Volume 10.1 November 2022

EMJ Diabetes

Review of EASD 2022

Interviews

David Leslie and Naveed Sattar share insights into their careers, research, and the future of the diabetes field.

Editor's Pick

Diabetic Ketoacidosis in Pregnancy: An Overview of Pathophysiology, Management, and Pregnancy Outcomes

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Editorial Board

Aims and Scope

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Front cover and contents photograph: Stockholm, Sweden, home of the **EASD 2022 © Jenifoto** / stock.adobe.com

Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

We are proud to bring you the 2022 issue of *EMJ Diabetes*, highlighting all the latest key topics from the 58th European Association for the Study of Diabetes (EASD) Annual Meeting, which was an event of outstanding quality that took place both online and in Stockholm, Sweden.

Along with the key highlights from this event, there are updates on the recommendations for the management of hyperglycaemia, which were jointly announced by the EASD and American Diabetes Association (ADA), as well as a session on telemedicine in diabetes, both of which have been summarised in this issue.

We are also proud to feature interviews with the past President of the Association of Physicians of Great Britain and Ireland (AOPBGI), David Leslie, and Naveed Sattar, who is Professor of Metabolic Medicine at the University of Glasgow, UK.

Our Editor's Pick for this issue is an excellent review article on diabetic ketoacidosis in pregnancy, which examines the potential etiopathogenesis, clinical presentation, and management of the condition in pregnancy. Alongside this are other highly engaging articles that focus on the chronic complications of diabetes and incretin-based therapy, among other topics.

This issue would not have come into fruition without the outstanding contributions of our authors, interviewees, peer reviewers, and Editorial Board, so, on behalf of the EMJ team, I would like to extend a big thank you to all of them. We would like to also thank you, our readers, for your continued support, and we hope to see many of you at next year's meeting in Hamburg, Germany.

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Foreword

Dear Colleagues,

It is my pleasure to welcome you to this issue of *EMJ Diabetes*, which is dedicated to recent developments in diabetes, including those presented at the 58th hybrid meeting of the European Association for the Study of Diabetes (EASD) in Stockholm, Sweden.

The full impact of the COVID-19 pandemic on people with diabetes is gradually becoming clear. People with diabetes (Type 1 even more than Type 2), like other people with chronic conditions, are at high risk of severe COVID-19. On an individual level, this risk is further exacerbated by diabetic complications and comorbidities that are often present in people with diabetes. Additionally, care (especially foot care) for people with diabetes has deteriorated in many countries. People with diabetes also appear to be at greater than average risk of the post-COVID syndrome, or 'long COVID'.

On the bright side, the therapeutic armamentarium for people with diabetes is continuously expanding. The efficacy of sodium-glucose co-transporter 2 inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists to decrease the risk of heart failure, renal failure, and cardiovascular disease is now well-established. Mineralocorticoid receptor antagonists such as finerenone are entering the arena, and appear to decrease risk of renal function deterioration in a safe manner. GLP-1 receptor and glucose-dependent insulinotropic peptide agonism can be combined in so-called twincretin molecules such as tirzepatide. Tirzepatide has now been shown to have greater efficacy with respect to weight loss and glycaemic control, compared with GLP-1 receptor agonists alone. Although these developments are of course extremely welcome, the high cost associated with these new medications is a serious concern in many countries facing economic pressures.

As always, I hope you will enjoy this issue of *EMJ Diabetes*.

Coen Stehouwer

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

EASD 2022

Review of the European Association for the Study of Diabetes (EASD) Annual Meeting

Location: Stockholm, Sweden, and online
Date: 20th–23rd September 2022
Citation: EMJ Diabet. 2022;10[1]:8-16. DOI/10.33590/emjdiabet/10054752. https://doi.org/10.33590/emjdiabet/10054752.

AFTER 2 years of virtual meetings, the 58th European Association for the Study of Diabetes (EASD) Annual Meeting took a hybrid form, with 7,716 participants onsite in Stockholm, Sweden, as well as 3,291 participants online. The programme of the congress was developed to cover the most recent developments and breaking news relating to diabetes research, covering the latest innovations and developments in the treatment of Type 1 and Type 2 diabetes (T2D), as well as their complications. Through symposia, debates, prize lectures, oral discussion sessions, and a dedicated e-learning track, a range of topics were discussed.

At the opening ceremony, President Stefano Del Prato reminded the participants not to forget the impact of the pandemic on people with diabetes, which has been identified as a risk factor for severe disease and death from COVID-19, with Type 1 diabetes leading to worse outcomes than T2D. Del Prato pointed out the inequality in the way the disease is dealt with, leading to higher mortality of the underprivileged, and affecting their daily delivery of care. Since the start of the pandemic, there has been a drop in diagnostic procedures such as measuring HbA1c, blood pressure, and lipids, accompanied by a reduction in the prescription of drugs for treating people with diabetes, thus putting patients at risk. Furthermore, the COVID-19 pandemic has had a significant impact on societies and healthcare systems.

Del Prato emphasised that we need a holistic, patient-centred approach to the management of diabetes. They stated: "Being a physician, being an investigator, being a researcher, means that we should really struggle, do our best, and be committed in order to ensure peace, prosperity, and progress." They stated it is also our duty to keep diabetes in the policy agenda. The EASD is committed to doing this in three ways: advocacy, research, and support. Finally, the pandemic has also had a

"The programme of the congress was developed to cover the most recent developments and breaking news relating to diabetes research, covering the latest innovations and developments in the treatment of Type 1 and Type 2 diabetes (T2D), as well as their complications."

major impact on the activity of scientific and professional organisations such as the EASD. The hybrid format of the meeting is an example of this; however, it has also led to the EASD engaging a broader audience, and expanding reach through social media.

Several prizes were presented at the opening ceremony, recognising contributions to diabetes science. The 54th Claude Bernard Lecture, in recognition of innovative leadership and lifetime achievements in diabetes research, was awarded to Michael Nauck. Next, Maike Sander received the 16th Albert Renold Prize for outstanding achievements in research on the islets of Langerhans. Michael Horowitz was awarded the 37th Camillo Golgi Prize for outstanding contributions in the field of the histopathology, pathogenesis, prevention, and treatment of the complications of diabetes. Further, the 57th Minkowski Prize was awarded to Martin Heni for research contributing to the advancement of knowledge concerning diabetes. Anette-Gabriele Ziegler won the 8th Diabetes Prize for Excellence, which recognises research leading to significant advances in the understanding, prevention, or treatment of diabetes or its complications. Finally, the 1st EASD-Lilly Centennial Anniversary Prize was awarded to Matthias Tschöp, to recognise their significant contribution through innovative approaches to the development and evolution of treatment and management of diabetes.

This issue of *EMJ Diabetes* includes summaries of highly relevant EASD press releases, covering topics such as dietary changes and risk of death in adults with T2D, anxiety among patients with diabetes, and the management of hyperglycaemia in patients with T2D.

We were delighted to be a part of this congress, and look forward to the next EASD meeting 2023 in Hamburg, Germany. Read on for more scientific highlights in our review of this congress. ●

"Being a physician, being an investigator, being a researcher, means that we should really struggle, do our best, and be committed in order to ensure peace, prosperity, and progress."

Anxiety Amongst Patients with Diabetes

NEW research, presented at the EASD Annual Meeting 2022 in Stockholm, Sweden, shows a burden of mental health issues in people with diabetes, and that the severity of anxiety may be linked to blood sugar management. Previous studies had shown that the rate of mental health disorders, including generalised anxiety disorder, are higher in people with diabetes compared to the general population; however, there has not been much research on the relationship between generalised anxiety and diabetes management.

Evelyn Cox from the Diabetes Research Company, San Francisco, California, USA, and colleagues, conducted an online survey, collecting data between October 2021 and November 2021 on anxiety, blood sugar management metrics, and demographic characteristics among 3,077 adults living with Type 1 or Type 2 diabetes (66% and 34%) in six countries: the UK, Sweden, the Netherlands, Italy, Germany, and France. The participants completed a Generalised Anxiety Disorder Questionnaire, screening for and measuring severity of anxiety. They were also asked for their most recent HbA1c levels, and those with glucose sensors were asked for the percentage of time spent in the target blood sugar range (70–180 mg/dL) on a typical day.

Participants in the Netherlands reported the lowest rates of anxiety (39%), while the UK and Italy reported the highest (51% and 63%, respectively). Males were less likely to experience anxiety than females (39% versus 57%) and those over the age of 45 years were less likely to experience it than those under the age of 45 years (34% and 59%, respectively). Furthermore, those who spent less than 70% of a day in the target range were almost twice more likely to experience moderate or severe anxiety compared to those who were in the target range 70% of the time or more (22% versus 14%). Those with lower HbA1c (≤7) were less likely to report moderate or severe anxiety than those with high HbA1c (>7).

> **"There is a need for a more integrated approach to diabetes management and mental health support in order to improve blood sugar metrics while minimising anxiety."**

Cox concluded: "It is crucial that people with diabetes who experience challenges with their mental health reach out to their healthcare providers or mental healthcare practitioners for support." There is a need for a more integrated approach to diabetes management and mental health support in order to improve blood sugar metrics while minimising anxiety.

Revolutionising Care for Diabetic Foot Ulcers with Early Surgical Intervention

EARLY percutaneous surgical intervention leads to improved outcomes compared to conservative treatment for patients with diabetic foot ulcers, according to new study data presented at EASD Annual Meeting 2022, held both virtually and live in Stockholm, Sweden, between 19th–24th September.

The study, led by Adrian Heald, Salford Royal NHS Foundation Trust, UK, enlisted a total of 33 patients diagnosed with diabetic foot ulcers±neuropathy, without an associated abscess, between April 2019 and April 2021. Of these 33 patients, 19 underwent a percutaneous orthopaedic procedure performed under local anaesthetic to adjust the foot mechanics, alleviate ulcer pressure, and ultimately improve healing. Tendo-Achilles lengthening was performed for those with a tight Achilles tendon plus ulcers on the foot sole (n=9) and toe tendon release was performed for those with ulcers at the toe apex and damaged flexor tendons (n=10). The remaining 14 patients were treated conservatively with combined medical and podiatric management.

Participants were followed-up for 1 year, and the authors found that all candidates in the percutaneous surgery group achieved ulcer resolution compared with only three out of 14 patients in the conservative management cohort. Additionally, there were no admissions for sepsis secondary to infected diabetic foot ulcers in the surgery group, compared with seven admissions in the conservative management group.

Furthermore, the results revealed that ulcer recurrence and amputation rates were lower in the surgery group (10%) than the conservative treatment group (66%) for both outcome measures. This improvement in outcomes was also reflected in death rates, with six deaths occurring in the conservative management group versus none in the surgery group.

Not only did the percutaneous surgical intervention yield improved outcomes across all measures, the cost of care for the surgical management group was 88% lower than the cost of care for the conservative management group. This is crucially important for patients and health services alike, with the high morbidity and mortality associated with diabetic foot ulcers and the rising costs of healthcare.

"This is crucially important for patients and health services alike, with the high morbidity and mortality associated with diabetic foot ulcers and the rising costs of healthcare."

Whilst the study included only a small number of patients, Heald concluded by urging other diabetic multidisciplinary foot teams to explore this treatment option. ●

Updates on EASD and ADA Recommendations for Managing Hyperglycaemia in Type 2 Diabetes

Updates on recommendations for the management of hyperglycaemia have recently been announced by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA). These recommendations update previous guidelines reported in 2018 and 2019 with changes including a shift in focus to patient-centred care, equity of care, and managing weight loss.

The new recommendations provide additional guidance on how to consider social determinants of health to improve equity of care and provide effective management of hyperglycaemia. Furthermore, they delve deeper into the importance of weight loss citing evidence from randomised controlled trials on the value of glucose-lowering medications in supporting weight loss. The report includes various recommendations for beneficial physical activity, including light exercise, resistance training, additional daily steps, 150 minutes of moderate to vigorous exercise per week, and strength training 2–3 times per week. It furthermore includes recommendations that patients should sleep between 6–9 hours per night.

Updates on glucose-lowering therapies are also provided, these include advice on higher doses of dulaglutide and semaglutide and specific information for comorbid conditions, such as atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease.

> **"These recommendations update previous guidelines reported in 2018 and 2019 with changes including a shift in focus to patient-centred care, equity of care, and managing weight loss."**

The general consensus of the recommendations highlights the importance of including patients in their own diabetes care, increasing considerations of social and economic circumstances, asking patients how they feel about their side effects to different potential medications, and encouraging them to play a more active role in determining care management plans. The recommendations also noted the potential benefits of implementing more aggressive and proactive treatment considering the potential use of combination therapy in first instance.

Red and Processed Meats Increase Type 2 Diabetes Risk

RED and processed meats are linked to a higher risk of Type 2 diabetes (T2D), according to new research that was presented at the EASD Annual Meeting 2022 in Stockholm, Sweden.

The most common form of diabetes, T2D, occurs when the pancreas cannot make enough insulin or the insulin that it does produce does not work properly. Being overweight or obese are two of the main risk factors, and T2D incidence is projected to increase; however, there are existing guidelines that recommend a specific plant-based diet and advise limiting animal product consumption.

Annalisa Giosuè, Department of Clinical Medicine and Surgery, University of Naples Federico II, Italy, and colleagues, reviewed 13 meta-analyses into links between diabetes and animal-based food, as animal proteins are not nutritionally equal. These meta-analyses included 175 estimates of how certain animal products may increase or reduce the risk of developing T2D.

Consuming 100 g/day of meat has a 20% increase of T2D risk, while 100 g/day of red meat (beef, lamb, and pork) saw a 22% increase and 50 g/day of processed meats (bacon, sausages, and deli meat) a 30% increase. However, white meats (chicken and turkey) only saw a 4% increase, while 100 g/day of fish and an egg a day had no association due to the low quality of evidence.

> **"Being overweight or obese are two of the main risk factors, and T2D incidence is projected to increase"**

While 30 g/day of cheese and 200 g/day of full-fat dairy products had no effect on T2D risk, 200 g/day of milk was associated with a 10% reduction in T2D risk and 100 g/day of yoghurt a 6% decrease. Further, consuming 200 g/day of total dairy saw a 5% reduction and 200 g/day of low-fat dairy a 3% reduction.

Giosuè concluded by saying that more "research is needed to achieve high quality of evidence required to give solid recommendations." However, the researchers' review shows that regularly consuming certain dairy products in moderation could reduce T2D risk. ●

Dietary Changes Lower Risk of Death for Adults with Type 2 Diabetes

THE RISK of death for people diagnosed with Type 2 diabetes (T2D) can be lowered by eating a diet high in omega-3, n-3 polyunsaturated fatty acids, wholegrains, fibre, and fish.

The systematic study and meta-analysis, which was first presented at 2022's EASD Annual Meeting in Stockholm, Sweden, examined 107 previously published prospective observational studies which focused on the impact of dietary factors and the risk of premature death for adults with T2D. Carried out by researchers in Germany, all dietary factors (including foods and food groups, macronutrients, micronutrients, secondary plant compounds, dietary patterns, and supplements) were investigated, along with the risk of death from all adults with Type 2 diabetes (>18 years) to June 2022.

Researchers included 72 studies in 45 meta-analyses, which compared the effects of high versus low intake, and evaluated the relationship between death from any cause and dietary factors across an average period of 10 years. The number of participants included in these studies varied, from 1,073 to 84,816.

The analyses concluded that there is a moderate certainty regarding the evidence of a protective association between patients with T2D eating diets rich in wholegrain, fibre, fish, omega-3, and n-3 polyunsaturated fatty acids, and premature death. Adding a single serving of 20 g per day of wholegrain from foods including rice, breakfast cereals, and bread was associated with around a 16% reduction in death, and an increase in fish consumption gave a 5% lower risk of premature death. Adding 5 g per day of dietary fibre (for instance, a medium-sized pear), and an increase of 0.1 g per day of n-3 polyunsaturated fatty acids from sources such as walnuts, flax seeds, and vegetable oil, lowered the risk of death by 14% and 13%, respectively.

Lead study author Janett Barbaresko, German Diabetes Center, Düsseldorf, Germany, commented: "Our rigorous assessment of the best currently available evidence indicates with reasonable certainty that eating a diet rich in wholegrains, fibre, fish, and polyunsaturated fatty acids, as well as consuming more vegetables and plant proteins, may help people with T2D live longer."

A limitation stressed by researchers is the lack of evidence regarding other dietary factors, including foods such as dairy, tea, and meat, and micronutrients including caffeine and vitamin D, in patients with T2D. This emphasises the need for more comprehensive studies to be carried out, so that clinicians can better understand the impact which dietary factors have on those with T2D, and the progression of their disease. ●

"The risk of death for people diagnosed with Type 2 diabetes can be lowered by eating a diet high in omega-3, n-3 polyunsaturated fatty acids, wholegrains, fibre, and fish."

COVID-19 Anxiety in Patients with Pancreas or Islet Transplants

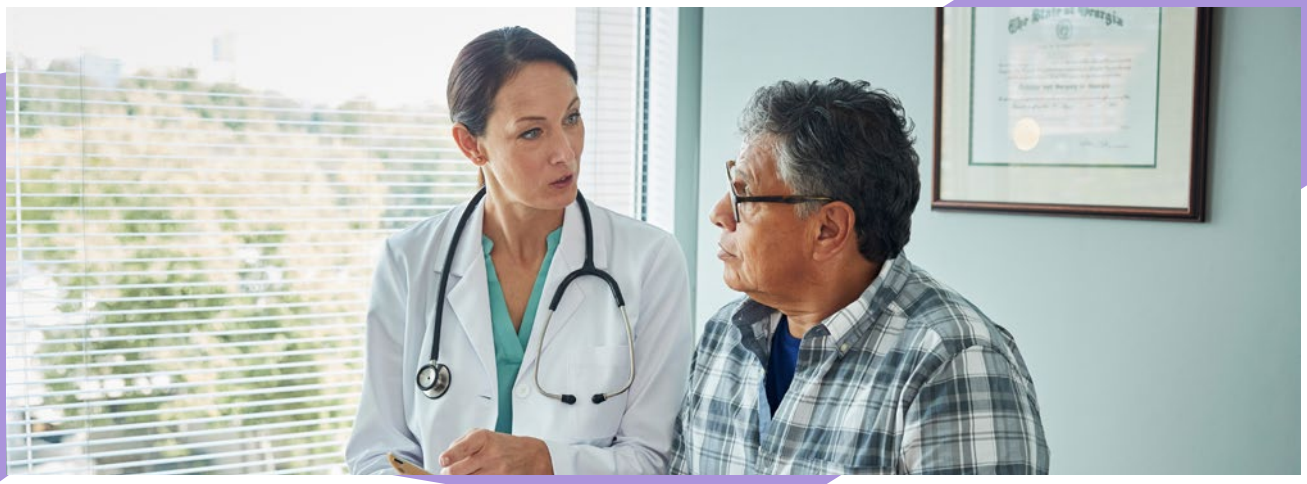
PATIENTS who had pancreas or islet transplants to treat Type 1 diabetes experienced high rates of stress and anxiety due to fear of becoming severely ill with COVID-19 during lockdown. These transplants involve transplanting β-cells, insulin-producing cells from the pancreas, which allows the patients to make insulin again. Nearly half of patients who had a transplant did not leave their house during the duration of the study, which was presented at EASD Annual Meeting 2022 in Stockholm, Sweden.

Researcher Cyril Landstra, Department of Internal Medicine, Leiden University Medical Centre, the Netherlands, and their team conducted a study with 323 participants, including 51 transplant recipients and 272 patients who had not had a transplant. They were asked to fill in a detailed survey about how lockdown affected them, their behaviour prior to the lockdown, physical activity, weight, and levels of anxiety, stress, and fear of COVID-19 infection in the spring of 2020, 8–10 weeks into lockdown.

The fear of contracting COVID-19 was 70% higher in transplant recipients than those who did not have a transplant. Additionally, glycaemic control worsened in transplant recipients, while it improved in patients who did not have a transplant. Those who had a transplant were three times more likely to stop going out for groceries than those who did not (52.1% versus 18.3%) and were also three times more likely not to leave their house at all (45.8% versus 14.0%). Furthermore, 26.8% of transplant recipients reported increased insulin use, 29.2% increased anxiety, 33.3% increased stress, 40.0% less physical activity, and 41.7% weight gain since the start of lockdown.

> **"Nearly half of patients who had a transplant did not leave their house during the duration of the study"**

While COVID-19 vaccines are now available, they do not work as well in patients who have received pancreas and islet transplants; therefore, the findings are still important to this day. Landstra said: "It's important that patients and healthcare professionals are aware of these unintended consequences and also that patients are aware that they can reduce their risk of severe COVID-19 through better diabetes self-management and a healthy lifestyle." ●



Adapting to Telemedicine in Diabetes

Author: Anaya Malik, Editorial Manager

Citation: EMJ Diabet. 2022;10[1]:17-19. DOI/10.33590/emjdiabet/10013792. https://doi.org/10.33590/emjdiabet/10013792.

EASD 2022

THIS year's European Association for the Study of Diabetes (EASD) Annual Meeting 2022 was a hybrid congress, which focused on inclusion and interaction within the global diabetes community whether participants attended in person in Stockholm, Sweden, or virtually.

In front of a live audience, Richard Holt, Professor in Diabetes and Endocrinology at University of Southampton, UK, delivered the presentation, '"I just called to say I love you..." Diabetes tools for telemedicine: What we learned from COVID-19 and beyond?' Holt spoke on how telemedicine has become increasingly popular in diabetes consultations, and how there has been a major rise in its use as a result of the pandemic. Holt reviewed the evidence on telemedicine for diabetes care, before exploring the practical issues experienced by patients and healthcare professionals during the pandemic, taking these as lessons to better inform how we can use telemedicine going forward. The COVID-19 pandemic has led to a rapid expansion of the use of telemedicine, and many have had to adapt to the use of this in diabetes care.

THE RISE OF TELEMEDICINE

Telemedicine is the process by which healthcare professionals evaluate, diagnose, and treat patients at a distance using telecommunications technology. First reports of the use of telemedicine date back to the 1950s when hospitals in the USA used the telephone as a medium of providing care for people. An upsurge in the use of telemedicine resulted from the advent of the internet, which made profound changes in the practice of telemedicine. Prior to the COVID-19 pandemic, there was a steady increase in the number of articles published on the use and effectiveness of telemedicine. Holt presented results from a PubMed® search that showed a steep increase in the number of articles published on the topic of diabetes in telemedicine in 2020 and 2021 compared to previous years. Holt explained that this was unsurprising given the rapid adaptation to telemedicine when face-to-face consultations were not possible.

THE DRIVE FOR TELEMEDICINE

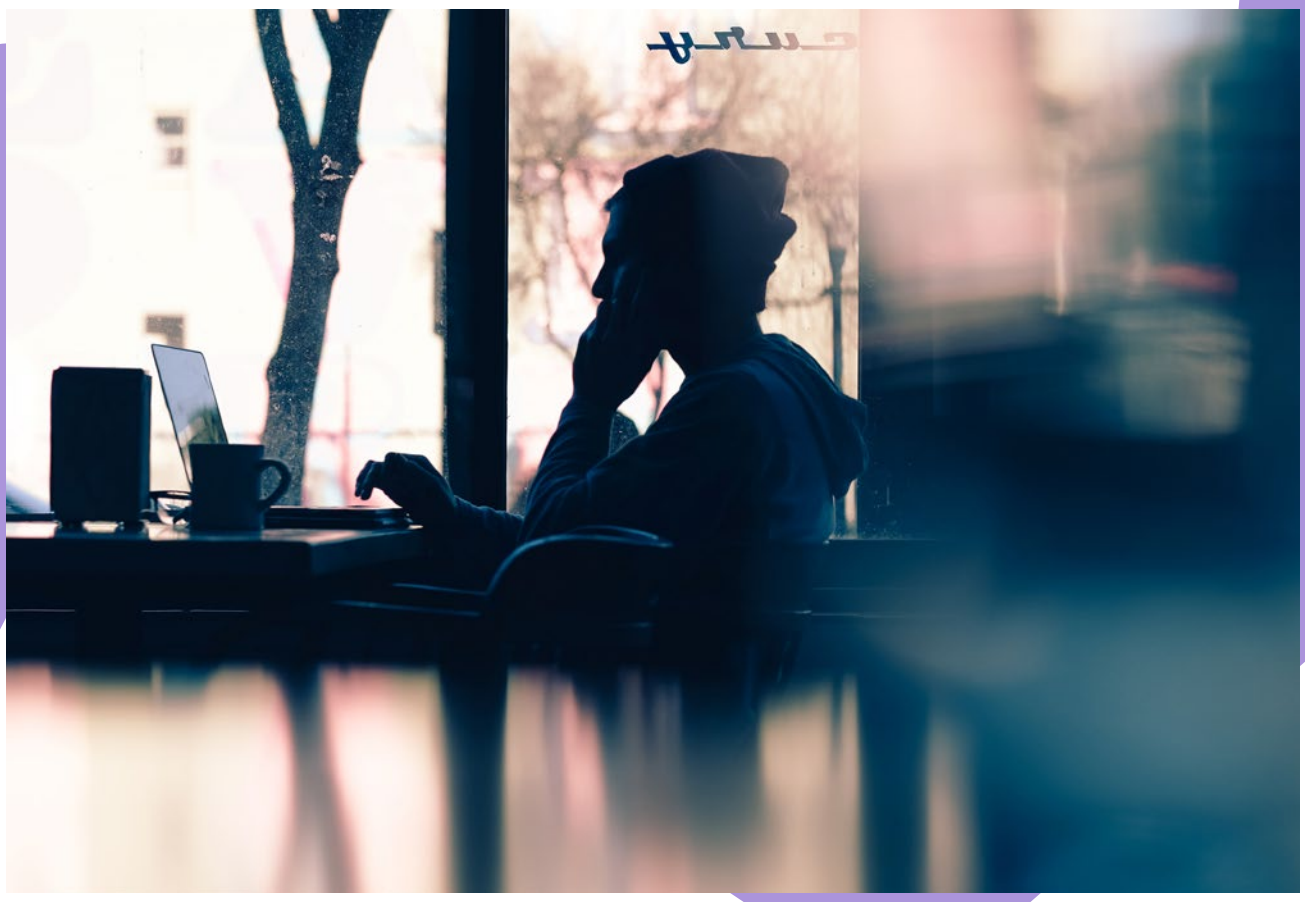
For patients, telemedicine offers convenience and flexibility: a telephone or video consultation is less time-consuming than an in-person appointment where travel time and expense must be accounted for. Patients are not obliged to take time off work, experience less interference with child or family responsibilities, and a sense of privacy is developed when people take appointments from the comfort of their own homes. Crucially, during the pandemic this meant people were not exposed to potentially contagious infections in doctor's surgeries or in hospitals.

