63]

Recent population studies have indicated a role of retinopathy in screening high-risk individuals (e.g., those who are overweight or have elevated fasting glucose or impaired glucose tolerance) for pre-diabetes.[64-67] Given the wide availability of fundus photography, as well as the ease of delineating retinal lesions, this strategy could be useful; however, this needs further validation and targeted studies in high-risk patients to warrant public health indication.[68] Moreover, an important consideration is the sensitivity of the ophthalmoscopic method. This is because a prevalence of retinal lesions as high as 9.8% using 6-field fundus photography was reported in the Blue Mountain Study,[69] in contrast to <1% in the Framingham Eye Study[70] and Göteborg[71] study in non-diabetic populations.

Community education and partnership in identifying patients at high risk of diabetes are needed, as well as awareness of diabetes in these groups. The development of targeted education modules for demonstration programmes targeted at the populations in their own languages would be beneficial. Furthermore, building the capacity of local community health workers that can teach patients about risk factors, take blood samples, participate in community-based surveillance, and utilise questionnaires to indicate symptoms-based or self-reported diabetes should be the main priority. Also, an increased awareness about post-stroke rehabilitation in patients with diabetes is needed, as these patients should be proactively educated about the risk of secondary stroke.[72,73]

CONCLUSION

There is an increasing need for improving surveillance of diabetes in the community and among primary healthcare networks because of the elevated risks associated with stroke in this subgroup of patients. The proposed shift towards population-based strategies (from patients with T2DM to those with pre-diabetes, metabolic syndrome, or insulin resistance), as well as using preventive measures for high-risk patients, could allow detection of those who are at increased risk of having a stroke. This approach would be helpful to improve the quality of life and reduce the burden of these chronic cardio-metabolic diseases. Furthermore, in the COVID-19 era, given the known risks of increased susceptibility to COVID-19 infections among patients with diabetes or pre-diabetes, as well as their poor clinical outcomes and increased mortality, it is imperative to explore alternative strategies to promptly identify patients at high risk, in order to maximise the opportunity to mitigate the ongoing impact of this devastating pandemic.[74-76] Strategies should also focus on disproportionate burden on vulnerable communities and those from low-resource settings.[75]

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Disparities in Diabetes Care

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Abstract

Disparities in the distribution of diabetes health have been reported by social class, age, gender, and ethnicity and may arise from an interplay of biological, clinical, and non-clinical factors. As well as being morally wrong, these differences in outcome will have a significant adverse effect on a nation's health. As a result, there have been international efforts to reduce inequalities, from the strategic organisation of healthcare to providers and patients themselves, with mixed effects. This article outlines the disparities in diabetes care and outcomes in different patient groups, and how the approach of integration of health and social care may help to overcome some of the adverse aspects of societal organisation that underpins disparities.

INTRODUCTION

Healthcare disparities and inequality are concepts that reflect aspects of differential healthcare access, disease and symptom management, and healthcare outcomes. Health inequalities can be defined as the "preventable, unfair and unjust differences in health status between groups, populations, or individuals that arise from the unequal distribution of social, environmental, and economic conditions within societies, which determine the risk of people getting ill, their ability to prevent sickness, or opportunities to take action and access treatment when ill health occurs."[1] Historically, disparities purely referred to a difference of some kind but, in recent years, the term has come to be synonymous with unfairness and inequality.

Having a focus on improving inequalities, rather than on raising the average health of the nation, is not just a question of fairness and social justice. Inequalities may be readily avoidable by governmental healthcare policy, as well as being economically advantageous to society. Globally, there is a large body of evidence documenting inequalities in access to healthcare and health outcomes in diabetes-related areas.[2-6] The distribution of health is determined by a wide variety of individual, community, and national factors. The Dahlgren and Whithead model (Figure 1) illustrates the contribution size of each layer to health, indicates the feasibility of changing specific factors, and the complementary action that would be required to influence linked factors in other layers.[2]

Inequalities in the distribution of health have been reported by social class, age, gender, and ethnicity. In all countries (whether low-, middle-, or high-income) there are wide disparities in the health status of different socioeconomic groups.[7] Evaluating outcomes by 'ethnicity' is

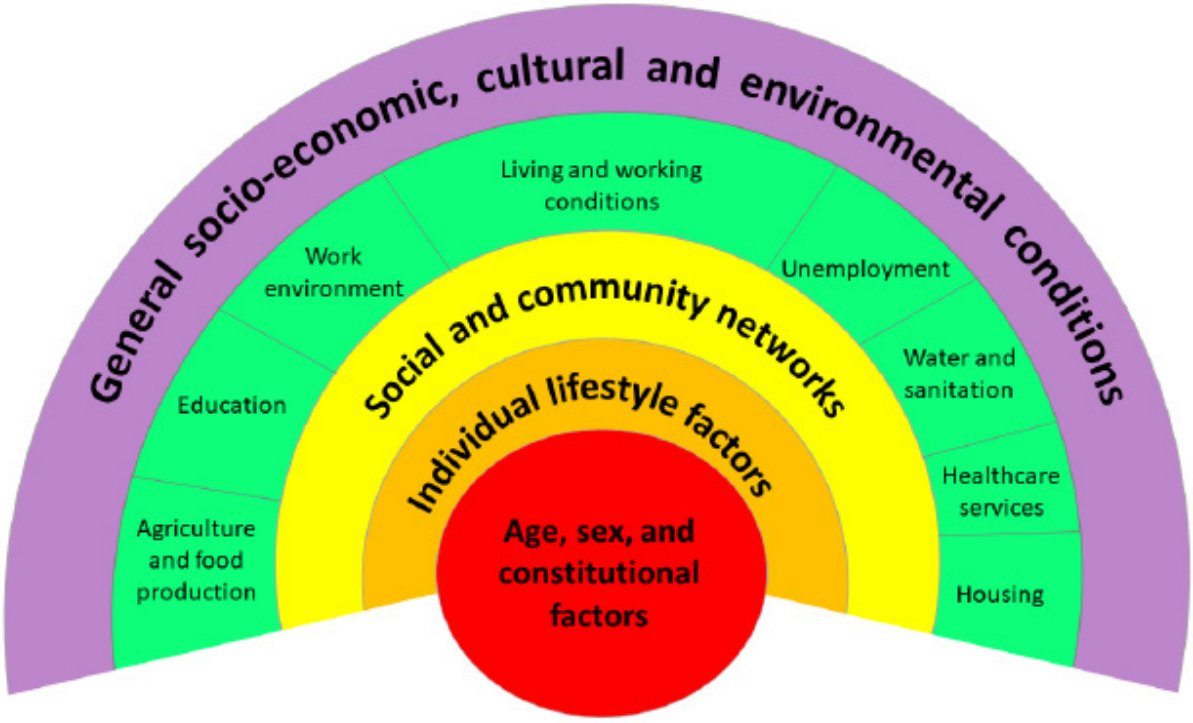

Figure 1: The Dahlgren and Whitehead model maps the relationship between the individual, their environment, and health.

more problematic in that the definition and interpretation of ethnicity is influenced by both historical value systems and the current social and political context. For example, reference to 'Asian' minority groups in USA (often south-east Asian diaspora) may differ to that of UK (often the Indian subcontinent).

Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) are both considered to be life-long conditions (with bariatric surgery and very low-calorie diets being notable exceptions leading to T2DM remission), whose aetiology has environmental and genetic contributions. From the outset, therefore, the impact on populations will be unequal. Diabetes is one of the most common chronic diseases and places a sizeable burden on patients, healthcare systems, and society. The International Diabetes Federation (IDF) estimate that nearly 700 million adults will be living with diabetes worldwide by 2045.[8] Diabetes is among the top 10 causes of adult mortality, and was estimated to have caused 4 million deaths globally in 2017.[9] The burden of morbidity and mortality from diabetes is unequally shared, and these disparities in diabetes outcomes arise from a complex interplay of biological, clinical, and non-clinical factors.[10] These factors will be explored in this article.

SEARCH METHODOLOGY

The authors searched English-language literature to identify all relevant studies in the last decade; from the year 2010 to the present date, regardless of publication status. They searched PubMed and Google Scholar databases, combining the terms 'diabetes' AND 'disparity' OR 'inequality' AND 'socio-economic' OR 'minority' OR 'ethnicity'. The authors have not covered gender disparities, which are extensively covered elsewhere.[11] They applied backward and forward snowballing to identify further papers. An extensive list was developed, and a shortlist was created based on the limitations of the length of the narrative review and importance of the marker. The last search was performed in June 2021.

EPIDEMIOLOGY OF DIABETES DISPARITIES

Inequalities in Diabetes Incidence

The incidence of T1DM increases towards the Northern and Southern poles of the world. Even within the UK, Northern areas of Scotland will have a higher incidence than in the South. Worldwide, disease onset of T1DM is associated with higher socioeconomic status (SES). In Europe, higher rates are reported in host White populations but increasing rates in second-generation migrants are reported.[12] T2DM is predisposed by obesity, which is itself socially patterned, with higher rates in lower socioeconomic groups. In the USA, diabetes is 60% more common in Black Americans than in White Americans,[13] and Indigenous American and Alaskan Native populations have diabetes prevalence twice that of the general population.[14] In the Pacific, diabetes disproportionally affects Hawaiian and Pacific Islander populations, the latter group having much higher rates in New Zealand than the White population.[15] Within Western European countries, the prevalence of T2DM is higher in ethnic minorities, particularly in those of South Asian, Middle Eastern, and North African origin.[10] Ethnic minority groups are also likely to develop T2DM at a younger age (up to 12 years younger), compared with their White counterparts.[10]

Disparities in Rates of Diabetes Complications and Control

Macrovascular

In a recent meta-analysis of worldwide studies (from USA, Canada, UK, and New Zealand), greater all-cause mortality in diabetes is not seen in Black or Asian populations compared with White populations. However, there remains a significantly greater mortality in the Māori population than the White population in New Zealand.[15] Behind this headline figure, there are differences in subtypes of cardiovascular disease. Cardiovascular disease is more prevalent in the Indigenous American and Alaskan Native populations than the non-Hispanic White population (14.7% compared with 12.2%, respectively).[14] Hispanic American participants have a lower risk of CVD than White participants (hazard ratio: 0.66 [95% confidence interval: 0.53–0.81]).[15] Black people with diabetes have an equivalent overall cardiovascular event rate to White people, but Black individuals tend to have an equal or lower risk of coronary heart disease.[15] This may relate to higher high-density lipoprotein cholesterol and lower triglyceride levels (unattributable to dietary difference)[16] compared with White people.[17] It is important to consider that rates can change with acculturation.[10]

The prevalence of diagnosed and undiagnosed hypertension among African American males (42.4%) and females (44%) ≥20 years of age in the USA is higher than the expected base rate of approximately 30%.[18] The origins of adult differences in hypertension begin early, with 13.8% prevalence of hypertension in African American youths versus 8.4% in the White subgroup and 10.4% in Hispanic populations.[19] Likely as a consequence of this, Black people in the USA between 45- and 64-years-old have a 3-fold higher risk of stroke compared to the White community.[20] Conversely, ethnic differences in risk of stroke have not been evident in the UK.[21,22]

Microvascular

Retinopathy

Predictors for diabetic retinopathy include older age (and younger age at diabetes diagnosis), male sex, Black and Asian race, socioeconomic deprivation, and occupation.[23] In the USA, rates of retinopathy are higher among non-White ethnic groups,[24] whereas in the UK, risk of retinopathy is equal in both Black and White populations[25] and lower in the South Asian community.[26] Adverse retinal outcomes including sight-threatening retinopathy in those with lower SES persist despite universal screening programmes.[27] Underpinning this microvascular burden is greater prevalence of vascular risk factors. Patients living in deprived areas will less often achieve glycaemic control targets and tend to have higher blood pressure and worse lipid profile control.[28]

Kidney disease

It is consistently reported that ethnic minorities have a higher prevalence of diabetes and chronic kidney disease than White individuals.[15,29] For example, in the USA, Hispanic individuals have a 2-fold and Black individuals a 3- to 4-fold

greater risk compared to White individuals.[15,30] In the UK, people of both South Asian and Black ethnic origin have 3- to 4-fold higher rates of acceptance onto renal replacement therapy than White individuals,[31] which can only be partly explained by a higher prevalence of T2DM and hypertension (in the Black population).