Healthcare professionals who adopt telemedicine may experience fewer missed appointments or cancellations, which may translate to better follow-up and therefore improved health outcomes. Appointments taken over telephone or video calls may be considered more time and cost efficient. A proof-of-concept randomised trial in 2013[1] showed that clinician time requirements could be reduced by 40% with remote management of diabetes. The practice of telehealth in medical consultations during and after the pandemic, however, did not always meet these expectations, Holt reflected.

"During the pandemic it was estimated that as a result of lack of face-to-face consultations there were as many as 60,000 cases of diabetes in the UK that were missed."

TECHNOLOGIES USED IN DIABETES TELEMEDICINE

An increasing number of technologies are being used in telemedicine for diabetes, and one can expect to see this range rapidly expanding in coming years. People are communicating using the telephone, social media, and email as a means of delivering care to patients. Patient portals now give people access to their health records and consultation history. Face-to-face diabetes self-management education has in part been moved online and apps have been developed to support clinical care. For example, DigiBete (DigiBete Ltd, Leeds, UK) is a video platform and app designed to support young people in the management of Type 1 diabetes, created in collaboration with the National Health Service (NHS) and by the Diabetes Team at Leeds Children's Hospital, UK. The platform



provides two-way communication with patients and clinics. For Holt, one of the tools that made the biggest impact in continuing care during the pandemic was the development of cloud-based management systems, for example LibreView (Abbott Laboratories, Chicago, Illinois, USA) or Dexcom Clarity (DexCom, Inc., San Diego, California, USA). These allow clinicians to look at glucose profiles of people with diabetes remotely.

HOW EFFECTIVE IS TELEMEDICINE IN DIABETES CARE?

A meta-analysis of 32 articles on telemedicine in primary healthcare for the management of patients with Type 2 diabetes demonstrated that telemedicine had a favourable effect on diabetes care.[2] Holt described the outcomes of the study, which showed that telemedicine interventions may help patients with Type 2 diabetes to effectively control blood glucose and improve self-management in primary healthcare. The analysis showed that telemedicine leads to a reduction in HbA1c, a reduction in fasting and post-prandial glucose, and reduction in blood pressure. The greatest reduction of HbA1c was observed after 6 months, but most studies that were analysed were 6 months in duration and the number of patients in shorter- and longer-term studies was small. Holt cautioned that more longer-term studies may be needed to look at effectiveness of telemedicine over a long period of time.

LIMITATIONS DURING THE PANDEMIC AND BEYOND

When face-to-face consultations could not go ahead in the UK, it was reported that estimated HbA1c did not change. However, during the pandemic it was estimated that as a result of lack of face-to-face consultations there were as many as 60,000 cases of diabetes in the UK that were missed.[3] Moin et al.[4] demonstrated that in Canada, there were less retinal examinations and less HbA1c and lipid measurements taken. The long-term consequences of this are as of yet unknown.

Practicalities often cause barriers to the smooth execution of delivering remote care. Healthcare professionals and patients may expect communication with reliable technology, data uploaded to the appropriate platform, clear expectations for the consultation, and a private space in which to discuss care. In reality, patients are often without the appropriate technology, for example a webcam, and are unprepared, in an inappropriate environment for a consultation, or do not answer the telephone.

To combat the factors that compromise the efficiency of delivering telemedicine in diabetes, Holt suggested further planning and evaluating of remote consultation services framework, improving competency of healthcare professionals, and embracing and acknowledging the novelty of the approach.

Telemedicine can be used to deliver effective diabetes care but cannot replace all in-person consultations, Holt concluded, suggesting a hybrid approach to health services. Nevertheless, healthcare professionals need to have the ability adapt in order to be able to deliver telemedicine in a way that maximises its impact. ●

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Weight Management, Micronutrients, and Supplements in Diabetes

These presentations took place between 16th–19th June 2022, as part of the 39th International Symposium on Diabetes and Nutrition, held in Anavyssos, Greece, and virtually

Speakers:

Michael Lean,[1] Jeffrey Mechanick,[2] Daniel West,[3] Andrea Hawkinson,[4] Simin Liu,[5] Philip Atherton,[6] Jose-María López-Pedrosa[7]

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5. Centre for Global Cardiometabolic Health, Brown University School of Public Health, Providence, Rhode Island, USA
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Meeting Summary

This year's 39th International Symposium on Diabetes and Nutrition in Anavyssos, Greece, hosted a series of presentations and plenary lectures with a focus on the effects of weight loss, micronutrients, nutritional supplements, and alternative dietary patterns in the prevention and management of Type 2 diabetes (T2D) and cardiovascular risk reduction. Michael Lean discussed how diabetes remission can be achieved through weight loss using a low-energy diet (LED) or very low-energy diet (VLED), accompanied by continued long-term support from

specialised healthcare professionals. Jeffrey Mechanick discussed the importance and impact of early intervention on T2D and cardiovascular disease (CVD). He emphasised that T2D should be seen not just at the point of disease, but on a spectrum from prediabetes to complications, with early interventions having significant impact on not only the progression of T2D, but also into the latter stages. Simin Liu presented an integrative multilevel framework for causal inference to personalise cardiometabolic health, highlighting recent work investigating the roles of dietary minerals, environment metals, and genomics in relation to cardiovascular disease and diabetes.

Several of the presentations included discussion of specific interventions. Daniel West discussed the use of whey protein (WP) and how it can help control postprandial glycaemic excursions (PGE) in people with T2D controlled on oral antihyperglycaemic drugs. Following this, Andrea Hawkinson discussed how a new supplement, mulberry leaf (*Morus alba*) extract (MLE), can significantly lower postprandial glucose response, as well as early insulin response, highlighting the need for further studies to evaluate its efficacy in people with T2D. Philip Atherton showed studies providing evidence that protein and essential amino acid (EAA) supplementation can help support muscle mass, which is especially essential for older people with T2D and sarcopenia. Finally, Jose-María López-Pedrosa spoke about how a supplement containing slow digestible carbohydrates (SDC), arginine, lysine, and β-hydroxy-β-methylbutyric acid (HMB) can help preserve muscle mass, as well as improve insulin resistance, in a rat model of diabetes.

Weight Management

Michael Lean

Weight gain and obesity are major drivers of T2D.[1-3]

Sustained Weight Loss Can Lead to Type 2 Diabetes Remission

T2D remission (an HbA1c <48 mmol/mol without the use of glucose lowering medications for 6 months), improvements in cardiovascular risk factors, and decreased T2D-associated mortality can be achieved through sustained weight loss.[4-7] As such, weight loss was a key recommendation of the 2010 Scottish Intercollegiate Guidelines Network (SIGN) guidance on the management of obesity, to which Lean contributed.[7]

Weight management is not only about weight loss, but also goal maintenance, prevention of weight gain, and minimising cardiometabolic risks.[7] To achieve such goals, Lean emphasised the need for people with T2D and with overweight or obesity to be supported with evidence-based weight-loss treatments.

The Utility of Very Low-Energy Diets

Evidence from an umbrella meta-analysis review of randomised controlled trials for achieving weight loss in people with T2D showed that a VLED (400–500 kcal/day) and LED (1,000–1,500 kcal/day) are associated with greater weight loss than control (reduced energy) diets, while high- or low-carbohydrate, or high-protein diets, are not.[8]

In the DiRECT trial, led by Lean and Roy Taylor, 149 patients were given a total diet replacement intervention (825–853 kcal/day) for 3–5 months, followed by 2–8 weeks of structured food introduction, all provided and monitored by trained practitioners. Antidiabetic and antihypertensive medications were discontinued at study initiation, but reintroduced if needed. Remission of diabetes was achieved by 46% of the intervention group versus 4% of a standard practice care control group (n=149; p<0.0001).[4]

Sustained Support is Needed

Few studies evaluating dietary intervention and diabetes remission have been carried out for ≥12 months and, among those, remission rates over time may not be sustained.[8] For instance,

a Mediterranean-type diet study showed HbA1c lowering and weight loss, and a T2D remission rate of approximately 15% at 1 year, but following this, reported that rates fell over time.[9]

While the DiRECT trial was successful, Lean highlighted that a VLED can be difficult to follow and sustain. The vital elements to success are the skill and empathy of a healthcare practitioner and long-term support by a team with a consistent message. As such, he called for diabetes and weight-loss management practitioners to work together.

Conclusions

Achieving and maintaining weight loss is key for people with T2D and with overweight or obesity, as it can lead to disease remission and reductions in cardiovascular and mortality risks.

A VLED, supported by trained practitioners, can help with weight loss, but sustaining weight management requires ongoing support.

Dietary Patterns and the Role of Nutritional Supplements or Products in Diabetes Care: An Overview

Jeffrey Mechanick

In a chronic disease model, genetic and environmental risk factors, along with social determinants of health and transcultural factors, can lead to a predisease stage, which, if unchecked, can manifest and lead to complications.[10]

Type 2 Diabetes Needs to Be Viewed as a Disease Spectrum Over Time

With this disease model in mind, insulin resistance, prediabetes, T2D, and associated cardiovascular/metabolic complications can be envisaged as a spectrum over time instead of in isolation.[11] As such, T2D interventions should occur in the early prevention stage as opposed to the active disease or complications stage, migrating preventive care from tertiary to secondary to primary settings, or even before.

Type 2 Diabetes Care Should Include a Structured Lifestyle Medicine Approach

According to Mechanick, a comprehensive care plan for a person with T2D must include a structured lifestyle medicine approach, with optimised nutrition and healthy eating patterns as a cornerstone. Dietary deficiencies with respect to micro- and macronutrients have been identified in people with T2D, and a review of diabetes-specific nutrition formulas provides clinical evidence for justification of their use.[12]

Nutrition Needs to Be Analysed as a Whole to Establish a Healthy Eating Pattern

Using a computer database, molecular components of food can be discovered.[13] However, Mechanick stated that nutrients should not be considered individually, but rather as a network analysis of a person's food metabolome that "can help identify the points that are opportunities for compounds to intervene to effect that network." By doing this, a healthy eating pattern can be suggested that will contain all the nutrients required.

In an American Association of Clinical Endocrinologists (AACE) guideline, Mechanick and colleagues laid out recommendations for the clinical use of dietary supplements and nutraceuticals.[14] These guidelines have been translated into recommendations in guidelines for T2D management and risk stratification.[15,16]

Conclusions

T2D should be envisaged as a spectrum from predisease to complications, so as to understand it in terms of a driver-based, chronic disease model.

By analysing and understanding a person's individual food metabolome, individualised recommendations can be given to help at any stage along the T2D spectrum.

Can Frequent Whey Protein Supplementation Improve Glycaemic Outcomes in Type 2 Diabetes?

Daniel West

T2D is associated with elevated fasting plasma glucose (FPG) levels and increased PGE.[17] Controlling this, according to West, is vital, as data shows that postprandial glucose response is not only a predictor of HbA1c levels[18] and contributor to glycaemic variability,[19] but also a predictor of future cardiovascular events[20] and economic burden.[21]

Whey Protein as a Means to Reduce Postprandial Glycaemic Excursions

One product being investigated with regard to its actions on reducing PGE is WP.[22] Recent studies have shown that WP slows gastric emptying, which in turn reduces the rate of digestion of glucose into the system[23,24] and hepatic glucose output.[24,25] WP has also been found to have a stimulating effect on insulin secretion, via stimulation of pancreatic β-cells,[26] eliciting an increase in glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide.[27,28] According to West, "all of these contribute to potentially improving postprandial glucose."

Clinical Trials of Whey Protein

In a clinical trial with WP, 15 people with T2D, controlled either with a sulfonylurea or metformin, ingested 50 g of WP isolate or a control formulation 30 minutes before a high-glycaemic index breakfast. Results showed the WP formulation compared with the control significantly suppressed PGEs, as assessed by incremental area under the curve (iAUC) at 0–30, 60–120, and 0–180 minutes, (-22%, -29%, and -28%, respectively). Additionally, the insulin iAUC at 0–30, 60–120, and 0–180 minutes were higher with the WP formulation compared with the control (96%, 107%, and 105%, respectively) as well as the total/intact GLP-1 response iAUC (154%/240%, 137%/332%, and 141%/298%, respectively).[27] This effect was less pronounced when WP was taken with a meal.[28]

In another study, the effect of WP on second meal effect was assessed in 11 males with T2D, controlled with lifestyle or oral antidiabetes medications. Participants consumed a supplemental drink of either 15 g of WP hydrolysate, intact WP, or placebo control, prior to consumption of a mixed-macronutrient breakfast and lunch. Compared with the control, the WP drink showed significant reductions in PGEs at both breakfast and lunch, but not at the evening meal when no drinks were consumed, suggesting there was not a second-meal effect. Notably, however, compared with the control, the WP hydrolysate drink was associated with a faster time to peak amino acid concentrations.[28]

Formulising a Whey Protein Supplement for Convenient Consumption

While the formulation used in this and the previous clinical study reduced PGEs, it was problematic due to the dose amount needed to be consumed, taste, and convenience. As such, West's team worked to formulise whey hydrolysate into a palatable drink. To trial this formulation, 18 participants with T2D, predominately male and controlled either with lifestyle or oral antidiabetes medications, consumed either the test WP drink or control (no WP) matched in taste and consistency. The drinks were consumed three times a day, within 10 minutes of a meal, for 1 week.[29] At the end of the intervention, the WP group compared with the control group showed approximately 10% less time spent hyperglycaemic (>10 mmol/L) and 2 hours per day more in euglycaemia. Additionally, supplement adherence was high (98%) and with no adverse events reported.[29]

West proposed that to determine long-term efficacy in patients with T2D on insulin or other oral antihyperglycaemic agents, longer-term studies are required with endpoints such as change in HbA1c, body mass, and impact on pancreatic β-cells.

Conclusions

Effective interventions targeting PGE in people with T2D are needed due to their association with improved glycaemic control and reducing cardiovascular risk and future cardiovascular events.

A Randomised, Placebo-Controlled Crossover Study to Evaluate Postprandial Metabolic Effects of Mulberry Leaf Extract, Vitamin D, Chromium, and Fibre in People with Type 2 Diabetes.

Andrea Hawkinson

Glycaemic management to reduce PGE in T2D is important, not just in terms of symptomatic management but also long-term cardiovascular risk reductions.[30]

Using Mulberry Leaf Extract to Control Postprandial Glycaemic Excursions

MLE, with origins in traditional Chinese medicine, contains sugar analogues (iminosugar alkaloids), with 1-deoxynojirimycin (1-DNJ) being the most abundant. 1-DNJ has been shown to slow glucose absorption by competitively blocking the active site of digestion and the polysaccharide-degrading enzymes, such as α-glucosidases.[31] Other glucose-lowering mechanisms of MLE have also been described, associated to other functional ingredients including rutin, caffeic acid, chlorogenic acid, and quercetin.

Clinical Study of Mulberry Leaf Extract

Methods

The double-blind, placebo-controlled, crossover study led by Mafauzy Mohamed from the Universiti Sains Malaysia (USM), Kubang Kerian, Malaysia, aimed to test the incremental effect of MLE on the reduction of postprandial glucose and insulin levels in people with T2D of Asian origin (data on file; NCT04877366).[32] There were two study sites (Singapore and California, USA) that enrolled adults (≥18 years) with T2D, either drug-naïve or metformin-treated (500–3,000 mg), with a HbA1c between 6.5% and 10.0%. Exclusion criteria included a BMI of ≥35 kg/m^2, FPG >200 mg/dL, and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2 (data on file).[32]

At each study site, participants received either a 2 g powder containing 250 mg MLE, 12.5 mg DNJ, 1.75 g fibre, 0.75 mg vitamin D_3, and 75 mg chromium or a placebo powder without MLE. The powder was sprinkled on top of a 350 kcal breakfast meal consisting of two slices of white bread, 20 g gouda cheese, and 250 mL apple juice (10.0 g protein, 6.5 g fat, and 55.4 g carbohydrates) and was consumed within 15 minutes. At the first study visit, all participants consumed either the test or placebo powder, with the alternative given at a second study visit (data on file).[32]

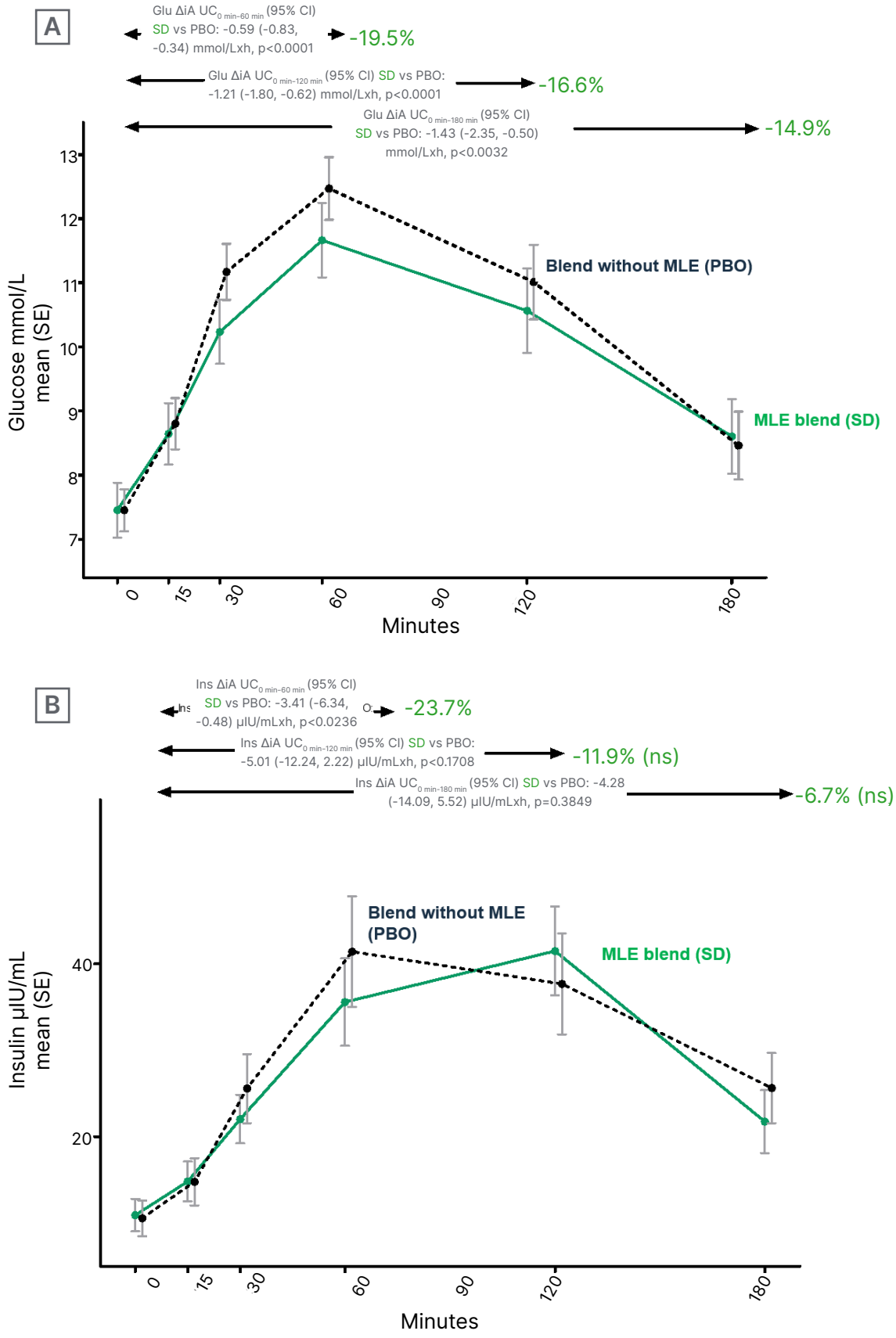
Blood glucose and insulin response were assessed over 3 hours (0, 15, 30, 45, 80, 120, and 180 minutes). The study's primary endpoint was to assess the effects of the MLE powder on the iAUC (0–1, 0–2, and 0–3 hours) of PGE. Secondary endpoints included assessment of the effects on iAUC of the postprandial insulin response. Sample size was calculated to show a difference of 15% in the iAUC of PGE between the two arms. The iAUC was calculated using the trapezoid rule and comparison of treatment means, using the mixed model approach with product, site, and period as fixed effects, and participants as random effect (data on file).

Results

A total of 30 participants were randomised, with 29 completing both interventions. Baseline characteristics between the two groups were similar, with an average age of 58.9±11.3 years, a mean BMI of 26.5±4.4 kg/m^2, and waist circumference of 92.9±11.2 cm. The overall mean FPG was 7.1±1.5 mmol/L, HbA1c was 54.1±5.1 mmol/mol, and systolic/diastolic blood pressure was 127±15/77±10 mmHg. There were some between-site differences, with the USA participants having a greater prevalence of obesity, and Singapore participants having slightly more dysglyceamia and lower estimated glomerular filtration rates (data on file).

Results (Figure 1) showed that the MLE blend, relative to placebo, significantly lowered the glucose iAUC curve by 19.5% at 1 hour (difference from control: -0.59 [95% confidence interval (CI): -0.83 and -0.34] mmol/L by hour; p<0.0001); 16.6% at 2 hours (difference from control: -1.21 [95% CI: -1.80 and -0.62] mmol/L by hour; p=0.0001); and 14.9% at 3 hours (difference from control: -1.43 [95% CI: -2.35 and -0.50] mmol/L by hour; p=0.0032). MLE also significantly reduced insulin response by 23.7% at 1 hour (difference from control: -3.41 [95% CI: -6.34 and -0.48] mIU/mL by hour; p=0.0236), but not at 2 hours and 3 hours, suggesting no overall effect on insulin response.

Figure 1: Effects of mulberry leaf extract on A) glucose and B) insulin trajectories.



AUC: area under the curve; Glu: glucose; Ins: insulin; MLE: mulberry leaf extract; ns: not significant; PBO: placebo; SD: standard deviation; SE: standard error of the mean; vs: versus.

One adverse event of fatigue, which lasted 4 days, was reported in the MLE group. Limitations of the study were that only a single dose was tested, the non-MLE ingredients in both formulations may have had an effect on glucose metabolism, and the study population only included adults of Asian origin (data on file).

Conclusions

Significant reductions on overall glycaemic burden and early insulin response following ingestion of the MLE-containing blend suggests the blend could be used as a dietary adjuvant to improve postprandial glucose response.

The findings support a reduced glucose gastrointestinal absorption effect of MLE, which could be mediated by DNJ. Longer-term studies are needed to understand the full translational metabolic impact of MLE.

An Integrative Multilevel Framework for Causal Inference to Personalise Nutrition for Cardiometabolic Health: Minerals and Metals?

Simin Liu

CVD-related deaths in the western world have fallen over the last 50 years due to advances in medicine and public health actions.[33] However, there are still a number of known risk factors identified by the America Heart Association (AHA) as being poorly controlled, including smoking cessation, physical inactivity, blood pressure ≥120/≥80 mmHg, BMI ≥30, lack of a healthy diet, total cholesterol ≥200 mg/dL, and FPG ≥100 mg/dL.[34]

The Need for Diversity in Diet

The U.S. Department of Agriculture (USDA) MyPlate initiative recommends that dietary patterns should be diverse and include a variety of nutrient-rich fruits, vegetables, whole grains, and protein.[35] These recommendations stem from the failing in findings from a study where only one component of the diet was controlled. A subgroup of females from the Women's Health Initiative Study participated in a large, USA-based, randomised controlled trial investigating dietary modification in postmenopausal females (aged 50–79 years; n=48,835). It was found that when energy from fat was lowered to 20% from ≥35%, there were no differences in primary outcome measures of coronary heart disease and total mortality occurrence. A confounding factor in the intervention, Liu highlighted, was that fat energy was mostly replaced with carbohydrates (half of which were sugar), not proteins.[36]

An Integrated View of Cardiometabolic Health

According to Liu, "there is no hope of identifying a gene that puts you at any substantial risk of developing disease without the environmental context of nutritional behaviour." Cardiometabolic health needs to be viewed on a multilevel, integrative basis to make causal inference (Figure 2). Over time, an intervention (e.g., food) that may produce an outcome of interest can be investigated for its biologically effective dose, biological effect, and impact on change in structure and function. Taking into account genetics and epigenetics can help improve measurements of exposure, mediators, modifiers, and outcomes, as well as predict outcomes or prognosis and identify targets and off-targets. These can all be used to personalise dietary interventions.

Gene–Diet Interaction

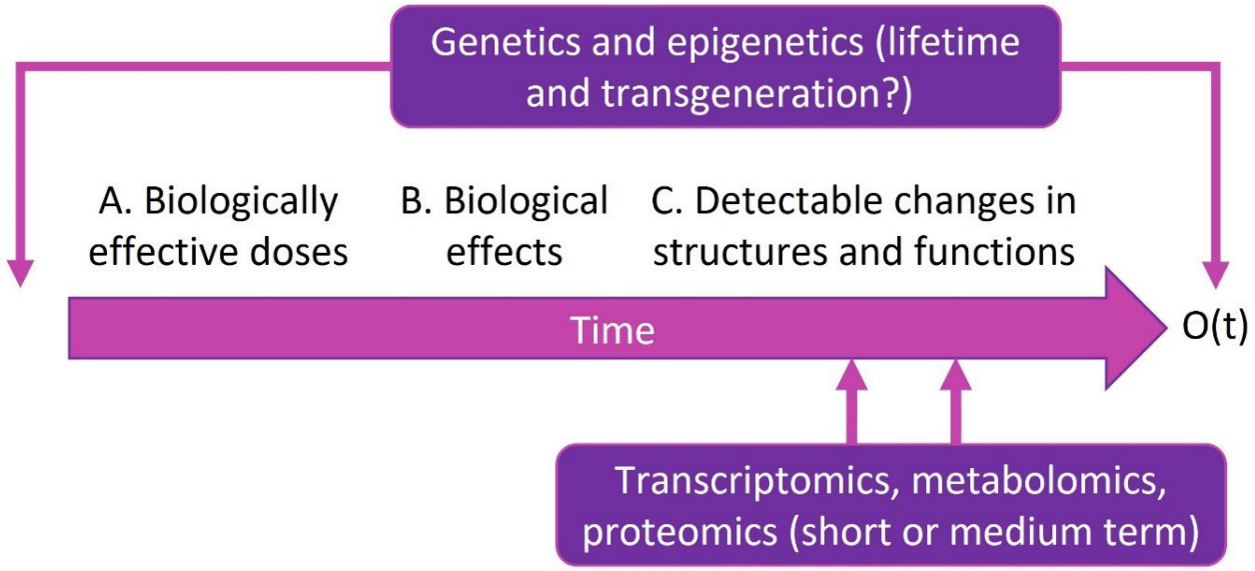
Using genetic analysis that takes all of these factors into account, it is now possible to identify some of the key regulatory drivers to explain different phenotypes in T2D and CVD.[37] For instance, *TRPM6* and *TRPM7* are genes that encode proteins involved in magnesium transport and were identified to be potential predictors of the risk of T2D after analysis, following magnesium supplementation in people who were low in this element.[38]

Conclusions

An integrated framework is needed that can enhance study design, analysis, and interpretation and allow for identification of effective prevention and intervention strategies at each phase of the life cycle, taking into account the concept of interaction.

Prevention of diseases such as T2D require definition of biological mechanisms and triggers. This can be helped by the use of biomarkers.

Figure 2: An integrative framework to evaluate causal relationships in diverse populations.



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O(t): outcome over time

Nutritional Interventions for Addressing the Interaction Between Diabetes and Sarcopenia

Philip Atherton

Lean body mass (LBM), including skeletal muscle, is continuously being remodelled throughout the day by the simultaneous process of protein synthesis and protein breakdown (turnover), also known as postprandial anabolism.[39] Researchers have shown that the timing and type of protein source can impact the rate of muscle hypertrophy and atrophy.[40]

The Actions of Protein on Insulin and Incretin Hormones

To further elucidate this concept, recent work by Atherton and colleagues showed that after approximately 45 minutes following protein consumption there is an insulin spike, even when carbohydrates are not consumed,[41] which is associated with anticatabolism.[42] Furthermore, in another study they carried out wherein participants ingested an EAA oral mixture, they observed an increase in GLP-1 and glucose-dependent insulinotropic polypeptide,[43] suggesting, according to Atherton, that "the insulin response we see is at least partially driven by an incretin response following essential amino acid administration."

Protein and Essential Amino Acid Supplementation in Older People

Maintenance of habitual protein intake is especially important in older individuals[44] as sarcopenia, defined as a reduction in muscle mass and function that can drive frailty, is more likely to occur.[45] A trial investigating effects of EAA supplementation on elderly participants with sarcopenia showed use of EAA supplementation for up to 16 months can help offset decline in LBM.[46] Moreover, a similar study showed that EAA supplementation was associated with an increase in muscle synthesis and muscle insulin-like growth factor-1.[47]

Age-related skeletal muscle decline is especially evident in people with T2D.[48] One trial showed that people with T2D who did not consume adequate amounts of protein had a significantly higher mean number of functional limitations and, overall, poorer diet quality.[49] This was found to be particularly true among people with insulin

resistance who were given EAA supplementation and showed an improvement in functional measures such as walking speed and balance tests.[50] Supplementation with just L-arginine, combined with exercise, in T2D has also been shown to improve fat-free mass and glucose tolerance.[51]

Atherton and colleagues hypothesised that targeting incretin hormones with nutrition could help rescue protein anabolism in elderly people. To test this, they infused GLP-1 into a group of males (mean±standard error of the mean age: 71±1 years) and showed a marked increase in microvascular blood flow following a meal, which was greater in the presence of GLP-1. In other words, "targeting GLP-1 in subjects with T2D might also have a muscle preserving function."[52]

Conclusions

Sarcopenia is an issue of concern in older people as well as older adults with T2D, which may be helped with sufficient protein and EAA intake.

Novel nutrient approaches might impact muscle outcomes via incretin effects.

β-hydroxy-β-methylbutyric Acid, Lysine, and Arginine: A Combination of Ingredients that Ameliorates Diabetes Muscle Loss and Its Complications in Streptozotocin-Induced Rats with Diabetes

Jose-María López-Pedrosa

Rats with Diabetes Model to Investigate Supplementation Effects

López-Pedrosa presented his group's study findings that evaluated the effects of a combination of dietary components, each shown to have a physiological effect, on skeletal muscle loss and metabolic changes in a diabetic rat model. This combination included SDC (which can decrease postprandial glycaemic and insulinemic responses),[53] HMB (which has been shown to increase muscle mass),[54] arginine (as discussed above),[51] and lysine (that can lower postprandial glucose and insulin responses).[55] T2D was induced in 12-week-old male Wistar rats via a high-fat diet and administration of a β-cell mass-reducing chemical agent (data on file).

The mice in the supplemental diet group, compared with mice on the high-fat diet, showed significantly less decline in muscle mass following the diabetes-inducing period along with a significant increase in expression of skeletal muscle glucose transporter 4. While there was an increase in FPG for both groups, it was significantly higher in the mice on the standard diet. Furthermore, the mice in the standard diet group experienced a decrease in fasting insulin levels, while those in the supplemental diet group had a significant increase. Overall, both groups showed a decrease in insulin sensitivity, but to a significantly lower degree in the supplemental group.

Additionally, while both groups experienced an increase in HbA1c, it was higher in the standard diet group, and the mice on the standard diet showed a slight increase in serum triglyceride/high-density lipoprotein:choline ratio, which is proposed to be a predictor of cardiovascular outcomes.[28]

Finally, isolation and analysis of pancreatic β-cells showed a significant increase in insulin production when exposed to a combination of HMB, lysine, and arginine only, suggesting this outcome is not dependent on SDC.

Conclusions

Supplementation with a mixture of SDC, HMB, arginine, and lysine, can preserve muscle mass and improve insulin resistance. Such supplementation might delay metabolic complications associated with diabetes progression.

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Implications of Elevated Postprandial Glucose and Nutritional Approaches for Postprandial Glucose Management with a Focus on Whey Proteins

This symposium took place on 19th September 2022 as part of the 58th Annual Meeting of the European Association for the Study of Diabetes (EASD), held in Stockholm, Sweden, and online

Chairperson: Ian J. Neeland[1,2]

Speakers: John L. Sievenpiper,[3,4] Bo Ahrén[5]

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Meeting Summary

This symposium took place at the 58th Annual Meeting of the European Association for the Study of Diabetes (EASD) in Stockholm, Sweden. The first speaker was John L. Sievenpiper, who discussed the pathophysiology of postprandial hyperglycaemia and how it may impact the risk of cardiovascular disease (CVD), peripheral vascular disease, insulin resistance, and other comorbidities in patients with Type 2 diabetes (T2D). Sievenpiper then reviewed various pharmacological interventions that target postprandial glucose (PPG) and insulin levels, including incretin therapies and α-glucosidase inhibitors, such as acarbose. Data presented showed that a low glycaemic index (GI) diet can improve glycaemic control and reduce cardiometabolic risk factors in patients with Type 1 diabetes (T1D) and T2D. Sievenpiper then presented data on novel non-pharmacological approaches that target PPG, including mulberry leaf *(Morus alba L)* extract (MLE), which has α-glucosidase inhibitor activity, reducing PPG and insulin responses to sucrose. The second speaker, Bo Ahrén, presented data on the effects of whey protein (WP) and branched-chain amino acids (BCAA) on PPG management and as a potential intervention for postprandial hyperglycaemia. They also discussed the mechanisms underlying the effects of WP, and highlighted data presented at the 2022 58th Annual EASD meeting by Johansen and colleagues on a novel micelle microgel technology. WP microgels (WPM) deliver highly concentrated and lower calorie doses of WP, with the potential to be developed clinically as therapeutics for T2D. The symposium concluded with a question and answer session between panel members and the audience. Ian J. Neeland was the meeting moderator.

Welcome and Introduction to the First Speaker

Ian J. Neeland

Neeland welcomed the delegates to the industry symposium and introduced the first speaker, Sievenpiper. Sievenpiper has established an internationally recognised research programme focused on using a combination of randomised controlled trials (RCT) and epidemiological approaches to address essential questions relating to clinical and public health measures regarding diet and the prevention

of cardiometabolic disease, with a particular interest in the role of sugars, the quality of dietary carbohydrates, and therapeutic plant-based diets. Sievenpiper has a direct role in knowledge translation, with appointments to nutrition guidelines committees as part of Diabetes Canada,the EASD, Canadian Cardiovascular Society (CCS), and Obesity Canada.

Implications of Elevated Postprandial Glucose

John L. Sievenpiper

Diabetes is a global epidemic. In 2021, more than 500 million people worldwide were living with diabetes, and this is projected to increase by 46% to 784 million by the year 2045.[1] Heart disease driven by the dual epidemics of obesity and diabetes remains the leading cause of death worldwide.[2]

Diagnosis of Type 2 Diabetes

The criteria for diagnosing T2D include a fasting plasma glucose (FPG) ≥7.0 mmol/L, a 75 g oral glucose tolerance test (2-hour plasma glucose) ≥11.1 mmol/L, a glycated haemoglobin (HbA1c) ≥6.5%, and random plasma glucose ≥11.1 mmol/L.[3-6] The known clinical effects of T2D are the basis for clinical follow-up evaluation and include tests for diabetic nephropathy, neuropathy, and retinopathy.[7-9]

Postprandial Glucose is the Gold Standard for Assessing Diabetes

Postprandial hyperglycaemia is one of the earliest manifestations in response to insulin resistance and insulin secretory dysfunction in the pathogenesis of T2D. Dysglycaemia presents earlier with PPG versus FPG.[10] In particular, β-cell dysfunction, which represents insufficient insulin secretion at a given level of insulin resistance manifesting as high glucose, is seen earlier with PPG than with FPG.[11]

The DETECT-2 Collaboration, which pooled nine studies of more than 44,000 individuals from five countries, showed that the 75 g oral glucose tolerance test is more sensitive and detects diabetes more effectively than with FPG or HbA1c, based on retinopathy.[12] The DECODE study included more than 29,000 individuals over 11 years of age, and found that the 2-hour PPG was associated with increased CVD mortality even within a normoglycaemic range.[13] The DECODE study also demonstrated that at any level of FPG, an elevated PPG is associated with increased CVD mortality.[14,15]

Pharmacological Interventions That Target Postprandial Glucose

There are several pharmacological interventions to target PPG, including incretin therapies, mealtime insulin, and α-glucosidase inhibitors, such as acarbose. Sievenpiper's colleague, David J.A. Jenkins, studied acarbose before the GI was recognised as a concept. In a randomised crossover study in 1981, four healthy individuals with a normal glucose tolerance were given a low dose of acarbose of 50 mg three times a day (TID) with meals and 25 mg TID with snacks. The study demonstrated that acarbose reduced PPG over 24 hours compared with placebo.[16]

The STOP-NIDDM trial randomised 1,429 individuals with impaired glucose tolerance (IGT) to high-dose acarbose (100 mg TID), and followed them for 3.3 years.[17,18] There was a 25% risk reduction in T2D with acarbose compared with placebo. In a prespecified secondary analysis of the trial, there was a 49% risk reduction in cardiovascular events with acarbose versus placebo.[19] A meta-analysis of seven studies powered to examine cardiovascular outcomes included 2,180 patients with T2D and found that acarbose was associated with reductions in myocardial infarction and total cardiovascular events in T2D.[20]

The Acarbose Cardiovascular Evaluation (ACE) trial, designed and powered to investigate coronary events, enrolled 6,522 Chinese patients with IGT and established coronary heart disease and found that low-dose acarbose (50 mg TID) reduced the risk of T2D but not cardiovascular events over a median 5-year follow-up.[21,22] The reduction in T2D confirmed the findings of STOP-NIDDM, but whether these findings translate to a real-world reduction in cardiovascular events downstream remains questionable.

Are There Guidelines-Based Nutritional Analogies of Acarbose?

The GI was first introduced by Jenkins et al.[23] in the early 1980s as a methodology to rank and classify carbohydrate foods as low (≤55), medium (56–69), and high (≥70) GI, based on their ability to raise blood glucose levels with glucose as the reference, which has a GI of 100.[23] The GI has since been incorporated into clinical practice guidelines from organisations such as the EASD and Diabetes Canada. Low GI foods are absorbed over the length of the small intestine, whereas high GI foods are absorbed proximally and at a faster rate, resulting in a significant and rapid rise in PPG levels and glucose variability. Major diabetes and CVD clinical practice guidelines worldwide recommend low GI/GL diets as an effective strategy for glucose management.[24]

Studies of low GI foods and acarbose indicate that acarbose can influence the GI of a meal, thereby possibly lowering the overall glycaemic load (GL). In 1979, a randomised study in eight individuals conducted by Jenkins et al.[25] compared placebo with guar gum (14 g) alone, acarbose (50 mg) alone, and guar gum (14 g) plus acarbose (50 mg).[25] Guar gum and acarbose produced similar 2-hour PPG reductions, with additive suppression in PPG when the two compounds were administered together.[25] The findings from a systematic review of RCTs and meta-analysis study, conducted by Jovanovski et al.,[26] supported that viscous fibre supplements provided glycaemic control beyond usual care and should be considered in the management of patients with T2D.[26] An average dose of approximately 13 g of viscous soluble fibre (β-glucan, guar, konjac mannan, psyllium) during 8 weeks led to a clinically meaningful 0.61% reduction in HbA1c.[26] These findings would meet U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) criteria for new drug development.

In 1980, further studies by Jenkins et al.[27] showed that legumes slowed carbohydrate digestion during a 3-hour period, which was reflected in a lower rise in PPG.[28] Moreover, a meta-analysis by Sievenpiper et al., which included 41 RCTs with 1,674 individuals, with and without T2D, found that pulses consumed as part of a low GI and high fibre diet reduced HbA1c by 0.48% in patients with T2D.

In addition to improving glycaemic control, low GI (≤55) diets have been shown to improve cardiometabolic risk factors in individuals with both T1D and T2D.[30] The systematic review and meta-analysis commissioned by the Diabetes and Nutrition Study Group to update the guidelines found meaningful reductions of 0.3% for HbA1c, a modest but clinically significant difference of 0.4 mmol/L for FPG, and approximately a 5% decrease in lipids.

In contrast, high GI/GL diets were associated with an increased incidence of diabetes in a meta-analysis of 24 prospective cohort studies with a 4-year to 22-year follow-up.[31] For GI, the combined relative risk (RR) was 1.27 (range: 1.15–1.40) per 10 unit increase and 1.87 (range: 1.56–2.25) across the global range, while for GL the combined RR was 1.26 (range: 1.15–1.37) per 80 g/day and 1.89 (range: 1.66–2.16) across the global range.[31] High GI/GL diets have also been associated with an increased incidence of coronary heart disease.[32] In a meta-analysis of 11 prospective cohort studies, including 350,000 individuals and 10,400 events over 11.4 years of follow-up, the overall RR for GI was 1.24 (range: 1.12–1.38) per 10 unit increase and 2.71 (range: 1.47–4.40) across the global range.[32] The RRs for GL were 1.44 (range: 1.25–1.65) per 65 g/day and 5.5 (range: 3.1–9.8) across the global range.[32]

Supplements That Target Postprandial Glucose

The MLE (*Morus alba L*) has been demonstrated to have α-glucosidase inhibitor activity and was investigated in a double-blind RCT of 38 healthy individuals.[33] Subjects were randomised to consume either 250 mg MLE, containing 12.5 mg of the active component deoxynojirimycin, or placebo and followed for 2 hours.[33] MLE was found to reduce PPG and insulin responses following administration of 75 g sucrose.[33]

In a crossover study that included 30 patients with T2D found that the same MLE combined with 1.75 g fibre, 0.75 µg vitamin D3, and 75 µg chromium reduced 3-hour PPG and insulin responses to a mixed meal tolerance test (55.4 g of carbohydrate [Figure 1]).[34]

In adults with prediabetes, significant results were also found with MLE (*Morus alba L*) when 38 individuals with IGT in a double-blind, parallel RCT were randomised to receive either 5 g/day (18 mg deoxynojirimycin) or placebo with a 4-week follow-

up and showed MLE reduced PPG and insulin responses to a mixed meal tolerance test.[35,36] Similar findings of α-glucosidase inhibition have been reported with another MLE product (*Morus nigra*) in patients with T2D.[37] In a controlled clinical study of 100 patients with T2D, 50 patients were treated with the MLE extract for 3 months, and 50 patients were treated with placebo.[37] At 3 months, fasting blood glucose and HbA1c were significantly reduced in the MLE-treated patient group.[37]

Conclusion

The epidemic of T2D and its downstream cardiometabolic complications threaten healthcare systems worldwide. PPG is the gold standard for diagnosing and probing the natural history of T2D. Pharmacological interventions that aim to lower PPG, such as α-glucosidase inhibitors, improve glycaemic control and cardiometabolic risk factors, and reduce incident diabetes. Guideline-based nutritional interventions aim to lower PPG (e.g., low GI/GL, viscous fibre, and pulses). These recommendations represent a nutritional analogy of acarbose, showing similar improvements in glycaemic control, cardiometabolic risk factors, and the reduction of diabetes and complications such as CVD. Supplements that target PPG, for example MLE, may share similar advantages; however, further studies and more data are needed.

Introduction to the Second Speaker

Ian J. Neeland

Neeland introduced the second speaker, Ahrén, who has been directly involved in the development of new targets and compounds for the treatment of T2D. Ahrén has a special interest in the development of new treatments based on the incretin hormone glucagon-like peptide 1 (GLP-1), and its inhibitory enzyme dipeptidyl peptidase 4 (DPP-4). Ahrén has published several original and review articles in the area of islet cell function with the special aim of understanding the regulation and mechanisms of normal pancreatic islet function, and the mechanisms and consequences of islet cell dysfunction as a key factor underlying T2D.

Nutritional Approaches for Postprandial Glucose Management Focus on Whey Protein

Bo Ahrén

Milk has 3.5 g of protein per 100 ml, which constitutes 20% of the energy provided by milk. There are two types of protein in milk: WP (approximately equal to 20% of the protein in cow's milk and 60% in human milk) and casein protein (approximately equal to 80% of the protein in cow's milk and 40% in human milk).

Constituents of Whey Protein

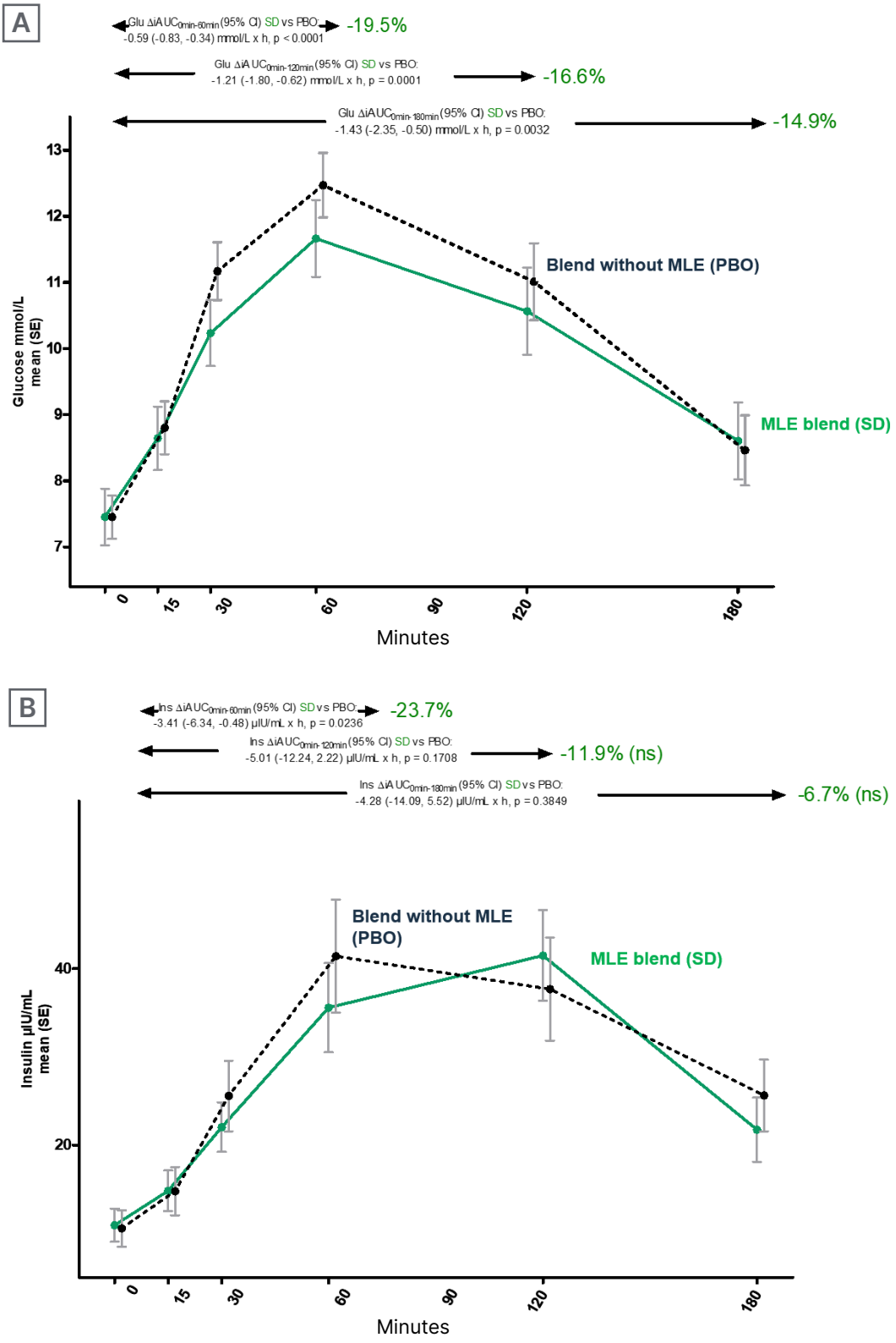
WP is the protein in the liquid remaining after milk has been coagulated during cheese production. This protein fraction is acid soluble and rapidly delivered to the gut after ingestion. WP consists of a mixture of proteins, the majority being β-lactoglobulin (approximately 50–60%), and the remaining including α-lactalbumin (approximately 10–20%), glycomacropeptide (12–20%), albumin (approximately 5–10%), and Igs (approximately 5–10%). WP contains a large fraction of the BCAAs leucine, isoleucine, and valine, which have been shown to play an important role in protein synthesis and other metabolic actions.[38] Today, WP is readily available as a supplement for muscle growth and development, but it also has the potential to treat PPG.

Branched-Chain Amino Acids Are Important for the Metabolic Action of Whey Protein

WP increases circulating levels of BCAA in T2D. This was demonstrated in an RCT by King et al.,[39] whereby 11 subjects with T2D were randomised to receive 15 g intact or hydrolysed WP before a breakfast meal.[39,40] Plasma BCAA concentrations were measured after breakfast alone, and prior to consumption of 15 g intact and hydrolysed WP before breakfast. After breakfast, there was no change in plasma concentrations of valine, leucine, and isoleucine, while concentrations more than doubled in 20–40 minutes when WP was consumed immediately before breakfast.[39]

The increased BCAA concentration following WP consumption is important because BCAAs are

Figure 1: Effects of mulberry leaf extract on glucose (A) and insulin trajectories (B).



AUC: area under the curve; CI: confidence interval; Glu: glucose; Ins: insulin; MLE: mulberry leaf extract; ns: not significant; PBO: placebo; SD: standard deviation; SE: standard error; vs: versus.

Adapted from Mohamed et al.[34]

potent stimulators of insulin secretion. BCAAs have been extensively studied in isolated islets and animal studies. In 2008, Kalogeropoulou et al.[41] compared the insulin response in 13 healthy subjects after receiving 2 g leucine with 25 g glucose versus 25 g glucose alone.[41] Leucine resulted in a doubling of the insulin concentration after glucose compared to glucose alone, which was associated with a reduction in glucose levels.

WP stimulates insulin secretion through three mechanisms. One, BCAAs directly stimulate islet β-cells to secrete insulin, and the other two effects are indirect, whereby WP bioactive peptides stimulate the secretion of the incretin hormones, gastric inhibitory polypeptide (GIP) and GLP-1.[42,43] Furthermore, WP inhibits the action of DPP-4, the enzyme responsible for GLP-1 and GIP inhibition, which leads to a sustained active concentration of GLP-1 after meal ingestion.[42]

Effects of Whey Protein on Glucagon-Like Peptide 1, Glucose-Dependent Insulinotropic Polypeptide, and Dipeptidyl Peptidase-4

In 2009, Ma et al.[44] conducted the first human study showing a marked increase in GLP-1 and GIP levels following WP consumption.[44] Eight subjects with T2D consumed 55 g WP either together with a breakfast meal or as a 30-minute preload in which GLP-1 and GIP concentrations were measured. Concentrations of GIP and GLP-1 increased after breakfast alone, but there was a potentiation of the response after WP was given with the test meal, concluding that WP was a particularly potent stimulator of GLP-1 when given as a preload.