Neuropathy and foot care

Despite a lower prevalence of clinical neuropathy in South Asian individuals compared to individuals of White or Black African or Caribbean ethnicity, in the UK people of an Asian background with T2DM appear at greater risk of painful diabetic neuropathy.[32]

There are international differences in the epidemiology of diabetic foot disease, which could be explained by the differences in economic viability and governmental infrastructures. However, there is also marked variation within countries. In the USA, the risk of foot ulceration and lower limb amputation tends to be greater in non-White people,[33,34] but in the UK this is not the case. Compared with White Europeans, Black individuals of African or Caribbean or South Asian descent have been found to have a reduced risk of lower limb amputation.[35,36] Socioeconomic disparities in diabetic foot care have been demonstrated, particularly in the USA, where there is a greater prevalence of lower-extremity amputations and peripheral vascular disease in lower-income regions and minority groups.[5]

CONTRIBUTORS TO DISPARITIES IN OUTCOMES

Biological Factors for Diabetes and Its Complications

Whether genetic factors contribute to ethnic inequalities in T2DM is unclear as there have been so few studies of ethnic minorities in Western countries. The interplay with the environment is not to be underestimated, as rates of T2DM are four times higher for those of Indian ancestry living in Western Europe compared to rates in the Indian subcontinent, and even higher for those of African descent.[10] Differences in fat distribution between the visceral and subcutaneous depots between ethnicities will affect insulin resistance and partly contribute to the higher rates of diabetes in the South Asian and Black African ethnic groups.[10] Higher post-prandial glucose, implicated in cardiovascular disease, has been reported in South Asians.[37,38] There remains uncertainty as to whether the predominant pathophysiological mechanism in the development of T2DM differs according to ethnicity, particularly regarding β-cell secretory capacity. Genetic markers for T2DM appear to differ between racial groups, but it remains uncertain as to how much these account for disparity in diabetes prevalence.[39] However, more data output for complication risk is needed. For instance, risk variants in the *APOL1* gene on chromosome 22, initially discovered in the African American population, are associated with an increased risk of kidney disease.[15]

Social Determinants of Health

SES is a multifaceted formulation that includes educational, economic, and occupational status. Each contributes overlapping properties to health. An individual's highest attained level of education is generally reached in early adulthood. Thereafter, their health will be driven by living conditions, better healthcare, and lifestyle (Figure 2).[40] Their income will dictate the built environment in which they live and their access to food and affordable healthcare. Their occupation may be associated with toxic environmental exposures and food availability.

People from lower SES may engage less with healthcare and have higher rates of non-attendance to appointments. Cumulatively, low SES can have the same adverse impact on health as smoking or low exercise levels.[41] The effect of macroeconomic factors on diabetes was well illustrated by the economic recession of 2008. Living in towns with higher household incomes led to the achievement of significantly better performance in diabetes care indicators.[42] More generally, there are no data as to whether changes in income, higher educational status, or different employment/occupational status improves diabetes outcomes.

Disparities in Quality of Healthcare and Access to Drugs and Technology

Those at highest need are reported to be the least likely to receive healthcare, a phenomenon known as Hart's inverse care law (Figure 3).

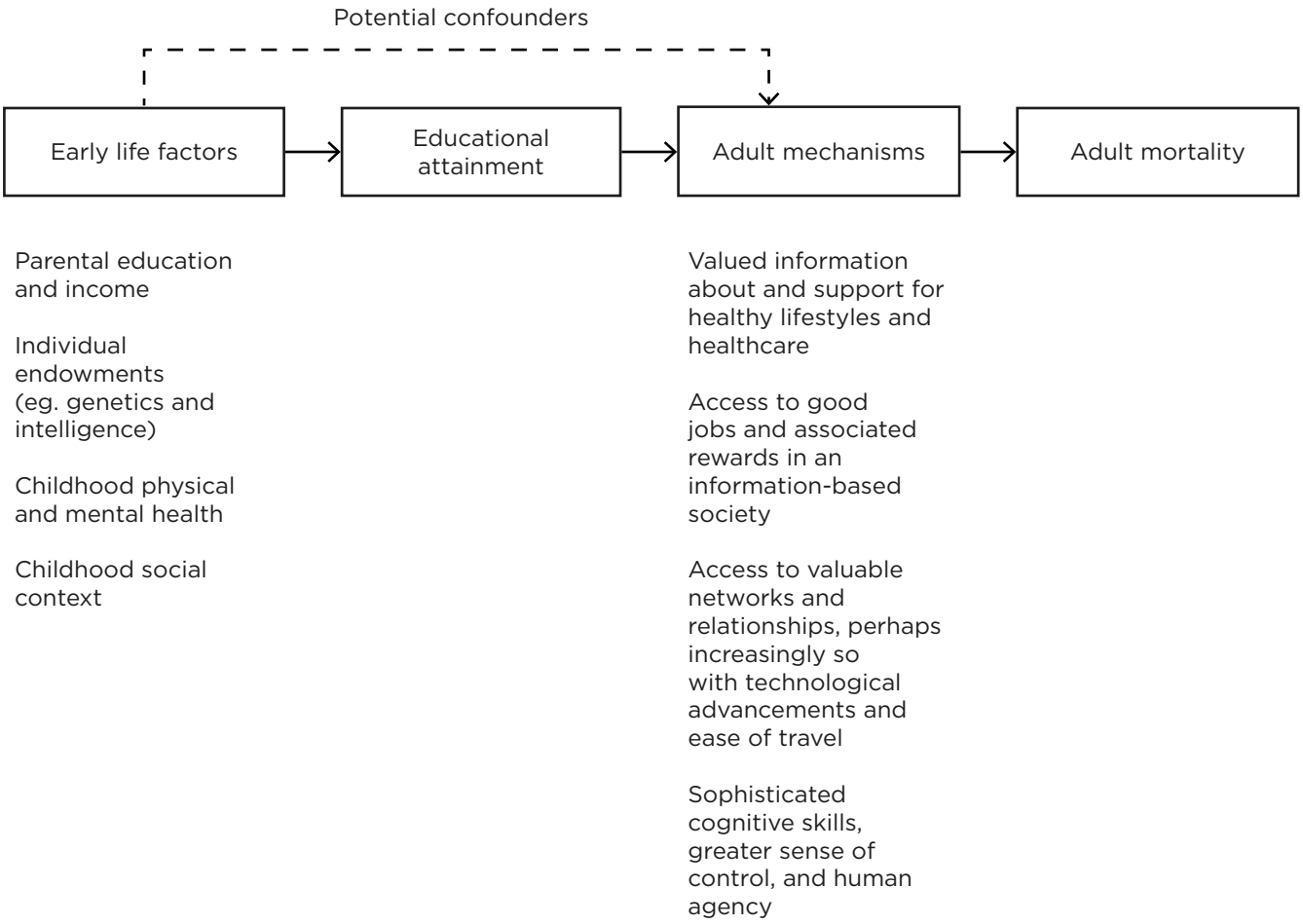

Figure 2: The relationship between educational attainment and adult mortality.