The inhibition of DPP-4 by WP was shown in 2006 by Gunnarsson et al.[42] in Ahrén's group. Mice were given 75 mg glucose alone or together with 75 mg WP. The WP and glucose treatment led to a significant potentiation of insulin levels and a reduction in glucose. Both GLP-1 and GIP were increased 15 minutes after after the WP and glucose treatment. Finally, the addition of WP to glucose led to a reduction in DPP-4 activity.

Whey Protein Delays Gastric Emptying and Reduces Postprandial Glucose

WP also delays gastric emptying by inhibiting muscle cell activity and through the release of GLP-1. In Ma et al.'s[44] 2009 study, discussed above, subjects consumed a radio-labelled mixed meal.[44] Scintigraphy was used to measure the amount of food remaining in the stomach after specific time periods.[44] Sixty minutes after subjects consumed the control mixed meal (no WP), 25% of the meal remained in the stomach.[44] When WP was given as a preload, 70% of the mixed meal remained in the stomach after 60 minutes.[44]

WP reduces PPG via several mechanisms.[42,43] It increases insulin secretion, which causes a reduction in hepatic glucose production and an increase in peripheral glucose utilisation, and it delays gastric emptying, which causes a delay in glucose absorption.

Effects of Whey Protein in Healthy Subjects and Patients with Type 2 Diabetes

Gunnerud et al.[45] conducted a dose–response study of WP in 12 healthy subjects who received 4.5, 9, and 18 g WP together with 25 g glucose.[45] WP reduced PPG and increased insulin and BCAA levels in a dose-dependent manner.[45] Ahrén conducted a randomised clinical trial with Jakubowicz and colleagues in Israel, in which 15 subjects with T2D were given 50 g of WP 30 minutes before a mixed breakfast meal.[46,47] Results showed a significant reduction in PPG, the incremental area under the curve (AUC) was reduced by 25%, and peak glucose levels were reduced from 16 mmol/L to 10–11 mmol/L.[46] Also, the AUC for insulin doubled and GLP-1 concentrations more than doubled.[46]

Several studies have been conducted on the effects of WP in T2D. The greatest efficacy has been observed when WP is taken 30-minute prior to a meal and at high doses (50–55 g), which while efficacious, contributes an extra 200–220 kcal.[44,46]

In 2017, the long-term effects of WP were investigated by Ahrén together with Jakubowicz.[48] A total of 19 subjects with T2D were given 28 g WP as a preload 15 minutes before a standardised breakfast every morning

for 12 weeks.[48] The results showed a persistent glucose reduction and increase in insulin and GLP-1 levels.[48] In addition, WP resulted in a reduction in both HbA1c and body weight.[48]

The reduction in body weight observed with WP consumption has been thought to be due to the bioactive peptides and BCAAs activating the satiety centre in the hypothalamus, resulting in an acute enhanced feeling of fullness and suppressed appetite, which over the long-term, has been associated with a reduction in body weight.[49] WP has also been shown to stimulate the release of gastrointestinal hormones involved in the regulation of appetite and satiety, including GLP-1, peptide YY (PYY), cholecystokinin, and ghrelin.[42,43,49,50]

Limitations of Traditional Whey Protein Formulas to Regulate Postprandial Glucose

Translating the benefits of WP to clinical use is challenging for two main reasons. One, the greatest efficacy has been observed when WP is taken as a preload 30 minutes prior to a meal; and two, a high dose of 50–55 g is required. With this type of regimen, compliance is a challenge and creates the burden of having to plan ahead, as well as contributes an additional 200–220 kcal. Therefore, to be able to use WP as an effective intervention, there is a need for a new format or technology that enables the use of a lower, more potent dose.

Micelle Technology to Administer Whey Protein

A novel formulation of WP has been developed, which allows for a smaller, more highly concentrated formula that is more readily absorbed.[51] Micelle technology generates WPM and reduces the size of WP into 250 nm micelles, producing a highly concentrated product delivered in a small volume. This highly concentrated WPM formula delivers a low dose of 10 g WP at only 40 kcal. The WPM formula acts quickly, within 10–15 minutes of consumption, and holds promise for translating the knowledge on WP into the clinic.

On behalf of Johansen et al., Neeland presented the study findings of this novel formulation as a short oral abstract presentation at the 58th EASD 2022 meeting.[51] In a randomised, placebo-controlled, crossover study, 26 adults with T2D were randomised to receive the WPM containing 10 g of WP (40 kcal) versus placebo (0 kcal). It was taken as a 125 mL shot, 15 minutes prior to consumption of a 250 g pizza lunch (622 kcal). Glucose, insulin, BCAA, and gut hormones (GLP-1, GIP, and PYY) were assessed.[51] The results showed that the 10 g WP premeal shot significantly reduced PPG levels, measured by iAUC.[51] The iAUC was reduced by 22% during the first 2 hours and 18% over 3 hours.[51] This was associated with an increase in early phase insulin secretion, which is critical for suppressing hepatic glucose production after a meal. The AUC was augmented by 61% at 1 hour and 14% at 3 hours. Regarding gut hormones, the AUC for GLP-1 increased by 66% during the first 2 hours. In contrast, there was no significant effect of WPM on PYY and GIP.[51]

The effects of WPM on gastric emptying were also examined using an acetaminophen (paracetamol) test.[51] Paracetamol was administered together with the meal, and levels were measured as an indirect marker of gastric emptying.[51] The results showed that plasma concentrations of paracetamol were reduced by 17% during the first 45 minutes compared with placebo, signalling a delay in gastric emptying with WPM administration.[51] Finally, the study showed that BCAA concentrations increased dramatically after WPM administration compared with placebo.

In another study by Johansen, a 125 mL premeal WPM shot (10 g; 40 kcal) was given to 102 subjects with T2D or prediabetes prior to consumption of a lunch meal.[52] Before WPM consumption and 15 minutes afterward, self-reported sensations were scored on a scale of 1–9 as hungry (1–3), satisfied (3–6), or full (7–9).[52] The number of subjects reporting that they were hungry significantly decreased following WPM, and the number stating they were satisfied significantly increased.[52]

Conclusion

WP degrades to a mixture of bioactive peptides and BCAAs and has been shown to stimulate the secretion of insulin, GIP, GLP-1, and PYY. Through several mechanisms, studies have demonstrated that WP can effectively reduce PPG in T2D,

with the greatest efficacy observed when WP is administered at high doses 30 minutes before a meal. A novel micelle technology allows for WP to be delivered as a highly concentrated formula in a smaller volume, which can be taken 15–30 minutes before a meal. WPM has been shown to reduce PPG, increase insulin, GLP-1, and BCAA levels, and increase satiety. Longer-term studies are needed to fully understand the impact and potential of this new technique.

Question and Answer Session

Ian J. Neeland, John L. Sievenpiper, and Bo Ahrén

The symposium concluded with a question and answer session among panel members and the audience. Topics included reduced body weight with WP despite increased insulin secretion, the effects of a general protein mixture versus WP, the epidemiology of WP intake and T2D prevalence, targeting low GI or low GL to lower PPG, the applicability of WP in T1D, and the mechanisms linking PPG excursion and acarbose with cardiovascular events.

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Abstract Highlights

The following highlights spotlight several standout abstracts presented at the 58th European Association for the Study of Diabetes (EASD) Annual Meeting, covering topics such as the effects of extended overnight fasting, the incidence of congenital heart defects in the offspring of females diagnosed with pregestational diabetes, and telehealth for the metabolic control of Type 1 diabetes.

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Combination of Dietary Weight Loss and Exercise May Improve β-Cell Function

β-CELL function may be improved by dietary weight loss in patients with Type 2 diabetes (TD2); however, it is unclear whether exercise in addition to diet therapy can play a role. This new research was presented at the EASD Annual Meeting 2022 in Stockholm, Sweden.

The new study assessed β-cell function at physiological conditions, using a mixed meal tolerance test, and at supraphysiological conditions, using the hyperglycaemic clamp. The researchers randomised 82 participants, who had T2D for less than 7 years and were overweight or obese, to 16 weeks of either standard care; dietary intervention; dietary intervention with exercise three times a week; or dietary intervention with exercise six times a week. The dietary intervention aimed to reach 25% calorie deficit and weight loss, while the exercise interventions consisted of resistance and aerobic training.

Primary outcome was the change in β-cell function, which was assessed with clamp-derived late-phase disposition index. The secondary outcomes were clam- and mixed meal-derived changes in β-cell function, insulin sensitivity from baseline to 16-week follow-up, and insulin secretion. Adherence to the diet (25–30% energy reduction) and exercise (>85%) was similar across all groups. Five participants were lost to follow-up.

All three intervention groups showed an improvement in late-phase disposition index. The mean difference from standard care was 58% for diet only, 105% for moderate volume exercise, and 137% for high volume exercise. While the high-volume exercise group showed a larger improvement compared to the diet group, there was no difference between moderate and high volume exercise, or between moderate exercise and diet. Furthermore, there was no difference in glucose-stimulated insulin secretion between the groups. The improvements in sensitivity were similar to those observed for the disposition index, and the observations during the meal test confirmed the hyperglycaemic clamp findings.

> **"The combination of exercise and dietary weight loss improves β-cell function more than diet alone or standard care."**

Authors concluded that the combination of exercise and dietary weight loss improves β-cell function more than diet alone or standard care. There was no significant difference between moderate and high-volume exercise, and it was mainly improved insulin sensitivity that led to the improvement in β-cell function. ●

Extended Overnight Fasting and its Effects

OVERNIGHT fasting is said to improve metabolic health; however, the mechanisms underlying these effects are inconclusive. Hepatic glycogen fluctuations, which can induce higher overnight fat oxidation, could be related to these mechanisms. For individuals with a high amount of ectopic fat accumulation, such as those with non-alcoholic fatty liver disease (NAFLD), increasing fat oxidation could be a therapeutic strategy.

Researchers from the Netherlands investigated whether prolonging overnight fasting from 9.5 to 16.0 hours reduces overnight hepatic glycogen and improves substrate metabolism in patients with NAFLD, when the total daily energy intake remains the same. The researchers recruited 11 patients with NAFLD and 10 age-matched, healthy controls. Food intake was restricted to 14.5 or 8.0 hours, recreating an overnight fasting period of 9.5 and 16.0 hours, respectively.

After a standardised lunch at 2:00 p.m. and at 6:30 a.m. the next morning, hepatic glycogen was measured in both groups with 13C-MRS, with nocturnal substrate oxidation being measured with a whole-room indirect calorimetry (respiratory chamber). Metabolic response to a meal was measured through a meal test, which was performed after the overnight fast with an indirect calorimetry (ventilated hood). Plasma metabolites were also assessed through drawing blood.

While prolonging overnight fasting led to lower nocturnal carbohydrate oxidation in all participants, hepatic glycogen levels were not affected. The researchers also noted higher fat oxidation in the patients with NAFLD and the control group. Regardless of the fasting time, individuals with NAFLD had a higher respiratory exchange ratio than the control group. However, the area under the curve for triglycerides was higher in those fasting for 16.0 hours than the 9.5-hour fast in both the NAFLD and control groups.

While no other post-prandial differences were noted during either of the fasting periods, these results suggest that extending overnight fasting can improve nocturnal substrate oxidation. The researchers concluded that changes in hepatic glycogen depletion did not mediate these improvements. ●

"For individuals with a high amount of ectopic fat accumulation, such as those with non-alcoholic fatty liver disease (NAFLD), increasing fat oxidation could be a therapeutic strategy."

Congenital Heart Defects in Children Following Pregestational Diabetes

A NATIONWIDE study carried out in France aimed to estimate the incidence of congenital heart defects (CHD) in the offspring of females diagnosed with pregestational diabetes. CHDs are the most common type of congenital issues in the children of this patient group.

The national French Medical Information System Program in Medicine, Surgery, and Obstetrics (PSMI-MCO) database was used to compare females with Type 1 diabetes (T1D) and Type 2 diabetes (T2D) to the general population. The secondary aim of the study was to investigate whether the association between CHD and maternal diabetes varied with diabetes types.

The study used a logistic model to estimate the risk factors for maternal-fetal prognostic indicators in females diagnosed with T1D and T2D. In the control population, this model was adjusted according to maternal age, prematurity, gender of the newborn, mode of delivery, and whether the infant was small or large for gestational age.

A large cohort of over 6 million mother and infant pairs was included in the study, using data recorded between 2012–2020. The rate of congenital malformations was found to be 6.2% in the control group (8.0 per 1,000 births), 8.0% in females with T1D (29.6 per 1,000 births), and 8.4% in females with T2D (27.4 per 1,000 births).

The risk of CHD was found to be 2.07 times higher with T1D (95% confidence interval: 1.91–2.24; p<0.001), and 2.20 times higher with T2D (95% confidence interval: 1.99–2.44; p<0.001). Caesarean section, premature birth, and small and large gestational age were associated with a higher risk of an infant having CHD.

"The study used a logistic model to estimate the risk factors for maternal-fetal prognostic indicators in females diagnosed with T1D and T2D."

The study concluded that a diagnosis of pregestational diabetes is a risk factor in the development of CHD in infants. It also found that there was no significant difference in cases of CHD regarding the type of diabetes the mother has. The final recommendation was that the modifiable risk factor of metabolic control could be harnessed in order to reduce the risk of CHD in infants.

Multimorbidity and Mortality in Patients with Type 1 Diabetes

PATIENTS with Type 1 diabetes (T1D) are at an increased risk of multimorbidity, which is associated with a decreased quality of life and an increased mortality. Patients with T1D are often affected by other chronic conditions at a young age, and these conditions lead to an increased risk of depression and severe hypoglycaemic episodes. Current data on multimorbidity, the coexistence of two or more chronic conditions or diseases, in patients with T1D is scarce, which is why a research team at the University of Helsinki, Finland, decided to study the prevalence of multimorbidity, and its impact on mortality in patients with T1D.

The study included 4,069 adult participants with T1D and analysed data from clinical records, registers, and questionnaires. Researchers defined the accumulation of diseases based on the number of chronic conditions at baseline from a list of 32 conditions, which were grouped into three subcategories: autoimmune disorders, vascular comorbidities, and other conditions.

At baseline, the prevalence of multimorbidity was 60.4% (n=2,458) and it increased with age; it was 31.1% in those under 30 years, 59.8% in those from 30–40 years, 74.8% in the 40–50 age group, 84.3% in the 50–60 age group, and 93.2% in those older than 60 years. Notably, there was no difference between males and females. Autoimmune disorders were observed in 12.7%, while vascular comorbidities were observed in 49.2%, and other conditions in 19.8%. The median follow-up was of 16.7 years, during which 784 (19.3%) participants died. Mortality was significantly increased by multimorbidity.

The study concluded that prevalence of multimorbidity is high and increases with age in patients with T1D. Due to vascular comorbidities and other chronic conditions, mortality is also increased; however, autoimmune disorders do not increase the risk. ●

"At baseline, the prevalence of multimorbidity was 60.4% (n=2,458) and it increased with age, as it was 31.1% in those under 30 years, 59.8% in those from 30–40 years, 74.8% in the 40–50 age group, 84.3% in the 50–60 age group, and 93.2% in those older than 60 years."

Telehealth as Effective as In-Person Care for Metabolic Control of Type 1 Diabetes

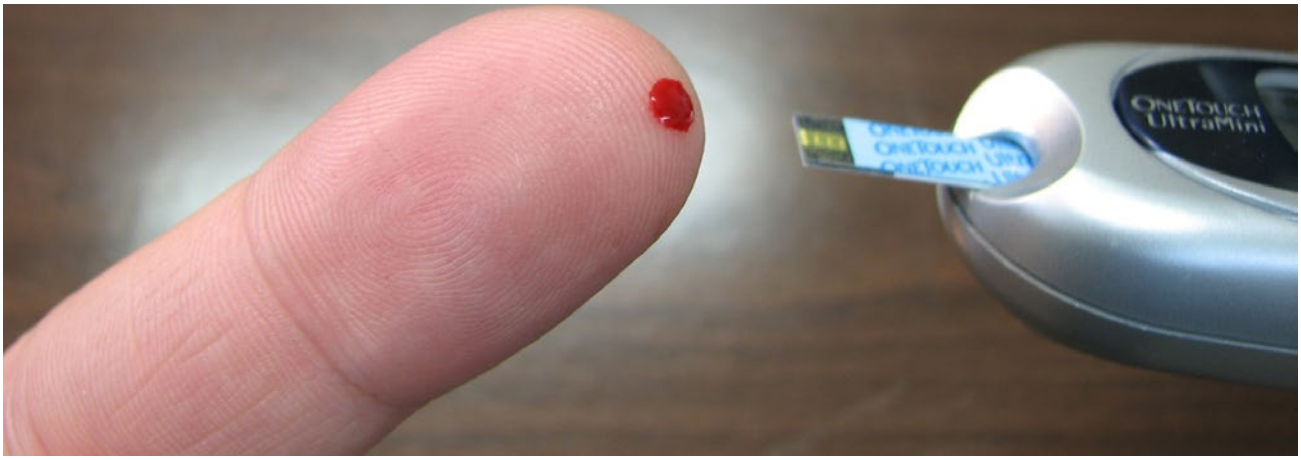
INCREASING evidence shows that telehealth (TH) is not inferior to in-person care for metabolic control of patients with Type 1 diabetes (T1D). The usage of TH has advantages such as decreasing time spent travelling and increasing accessibility, allowing for more frequent visits. This has been especially important since the COVID-19 pandemic, and in rural zones.

A new study aimed to compare the changes in HbA1c between in-person visits and TH after 6 months. Secondary objectives were comparison of hypoglycaemic events, glucometric parameters, direct and indirect costs, EsDQoL questionnaire, and patient satisfaction. The researchers carried out a randomised, controlled study. The 55 participants were split into two groups: a conventional group (29 subjects), submitted to standard in-person visits in an outpatient clinic, lasting 30 minutes, at baseline, 3 and 6 months; and a TH group (26 subjects), submitted to a teleconsultation of 10 minutes in months 1, 2, 3, and 4, as well as an in-person visit at baseline and 6 months.

After 6 months, the mean change in HbA1c was -0.05% in the TH group, versus 0.2% in the conventional group. The conventional group spent 93.2 minutes +12.0 with the endocrinologist, versus 102.9 minutes +7.6 in the TH group. Furthermore, 46% of participants preferred a combination of both in-person and TH visits. The researchers did not detect any severe hypoglycaemia.

Authors concluded that TH is comparable to in-person visits when it comes to HbA1c levels, with a significant improvement in EsDQoL and time in range. While TH implies increased costs for the national care system, it leads to a decrease in direct and indirect costs for the patients. More research is needed to determine efficient timings of visits, as well as long-term cost analysis.

"After 6 months, the mean change in HbA1c was -0.05% in the TH group, versus 0.2% in the conventional group."



SARS-CoV-2 Increases Risk of Type 1 Diabetes in Children and Adolescents?

NEW research has revealed that there could be an increased risk of developing Type 1 diabetes (T1D) following severe acute respiratory syndrome virus 2 (SARS-CoV-2) infection in children and adolescents.

A research team, led by Hanne Løvdal Gulseth, Norwegian Institute of Public Health, Norway, analysed data obtained from the Norwegian preparedness register for 1,202,174 children and adolescents to evaluate the link between SARS-CoV-2 infection and risk of developing T1D in response to several case reports indicative of the link between the two. The individuals enrolled were followed-up from the COVID-19 pandemic outset on 1st March 2020 until the first of either a diagnosis of T1D, their 18th birthday, death, or the 22nd of March 2022.

The study used a full population cohort and a test-negative design and utilised Cox regression analysis, with SARS-CoV-2 PCR positivity as a time-dependent exposure to estimate unadjusted hazard ratios (HR) and HRs adjusted for age, geographical area, non-Nordic country of origin, sex, and socio-economic status. Separate analyses were performed if a diagnosis of new onset T1D was made ≤30 days or ≥31 days following SARS-CoV-2 infection.

Of the 1,202,174 children and adolescents enrolled, 424,354 experienced SARS-CoV-2 infection, with 990 incident diagnoses of T1D. The full population cohort adjusted HR for T1D diagnosis ≥31 days following SARS-CoV-2 infection was 1.57 (95% confidence interval: 1.06–2.33) compared 1.63 (95% confidence interval: 1.08-2.47) for the test-negative cohort.

> **"These results highlight the association between SARS-CoV-2 infection and the increased risk of developing T1D in children and adolescents."**

These results highlight the association between SARS-CoV-2 infection and the increased risk of developing T1D in children and adolescents. The researchers recommend that further studies are required and should include assessment of different SARS-CoV-2 variants, as well as longer-term follow-up. ●

Interviews

David Leslie and Naveed Sattar share insights into their careers, research, and the future of the diabetes field. Covering fascinating topics including autoimmunity and cardiometabolics.

Featuring: David Leslie and Naveed Sattar

David Leslie

Professor of Diabetes and Autoimmunity, Centre of Diabetes, Queen Mary University of London, UK; Consultant Endocrinologist, Barts Health NHS Trust, London, UK

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Q1 How did you first become interested in a career in medicine, specifically in your specialism in diabetes and autoimmunity?

I became interested in medicine because I loved biology, particularly human biology. I would have liked to have done genetics, but it seemed to me that genetics was not very well developed at that stage. At that point, colleagues of mine said to me, "David, you're not going to study snails, are you?" And then I thought the lack of acknowledgment and reputation if I was studying snails compared to being a doctor was not appropriate. I didn't hear angels singing or anything like that, there were no choirs! I was just very interested in biology. I was very unsure as to what to do.

I really wanted to do cardiology but in those days, which was back in the 1970s, there were literally no jobs, and I mean no jobs. I can remember at that time, that the President of the European Society of Cardiology (ESC) was aged about 43 and still a senior registrar; Douglas Chamberlain, whom I later worked with. It just seemed crazy, but there were just no jobs.

I then applied for two jobs, one which everyone thought I would get in chest diseases, and the other at King's College Hospital, London, UK, in diabetes, as King's was considered the best place to go for this. No one thought I'd get the job at King's because there was a very good candidate who was much more senior than me,

"I think really when you reach my age, you're more interested in trying to help people develop themselves rather than yourself."

but in the event, I got on enormously well with the person who ran the department, David Pyke. David became my colleague, mentor, and friend, really a father figure. And really, that was that. The decision as to whether I did chest diseases or diabetes was actually out of my hands because the interview at King's was one hour before the interview at the Royal Brompton Hospital, London, UK. I was dead certain that I would get the job at the Royal Brompton Hospital, but not at King's, but, I went to the King's interview, they offered it to me, and they said, "you have to make up your mind now!"

Q2 You were the first clinician to report many things; for example, early environmental events as a cause of Type 1 diabetes, early glucose changes during pregnancy being associated with congenital malformations, and persistent changes in the immune system as a predictor of diabetes. How does it feel to have been so instrumental in your field, and to have positively changed diabetes diagnosis and care for so many patients?

I love the excitement of discovering things, but no one discovers it entirely by themselves. Every single thing I've done has been with other people, and everything that I've done was just a race as to who got there first! I remember the early environmental story that I did with the late Bob Elliot, a New Zealander; he had the data, and I had the ideas. I said to him, "why don't we look at all of your data and see when these guys are developing this particular protein (an autoantibody)?" And he said, "oh, that's an interesting idea," and that was it. Most got the autoantibody before they were aged 5 years, so we wrote our paper up. I think that's pretty typical of all these things; you're never by yourself, always with people. At the end of the day, it's just a question of how much you try and claim it as your own, and whether you got there more or less first.

Q3 You were the Principal Investigator for three studies: Blueprint Epigenome, Action LADA (Latent Auto-Immune Diabetes in Adults), and EXALT. Could you tell us briefly what these studies are looking into, and why this is important in diabetes and autoimmune disease care and understanding?

Well, these are all European Union (EU)-funded studies, so that has a certain cachet. I was indeed the principal investigator for these three studies. The first one, Action LADA was about latent auto-immune diabetes in adults (LADA), and followed from the idea that there might be people in adult life who have Type 1 diabetes. Some people still think that Type 1 diabetes is a childhood disease, but the evidence is that adult-onset Type 1 diabetes is the most common form of presentation and it often presents in adults who do not initially require insulin. So, the most prevalent presentation of Type 1 diabetes is an adult with non-insulin requiring diabetes. That's where we are.

The Blueprint Epigenome study was awarded the largest sum of money ever given by the EU. It was about 30 million EUR to identify the so-called epigenome of the human body. To put it simply, my nose looks like a nose and my ear looks like an ear, but the genes are exactly the same genes. So, what's happened? And the answer is epigenetics; certain genes in my ear are switched off, and others switched on. That's epigenetics.

Some people say the difference between identical twins is epigenetics. It's the way a gene is expressed. There are lots of little markers put on these genes and they are expressed in different ways, and that's what we're doing. We published a number of papers on the subject. It's a fascinating subject. It's just in its infancy stage and there's going to be a lot more to come, too. I was interested in identical twins, which is what we used for that programme, and I was particularly interested in why one twin had diabetes and the other did not, even though they were identical

genetically. The implication was that it was a sort of epigenetic difference, and I suspect there is and that's what we're going to find one day. We're still analysing our data. The third EU grant was for immune therapy, which was an attempt to use a form of immune therapy to change the process of Type 1 diabetes. We did an initial early phase study, then a Phase IIa, and right now we're doing a Phase IIb study, where we're giving the treatment to people with recently diagnosed Type 1 diabetes to see if we can modify the disease process. If it works, we'll start looking at people at a very early stage of diabetes, perhaps even before they develop clinical diabetes because we can now predict the disease very well, even before the onset of clinical symptoms of diabetes.

Q4 Looking at professorships you hold, you're an Emeritus Professor to both Central South University in China, as well as a Chair at the University of Rome in Italy. In what ways do these positions aid your research, and the research carried out within these institutions?

I'm an Emeritus Professor in China, so I do a lot of work there. But in Rome, I'm the lead Professor of the International Medical Faculty. I've had a long association in Rome, and the person in charge of the department there also works with me in London. I enjoy this international collaboration; it's always been exciting, and they have a fantastic university set up both in China and in Rome. In Rome, we are promoting Italy's first English language-based medical course, and so that's been very entertaining. The engagement with China was for a more intellectual reason, because the incidence of Type 1 diabetes is highest in Northern Europe and lowest in China. I was interested in whether that difference is likely to be either genetic or environmental. It turns out that China does have a lower frequency of classic adult-onset Type 1 diabetes than we do in Europe. Globally, Northern Europe is the exception with its high disease incidence, not the rule. The reason Northern European children have a very high frequency of Type 1 diabetes is probably genetic because here we have a lot of high-risk disease-associated genes, but in the rest of the world, where they have low-risk genes or moderate-risk genes, it's not so high, and that's why there is this differential.

When it comes to more slow-onset disease, those presenting with non-insulin requiring Type 1 diabetes, that disease form is almost as prevalent in China as it is in Europe. I think in Europe, people who are diagnosed at a young age with Type 1 diabetes have a strong genetic component, but the older you are, the less genetically determined the disease. That observation is in line with what we found in identical twins. We found if you were diagnosed, as a twin, when you were young, let's say under the age of 10, then about 50–60% of your co-twins develop the disease, but if you are over 15 years of age, then only about 10–20% develop the disease. There's much, much less penetrance of the disease genes as you get older.

Q5 As an educator, where do you believe your focus will lie in the future?

My focus is increasingly turning to things beyond my future. I'm not looking to progress. I think my colleagues would be horrified if they thought that I was looking to hang around for 20 years or more. I think really when you reach my age, you're more interested in trying to help people develop themselves rather than yourself. With that in mind, one of the things I really am proud of is setting up a consortium called T1DUK, which is a consortium of the top research workers on Type 1 diabetes in Britain. Initially, only a few people joined me, and then gradually everyone joined in. We have this fantastic network now around Britain, with the T1DUK Consortium involved, not just in developing trials to try and prevent Type 1 diabetes, but also in developing ways of trying to expand our knowledge of the disease, and I'm really proud of that. And I think that's what guys of my age should be doing, looking to help other people. These guys in T1DUK are doing fantastic things, I mean, much more as a group than I could ever have done as an individual.

"I believe that the study of diabetes has always been a very academic sort of subject, really. A great area to go into if you are interested in making discoveries and making a difference."

Q6 What new advances in diabetes management are you most excited about and why?

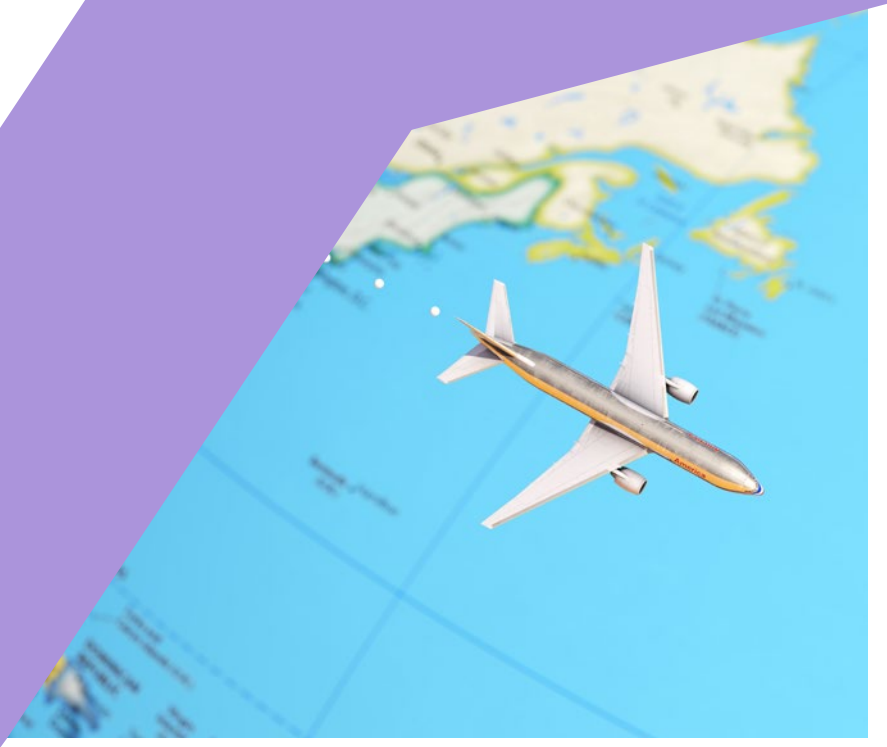
I suppose we assume that there are two main types of diabetes, Type 1 and Type 2, but actually, I don't think there are two main types. I think there are many types of diabetes, so I think there's huge heterogeneity. This disease in children is different from the disease in adults, and that is true for Type 1 diabetes and for Type 2 diabetes. Some people with Type 2 diabetes are young and thin when they're diagnosed; others are older and obese. Only recently have we come to appreciate these differences. As we do so, we will start understanding that there are different ways you can treat the disease. I'll just give you one example: the standard treatment of Type 2 diabetes is metformin but actually in people who are under the age of 25 when they're diagnosed with Type 2 diabetes, 50% of them respond to metformin, whereas about 88% of older people respond. These are the sort of differential assessments that we're going to have to start understanding, appreciating, and coming to terms with, because suddenly we've got a lot of drugs available to us. And in the same way, we're now looking to maybe apply that sort of heterogeneity to Type 1 diabetes, as the therapy you use might be different in those who are very young compared with older-onset cases.

Q7 How has the COVID-19 pandemic affected your career in the field of diabetes research, and have there been any unforeseen benefits to this?

No unforeseen benefits whatsoever, apart from the fact that I think hybrid meetings have definitely got some value. I think the value is constrained by the fact that there's no dialogue. Even with us here, I'm answering your questions, but we're not actually having a dialogue, and I think that's true of all these virtual calls; they curtail dialogue. In terms of the future, it's dialogue that counts because it's that casual discussion in the pub or in the coffee shop that actually leads to better things. On the other hand, in terms of where we are at the moment, it's fantastic to be able to look at a talk that you would have missed if you'd been at the meeting, go back to it and look at the slides, to think about it in more detail. The hybrid presentations are great for the present, for learning where we are right now. But they're hopeless for looking into where we're going in the future.

Q8 What advice would you offer to someone considering a career in the field of diabetes and autoimmunity?

They need to decide if they're going to be an academic or not. If you're going to be an academic, then I think it's a very interesting and exciting field, and I think it's got a great future because there are so many unanswered questions. The thing that makes diabetes exciting is the fact that it's so prevalent. Most people by the age of 80 are either at risk of diabetes or have it, and it's going to get worse; that's just the reality. Diabetes is a condition with severe consequences, in need of better management, and for somebody that wants to do medicine, that's a very exciting prospect. I believe that the study of diabetes has always been a very academic sort of subject, really. A great area to go into if you are interested in making discoveries and making a difference.



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Q1 What led you to pursue a career in medicine, particularly metabolic and cardiometabolic medicine?

To be honest, I had no idea what I wanted to do after school, and medicine was popular amongst Asian families if children were deemed bright enough. So I sort of funnelled into this direction. After medical school and my first year of house jobs, I actually left medicine as I did not enjoy it up to then. Instead, I became an accountant for 6 months. However, a few weeks of auditing brought me to my senses, and I returned to medicine promptly.

I wished I had done cardiology as I miss the chance to use practical skills, but clinical biochemistry was one of the few subjects I really enjoyed at medical school. Therefore, on returning to medicine, I was lucky enough to move into a registrar post in this specialty. Cardiology seemed too high a bar to me as I did not trust my clinical skills at that time. In the early weeks of clinical biochemistry, an older consultant (Alastair Glen) introduced the idea of research by handing me some data on different types of fatty acids measured in thousands of pregnant women. Glen told me to make something of it. It was an amazing spark that led me to completely different ways of thinking. I guess I have never looked back since.

Q2 Which have been the most exciting advances in your field since you began to practise in the 1990s?

Probably statins. My unit led the world's first primary prevention trial of statins, called WOSCOPS, led by the energetic James Shepherd, who gave me my registrar post. This seminal trial, which came soon after the first secondary prevention trial, changed people's way of thinking about cholesterol and heart disease. Now, nearly 30 years later, statins are amongst the most commonly prescribed drugs in medicine. I have also gained much by association with these trials. I still work on some of the data my senior colleagues generated in this trial and the later PROSPER trial (statins trial in elderly patients). In fact, we helped with a recent paper on statin-associated muscle side effects, which was published a few days ago.[1]

"One of my first grants, which I conceived, came from the recognition that high insulin levels in females with polycystic ovary syndrome could be driving their infertility."

Q3 What is the one moment in your career that you are most proud of, and why?

Being awarded the Minkowski Lecture, which I delivered to an audience of nearly 5,000 people in a massive stadium in Lisbon, Portugal, at the opening lecture of the European Association for the Study of Diabetes (EASD) Annual Meeting in 2011. The happiness came as my parents and sister were in attendance, and I do not think they realised I could actually talk comfortably to such big audiences. They were blown over and I could actually see my late, beloved dad crying whilst he was listening to me talk. It was an emotional experience, shared with parents and friends. I only wish I had convinced my wife and kids to come over.

Q4 Throughout your career, you have worked across a number of different disciplines. Could you detail how this cross-collaboration comes to be, and list some of the positives which working with other disciplines brings to both research and practice?

I have been lucky to dip into many disease areas clinically, in research, and by working with close colleagues from different specialities. When one does this, and reads some of the wider literature, it becomes clear there are overlaps in risk factors and complications that one can apply across disciplines. One of my first grants, which I conceived, came from the recognition that high insulin levels in females with polycystic ovary syndrome could be driving their infertility. Therefore, we set up one of the first and largest trials at that time of the diabetes drug metformin, which lowers insulin levels. I owe a great debt of gratitude to Richard Fleming, who helped me run this trial, and Ian Greer, who took my initial ideas and helped mature them into two useful reviews on this topic.[2,3] Greer told me to submit both these reviews for publication. Amazingly, both were accepted. So, one thing I have learned is to trust your instincts, as you never know what may happen.

Q5 Several of the findings you have made have been implemented into clinical practice. Please detail one or two of these, and let us know how you feel they have improved the healthcare of patients.

I was one of the first to discover that statins may actually increase the risk of developing diabetes. This side effect does not negate the enormous benefits of statins on the prevention of heart disease; however, it does mean people who are at higher risk of diabetes need to be told to also take lifestyle issues seriously. By doing so, they will not only lower their heart disease more on top of the effect of statins, but they will also attenuate any associated risk of developing diabetes coming from starting statins. This information is now in National Institute for Health and Care Excellence (NICE) guidelines.

I have also helped discover that excess liver fat may be linked to diabetes. My paper on diabetes that looked at liver function tests was noted by Roy Taylor around 2008.[4] Approximately 10 years later, Taylor and Lean invited me to help on the design and execution of the DiRECT trial, which proved that early Type 2 diabetes can be reversed in the vast majority of patients with sizeable weight loss, a finding with profound clinical implications, now used in the National Health Service (NHS), as well as research implications. We have since repeated this type of intervention in South Asians with results to come soon.

Q6 The COVID-19 pandemic has impacted healthcare worldwide. How has it affected your practice, and have you noticed any correlations between the disease and the prevalence of different metabolic conditions?

COVID-19 impacted people with diabetes much more than those living with a prior heart attack. We now know risk factors such as excess weight, higher blood pressure, higher sugar levels, or poor kidney function are all risk factors for worse COVID-19 outcomes.

> **"There are also many indirect effects of the pandemic, such as a reduction in physical functioning of many people through weight gain and lower levels of activity."**

There are also many indirect effects of the pandemic, such as a reduction in physical functioning of many people through weight gain and lower levels of activity. This likely means that even more people have been pushed into chronic disease, or that their diseases have progressed more rapidly. New data emerging all the time tells us this, including the ever-increasing numbers attending emergency departments throughout the country.

We need a lifestyle revolution in the UK, but this requires careful planning and investment. I am worried that if we do not do this, more and more people will live with multiple chronic conditions, putting ever increasing pressure on the NHS and its doctors, nurses, and allied health staff.

Q7 Are there any metabolic conditions which you feel have a lack of awareness?

If we include conditions that obesity is a risk factor for, then many conditions are relevant. This includes diseases such as hypertension, heart failure, psoriasis, fatty liver disease, gout, sleep apnoea, many types of cancer, lung disease, and the vast majority of reproductive health outcomes, to name but a few. So, the list is incredibly long, which is why we must be much more focused on tackling and preventing obesity.

Q8 Which new technologies and recent breakthroughs do you expect will make a real difference in your field in the near future?

I think we are getting progressively better at helping people make positive lifestyle changes; however, more can be done. The old way of just telling people to lose weight does not work and people need much simpler advice on exactly what changes they can make and how to make them. I am working hard on this. In terms of medicines, we are at the beginning of a new generation of weight loss drugs based on the class of drugs called glucagon-like peptide 1 receptor agonists. I like to think of them as chemical appetite suppressants, although they are more complex than that. Even so, some of the newer drugs linked to this class can now help people lose 15–20% of their body weight, which is a major breakthrough. This means people of 100 kg can lose up to 20 kg or nearly 7 units of BMI with these drugs. The implications of such weight loss could be enormous and several major trials due to report over the next 5 years should confirm the types of gains that could be achieved with this class. If these results go to plan, then such drugs could improve the lives of many patients. However, the cost of these new drugs is high; therefore, health authorities will have to work out who gets them initially. Over time, costs should reduce, and more patients could benefit. Of course, I would prefer we prevented obesity rather than having to treat people once they have excess adiposity. However, with so many now living with obesity, we cannot deny there is great need out there.

Q9 As an educator, where do you feel your focus will lie in the coming years?

As you can see from my preceding responses, it will be improving lifestyle education across the board so that it is no longer ignored but rather becomes the norm, so that all health professionals are able to give rapid, consistent, and evidence-based advice on the range of measures (tools) available to help people improve their diets, activity levels, or sleep habits. Of course, the food industry needs to help too. Hopefully, we can develop partnerships whereby healthier foods become the norm whilst companies still make profits, even if such profits are less than they were in the past with the selling of less healthy foods. There has to be some give and take for all parties.

Q10 What advice would you give to someone hoping to start a career focused on metabolic medicine?

Metabolic medicine opens the potential to work in many different areas and to engage in many types of research. I would try to gain exposure to many different types of clinics so that you become comfortable treating several diseases. This will allow better research but also, as more and more people have multiple conditions, familiarisation with different but linked diseases, enabling better and more efficient care to be delivered. In fact, we need many more doctors working across linked disciplines to improve care. If we can achieve this, more doctors will appreciate the common links between conditions and that some common solutions are available to prevent, delay, or slow many diseases. My personal preoccupation is better weight management across the life course of many chronic diseases. I am working hard, as are many others, to champion this as a major goal for the NHS and wider society.

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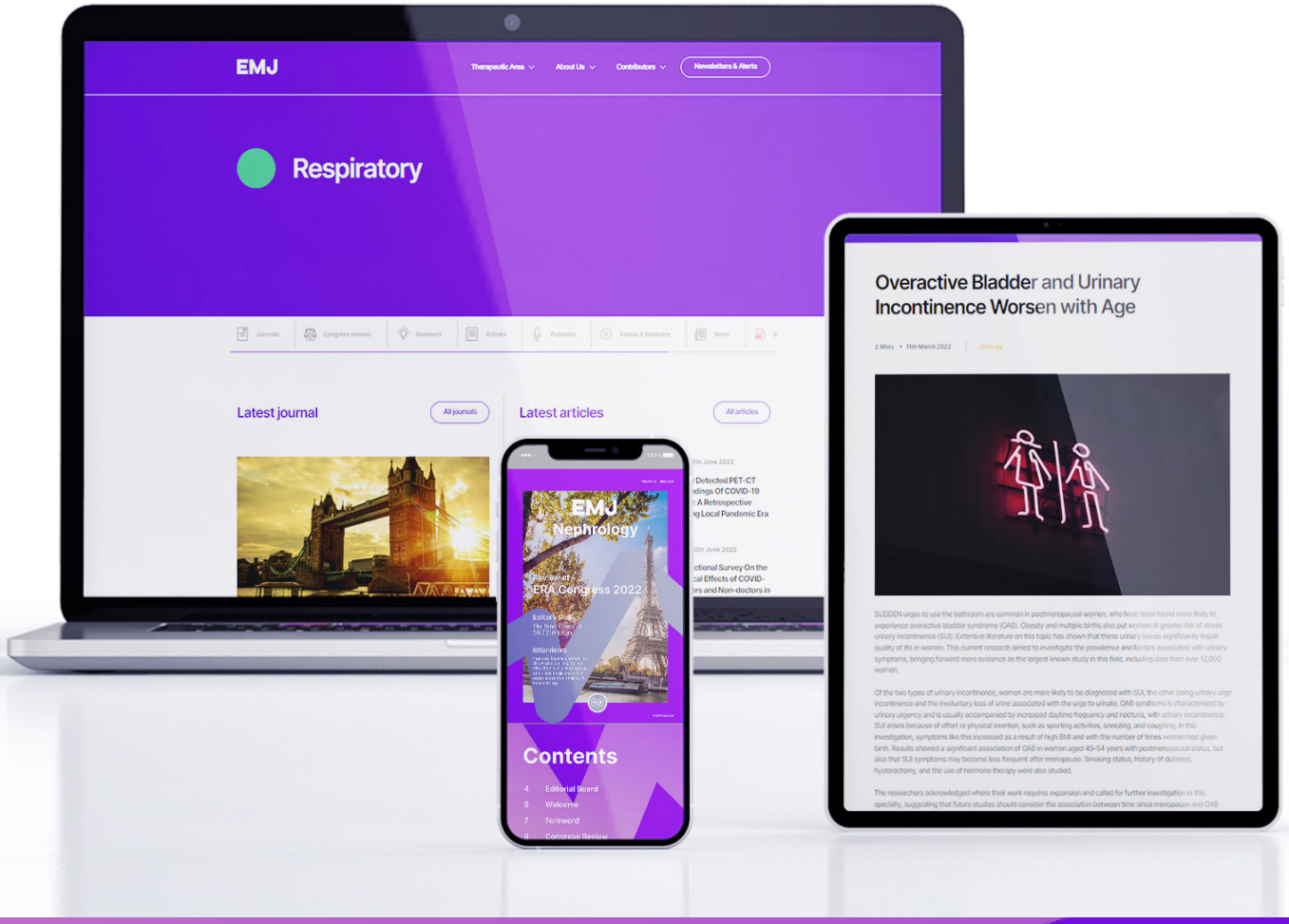

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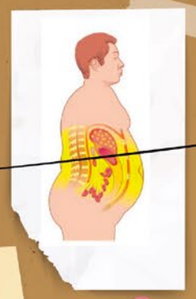
OBESITY INCREASES TYPE 2 DIABETES RISK

MECHANISMS BY WHICH OBESITY LEADS TO T2DM

Caloric overload } Trigger



Liver fat accumulation

Hepatic insulin resistance

Pancreatic fat accumulation

β-cell lipotoxicity

High insulin gluconeogenesis

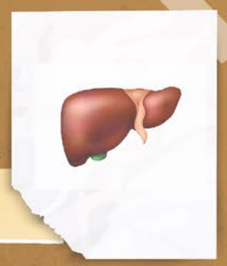
Impaired insulin secretion

Hyperinsulinaemia

Hyperglycaemia

Muscle insulin resistance } Trigger

LIVER CYCLE



PANCREATIC CYCLE

OBESITY AND T2DM RISK IN NUMBERS

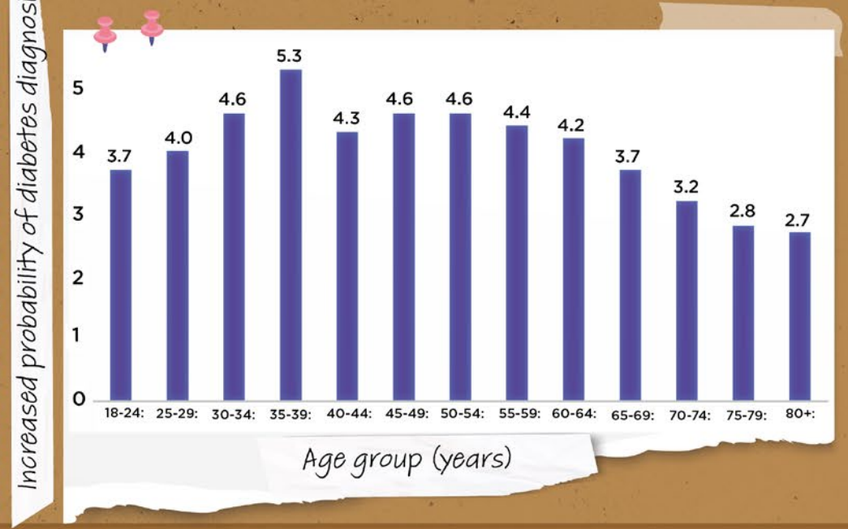
80-85% of risk for developing T2DM can be attributed to obesity[2]

80x greater likelihood of developing T2DM when obese, compared with BMI <22[2]

90% of adults with T2DM are overweight or obese[3]

5% reduction in bodyweight + regular exercise reduces risk of T2DM by >50%[4]

IMPACT OF OBESITY ON DIABETES RISK BY AGE



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FUTURE PROJECTIONS

2016:
estimated 41 million overweight children under 5

2040
642 million people expected to be living with diabetes

Diabetic Ketoacidosis in Pregnancy: An Overview of Pathophysiology, Management, and Pregnancy Outcomes

Editor's Pick

While this issue features a wide variety of topics, including the development of twincretins, which an important new therapeutic principle, I would like to draw your attention to this particular review on diabetic ketoacidosis in pregnancy. This review makes an important point on diabetic ketoacidosis in pregnancy, which can occur at relatively mild levels of hyperglycaemia and present with non-specific symptoms, making the condition difficult to recognise. Therefore, a high index of suspicion is needed.

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Abstract

Diabetic ketoacidosis (DKA) is an obstetrical emergency that is associated with an elevated risk of adverse pregnancy outcomes. This includes pregnancy loss in up to 1 in 3 cases. Due to the normal metabolic changes that occur during pregnancy, females who are pregnant are more vulnerable to DKA, and it can occur at lesser than expected degrees of hyperglycaemia. Presenting symptoms can be non-specific and include nausea and vomiting, fatigue, polydipsia, and polyuria. DKA may be the first presentation of previously undiagnosed diabetes. Therefore, high index of suspicion, along with prompt diagnosis and management, is essential. The cornerstones of management include intravenous insulin, intravenous fluids, and electrolyte replacement. Treatment generally follows the principles for DKA management outside of pregnancy, with some additional considerations. Close

maternal and fetal monitoring is essential, and intensive care unit admission is typically required to adequately achieve this goal. In all situations, a thorough investigation should occur to address the underlying cause of the DKA and prevent further episodes. This review article outlines the potential etiopathogenesis, clinical presentation, and management of DKA in pregnancy.

Key Points

1. DKA in pregnancy is an obstetric emergency that leads to increased risk of maternal and fetal mortality without prompt diagnosis and management. Pregnant individuals with diabetes are at higher risk of developing DKA than non-pregnant individuals with diabetes, and DKA can occur at lower levels of hyperglycaemia.

2.Timely recognition and management of DKA in pregnancy are crucial for optimising outcomes. Patients should be managed with intravenous insulin, intravenous fluids, and electrolyte replacement, and should have close maternal and fetal monitoring throughout.

3. Identifying DKA precipitants is important not only for treatment, but for reducing the risk of future recurrence. Improved understanding and evaluation could help with development of pregnancy-related DKA prevention strategies in the future.