Reproduced with permission from Hayward et al.[40]

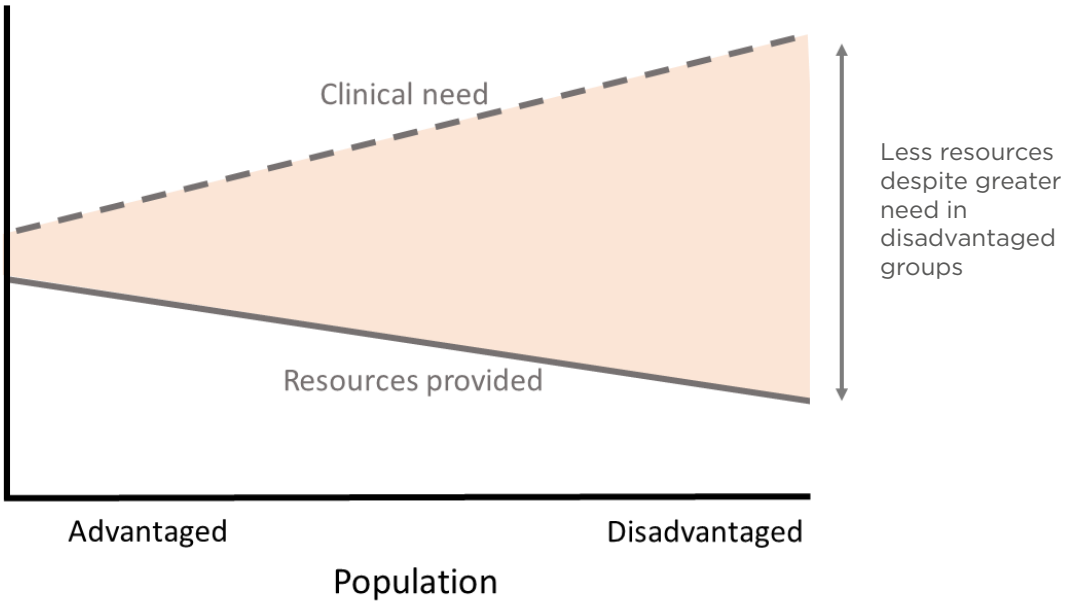

Figure 3: Hart's inverse care law.

In contrast, socially disadvantaged people in high-income countries may receive more healthcare, but it is of worse quality and insufficient quantity to meet their additional needs, known as the 'disproportionate care law'. In addition to the availability of healthcare services and the quality of the services offered, Goddard and Smith highlighted two other reasons for variations in access to healthcare: direct and/or indirect costs of healthcare, and the quality of information provided to all population groups.[43] Groups who are considered hard to reach tend to access health services less frequently and suffer poorer health outcomes. Such people may include minority ethnic groups, the homeless, asylum seekers, the unemployed, the elderly, people with learning disabilities, and people with mental health or substance misuse problems. These individuals may ill-afford access to healthcare and/or be provided with unsuitable information.

In a 2016 publication, the IDF reported that access to diabetes drugs in developing countries was a particular concern.[4] For instance, metformin is usually the first-line treatment for T2DM, but comprehensive government provision of metformin was limited to 10% of low-income countries versus 72% of high-income countries.[4] Access to sulfonylureas and dipeptidyl peptidase 4 inhibitors fared worse, with none of the low-income countries having government provision. Similar trends existed for insulin. Consequently, people from low-income countries can spend up to two-thirds of their disposable income to pay for insulin and essential consumables associated with insulin administration such as needles and glucometers, both of which were sparser than insulin.[4]

Disparities in prescribing trends also exist within developed countries. In the UK and Australia, SES is a key determinant of disparity in glycaemic control and for the prescription of newer therapies for T2DM.[6] Ethnicity also leads to variable prescribing. In the UK, people of Asian ethnicity were 32% less likely to be prescribed sodium–glucose co-transporter-2 inhibitors and 63% less likely to be prescribed glucagon-like peptide-1 agonists.[28] One factor that may affect prescribing is the reliance on BMI in therapeutic decision trees. According to the World Health Organization (WHO) classifications, a BMI of 30 kg/m^2 is considered obese. However, this threshold is not suitable for people with Black, Asian, and minority ethnic backgrounds, who have the same risk for T2DM and at a BMI of 27 kg/m^2 and 22 kg/m^2, respectively, as their White counterparts would with a BMI of 30 kg/m^2.[10] As prescribing of glucagon-like peptide-1 agonists is often based on BMI, this will have the effect of discriminating against the non-White population.

Many diabetes drugs require dose reduction or cessation with kidney impairment. Calculations for the estimated glomerular filtration rate adjust for ethnicity, which may itself entrench disparity. A recent study showed that removal of race adjustment may increase diagnoses of chronic kidney disease among Black adults and, thereby, enhance access to specialist care. However, such a change may also prompt drug contraindications or dose reductions for individuals who are reclassified to advanced stages of chronic kidney disease.[44] Consequently, people from African Caribbean backgrounds may have an underestimate of the estimated glomerular filtration rate and, thus, may be wrongly denied access to therapy such as sodium–glucose co-transporter-2 inhibitors.[28,44]

Recent advances for T1DM diabetes include continuous glucose monitoring devices and insulin pump therapy. Significant variations exist in access to such technologies, which are associated with suboptimal glycaemic control. Increasing age is negatively correlated with computer literacy, hence the increase in diabetes technology use has primarily benefited young and middle-aged individuals.[45] Regional variation in provision also affects use. There is a ten-fold variation in insulin pump use across specialist centres in the UK.[46] People from lower SES groups tend to have reduced computer use and computer experience, although this has lessened in recent years.[47] This digital divide restricts access to technologies where home-based uploading of data is required. The uptake of virtual consultations for diabetes during the COVID-19 pandemic may exacerbate this disparity in computer-access and literacy.