INTRODUCTION

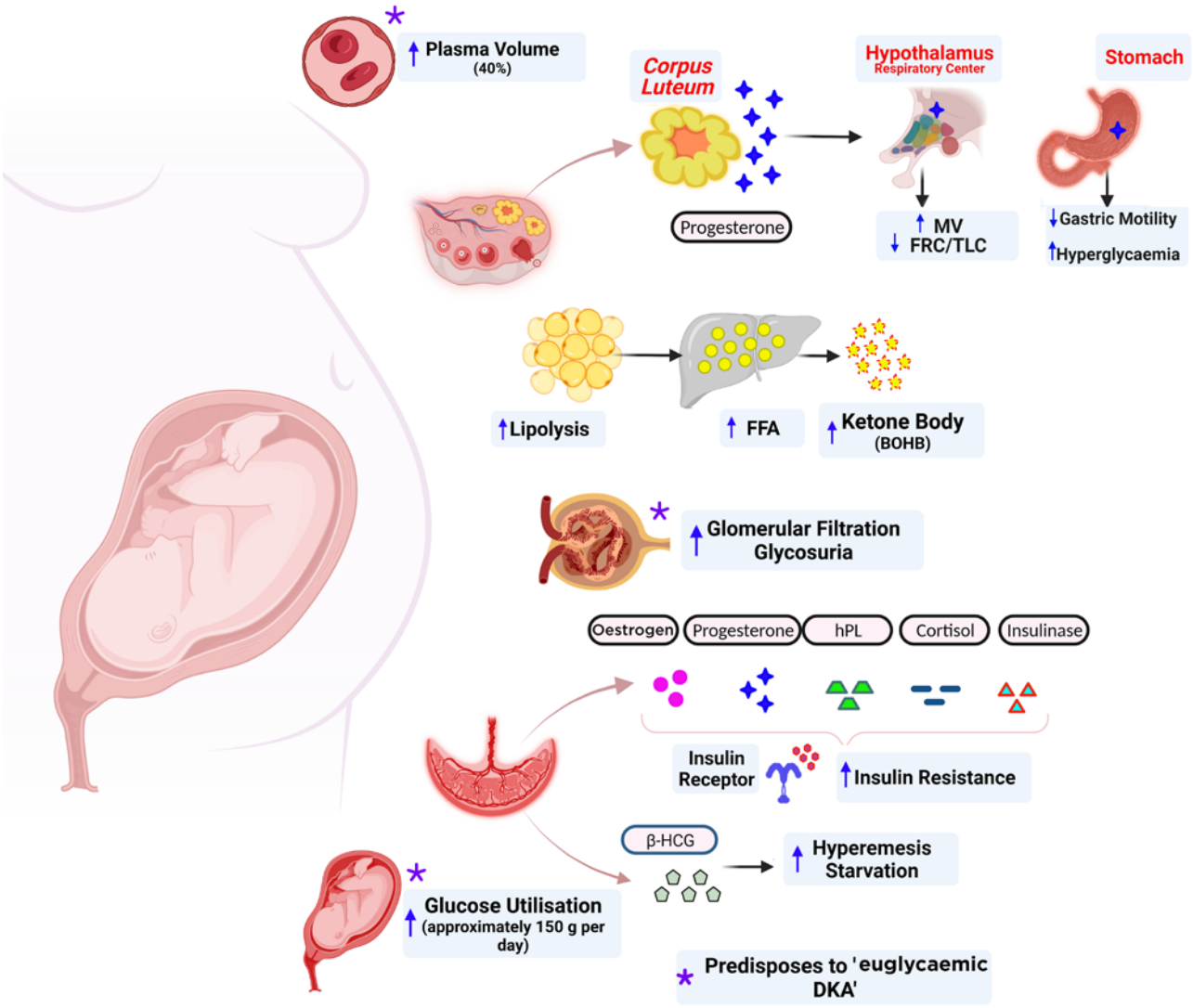
Diabetic ketoacidosis (DKA), characterised by the triad of acute hyperglycaemia, metabolic acidosis, and ketosis, is an acute life-threatening but preventable complication of diabetes.[1,2] The Centers for Disease Control and Prevention (CDC) reported that the age-adjusted rate of DKA hospitalisation has increased by 54.9%, from 19.5 to 30.2 per 1,000 people, at an average annual rate of 6.3% from 2009 to 2014. The rates were highest in individuals less than 45 years of age. However, the in-hospital case-fatality rates have declined overall by 63.6%.[1] Although DKA is typically encountered in patients with Type 1 diabetes, it can occur in patients with any form of diabetes. In fact, the Phase II Fremantle Diabetes Study from the UK, with 1,724 hospitalised patients, showed the overall incidence of DKA was 35.6/ 10,000 person-years for Type 1 diabetes; 13.3/10,000 person-years for Type 2 diabetes; 121.5/10,000 person-years for adults with latent autoimmune diabetes; and 446.5/10,000 person-years for secondary diabetes.[3]

DKA in pregnancy is an obstetrical emergency. Quality data are unavailable regarding the incidence and prevlance of DKA in pregnancy according to subtype of diabetes; however, it appears to complicate 5–10% of all pregnancies with pregestational diabetes, and can also occur in females with gestational diabetes.[4-6] Without prompt diagnosis and treatment, DKA can be associated with maternal and fetal mortality. However, with an improved understanding of the disease and appropriate management, the associated maternal–fetal morbidity and mortality have improved over the years.[4] It is critical to have a very high index of suspicion for DKA during pregnancy, as the symptoms can be misleading and can present without an extreme increase in plasma glucose concentration.[7,8] Furthermore, females may not have a diagnosis of diabetes prior to presenting with DKA.

WHAT IS THE PATHOPHYSIOLOGY OF DIABETIC KETOACIDOSIS?

DKA results from an increased glucagon to insulin ratio, with a concomitant increase in counter-regulatory hormones (cortisol, growth hormone), resulting from an absolute or relative insulin deficiency leading to abnormal carbohydrate, protein, and fat metabolism. Because of hypoinsulinaemia, relative cellular hypoglycaemia ensues, resulting in the

Figure 1: Mechanisms underlying the development of diabetic ketoacidosis in pregnancy.



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BOHB: β-hydroxybutyrate; DKA: diabetic ketoacidosis; FFA: free fatty acid; FRC: functional residual capacity; HCG: human chroionic gonadotropin; hPL: human placental lactogen; MV: minute ventalition; TLC: total lung capacity.

stimulation of counter-regulatory response. With increased delivery of gluconeogenic precursors (e.g., alanine and glutamine from protein catabolism, glycerol from lipolysis, lactate from muscle glycogenolysis), hyperglycaemia occurs from enhanced endogenous hepatic glucose production, which may be further compounded by renal gluconeogenesis.[2,9] In addition to growth and other counter-regulatory hormones, epinephrine activates hormone-sensitive lipase in adipose tissue, leading to enhanced synthesis of nonesterified fatty acids (a substrate for ketogenesis in the liver). Furthermore, hyperglucagonaemia (and hypoinsulinaemia) activates carnitine acyltransferase 1, the rate-limiting enzyme for ketogenesis, eventually contributing to high anion gap metabolic acidosis.[10] Osmotic diuresis and multiple electrolyte disturbances follow, leading to hypovolemia and hypertonicity.[2]

WHY DOES PREGNANCY PREDISPOSE TO DIABETIC KETOACIDOSIS?

There are several pregnancy-related alterations to the metabolic milieu that prime females (with and without diabetes) for DKA development (Figure 1).

Pregnancy is considered an insulin-resistant state whereby insulin sensitivity decreases by 56% by 36 weeks of gestation. Contributors to insulin resistance include increased maternal concentrations of serum oestrogen, progesterone, cortisol, human placental lactogen, TNF-α, and prolactin.[11,12]

Pregnancy is characterised by fasting hypoglycaemia, with associated hyperinsulinaemia.[13] In some cases, elevated human chorionic gonadotropin during early pregnancy is associated with hyperemesis, which could contribute to a relative state of hypoglycaemia, facilitating a state of starvation ketosis.

The fetoplacental unit can utilise up to 150 g per day of glucose to meet the demands of the growing fetus.[14] Hence, to meet this increased need, maternal insulin resistance could possibly be a physiological adaptation. Studies have shown enhanced expression of glucose transporter 1, especially in females with gestational diabetes, which increases glucose uptake by the fetoplacental unit.[15,16]

In addition to the cellular antagonising properties of progesterone to insulin, progesterone decreases gastrointestinal motility, thereby enhancing hyperglycaemia.

Progesterone also increases minute ventilation by 30–50%, leading to a state of respiratory alkalosis, which is potentiated by bibasilar alveolar collapse from the gravid uterus, decreasing both functional residual capacity and total lung capacity by 10–20%.[17-20]

Renal compensation of respiratory alkalosis through enhanced bicarbonate excretion decreases the buffering capacity during an acidotic state.

Compared with females without diabetes, plasma concentrations of free fatty acids and β-hydroxybutyrate (BOHB) are significantly higher during all trimesters of gestation in females with both pregestational diabetes and gestational diabetes.[21,22]

Intriguingly, all females who are pregnant are at risk of ketosis, even without underlying diabetes. This was demonstrated in a prospective study comparing females who were pregnant without diabetes who fasted during Ramadan to age-matched non-fasting females who were pregnant. The fasted group were documented to have significantly higher rates of ketosis (11.3% versus 5.0%) and worsening clinical complaints (nausea, vomiting, and dizziness).[23]

Taken together, these metabolic changes mean that DKA can develop faster and at lower glucose concentrations during pregnancy. In fact, 'euglycaemic DKA', broadly defined as plasma blood glucose concentration <14 mmol/L (252 mg/dL), has been well described during pregnancy.[24] In addition to the general explanations for the aetiology of DKA in pregnancy (outlined above), additional potential contributors to euglycemic DKA include significantly increased glomerular filtration rate (increased by approximately 60%) during pregnancy with associated glycosuria;[14,25] enhanced maternal (oestrogen and progesterone), and fetal (anabolic state) glucose utilisation;[25] and a concomitant increase in plasma volume by 40% compared with the pre-pregnancy state, leading to a dilutional effect.[25]

Hence, all females who are pregnant, regardless of the type of diabetes, are at risk of developing DKA and the underlying pathophysiological mechanisms leading to DKA in different subtypes of diabetes are presumably similar.

WHAT ARE THE RISK FACTORS FOR DIABETIC KETOACIDOSIS IN PREGNANCY?

A 10-year retrospective review of 37 hospitalisations for DKA during pregnancy in a tertiary care centre demonstrated that hyperemesis and β-sympathomimetic drugs were associated with 57% of DKA episodes, with non-compliance and physician management errors occurring in 24%.[26] Multiple other studies have documented additional risk factors, including

concurrent infections, insulin device failure, missed insulin doses, maternal gastroparesis, and undiagnosed diabetes.[27-31] Use of glucocorticoids for fetal lung maturation towards the later part of pregnancy in conjunction with maternal insulin resistance can markedly increase the risk for DKA. Hence, careful monitoring of blood glucose concentration and timely treatment of hyperglycaemia following glucocorticoid administration is warranted.

CLINICAL PRESENTATION OF DIABETIC KETOACIDOSIS

The clinical signs and symptoms associated with DKA can often be misconstrued as normal pregnancy. For example, as nausea and vomiting is associated with >70% of all pregnancies, underlying DKA could potentially be missed if not suspected.[32] Common clinical symptoms of DKA in pregnancy include nausea, vomiting, and abdominal pain.[4] Patients can also present with generalised fatigue, polyuria, and polydipsia secondary to hyperglycaemia, evidence of volume depletion including dry mucous membranes, increased skin turgor, tachycardia, and hypotension. In severe cases, rapid, shallow breathing (Kussmaul's respiration) with the classic fruity odour from ketones could be present. Patients with severe DKA can also present with altered mental status, lethargy, and disorientation. Rarely, patients can develop cerebral oedema, causing obtundation and coma. As symptoms are non-specific and females may not have a prior diagnosis of diabetes at presentation, DKA should be considered in any individual who is pregnant and who is unwell.

LABORATORY FINDINGS AND DIAGNOSTIC CRITERIA FOR DIABETIC KETOACIDOSIS

Venous blood collection for plasma glucose, serum electrolytes, renal function (including blood urea nitrogen and serum creatinine), serum osmolality, serum ketones (quantitative or qualitative based on the availability), blood gas, and urine (mid-stream preferably) for a urinalysis and urinary ketones should be collected as part of the initial evaluation.[33] The Joint British Diabetes Society's (JBDS) diagnostic criteria for DKA in pregnancy include positive urinary ketones more than (++) or serum ketones >3.0 mmol/L (in high-risk cases, serum ketones >1.5 mmol/L) and evidence of metabolic acidosis with a venous blood pH <7.30 and/or bicarbonate <15 mmol/L.[34] In addition, an anion gap (Na^- [Cl^+ HCO3]) of >12 mmol/L indicates the presence of an increased anion gap metabolic acidosis.[33]

While evaluation of ketonaemia via nitroprusside test (serum and urine) is highly sensitive, it helps estimate only acetone and acetoacetate levels but not BOHB, which is elevated in a >10:1 ratio compared with other ketoacids during an insulin-deficient state.[33] Hence, quantitative assessment of BOHB is helpful if available. Serum electrolyte concentrations, particularly potassium and phosphate concentrations, should be carefully monitored. They can initially be 'pseudonormal' during early stages of DKA due to transcellular shifts (from insulin deficiency) and associated hypertonicity while masking a total body deficit. About 16–25% of patients with DKA can have a non-specific elevation of serum amylase and lipase concentration.[35]

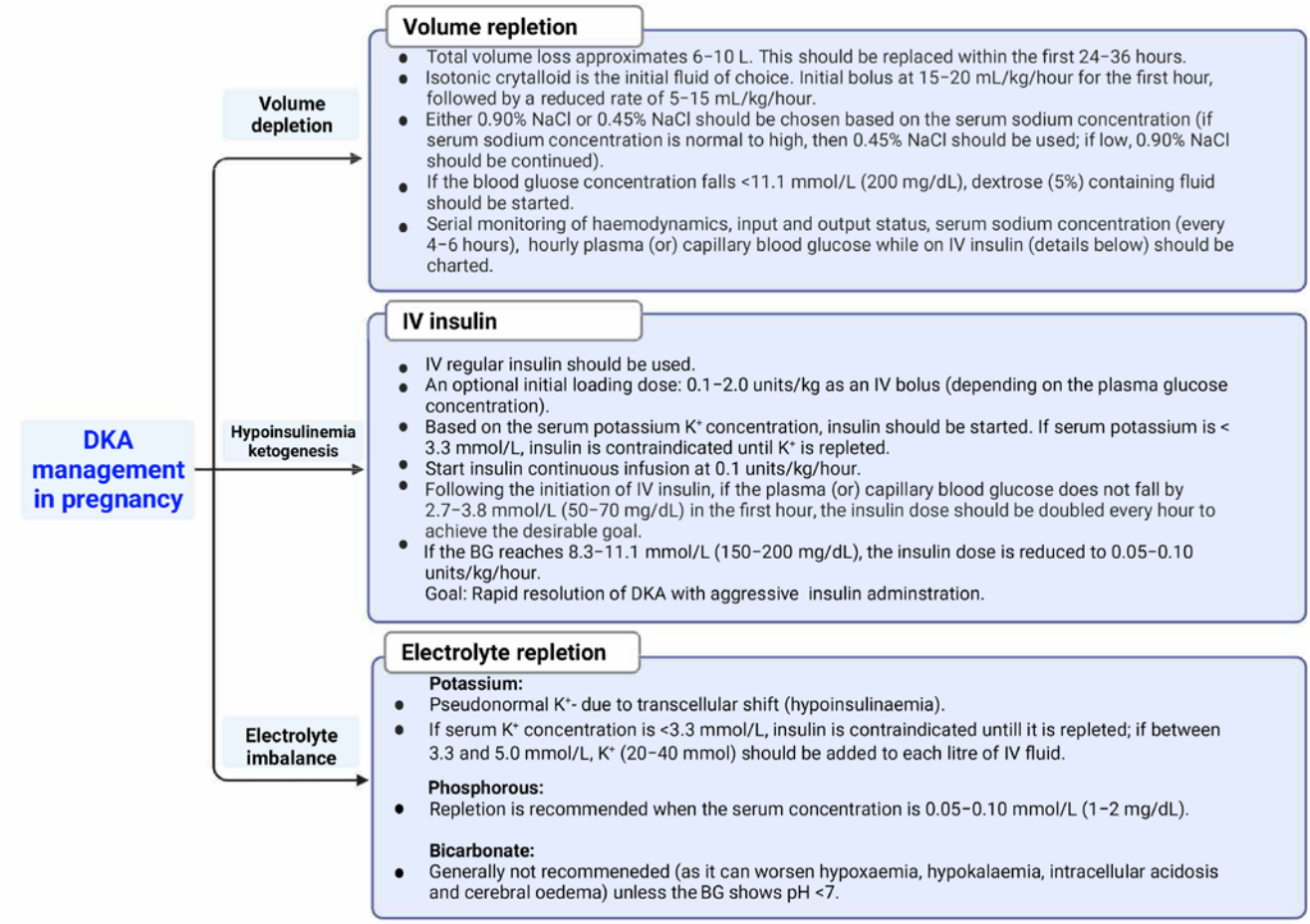
MANAGEMENT OF DIABETIC KETOACIDOSISIN PREGNANCY

Guidelines for the management of DKA in females who are pregnant are broadly the same as that of an individual who is not pregnant, and is similar for all subtypes of underlying diabetes, including identification and treatment of precipitating factors, fluid replacement, insulin therapy, and electrolyte repletion (Figure 2). In addition, fetal monitoring is warranted to identify any deleterious consequences of maternal acidosis on the fetus. All patients who are pregnant with confirmed or suspected DKA should, therefore, be admitted to highly specialised units (preferably intensive care units) capable of managing DKA and providing continuous fetal monitoring.

Identify and Treat the Underlying Cause

When DKA is confirmed, every attempt should be undertaken to determine the possible precipitating factor(s). A comprehensive history to evaluate for factors such as underlying infection, cardiovascular event, use of glucocorticoids, insulin omission or malfunction of insulin delivery systems, and use of expired

Figure 2: Management of diabetic ketoacidosis during pregnancy.



BG: blood gas; DKA: diabetic ketoacidosis; K+: potassium; IV: intravenous; NaCl; sodium chloride.

insulin should be obtained. An individualised workup should subsequently be completed.

Fluid Management

Osmotic diuresis secondary to hyperglycaemia can lead to significant volume depletion, as high as 10 L. Volume resuscitation improves hyperglycaemia and enhances peripheral insulin action blunted by hyperosmolarity and hyperglycaemia (in patients with normally functioning kidneys).[33] One of the primary management goals should be the replacement of total volume loss within the first 24–36 hours of presentation. Isotonic fluid, 0.9% sodium chloride (NaCl), is the recommended initial crystalloid but can be guided by the haemodynamic status on presentation.[4,34] About 50% of the fluid should be replaced within 24 hours of presentation. A widely followed protocol is to start isotonic crystalloids at the rate of 15–20 mL/kg/hour (approximately 1.0–1.5 L for a 70 kg adult) for the first hour, followed by a decreased rate of 5–15 mL/kg/hour. The decision to continue 0.90% NaCl versus 0.45% NaCl should be made based on serum sodium trends (rapid improvement of corrected serum sodium can increase the risk for cerebral edema), serum osmolality, and urine output.[36] For example, following initial resuscitation, 0.45% NaCl could be substituted at the rate of 250–500 mL/hour if the corrected serum sodium is normal or elevated; whereas, if low, 0.90% NaCl should be continued with serial monitoring of sodium. The total fluid requirement may be relatively lower compared with an individual who is not pregnant.[34]

Furthermore, individuals with kidney disease, heart failure, or pre-eclampsia may need a more conservative approach to fluid replacement,

which should be individualised according to initial tolerance and overall clinical status. Once the blood glucose concentration reaches 11.1 mmol/L (200 mg/dL), dextrose containing fluids (5% or 10% dextrose) should be initiated to prevent hypoglycaemia while continuing intravenous (IV) insulin therapy, as the goal is to inhibit ongoing ketogenesis that was driven by hypoinsulinaemia.[4] Successful fluid resuscitation is reflected by improvement in volume status, haemodynamics, serum sodium concentration, blood glucose concentration, and overall clinical status.

Intravenous Insulin

Continuous IV insulin infusion therapy is the mainstay of DKA management to correct the underlying metabolic derangement. The goal of IV insulin therapy is not only to control hyperglycaemia (by promoting glucose uptake at the periphery and inhibiting gluconeogenesis) but also to suppress ongoing ketogenesis. Insulin should be initiated based on serum potassium concentrations, along with fluid resuscitation. Adequate initial volume resuscitation prior to initiation of insulin therapy could potentially enhance insulin sensitivity and decrease insulin requirement. The initial loading dose of 0.1–0.2 units/kg as an IV bolus is endorsed by the American College of Obstetricians and Gynecologists (ACOG).[4] However, the JDBS recommends starting fixed-rate insulin at 0.1 unit/kg/hour.[34] Studies outside of pregnancy have shown no difference in the rate of plasma glucose concentration or anion gap improvement, the incidence of hypoglycaemia, length of hospital stay, and the overall outcome of DKA when treated using continuous insulin infusion therapy, with or without the initial IV bolus.[36-38]

A continuous IV insulin infusion at the rate of 0.1 unit/kg/hour should be initiated (with or without the initial bolus) only if the serum potassium concentration is >3.3 mmol/L, and should be delayed until hypokalaemia is appropriately corrected. Plasma or capillary blood glucose concentration should be assessed on an hourly basis. If the plasma/capillary blood glucose concentration does not fall by at least 2.7–3.8 mmol/L (50–70 mg/dL) in the first hour, the insulin infusion rate must be doubled, and this titration of insulin should be carried out every hour until a steady-state blood glucose concentration is achieved. Once the plasma/capillary blood glucose concentration reaches 11.1 mmol/L (200 mg/dL), in addition to dextrose-containing fluids (to avoid hypoglycaemia), the insulin infusion dose needs to be reduced to 0.05–0.10 unit/kg/hour. The eventual goal is to maintain a blood glucose concentration between 5.6–8.3 mmol/L (100–150 mg/dL), with the smallest insulin dose possible, until complete inhibition of ketogenesis is achieved, as evidenced by the normalisation of the anion gap (if normal renal function).[4] While IV insulin is ongoing, periodic monitoring and replacement of electrolytes, especially potassium, is essential. Temporary discontinuation of insulin may be needed to facilitate potassium repletion.

Once the anion gap normalises, the transition from continuous IV insulin to subcutaneous insulin with a 2–4 hour overlap is made, primarily to prevent rebound hyperglycaemia. However, it is reasonable to continue the long-acting insulin throughout DKA treatment if the patient is on a known multiple daily injection insulin regimen.[34] This practice can reduce the risk of rebound hyperglycaemia and recurrent DKA, which can occur with premature discontinuation of IV insulin and/or inadequate overlapping with subcutaneous insulin. If the patient was on an insulin pump, it should be restarted following DKA resolution.

Electrolyte Replacement

Hypoinsulinaemia, hyperosmolarity, and acidosis associated with DKA cause total body potassium deficit despite normal serum potassium concentration (due to transcellular shift). Therefore, rapid correction of DKA could potentially increase the risk of hypokalaemia and life-threatening cardiac arrhythmias, warranting close monitoring of serum potassium. If the initial serum potassium concentration is <3.3 mmol/L (as opposed to >5.5 mmol/L), IV insulin therapy is contraindicated until potassium is adequately repleted. However, fluid resuscitation should be initiated regardless of the serum potassium concentration. Certainly, potassium could be added to the intravenous fluid simultaneously to ensure that serum potassium is maintained within the acceptable range of 3.3–5.5 mmol/L.[4]

Hypophosphataemia can also ensue with aggressive fluid hydration and insulin treatment due to transcellular shift. Usually, severe

hypophosphataemia is rare, and replacement is indicated when the concentration is 0.05–0.11 mmol/L (1.00–2.00 mg/dL). Rapid or over-correction of phosphate can precipitate hypocalcaemia and, hence, careful monitoring of serum calcium is warranted.[39,40]

The use of bicarbonate in patients with DKA is controversial as it increases the risk of hypoxaemia, hypokalaemia, intracellular acidosis, and cerebral oedema.[33,36] Bicarbonate treatment is not recommended unless the patient has severe metabolic acidosis with a pH <7.0 and should be done under expert supervision.

MONITORING RESPONSE TO DIABETIC KETOACIDOSISTREATMENT

During DKA treatment, patients' capillary blood glucose should be monitored hourly while on IV insulin therapy, and serum electrolytes for potassium, phosphorous, and calcium concentration and anion gap every 4 hours. The JDBS endorses monitoring venous bicarbonate and potassium at 1 hour, 2 hours, and then every 4 hours.[41] However, monitoring serum bicarbonate may be helpful only during the first 6 hours following the initiation of the DKA protocol because of increased incidence of hyperchloraemic metabolic acidosis (normal anion gap) secondary to administration of isotonic crystalloids (NaCl) for volume resuscitation.[33] Clearance of urinary ketone lags behind the clearance from the blood and, hence, monitoring serum anion gap is advisable (when renal function is normal). The recommended metabolic targets to achieve during DKA treatment include an increase in venous bicarbonate concentration by 3.0 mmol/L/hour; a decrease in capillary blood glucose level by 3.0 mmol/L/hour (54 mg/dL/hour); and a decrease in blood ketone concentration by 0.5 mmol/L/hour.[34] Strict criteria to determine DKA resolution in pregnancy are not established; however, one can generally consider biochemical resolution if the following parameters are satisfied: serum ketone concentration <0.6mmol/L; calculated anion gap ≤12.0 mmol/L; venous pH >7.3; and serum bicarbonate concentration >15.0 mmol/L.[33,42]

FETAL MONITORING DURING DIABETIC KETOACIDOSIS

Severity of maternal DKA determines the severity and frequency of fetal heart rate changes. However, in most cases, these changes are reversible following the correction of maternal acidosis.[43] Continuous fetal monitoring is recommended if the pregnancy is >24 weeks of gestation during the DKA episode.[44] Initial fetal heart rate tracing during the DKA episode can show decreased or absent variability, absent accelerations, or late decelerations. In addition, Doppler ultrasound studies using pulsatility index have demonstrated transient alteration in blood flow, particularly redistribution of blood flow in the middle cerebral (reduced) and umbilical arteries (increased).[43,45] There are no clear recommendations for the duration of continuous fetal monitoring; however, in most centres, it is continued until the resolution of DKA with frequent monitoring post resolution. Typically, DKA is not an inidication for delivery but this decision should be made on a case-by-case basis.

WHAT ARE THE OUTCOMES FOLLOWING DIABETIC KETOACIDOSIS IN PREGNANCY?

The maternal and fetal outcomes reported in previously published retrospective studies and case series of DKA in pregnancy are outlined in Table 1.[7,14,24,29,46-51]. Original studies were chosen through literature search in the PubMed database using combinations of the following key search terms: "diabetes", "gestational diabetes", "GDM", "Type 2 diabetes", "hyperglycemia", "ketoacidosis", "pregnancy". The reference list of included articles were also examined to identify articles not retrieved using this search strategy. Case reports and case series with less than five patients were not included in this review. There were no conveivable differences nor any detailed reports about maternal and fetal outcomes following the DKA events in different diabetes category.

Maternal Outcomes

The overall maternal mortality associated with DKA is <1%. However, similar to individuals who are not pregnant, DKA can be associated with significant morbidity, including hypotension

Table 1: Prior published studies of diabetic ketoacidosis in pregnancy (case reports excluded).