INTERVENTIONS TO REDUCE DISPARITIES

Interventions to reduce disparity can occur at various levels, as depicted on the Dahlgren and Whitehead model (Figure 1), from the individual to wider-scale healthcare and societal organisation.

Healthcare Organisation

The principal determinants of inequalities in health are national socioeconomic factors and the physical and social environment.[48] The complexity of the causes of inequalities in health means that multifaceted and, therefore, multi-sectoral action is required to tackle the problem. A key component is the organisation of the healthcare system and interventions here have the potential to effect significant changes in healthcare processes and health outcomes. Provision of universal coverage is a necessary, but not sufficient, requirement for achieving equity in healthcare. In diabetes, supporting evidence comes from population-based studies: having health insurance is the strongest predictor of whether individuals have access to diabetes screenings and care.[49]

National retinopathy screening programmes can help to equalise access to ophthalmic support and ensure people of all ages have regular risk-stratification to prevent worsening retinopathy and blindness. A difficulty in determining the effect of screening programmes or preventive therapy is the 'healthy user effect'. This arises as healthier patients are more likely to attend screening programmes and/or more likely to request prescriptions for preventive therapies. Non-attendance to screening appointments exhibits a bimodal distribution, with higher rates in those between 16–30 years of age and a second peak in patients over the age of 90 years.[30] Automated appointment reminders aim to improve this but fall foul of disparities in computer literacy.

Pay-for-performance strategies, which financially reward the achievement of targets such as blood pressure and cholesterol, were introduced to strengthen primary care in UK but have been found to fall short of addressing the disparities in diabetes management between minority ethnicity groups.[50]

Approaches for Medical and Social Care Integration

Given that diabetes is predominantly managed in the community, successful interventions should be based in the community setting. Two main types of intervention to address social determinants of health are compensatory interventions, which provide support to enable individuals to fill gaps and access otherwise inaccessible or unavailable resources; and root cause interventions, which are designed to change underlying structures or systems, rather than compensate for them.[51]

An example of the former is the National Diabetes Prevention Plan in the USA and the National Health Service Diabetes Prevention Programme (NHS DPP) in the UK. Each supports those at high risk of T2DM to reduce their risk via a supported lifestyle intervention to achieve a healthy weight, improve nutrition, and increase physical activity. The standardised training of facilitators and certification serves to reduce disparity in quality between centres. A root cause approach to diabetes prevention may instead include components such as residential environment planning, allowing for walking and cycling, or the restriction of unhealthy businesses (e.g., fast foods) in low-income areas.[52]

Individual Healthcare Providers

Most interventions to reduce diabetes disparities by SES have been conducted in industrialised countries.[53] Positive interventions include cultural tailoring of the intervention; community educators or lay people leading the intervention; one-on-one interventions, incorporating treatment algorithms; and high-intensity interventions (at least 10 appointments) delivered over a long duration (≥6 months). Less useful interventions were didactic teaching or interventions focused only on diabetes knowledge.[53] One possible mediator of ethnicity on health disparity is the presence of a language barrier. Interpreter services in the USA have led to a greater frequency of health visits and completed prescriptions[54] and, in the UK, patients with language barriers seen at language-concordant providers in primary care have reduced diabetes-related hospital admissions.[55]

Patients

Structured education and self-management are considered vitally important for diabetes care and yet self-deterministic interventions may widen inequalities, as disadvantaged groups are less likely to participate.[56] Approaches that address financial burden as well as work and environment-related factors are essential for enhancing diabetes self-management.

Individual behaviours relating to food choice, inactivity, smoking, and alcohol need to be addressed. Smoking is significantly more common in socioeconomically deprived areas. Although rates are declining, this has been slower in disadvantaged groups.[57] Differences in alcohol-related harm exist across Europe, where consumption of alcohol is the highest per capita in the world.[58] In general, alcohol-related harm is greater in people from lower SES groups, even if consumption is equal to more affluent counterparts.[58] Education may paradoxically worsen inequalities of alcoholism, whereas measures limiting the availability of alcohol, including price rises and licence restrictions, has a disproportionate effect on lower SES groups.[58]

CONCLUSIONS

Disparities in diabetes care continue to exist between and within nations. These disparities lead to higher-risk groups having less access to optimal treatments for both T1DM and T2DM. They also contribute to the variation in microvascular and macrovascular complication rates. It is important, morally and for societal health at large, that these inequalities are addressed. Differences in morbidity between ethnic minority populations in North America and the UK are unlikely to be attributed to genetic differences but, rather, they infer differences in healthcare systems and healthcare access. Strategies to reduce health inequalities must be based on a societal healthcare policy. The implementation of strategies will need to be intersectoral and multidisciplinary. It is vital that interventions must be adequately funded and comprise of tailored interventions that are culturally sensitive, local to the individual with diabetes, and not didactic in nature.

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Socio-demographic Determinants of Attendance in Diabetes Education Centres: A Survey of Patients' Views

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Abstract

Introduction: Diabetes is a global medical condition associated with a huge human and financial cost. However, early detection and appropriate pharmacological and non-pharmacological interventions, such as structured patient education, are useful measures to reduce its impact. Although the benefits of educational intervention are well recognised as a key component of empowerment, motivating attendance in diabetes education centres remains problematic, and this has a negative impact on healthcare finances.

Objective: This survey study sought to identify the socio-demographic determinants of attendance at diabetes education centres.

Methods: A questionnaire survey of 207 patients from four diabetes education centres was conducted.

Results: In predicting attendance from demographic variables, the regression analysis showed that the participants that were living alone are less likely to attend, while participants who have a flexible working environment are more likely to attend the sessions.

BACKGROUND

People with long-term conditions such as diabetes are at greater risk of comorbidity, and anecdotal evidence suggests that it can increase the burden of ongoing COVID-19 pandemic infection.[1-3] Diabetes is characterised by elevated blood glucose levels,[4] and consistently high levels of glucose can lead to life threatening complications such as nephropathy, retinopathy, and gangrenous foot ulcers.[3] Thus, diabetes has a negative physical, psychological, social, and economic impact on the affected individual.[5] Despite significant advancements in diabetes care, there has been a global upsurge in the prevalence of diabetes within the last decade.

The development of structured patient education as a form of therapy has a positive impact on diabetes management, and has tremendously improved the level of awareness, consequently helping to reduce avoidable complications.[6] Nevertheless, attendance at diabetes education

centres is important to achieve the goal of educational intervention. Evidence indicated that barriers to attendance at diabetes education centres are due to various factors, such as demographic characteristics of the patient and organisation of care.[5-7] The individual is unique, with varying socio-demographic characteristics that may either influence or hinder attendance. Although some studies have identified the socio-demographic characteristics of non-attenders, there is little research to discern whether these factors can be used to predict attending behaviour.

RESEARCH DESIGN AND METHODS

A survey of two groups of patients was conducted in four selected hospital sites in the South East of England. These settings were chosen because of the number of attritions from diabetic education sessions and its demographical differences. The research followed the principles outlined in the Declaration of Helsinki, and was conducted according to the ethical codes guiding research in England.[8,9] Ethics approval for this study was granted by Berkshire Research Ethics Committee. Similarly, the participant's consent was sought at the beginning of each data collection stage, with freedom to withdraw at any time.[10] The aim of this study was to examine the influence of socio-demographic characteristics on attendance, and to discern whether these factors can be used to predict attending behaviour.

The access to the participants was gained through the general practitioners' register in the primary care trust, and a purposive sample of 207 newly diagnosed patients with diabetes were surveyed. The criterion for selecting eligible patients was all the recently diagnosed patients who had been referred to diabetes education centres for a structured patient education programme within the last 12 months. The researcher performed a power calculation to determine the required sample size for the questionnaire.[11,12] The calculation was based on Cohen's (1988) effect size guide (correlations: small=0.1; medium=0.3; large=0.5). It was calculated that a total number of 176 participants (n=88 in each group) would be needed to generate a moderate effect size of 0.3 at a power rate of 0.95, which was sufficient for this study.

The instruments were administered to attenders through face-to-face interactions during diabetes education sessions, while postal technique was used for non-attenders and data analysis was carried out in three phases.[11,13] In addition to descriptive statistics such as frequency distribution, percentages, cross tabulations, and correlations between variables that are deemed to be important in answering the research questions, Chi-square was used to compare both groups, and therefore show if there were differences between the expected and observed frequencies between the two groups. Finally, logistic regression was used to produce a model that predicts which variables might lead to non-attendance.[11,12,14] As the exact p-value will be reported in the text, the α level used as a significance criterion for all the statistical tests is $p \leq 0.05$. From a positivist perspective, Statistical Package for the Social Sciences (SPSS) software (IBM, Armonk, New York, USA) was employed to analyse the quantitative data, and the results are presented below.[12]

SOCIO-DEMOGRAPHIC DATA

Age Distribution of Participants

Table 1, showing the age distribution of participants, revealed that the age distribution of majority of the participants ranged between 41 years and 65 years (n=137, 66%) and approximately one-fifth (n=39, 19%) were over 66 years of age. There was an equal number of females (n=7) in both groups within the age range of 40 years and below. Of the 31 participants who were under 40 years, n=19 were living alone, while n=7 were living with family. The majority of the middle-aged participants within the age range of 40 years to 65 years were living with a partner. Nevertheless, Chi-square analysis of this data showed no statistically significant association between the age of both groups and attendance behaviour: X^2 (2; N=207): 3.39, p=0.183.

Gender of Participants

As shown in Table 1, the gender distribution of both groups is similar. However, there were fewer males (n=10) than females. In all, 42 males were White, 23 were Asian/Asian British, and 20 were Black/Black British, while 66 females were White, 29 were Asian/Asian British, and 7 were

Table 1: Patient socio-demographic data.

Characteristics	Participants		Pearson Chi-squared
	Attenders (N=102)	Non-attenders (N=105)	
Age in years			
40 years and below	n=11 (10%)	n=20 (19%)	p=0.183 (p>0.05)
41–65 years	n=73 (72%)	n=64 (61%)	
66 years and above	n=18 (17%)	n=21 (20%)	
Gender			
Male	n=52 (51%)	n=46 (44%)	p=0.203 (p>0.05)
Female	n=50 (49%)	n=58 (55%)	
Ethnicity			
White	n=67 (65%)	n=42 (40%)	p=0.002 (p<0.05)
Asian/Asian British	n=16 (16%)	n=36 (34%)	
Black/Black British	n=13 (13%)	n=14 (13%)	
Mixed race	n=2 (2%)	n=4 (4%)	
Chinese	n=1(1%)	n=6 (6%)	
I have flexible work commitments			
Yes	n=78 (76%)	n=43 (41%)	p=0.001 (p<0.05)
No	n=24 (24%)	n=59 (56%)	
Living arrangements			
Living alone	n=13 (13%)	n=46 (44%)	p=0.001 (p<0.05)
Living with partner	n=64 (63%)	n=49 (47%)	
Living with family	n=24 (23%)	n=7 (6%)	
Other	n=0 (0%)	n=3 (3%)	
Family history of diabetes			
Yes	n=29 (28%)	n=64 (61%)	p=0.001 (p<0.05)
No	n=73 (72%)	n=39 (37%)	
I can communicate well in English language			
Yes	n=98 (96%)	n=96 (91%)	p=0.077 (p>0.05)
No	n=3 (3%)	n=9 (9%)	
I have a specific learning need			
Yes	n=4 (4%)	n=11 (10%)	p=0.052 (p>0.05)
No	n=98 (96%)	n=91 (87%)	

Black/Black British. Out of this number, a higher number of males in the non-attenders group (n=21) were living alone as compared to the attenders (n=7). Overall, the data on male/female ratio of the participants in both groups showed no statistically significant association between gender and attendance behaviour: χ^2 (1; N=206): 0.94, p=0.203.

Ethnic Origin of Participants

Table 1 shows that slightly more than half (n=109, 53%) of the participants were from a Caucasian background, and a quarter were Asian (n=52, 25%). Other minority ethnic groups constituted less than a quarter (n=41, 20%) of the participants. The majority of the White participants (n=75) did not have a family history of diabetes, while

more than half of Asian participants (n=36) had a history of diabetes in their family. The data revealed that more White participants among the attenders (n=54) have flexible working commitments as opposed to the non-attenders (n=19). The Pearson Chi-square analysis of this data indicated an association that achieved statistical significance between attendance behaviour and ethnicity: χ^2 (5; N=202): 18.68, p=0.002.