Year	Authors	Number of patients	Maternal age at DKA episode (mean)	Number of patients with pre-existing diabetes (%)	Average gestation at time of DKA (weeks)	Fetal mortality (%)	Maternal Mortality (%)
1993	Kilvert et al.[46]	9	27.4	9 (100.0)	23.5	22.0	0
1993	Montoro et al.[47]	20	25.0	20 (100.0)	26.5	35	0
1996	Cullen et al.[48]	11	N/A	N/A	26.0	9.0	0
1996	Chauhan et al.[7*]	51	19.6	51 (100.0)	30.6	35.0	0
1996	Chauhan et al.[7*]	9	20.5	9 (100.0)	32.2	10.0	0
2003	Schneider et al.[29]	11	26.3	7 (63.7)	28.4	27.0	0
2008	Guo et al.[14]	8	30.0	N/A	24.8	37.5	0
2017	Bryant et al.[49]	33	25.0	28 (84.0)	17.0	26.7	0
2017	Morrison et al.[50]	62	28.2	61 (98.3)	24.2	15.6	0
2021	Diguisto et al.[24]	82	N/A	75 (91.5)	25.0	16.0	0
2022	Eshkoli et al.[51]	8	27.5	8 (100.0)	26.6	25.0	0

*Two historical cohorts are reported in this study: Cohort 1 (n=51) from 1976 to 1981 and Cohort 2 (n=9) from 1986 to 1991.

DKA: diabetic ketoacidosis; N/A: not available.

Box 1: Clinical Pearls: Diabetic ketoacidosis in pregnancy.

1. DKA is an obstetric emergency frequently associated with pregnancy loss.
2. In pregnancy, DKA can occur at lower than expected maternal glucose concentrations and symptoms can be non-specific.
3. Management includes intravenous insulin, intravenous fluids, and electrolyte replacement.
4. Identifying the precipitating cause is important, and may reduce risk of recurrence.

DKA: diabetic ketoacidosis.

(from severe dehydration), organ dysfunction (from acidosis), and cardiac dysrhythmias (from electrolyte abnormalities, including hypokalaemia) in a female who is pregnant. All these metabolic changes could potentially be prevented and/or reversed following the prompt initiation of treatment. Cerebral oedema with neurological symptoms is a rare but serious complication of severe DKA (in the population that is not pregnant) with a >70% mortality rate (particularly encountered in children).[2]

Fetal Outcomes

The reported fetal mortality ranges from 9–36%.[7,46-48,52] Various hypotheses have been postulated outlining the pathophysiology of fetal demise. Both ketones and glucose cross freely across the placenta.[53] Fetal hyperglycaemia due to maternal hyperglycaemia leads to fetal osmotic diuresis. Furthermore, fetal acidaemia, from transfer of ketoacids across the placenta, can lead to vasoconstriction of the uteroplacental blood vessels. In addition, a decrease in 2,3 bisphosphoglycerate (decreased phosphate) could decrease the fetal oxygen delivery (leftward shift of maternal oxy-hemoglobin curve with increased oxygen affinity). Fetal cardiac arrhythmias can develop in the setting of electrolyte disturbances, particularly hypokalaemia. Despite the deleterious consequences, all these adverse outcomes can be prevented or even reversed with proper treatment of DKA. In addition to the immediate sequelae of DKA, data have associated ketone body exposure with a negative impact on long-term neurodevelopmental abnormalities, particularly intelligence and psychomotor development.[54-56] However, the biological mechanism is not clear.

DIABETIC KETOACIDOSIS PREVENTION

The measures to prevent maternal and fetal adverse outcomes due to DKA should begin during preconception counseling. It is imperative to prepare a female with diabetes for pregnancy through adequate education about the importance of diabetes control prior to pregnancy. Close monitoring and regular insulin titration are critical during pregnancy. In addition, females should receive education on precipitating factors, signs, and symptoms of DKA, home monitoring of urine ketones, and how to seek help on time. A multidisciplinary team involving an endocrinologist (trained in managing diabetes in pregnancy), high-risk obstetrician, maternal-fetal medicine specialist, and diabetes educators should ideally be involved in caring for a females who are pregnant with diabetes.

CONCLUSION

DKA in pregnancy is an obstetrical emergency associated with poor pregnancy outcomes. Compared with an individual who is not pregnant, a female who is pregnant with diabetes is at higher risk of developing DKA, and the condition can occur with lesser degrees of hyperglycaemia. DKA can also be the first presentation of diabetes in pregnancy. A high index of suspicion along with prompt diagnosis and management are critical to ensure optimal outcomes (Box 1). Further studies are warranted to develop improved strategies to prevent DKA during pregnancy and clarify the long-term sequelae of ketosis on offspring of females with DKA.

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Next Step in Incretin-Based Therapy: From Single to Dual Agonism

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Abstract

The twin epidemics of Type 2 diabetes (T2D) and obesity will continue to bring significant health challenges in the coming decades. Randomised controlled trials of glucagon-like peptide 1 (GLP-1)-based therapies showed high glycaemic efficacy with clinically meaningful weight loss, and have been considered as game-changers in the diabesity population. Emerging evidence has demonstrated that co-administration of glucose-dependent insulinotropic peptide (GIP) and GLP-1 results in enhanced insulinotropic effect in an additive way with significant glucagonostatic response, compared with the administration of each hormone separately. These findings have driven the choice to pursue incretin-based dual agonist therapies, known as 'twincretin'. Observations from the global registration Phase III trials suggest that tirzepatide (a novel dual GIP/GLP-1 receptor agonist) represent advancement over current GLP-1 analogues, providing enhanced glycaemic and weight benefits with similar gastrointestinal tolerability. However, data are limited from patients with a range of ethnicities, and several questions remain unanswered.

Key Points

1. Co-administration of GIP and GLP-1 results can produce an enhanced insulinotropic effect compared to the administration of each hormone separately.

2. Results on the long term efficacy, safety, and tolerability, from ongoing Phase III clinical trials will impact the therapeutic prospects and future directions of incretin-based agonist therapy.

3. Incretin-based dual agonist therapy may offer an alternative to stringent dietary restriction and challenge the success of bariatric surgery in the diabesity community

INTRODUCTION

The incretin effect, an augmented prandial insulin response, is mediated mostly by the hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), which are released from the intestines after meals.[1] This effect is part of the entero-insular axis of glucose homeostasis, and is responsible for 50–65% of total insulin secretion after a meal.[2] The first incretin described in 1973 was GIP, and GLP-1, the second incretin, was discovered later in 1987.[3,4] GLP-1 and GIP are the two most widely studied incretins. GIP perhaps makes a greater contribution to the physiological insulin response to meals than GLP-1, but therapeutic development to date has focused on GLP-1, as the insulinotropic effect of GIP is markedly attenuated in Type 2 diabetes (T2D).[5] GLP-1 receptor agonists (GLP-1RAs) are established glucose-lowering agents that potentiate insulin secretion in response to glucose, and suppress glucagon secretion. GLP-1RAs are associated with greatest weight loss, and have shown their ability to decrease the risk of cardiovascular (CV) events in individuals with T2D at risk of CV disease.[6] Nevertheless, renewed interest in the therapeutic potential of GIP emerged, with studies showing that improving glycaemic control with another agent such as insulin could restore the insulinotropic potency of GIP.[7,8] The novel concept of combining a GIP with a GLP-1RA takes incretin-based therapy to a new level. This review will explore whether complementary mechanisms of action of combined GLP-1 and GIP receptor agonism could be effective and safe new options that are superior to pure GLP-1RAs as therapy for metabolic disorders.

GIP PHYSIOLOGY: SIMILARITIES AND DIFFERENCES WITH GLP-1

GIP is a 42-amino acid peptide secreted from intestinal K cells that are located mainly in the proximal small intestine. Like GLP-1, GIP is released after ingestion of nutrients, and promotes meal-stimulated insulin secretion in a glucose-dependent manner by receptor binding to pancreatic β-cells.[9] However, GIP has a distinctly modulatory effect on glucagon by inhibiting its secretion instates of hyperglycaemia, but increasing glucagon release during hypoglycaemia. The half-life of GIP and bioactive GLP-1 is only a few minutes because they are inactivated by the enzyme dipeptidyl peptidase 4.[10] GIP also targets bone, acutely inhibiting bone resorption.[11] Unlike GLP-1, GIP exerts anabolic actions at the level of adipose tissue leading to accumulation of body fat.[12] The effect of GIP on the gastrointestinal (GI) tract is incompletely understood; while GLP-1 slows gastric emptying,[13] this effect is not confirmed for GIP.

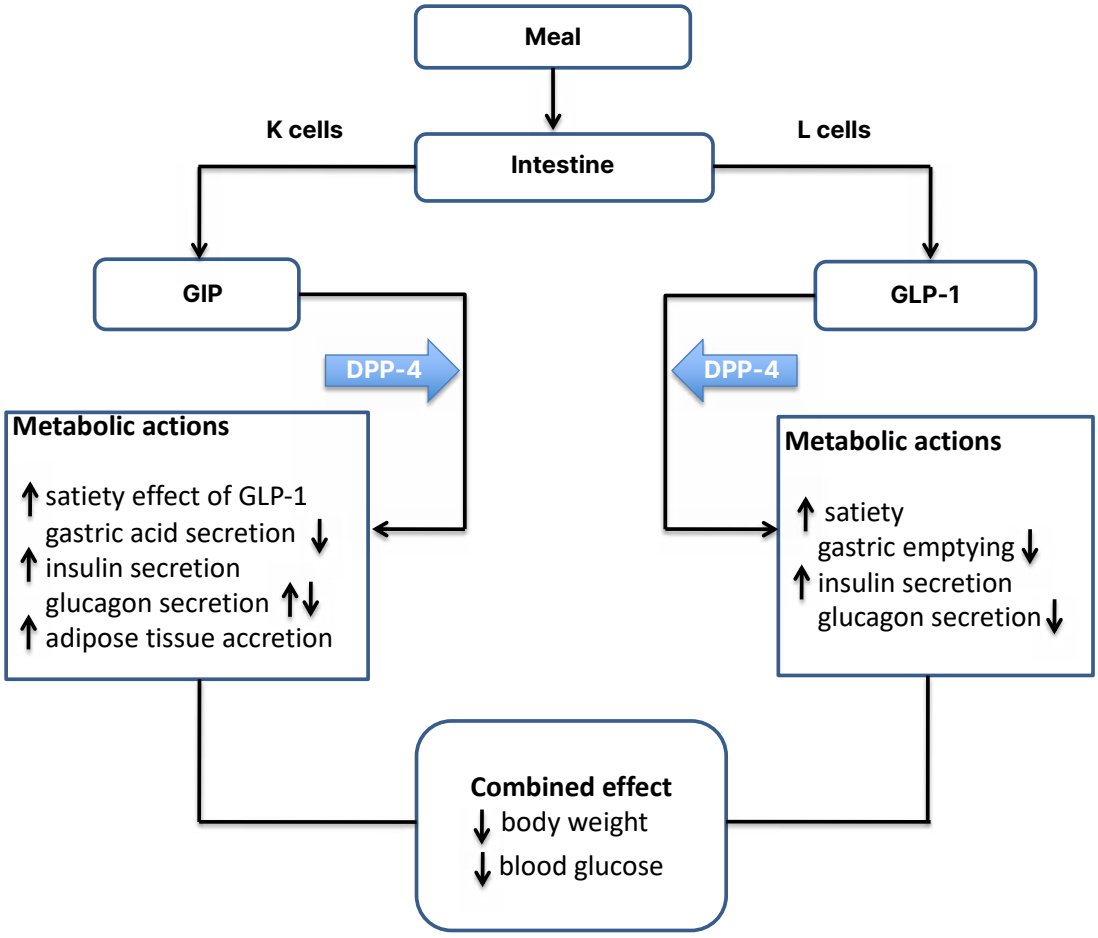
Clinical studies exploring the effect of GIP on food intake are limited. However, GIP appears to synergise the central satiety effect and weight loss linked with GLP-1. GIP might also improve cognitive function and certain aspects of lipid profile, but its CV effects are not yet fully elucidated. The superior metabolic benefits observed with concomitantly targeting GLP-1 and GIP receptors garnered interest in developing unimolecular drugs that would combine the actions of GLP-1 and GIP (Figure 1).

CONCEPT OF TWINCRETINS IN MANAGEMENT OF TYPE 2 DIABETES

It has been postulated that the glucose-lowering effects of simultaneous GLP-1R agonism might help overcome resistance to GIP action in T2D, thus enabling greater glucose-lowering effects when combined. In principle, treatment with a GIP and a GLP-1 RA together would augment glucose lowering while providing defence against hypoglycaemia. Besides, GLP-1 and GIP appear to activate distinct hypothalamic mechanisms coupled to reduced food intake,[14] providing a greater degree of weight lowering than that seen with GLP-1 alone. Although pharmacological levels of GIP can increase glucagon secretion and promote adipose tissue deposition, these effects can be countered by inhibition of glucagon secretion and reduction of food intake linked with GLP-1.[15] Altogether, this has brought the novel concept of incretin-based dual agonist therapy.

The first 'twincretin' was a unimolecular dual GLP-1R/GIP receptor (GIPR) agonist. It demonstrated superior dose-dependent weight loss and reductions in blood glucose levels, with decreased food intake relative to exendin or liraglutide in rodents and monkeys.[16] The leading agent among unimolecular GLP-

Figure 1: Metabolic actions of GLP-1 and GIP on key target tissues.



Upward arrows denote an increase, downward arrows denote a decrease.

GIP: glucose-dependent insulinotropic peptide; GLP: glucagon-like peptide 1.

1/GIP co-agonists is tirzepatide, a 39 amino acid synthetic peptide with agonist activity at both the GIP and GLP-1 receptors, with a higher affinity to GIPR.[17] Its structure, which is primarily GIP sequence-based, includes a C20 fatty di-acid acyl chain that extends the duration of action, thereby allowing once-weekly subcutaneous administration. Initial clinical evaluation of tirzepatide included a series of randomised, placebo-controlled Phase I trials designed to assess the safety, tolerability, pharmacodynamics, and pharmacokinetics of the molecule in humans.[17] In Phase II studies, weekly doses of tirzepatide ranging up to 15 mg, resulted in up to 2.4% reductions in HbA1c and weight loss of up to 11.3 kg in individuals with T2D.[18] Tirzepatide induced greater improvements compared with dulaglutide in a study that measured different markers of β-cell function and insulin sensitivity.[19] It was also associated with improvements in lipoprotein profiles.[20] Tirzepatide is the first twincretin to enter global Phase III trials.

TIRZEPATIDE: EFFICACY IN PHASE III CLINICAL TRIALS

After the promising results in Phase I and Phase II trials, the SURPASS clinical trial programs were designed to assess the efficacy and safety of Tirzepatide as a treatment to improve glycaemic control in patients with T2D. The SURPASS Phase III clinical trials (Table 1)[21-29]

Table 1: Overview of the SURPASS Phase III clinical trials of tirzepatide for the treatment of Type 2 diabetes.

Trial name/ publication date	Baseline characteristics and trial duration	Comparator group	Primary outcome	Results	Remarks
SURPASS 1[21] October 2020	Treatment naïve population 472 participants Duration: 40 weeks	Tirzepatide 5, 10, and 15 mg versus placebo	Change from baseline in HBA1c	Mean HbA1c decreased from baseline by 1.87% with tirzepatide 5 mg 1.89% with tirzepatide 10 mg and 2.07% with tirzepatide 15 mg versus +0.04%with placebo	Significant weight loss was seen and side effects were consistent of GLP 1 analogues
SURPASS 2[22] February 2021	On Metformin monotherapy 1,881 participants Duration: 40 weeks	Tirzepatide 5, 10, and 15 mg versus semaglutide 1 mg	Change from baseline in HBA1c	Mean HbA1c decreased from baseline by 2.01% with tirzepatide 5 mg 2.24% with tirzepatide 10 mg and 2.3% with tirzepatide 15 mg versus 1.87% with semaglutide (p <0.05 for all doses)	Tirzepatide at all doses was noninferior and superior to semaglutide. Reductions in body weight were greater with tirzepatide than with semaglutide.
SURPASS 3[23] January 2021	On metformin ± SGLT2i 1,420 participants Duration: 52 weeks	Tirzepatide 5, 10, and 15 mg versus degludec	Change from baseline in HBA1c	Mean HbA1c decreased from baseline by 1.93% with tirzepatide 5 mg 2.2% with tirzepatide 10 mg, and 2.37% with tirzepatide 15 mg versus 1.34% with degludec (p <0.001 for all doses)	All three tirzepatide doses decreased bodyweight (-7.5 kg to –12.9 kg), whereas insulin degludec increased bodyweight by 2.3 kg
SURPASS 4[24] June 2021	Established cardiovascular disease or a high risk of cardiovascular events On 1-3 oral medication (Metformin, SU, SGLT2i) 1,995 patients Duration: 52 weeks	Tirzepatide 5, 10, and 15 mg versus glargine	Change from baseline in HBA1c	Mean HbA1c decreased from baseline by 2.43% with tirzepatide 10 mg, and 2.58% with tirzepatide 15 mg versus 1.44% with glargine (p <0.001 for both doses)	Adjudicated MACE-4 events (cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina) occurred in 109 participants and were not increased on tirzepatide compared with glargine (hazard ratio: 0.74; 95% confidence interval: 0.51–1.08)
SURPASS 5[25] February 2021	On glargine ± metformin 475 patients Duration: 40 weeks	Tirzepatide 5, 10, and 15 mg versus placebo	Change from baseline in HBA1c	Mean HbA1c decreased from baseline by 2.4% with tirzepatide 10 mg, and 2.34% with tirzepatide 15 mg versus 0.86% with placebo (p <0.001 for both doses)	Significant weight loss was seen and side effects were consistent of GLP 1 analogues
SURPASS 6[26] August 2022	On glargine ± metformin 1,182 patients Duration: 52 weeks	Tirzepatide 5, 10, and 15 mg versus lispro	Change from baseline in HBA1c	Results awaited	

Table 1 continued.

Trial name/ publication date	Baseline characteristics and trial duration	Comparator group	Primary outcome	Results	Remarks
SURPASS J MONO[27] April 2021	Treatment naïve or on metformin monotherapy 636 patients Duration: 52 weeks Japanese study	Tirzepatide 5, 10, and 15 mg versus dulaglutide 0.75 mg	Change from baseline in HBA1c	Mean HbA1c decreased from baseline by 2.55% with tirzepatide 10 mg, and 2.88% with tirzepatide 15 mg versus 1.29% with dulaglutide 0.75 mg (p <0.001 for both doses)	All doses of tirzepatide were superior to dulaglutide for weight loss
SURPASS J combo[28] March 2021	On monotherapy 441 patients Duration: 52 weeks Japanese study	No active comparator	Number of participants with ≥ 1 SAE	Results awaited	
SURPASS AP Combo2[9] February 2022	On metformin ± SUs 956 patients Duration: 40 weeks	Tirzepatide 5, 10, and 15 mg versus glargine	Change from baseline in HBA1c	Results awaited	

SAE: serious adverse effects; SU: sulfonylurea

are mostly multicentric and global; only two studies are from Japan and one study is from the Asia–Pacific region. These trials included patients with different background therapies; for example, SURPASS 1 included treatment of naïve patients, whereas others included patients on different oral anti-diabetic agents (metformin, sulfonylurea, pioglitazone, SGLT-2 inhibitor, and/or insulin). SURPASS 1, SURPASS 5, and SURPASS J-combo are placebo controlled, while others have active comparators: for example GLP-1RAs (dulaglutide and semaglutide), long-acting insulin analogues (glargine and degludec), or short-acting insulin analogue (lispro). The SURPASS trials are designed to evaluate once-weekly tirzepatide doses of 5 mg, 10 mg, and 15 mg with a dose escalation algorithm: starting dose at 2.5 mg weekly for the first 4 weeks, then dose increment of 2.5 mg every 4 weeks until the maintenance dose of 5 mg, 10 mg, or 15 mg is achieved. Other than the SURPASS J-combo trial, the primary endpoint for each of the studies was the change in HbA1c from baseline. To date, the results of SURPASS 1–5 have been available, and it has been shown that tirzepatide lowers HbA1c significantly better than placebo, semaglutide, degludec, glargine, and placebo, respectively. In addition, there was significant weight loss seen as compared with placebo, insulin, or semaglutide. The SURPASS 2 trial was a head-to-head comparison with one of the most effective GLP-1 analogues, semaglutide, in patients only on metformin. This trial showed noninferiority and superiority to semaglutide for HbA1c reduction, as well as for weight reduction. In a recent meta-analysis which included data from six randomised control trials involving 3,484 patients, tirzepatide showed impressive glycaemic efficacy and weight loss data over 1 year of use.[30] The results of SURPASS J-combo, SURPASS AP, and SURPASS 6 are awaited.

SAFETY AND TOLERABILITY OF TIRZEPATIDE

Overall, the safety profile is at par with the existing GLP-1RAs. The most common side effects reported in SURPASS 1 trial (as compared with placebo) were abdominal discomfort, nausea, diarrhoea (12–18%), injection site reactions (2–3%), and hypersensitivity (1–2%); however, all side effects were mild. Although there was rise in the amylase level with tirzepatide treatment compared with placebo, there was no confirmed case of pancreatitis. Furthermore, no treatment emergent diabetic retinopathy or medullary carcinoma of the thyroid was reported. When compared head-to-head with semaglutide in the SURPASS 2 trial, nausea was reported in 17–22% of patients who received tirzepatide, and in 18% who received semaglutide. Diarrhoea was reported in 13–16% and 12%, respectively, and vomiting in 6–10% and 8%, respectively. This indicates that the GI side effects of tirzepatide and semaglutide are comparable. Pancreatitis and cholelithiasis were reported in small number of patients (<1%), and were similar in both groups. When compared with degludec in the SURPASS 3 trial, GI side effects were more common in the tirzepatide group, but hypoglycaemia was more common in people treated with degludec (1–2% versus 7%). Although the dedicated CV outcome trial (CVOT) is still underway, adjudicated 4-P MACE was evaluated in the SURPASS 4 trial, and there was no increase in CV death, myocardial infarction, stroke, or hospitalisation for unstable angina in the tirzepatide group as compared with glargine (hazard ratio: 0.74; 95% confidence interval: 0·51–1·08).[25] Satter et al.[31] demonstrated similar safety in 4-P MACE in a meta-analysis which included 4,487 participants treated with tirzepatide and 2,328 participants in control arm from seven trials which lasted more than 26 weeks duration.

THERAPEUTIC PROSPECTS

To date, the efficacy and safety trials of tirzepatide are mostly published. However, dedicated data from Japan and the Asia Pacific region (SURPASS J-combo and SURPASS AP-combo) are yet to come. The results of the ongoing SURPASS-CVOT trial will be published in 2024 (Table 2).[32-37] This large trial is likely to provide more clarity on whether dual agonism through tirzepatide lead to even greater benefits in patients with T2D and established CV disease than a GLP-1RA based approach. As there was clear evidence of clinically significant weight loss from the Phase III trials, tirzepatide has been planned to be evaluated as an anti-obesity drug in non-diabetic (SURMOUNT 1 trial), and diabetic (SURMOUNT 2 trial) populations, and on those who are already on intensive lifestyle programmes (SURMOUNT 3 trial). Of these, the SURMOUNT 1 trial[33] has recently been published, which found significant weight loss with all three doses of tirzepatide compared with the placebo in non-diabetic individuals. This indicates tirzepatide may be a potential therapeutic option for individuals living with obesity. Another two trials are currently ongoing. The SUMMIT trial will document safety and efficacy of tirzepatide in heart failure patients, and the SYNERGY-NASH trial will provide specific data on the benefit of treatment with tirzepatide in people with non-alcoholic steatohepatitis. If the results of these trials are positive, it will open a new horizon in the management of T2DM, obesity and non-alcoholic steatohepatitis.

OUTSTANDING QUESTIONS AND FUTURE DIRECTIVES

Although there is a lot of evidence at present with this novel molecule, many unanswered questions remain. Firstly, it is not clear how much GIPR stimulation contributes to the effects of tirzepatide, and what should be the ideal ratio of GIP/GLP-1 action of this co-agonist for the best results. Secondly, do these unimolecular agents target both receptors in the same cell, different cells in different tissues, or both? Thirdly, the action of GIP on β-cells has a tachyphylaxis effect; what will be the effect of tirzepatide in this regard? Furthermore, a layer of complexity underlying the logical development of GIP/GLP-1R co-agonists grow from numerous studies, indicating that GIPR antagonism may be metabolically beneficial as well. Nevertheless, GIPR antagonist is now available on the market with promising initial results, and can be utilised to understand the clinical benefits seen with tirzepatide. Lastly, the future positioning of dual GIP/GLP-1RA against GLP-1RA in the treatment landscape of T2D needs to be better defined. The positioning of tirzepatide in the therapeutic

Table 2: Published and ongoing trials on tirzepatide for cardiovascular safety, obesity, and non-alcoholic fatty liver disease.

Trial name/ expected publication date	Baseline characteristics and trial duration	Comparator group	Primary outcome	What the study aims to establish/results
SURPASS CVOT[32] October 2024	On oral or injectable anti-diabetic medication 12,500 participants Event-driven trial	Tirzepatide maximum tolerate dose up to 15 mg versus dulaglutide 1.5 mg	Time to first occurrence of a component of event of 3 P MACE	Cardiovascular safety of tirzepatide in a head-to-head trial with dulaglutide
SURMOUNT 1[33]	Non-diabetic obese individuals 2,539 participants Duration: 72 weeks	Tirzepatide at one of three doses (5 mg, 10 mg, or 15 mg) versus placebo	Percentage change in body weight from baseline to week 72 and percentage of patients achieving at least a 5% weight reduction by week 72	Tirzepatide in all three doses was superior to placebo in reducing body weight
SURMOUNT 2[34] April 2023	Diabetic obese individuals 900 participants Duration: 79 weeks	TIrzepatide versus placebo	Percent change from randomisation in body weight	Efficacy of tirzepatide as anti-obesity drug in diabetic individuals
SURMOUNT 3[35] May 2023	Non-diabetic obese individuals who are on intensive lifestyle programmes 800 participants Duration: 104 weeks	Tirzepatide versus placebo	Percent change from randomization in body weight	Efficacy of tirzepatide in maintaining body weight or adding to weight loss after an intensive lifestyle modification programme
SYNERGY NASH[36] December 2023	NASH (Stage 2 or 3 fibrosis, histology proven), BMI >27 kg/ m2 196 participants Duration: 52 weeks	Tirzepatide versus placebo	Percentage of participants with absence of NASH with no worsening of fibrosis on liver histology	Efficacy and safety of tirzepatide in treatment of NASH
SUMMIT[37] November 2023	Obese, heart failure with preserved ejection fraction 700 participants Duration: 52 weeks	Tirzepatide versus placebo	All-cause mortality, heart failure events, 6-minute walk test distance, and Kansas City Cardiomyopathy Questionnaire	Efficacy and safety of tirzepatide (LY3298176) in participants with heart failure with preserved ejection fraction and obesity

NASH: non-alcoholic steatohepatitis

algorithm will likely be influenced by emerging informations on CV outcomes, non-alcoholic fatty liver disease, kidney protection, and durability of effects. One promising aspect of incretin-based dual agonist therapy (e.g., tirzepatide) is that it might offer an alternative to stringent dietary restriction, and could challenge the success of bariatric surgery in the diabesity community.