Type of Working Environment of the Participants

From the data in Table 1, 24 (24%) of the participants who attended the session had an inflexible work environment whilst more than three-quarters (n=78, 76%) had a flexible work environment. Against this figure, the data for non-attenders revealed that more than half of them (n=59, 56%) did not have a flexible working environment and (n=43, 41%) did, whilst (n=3, 3%) did not answer the question. Unlike the non-attenders with a close margin, the margin between those that had flexible working environments (76%) and those that did not have flexible working environments (24%) amongst the attenders is very wide. This data shows an association that is statistically significant between working commitments and attendance behaviour: χ^2 (1; N=204): 24.88, p=0.001.

Living Arrangements of the Participants

The living arrangements of participants who attended the session revealed that almost two-thirds (63%) were living with a partner while less than half (47%) of non-attenders were living with a partner. On the other hand, a greater number of non-attenders were living alone n=46 (44%) as opposed to n=13 (13%) amongst the attenders. The overall data showed that more participants who were living with a partner (n=112) or living with a family (n=30) had a flexible work environment as compared to those living alone (n=59). An association that achieved statistical significance was observed between the living arrangements and attendance between the two groups: χ^2 (3; N=206): 32.71, p=0.001, as shown in Table 1.

Family History of Diabetes amongst Participants

More attenders did not have a family history of diabetes, while almost two-thirds of non-attenders (n=64, 61%) had a history of diabetes in their family (Table 1). Although more than half of the total number of participants had no family history of diabetes (n=112, 54%), the majority of them were attenders (n=73, 65%), showing a statistically significant association between family history and attendance behaviour between the two groups: χ^2 (1; N=205): 23.49, p=0.001.

Level of Communication of the Participants

As shown in Table 1, only a minority of participants have problems with speaking English. Out of this minority (n=12), the number of non-attenders (n=9) who could not communicate well in the English language was triple in the number of attenders (n=3). This study found no statistically significant association between communication and attendance behaviour: χ^2 (1; N=206): 2.94, p=0.077, as the majority of both groups can communicate well in the English language.

Learning Requirements of Participants

The question on socio-economic data presented in Table 1 showed that an overwhelming number of both groups had no specific learning needs (n=189, 91%), which unsurprisingly revealed no statistically significant association between learning needs and attendance behaviour: χ^2 (1; N=204): 3.53, p=0.052. Out of 15 participants who had a specific learning need, n=9 were female and n=6 were male.

ANALYSIS OF FINDINGS

A total of 207 participants completed the questionnaire, and the sample comprised 102 participants who attended the sessions and 105 participants who did not attend. Table 1 shows a breakdown of the socio-demographic characteristics of the participants. The majority of both attenders and non-attenders fell between the age range of 41 years and 65 years (73 versus 64; p>0.05) and this reflects the epidemiology of Type 2 diabetes mellitus.[15,16] Differences in ethnicity were observed for non-attenders versus attenders[17] (Caucasian: 67 versus 42;

Asian 16 versus 36; p<0.05) while the gender distribution of both groups was similar (p>0.05). A significantly higher percentage of attenders had a flexible work environment (78 versus 43; p<0.05) and more non-attenders were living alone (46 versus 13; p<0.05), while more attenders did not have a family history of diabetes[6] (73 versus 39; p<0.05). Data from the study revealed no significant differences in their level of communication and specific learning needs (p>0.05).

The series of Chi-square tests of association between attending behaviour and the various socio-demographic variables identified four variables that showed statistically significant associations; therefore, logistic regression was performed on: ethnicity, living arrangements, family history of diabetes, and flexibility of working environment (Table 2). The results in Table 2 show that living arrangements (p<0.001), employment (p<0.001), and family history of diabetes (p=0.05) added to the prediction, while ethnicity (p>0.05) did not add significantly to the model. The category 'living arrangements 1' (living with family) is a significant predictor of attendance (p=0.004) and the odds ratio is 3.33. This indicates that the participants who were living with family are three-times more likely to attend.[12] Equally, the category 'living arrangements 2' (living with partner) is also a significant predictor (p=0.001) and the odds ratio is 16.35, denoting that participants who were living with partners are 16-times more likely to attend the session than those who do not. However, category 'living arrangements 3' (living alone) is not a significant predictor (p=0.999). Employment is also a significant predictor (p=0.001), and the odds ratio is 4.38. This shows that participants

Table 2: Logistic regression analysis of demographic data of the participants (N=207).

95% CI for Exp(B)							
Independent variable	**B**	**SE**	**Wald test**	**Sig**	**OR**	**Lower**	**Upper**
Living Arrangements	N/A	N/A	20.063	0.000	N/A	N/A	N/A
Living with family	1.201	0.4220	8.113	0.004	3.330	1.450	7.590
Living with partner	2.794	0.6360	19.292	0.000	16.350	4.690	56.880
Living alone	N/A	27,243.7600	0.000	0.999	0.00	0.000	20.174
Ethnicity	N/A	N/A	8.401	0.038	N/A	N/A	N/A
White	-1.113	0.4620	5.803	0.016	0.328	0.133	0.813
Asian/Asian British	-0.219	0.5690	0.148	0.701	0.803	0.263	2.450
Black/Black British	-1.367	0.6860	3.972	0.046	0.255	0.066	0.978
Flexible working	1.478	0.3700	15.973	0.000	4.380	2.123	9.040
Family history of diabetes	-0.722	0.3688	3.847	0.050	0.456	0.236	1.000
Constant	-1.212	0.5000	5.877	0.015	0.298	N/A	N/A

Model x^2=78.19, p<0.001.

Pseudo R^2=0.43 (Nagelkerke R-square). B: coefficient for the constant; CI: confidence interval; Exp(B): exponentiation of the B coefficient; N/A: not applicable; OR: odds ratio; SE: standard error.

who have a flexible working environment are four-times more likely to attend the sessions.[12] The logistic regression showed that ethnicity and family history of diabetes were not significant predictors of attendance.

DISCUSSION

There were similarities in age and gender with variations in living arrangements, ethnicity, employment, and family history of diabetes. The findings showed a wide ethnic variation between the two groups of patients within the four localities, and this reflects Britain's multi-cultural society.[18,19] It is reasonable to assume that ethnicity is going to be a predictor of attendance; however, ethnicity was not a significant predictor in this sample ($p>0.05$), with an odds ratio of less than 1. Different cultural backgrounds have different expectations, and there is a link between culture and perception to healthcare utilisation;[20] therefore, this finding is surprising. However, in addition to English language sessions, the provision of education in an area of the Trust with a high ethnic minority covers a separate session in another language (Punjabi). The findings suggest that communication and learning needs was not a significant barrier in this sample, and this contradicts the studies of Rhee et al.[21] and Graziani et al.,[22] which revealed that a low level of education and an inability to read well constitute a significant obstacle to attendance. It is important to establish that both studies were conducted outside the UK, and it could be partly due to availability of education sessions in some other languages.

The model suggested that, although three socio-demographic variables have value in predicting attendance behaviour, the two key predictors for the sample in this study are living arrangements and working environment. This finding is compatible with Hsu and Gallinagh,[23] who found that living alone was associated with a low uptake, but found no association between attendance and age. Similarly, several authors have identified work and a family history of diabetes as barriers to attendance,[7,22,24-26,] and this is congruent with the findings of this study. Whilst family history of diabetes achieved significance ($p=0.05$) in this study, the odds ratio was low; however, it does merit further research in the future in terms of its predictive ability.[12] Evidence from epidemiological studies[27-29] is increasingly suggesting a link between socio-demographical characteristics of the patient and compliance to healthcare interventions. Changing behaviour is a complex process;[5,30] therefore, the authors' study suggested the need to recognise the impact of socio-demographical factors as an important modifier in the change process.

LIMITATIONS OF THE STUDY

The use of purposive sampling technique and small sample size of participants in the current study suggest that it cannot be generalised to non-attenders in clinical settings in the UK. With a response rate of 25.8% among the non-attenders after three repeated follow-up questionnaires, there is a possibility that valuable information could have been missed from those that have decided not to participate in the study. Additionally, there may be a self-report bias. These limitations of survey study are well documented in literature;[14,31] however, this research has thrown more light on this phenomenon of non-attendance in diabetes education centres.

SUMMARY

Although both the national and international response to diabetes prevention and management includes empowerment, it has always been challenged by the number of wasted appointments. This study has contributed to the body of knowledge on non-attendance in clinical practice and the findings confirm the importance of considering demographic characteristics when providing educational intervention (Box 1). Thus, expanding the understanding of these factors is crucial for healthcare providers and educators to identify additional support that the patients may require when devising healthcare interventions. In all, the implications of this result should be interpreted within the context of the limitations of the project. Additionally, the authors recommend conducting a further large-scale study covering several hospital trusts across the country.

Box 1: Implications for practice.

- Barriers to attendance are complex and sometimes beyond the control of patients.
- Recognising individual uniqueness is important to promote patient engagement.
- Considering patient's socio-demographic data is important to aid concordance.
- Poor healthcare utilisation has a negative financial impact on the NHS and the taxpayers.

NHS: National Health Service.

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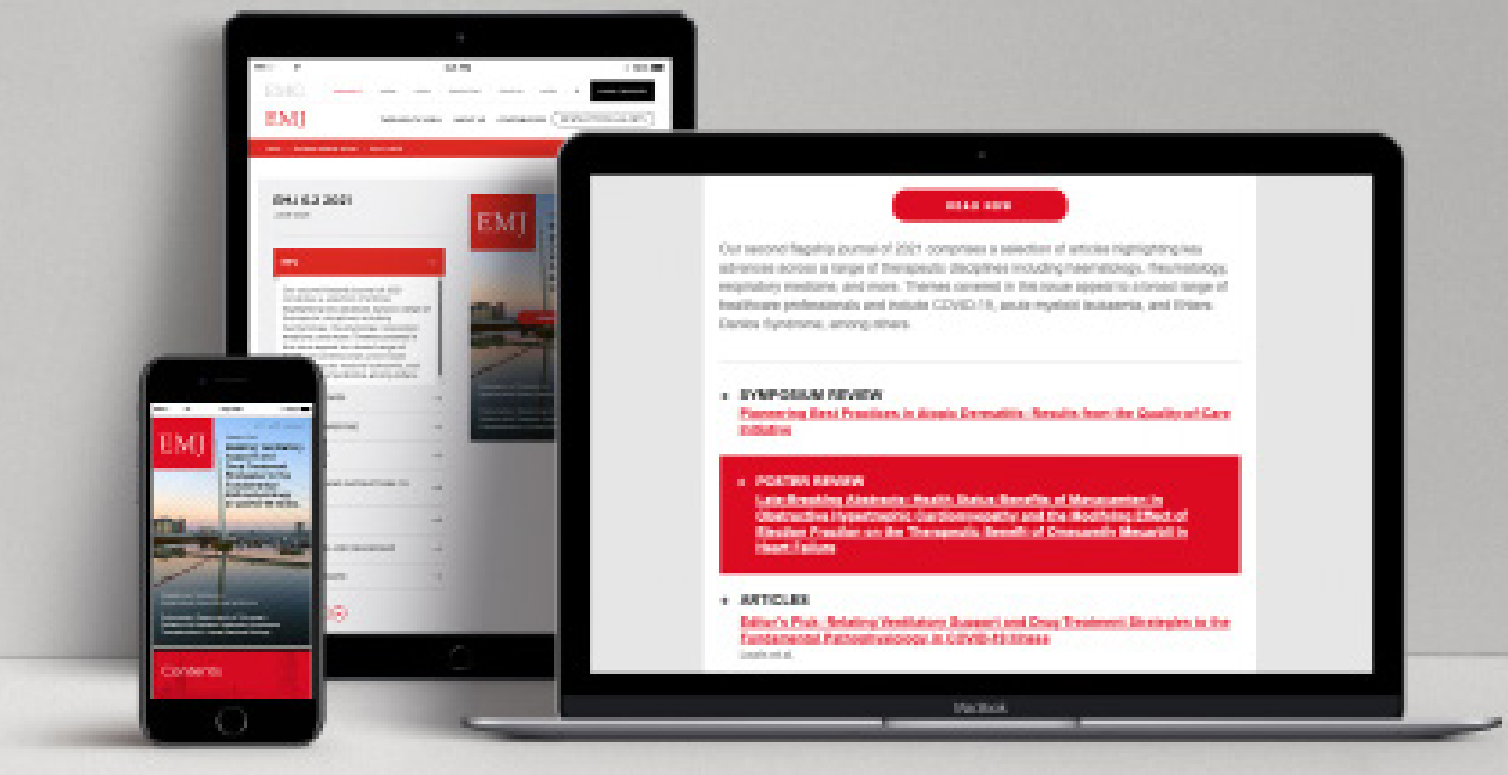

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