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Comorbidity of Anxiety and Depression with Hypertension, Diabetes, and Cardiovascular Disease: A Selective Systematic Review from India

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Abstract

Context: Non-communicable diseases (cardiovascular diseases, hypertension, and diabetes) and comorbid common mental disorders are of public health concern because of their high morbidity and mortality rates. The authors undertook a systematic review of studies that reported the prevalence of common mental disorders among non-communicable diseases, specifically in India.

Evidence acquisition: Relevant databases (Medline, Google Scholar, EBSCO, and ProQuest) were searched until May 2021. Descriptive and observational studies from the mentioned databases were included.

Evidence synthesis: Of the total 6,515 studies, the electronic literature search identified 4,307 studies. Manual cross-referencing identified an additional 2,208 studies. Only 17 studies met the criteria and were included for the review.

Findings: Twelve studies focused on the prevalence of anxiety and depression in patients with diabetes, four studies focused on cardiovascular disease, and one on the prevalence of depression in hypertension. The prevalence of anxiety disorder and depression was 3.9–44% and 8–44%, respectively.

Conclusion: High prevalence of anxiety and depression is seen in people with diabetes, indicating these are of serious public health concerns in India.

Key Points

1. Common mental disorders and non-communicable diseases (NCD) are interlinked, and the pathways of comorbidity have been described to be reciprocal.

2. This systematic review of Indian studies illustrates the high prevalence of anxiety and depression in NCDs, specifically in diabetes.

3. The findings of the review highlight the need to focus on the integration of services in healthcare to improve the screening and identification of common mental disorders in people with NCDs.

INTRODUCTION

Non-communicable diseases (NCD) are defined as medical conditions that cannot be transmitted.[1] They are characterised by a chronicity of at least 3 months and are progressive in nature. The conditions categorised as NCDs are cardiovascular diseases (CVD), respiratory diseases, obesity, gastrointestinal disorders, diabetes, cancer, and endocrine and metabolic disorders.[2] NCDs such as heart diseases, cancer, stroke, and diabetes are the leading cause of mortality in the world.[3] The combined burden of these diseases is rising fast among lower-income countries.

According to the Global Status Report on NCDs (2010), 80% of CVD and diabetes, and 90% of deaths from chronic obstructive pulmonary disease, occur in low- and middle-income countries.[4] The recent edition (2020) indicates that 70% of deaths worldwide are due to NCDs.[4]

The modifiable risk factors associated with NCDs are tobacco use, physical inactivity, unhealthy diet, and the harmful use of alcohol.[4] Tobacco accounts for 7.2 million deaths every year, more than 3.3 million annual deaths have been attributed to alcohol use from NCDs, including cancer, and 1.6 million deaths can be attributed to insufficient physical activity.[5] These risk factors lead to metabolic and psychological changes in the body, such as raised blood pressure, overweight/obesity, hyperglycaemia, and hyperlipidaemia.[4]

There have been increasing calls to include common mental disorders (CMD) such as depression and anxiety under the umbrella of NCDs. However, the prevention and control of both diseases remain separate and independent. CMDs typically include anxiety, depression, and somatic complaints and cause limitations in daily activities.[6] CMDs are identified as the leading contributors of disability globally, but they are less likely to receive treatment.[7] This reflects stigmatisation, and they are undetected most of the time.[7,8] The aetiological factors for CMDs can be psychological, social, and biological. The causal mechanism of the risk factors of NCDs and CMDs also operate at the individual level (genetic factor), psychological level, and societal level (social determinants). Thus, CMDs and NCDs are interlinked and highly comorbid. The pathways of comorbidity have been described to be bidirectional in nature.[9,10] For example, diabetes elevates the risk of depression and vice versa.[11] These conditions share common diathesis contributing to the onset of other comorbid conditions.[12] The psychological burden of being ill and associated health factors can act as triggering factors in the development of depression and anxiety among patients with diabetes.[13] Similarly, depression leads to unhealthy dietary practices, less physical activity, tobacco use, harmful use of alcohol, and weight gain, which are risk factors for diabetes. Risk factors for NCDs tend to cluster together.[8]

Depression and anxiety have also been recognised as systemic illnesses that negatively affect physical health.[14,15] People with CMDs may use nicotine and alcohol, which can further affect their physical health. This not only contributes to NCDs but also increases the burden of depression and anxiety. Tobacco and alcohol use are also linked with common and severe mental illness. Along with NCDs, from a societal perspective, tobacco use in mental disorders might be a significant contributor to premature mortality.[16]

The likelihood of depression tends to double for patients with diabetes, when compared with the general population without diabetes.[17,18] Patients with diabetes may have excessive fear and worry about the disease, which can result in anxiety, and anxiety disorders are associated with hypertension.[19,20] Hypertension may trigger an anxiety disorder and, conversely, an anxiety disorder may lead to hypertension.[21] Studies suggest that individuals experiencing depression are at risk of developing hypertension, and are predisposed to stroke and ischaemic heart disease (IHD).[22,23] They are more likely to develop CVD and have a higher mortality rate. Hypertension is also an important risk factor for the development of coronary heart disease.[24] There exists a graded relationship among both: the more severe the depression, the higher the risk of mortality and other cardiovascular events. The economic indicators relating to CVD and depression are high medical cost, increased health service utilisation, and less productivity. These factors contribute to poor quality of life (QoL).[25]

There is also evidence that lifestyle risk factors such as diet, physical inactivity, smoking, and alcohol use, besides non-modifiable risk factors such as age, poverty, and gender, contribute to comorbidity.[12] It is also evident that depression and anxiety are prevalent in people with physical comorbidities, specifically in South Asia.[26] There is an increasing trend in the prevalence of both CMDs and NCDs in developing countries such as India.[26] Major risk factors of NCDs in India are high systolic blood pressure, high fasting plasma glucose, and high BMI.[27] In 2013, there were an estimated 65.1 million diabetes cases; this is expected to increase up to 109.0 million in 2035.[28] The World Economic Forum (WEF) estimated that countries such as Brazil, China, India, and the Russian Federation lose more than 20 million productive life years annually to NCDs.[3]

Most of the time, depression goes undetected despite its high prevalence in NCDs. Patients do not receive adequate treatment, which further deteriorates their physical health. This suggests addressing the risk factors and integrated management of mental disorders and NCDs. In view of this, it is important to screen patients for NCDs and CMDs. Thus, this study aimed to review the literature from India on the prevalence of CMDs in NCDs and vice versa.

OBJECTIVES

- To study the prevalence of anxiety and depression in hypertension, diabetes, and CVD in India; and
- To study the prevalence of hypertension, diabetes, and CVD in anxiety and depression in India.

METHODS

Evidence

Electronic databases such as PubMed, Medline, EBSCO, CINAHL, ProQuest, and Google Scholar were searched for the time period of 1980 to May 2021. The keywords used for the search strategy were "prevalence," "anxiety," "depression," and "hypertension;" "prevalence," "anxiety," "depression," and "diabetes mellitus;" and "prevalence," "anxiety," "depression," and "cardiovascular diseases." The evidence was screened for inclusion criteria using a three-stage approach: reviewing the title, abstract, and full text. The authors included studies that were published between 1980 and May 2021 in indexed and non-indexed journals, and descriptive and observational studies that allowed an estimation of the prevalence of CMDs and NCDs. For this review, NCDs included hypertension, diabetes, and CVD, whereas CMDs included anxiety and depression. The authors included studies from inpatient, outpatient, and community settings, and whose participants were adults (age >18 years) from India. Studies that did not relate to NCDs and CMDs, and those that were randomised control trials or reviews (systematic or non-systematic), were excluded. Studies conducted only amongst the elderly or adolescents were also excluded.

Data Extraction

Microsoft Excel was used to enter the extracted information for the review. The data extraction form included authors' names, publication year, study design, participants' profile, sample size, measurements, and outcomes. One author (Rajan) conducted the screening independently by reviewing articles and abstracts. Full-text articles of the abstracts that met the inclusion criteria were then reviewed by two independent

authors (Rajan and Chaturvedi). Data of these studies were extracted by two independent authors (Rajan and Krishna). Discrepancies in article inclusion, data extraction, and bias assessment were resolved by consensus or by referring to the third author (Muliyala).

Risk of Bias

The quality of the included studies was assessed by the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.[29] Three independent authors (Muliyala, Krishna, and Rajan) assessed the quality of studies, and disparities were resolved by consensus. The quality rating was based on the total number of "yes" responses and was rated as follows: poor: <50%; fair: 50–75%; and good: ≥75%.

RESULTS

A total of 17 studies that met the inclusion criteria were reviewed. Figure 1 illustrates the screening and selection process in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Of the total 6,515 studies, the electronic literature search identified 4,307 studies. Manual cross-referencing additionally identified 2,208 studies. After removing 100 duplicate studies, 6,415 were screened and 6,397 were excluded as they did not meet the inclusion criteria. The full text was only reviewed in the remaining 25 studies. Further, eight studies were excluded as they did not concur with the inclusion criteria, resulting in 17 studies for the review.

The characteristics of the included studies are provided in Table 1.

REVIEW OF THE INCLUDED STUDIES

All the studies included in this review were conducted in hospital settings and were observational studies. Out of the 17 studies, only one had respondents enrolled from an inpatient setting. Overall, 12 studies assessed the prevalence of depression and/or anxiety in NCDs, particularly in diabetes. Three studies evaluated the prevalence of depression in CVD. Only one study looked into the prevalence of CMD in NCD (diabetes, hypertension, and CVD).

Despite the aetiological differences, many studies have not distinguished between different types of diabetes. Only one study focused on Type 1 diabetes (T1D) and Type 2 diabetes (T2D) separately;[32] 11 studies have focused only on T2D.

Studies That Assessed Depression and Anxiety Disorders in Diabetes

The prevalence of depression in patients with diabetes ranged from 8% to 46%. Risk factors of NCDs such as smoking and alcohol use were also reported in three studies. The sample size varied from 50 to 10,450. Depression was identified by diagnostic interview: International Classification of Diseases (ICD) and Diagnostic and Statistical Manual of Mental Disorder (DSM-IV) in two studies; Physical Health Questionnaire-9 (PHQ-9) in five studies; Hamilton Rating Scale for Depression-17 (HAM-D-17) in three studies; Hamilton Depression Rating Scale (HDRS-21) in one study; Beck Depression Inventory (BDI) in one study; Primary Care Evaluation of Mental Disorders (PRIME-D) in one study; and Hopkins Symptom Checklist (HSCL) in one study. Studies were from Northern (10), Southern (six), and Western (two) regions of India. The prevalence of anxiety disorder and depression in any NCD were 3.9–44.0% and 8.0–46.0%, respectively.

Four studies reported an association between the duration of diabetes and the prevalence of depression, as the incidence of diabetic complications increased with illness duration.[31,41,42,45] A higher prevalence of depression was reported in one of the studies among patients having uncontrolled diabetes (glycated haemoglobin test: HbA1c).[45] Two studies concluded that patients diagnosed with T2D and depression had poor QoL compared with those without depression. Health-related QoL was adversely affected by the presence of depression.[46] Negative correlation was reported between HbA1c and QoL in one of the studies. This supports the view that patients with poor control of blood glucose levels have a worse QoL. One of the studies reported that 67% of patients with diabetes were overweight or obese.[45] Two studies indicated that depression was significantly associated with older age,[34,39]

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart

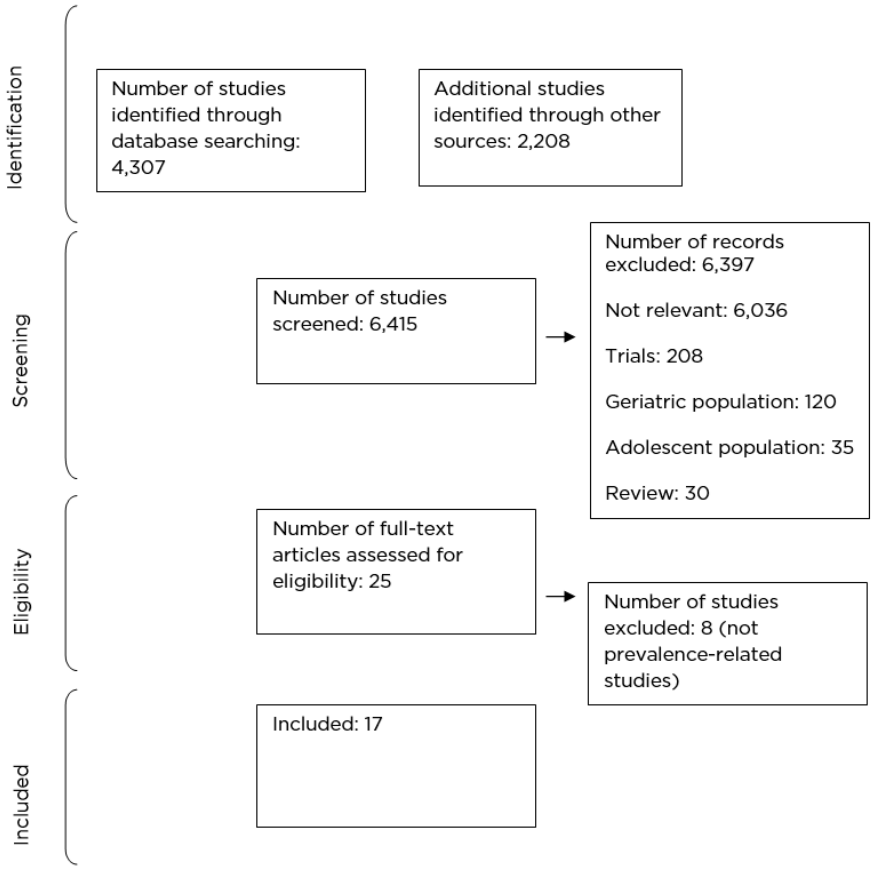

Table 1: Characteristics of studies included in the review.

Author (year)	Methods			Prevalence	Remarks/socio-demographic correlation
	Design/site of data	Tools and questionnaires used for CMD	Method to diagnose NCD		
Shruthi et al.[30] (2018)	Cross-sectional study N=248 Hospital	MINI and HAM-D	WHO criteria of presence of typical myocardial ischaemic pain, electrocardiographic changes, and cardiac biomarkers	Diabetes: 67.30% Hypertension: 65.33% Depression: 44.00%	Nicotine consumption (smoke form) was found in 66.1% of patients and alcohol use was found in 56.0% of patients
Balhara, Sagar[31] (2011)	Cross-sectional study N=77 Hospital	Brief patient health questionnaire, and HADS	HbA1c levels, fasting blood glucose, and postprandial blood glucose	Depression: 16.9 % Generalised anxiety disorder: 3.9%	HADS anxiety scores were found to be related to HbA1c levels (correlation-coefficient: 0.41; p=0.03) and postprandial blood glucose levels (correlation coefficient: 0.51; p=0.02).

Table 1: Continued.

Chaudhary et al.[32] (2017)	Cross-sectional study N=50 Hospital	HAM-D and HAM-A	N/A	Depression among patients with T1D: 38% Depression among patients with T2D: 42% Anxiety among patients with T1D: 44% Anxiety among patients with T2D: 34%	Depressive symptoms were found to be more prominent in patients with T2D compared with patients with T1D
John[33] (2013)	Cross-sectional observational study N=130 Hospital	MMSE or HMSE, SCID-I, and health-related quality of scale (EQ-5D)	ECG and cardiac enzyme studies	Depression: 34.6% Anxiety: 36.9%	Prevalence of dysthymia: 30.0% Panic disorder: 3.1% Generalised anxiety disorder: 3.8% Adjustment disorder: 7.7%
Joseph et al.[34] (2013)	Cross-sectional study N=230 Patients with T2D in hospital	PRIME-MD PHQ-9	Recordings of blood investigation and anthropometric measures	Depression: 45.2%	Categorisation of depression: moderate depression (30.9%) and severe depression (14.3%) Average duration of time since the detection of diabetes was 12.10±7.35 years
Kulkarni et al.[35] (2014)	Cross-sectional study N=282 Hospital	PHQ-SADS	Diagnosed by physician	Anxiety: 19.1% Depression: 29.1%	Prevalence of somatisation: 35.1%
Mathew et al.[36] (2012)	Cross-sectional study N=80 Hospital	MDI, BDI, and the DSM-IV	Diagnosed by physician	Depression: 38.8%	Multiple linear regression models showed that the presence of depression increased HbA1c by an average of 0.94% after adjusting for age and sex
Poongothai et al.[37] (2015)	Cross-sectional study N=1,505 Hospital	PHQ-12	Anthropometric measures and blood investigation	Depression: 16.6%	N/A
Raval et al.[39] (2010)	Cross-sectional study N=80 Hospital	PHQ-9, self-report version of PRIME-MD	Diagnosed by physician and anthropometric measures and blood investigation	Depression: 41%	Depression was strongly associated with age
Singla et al.[40] (2012)	Cross-sectional study N=91 Hospital	MINI Neuropsychiatric Scale	Pre-diagnosed diabetes by physician, routine biochemistry	Depression: 8%	Family history of diabetes was present in 60.43% of patients, 6.59% were active smokers, and 46.15% were obese

Table 1: Continued.

Rajput et al.[38] (2016)	Cross-sectional case–control study design N=820 Hospital	HAM-D and HAM-A	Diagnosed by physician and anthropometric measurements were recorded	Depression in patients with diabetes: 26.3% Depression in patients without diabetes: 11.2% Anxiety in patients with diabetes: 27.6% Anxiety in patients without diabetes: 12.7% Comorbid depression and anxiety in patients with diabetes: 21.0%	N/A
Raval et al.[39] (2010)	Cross-sectional study N=80 Hospital	PHQ-9, self-report version of PRIME-MD	Diagnosed by physician and anthropometric measures and blood investigation	Depression: 41%	Depression was strongly associated with age
Singla et al.[40] (2012)	Cross-sectional study N=91 Hospital	MINI Neuropsychiatric Scale	Pre-diagnosed diabetes by physician, routine biochemistry	Depression: 8%	Family history of diabetes was present in 60.43% of patients, 6.59% were active smokers, and 46.15% were obese
Thour et al.[41] (2015)	Cross-sectional study N=73 Hospital	PHQ-9	Pre-diagnosed diabetes by physician	Depression: 41%	Categorisation: severe depression (4%); moderate depression (10%); mild depression (27%) Depression was significantly more prevalent in rural subjects (57%) when compared to urban ones (31%; p=0.049)
Kanwar et al.[42] (2019)	Cross-sectional study N=202 Hospital	Case record form, (Brief IPQ), ICD-10, HAM-D, HAM-A, and MINI	Routine blood investigation	Depression: 41.9% Other psychiatric comorbidity: 58.4%	Depression was higher in female patients and persons aged >50 years
Bhatt et al.[43] (2015)	Observational, single-centre study N=6,867 Hospital	MADRS and SF-36	N/A	Depression: 39.8%	N/A

Table 1: Continued.

Weaver, Madhu[44] (2015)	Cross-sectional study N=184 Hospital	HSCL	Finger-stick blood test, pre-diagnosed diabetes by physician	Depression: 19% Anxiety: 26%	N/A
Guruprasad et al.[45] (2012)	Cross-sectional study N=210 Hospital	BDI	GPE, pre-diagnosed diabetes by physician	Depression: 27.6% Comorbid hypertension with depression and diabetes: 51.7% IHD: 25.9% Obesity and diabetes: 15.5% Tobacco use: 65.5%	N/A
Das et al.[46] (2013)	Cross-sectional study N=195 Hospital	HAM-D, Q-LES–Q, and SF	Diagnosed by physician	Depression: 46.15%	Categorisation: mild depression (32.2%); moderate depression (36.7%); severe depression (14.4%); very severe depression (16.7%)

BDI: Beck Depression Inventory; Brief IPQ: Brief Illness Perception Questionnaire; CMD: common mental disorders; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders IV ed. 2000; GPE: General Physical Examination; HADS: Hospital Anxiety and Depression Scale; HAM-A Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; HbA1c: glycated haemoglobin; HMSE: Hindi Mental Status Examination; HSCL: Hopkins Symptoms Checklist; ICD-10: International Classification Of Diseases, Tenth Revision; IHD: ischaemic heart disease; MADRS: Montgomery–Åsperg Depression Rating Scale; MDI: Major Depression Inventory; MINI: Mini International Neuropsychiatric Interview PLUS 5.0.0; MMSE: Mini Mental Status Examination; N/A: not applicable; NCD: non-communicable diseases; PHQ-SADS: Patient Health Questionnaire-Somatic, Anxiety, and Depressive Symptoms; PHQ-9: Patient Health Questionnaire-9; PHQ-12: Patient Health Questionnaire-12; PRIME-MD: Primary Care Evaluation of Mental Disorders; Q-LES–Q: Quality of Life Enjoyment and Satisfaction Questionnaire; SCID-I: structured clinical interview for DSM-IV Axis I Diagnosis; SF: Short Form; SF-36: Short Form Health Survey-36; T1D: Type 1 diabetes; T2D: Type 2 diabetes; WHO: World Health Organization.

female gender,[34] and complications due to T2D or other comorbidities such as hypertension and being overweight.[34,38,39] Conversely, two studies reported that gender was not associated with depression.[38,39] One of the studies indicated that depression was more prevalent in rural populations than urban.[41] One of the studies showed that depression was significantly associated with retinopathy, nephropathy, and IHD.[38] Another study reported that depression was strongly associated with age, central obesity, neuropathy, and nephropathy; however, it also found that depression was not significantly associated with gender.[39]

Studies That Assess Depression and Anxiety Disorders in Hypertension

Out of 17 studies, only one, conducted in a hospital in Mangalore, India, reported a prevalence of depression in patients with hypertension as 28%.[35]

Studies That Assess Depression and Anxiety Disorders in Cardiovascular Diseases

Among the four studies that assessed the prevalence of depression in CVD, one focused on IHD in general, two focused on acute coronary artery disease, and one focused on carotid artery intima-media thickness. One study assessed the relationship between IHD and QoL. Poor QoL was reported among patients with IHD and comorbid anxiety and depression.[33] In one of the studies, depressive symptoms were associated with functional and structural markers of atherosclerosis, common carotid intima-media thickness, and augmentation index.[37]

DISCUSSION

In this review, the authors have presented a comprehensive summary of existing research on the comorbidity of CMDs (anxiety and depression) and NCDs (hypertension, CVD, and diabetes) in India. The data presented in this review reflects the high prevalence of anxiety and depression in NCDs, specifically diabetes. The prevalence of depression in patients with diabetes in the present study was 8–46%. Studies that were based in the USA and the Netherlands, which were included in a systematic review on the epidemiology of diabetes and depression, conducted among patients with diabetes, reported the prevalence rate of depression as 32.1% and 19.3%, respectively. Though these are from high-income countries, they are within the range of the present study.[47] The estimated prevalence of depression in patients with hypertension in one of the meta-analyses was reported to be 21.3%, and the range of point prevalence of 41 studies was observed to be between 0.5% and 73%.[48]

Twelve studies included in the review examined the prevalence of CMDs in diabetes. Diabetes and psychiatric disorders share a bidirectional association, both influencing each other in multiple ways.[49] People with diabetes are two-times more likely to develop depression relative to people without depression, and patients with depression have poorer clinical parameters and outcomes of diabetes because of poor medication compliance and dietary practices.[50]

It has also been reported that comorbid anxiety and depression in people with diabetes also leads to medical complications of diabetes, work disability, and poor QoL.[51] Patients with diabetes are likely to face challenges at physical, emotional, psychological, social, occupational, and interpersonal levels.[52] The complications associated with the management (medication dosing, monitoring blood glucose, eating patterns, and physical activity)[53] of diabetes can lead to negative emotions such as worry, fear, and anger, which result in poor QoL.[50] Among the studies reviewed, 11 have focused on T2D despite the aetiological differences. T1D is an autoimmune condition, whereas T2D is linked with genetic and lifestyle choices.[54] Both types of diabetes lead to health complications. Depressive symptoms seem to be slightly more prevalent in T2D compared with T1D.[11]

The co-occurrence of NCDs and CMDs has been associated with elevated symptom burden, functional impairment, and a decrease in QoL.[9] The authors found that the prevalence of anxiety and depression was higher in females compared with males, similar to the studies done elsewhere.[55] Depression was identified either by diagnostic interviews or diagnosis by a general practitioner (n=2). The tools used in the studies were PHQ-9, HAM-D, and BDI, which are widely used in clinical practice and research. PHQ is a screening tool commonly used in primary care, HAM-D is a widely used clinician-administered depression assessment scale, and BDI is a self-reported inventory to measure the severity of depression. It is reported that the estimate of depression prevalence depends upon the assessment tools (standardised interview or self-report questionnaires, classification of depression, and diabetes type).[11] Depression assessed with self-report questionnaires is found at a rate two-times higher than when assessed with standardised interviews.[17,53] The overall quality of the studies included in the systematic review was good. In the risk of bias assessment, most studies were categorised as good (n=14). All the studies used standardised tools that were reliable and valid for assessment.

CMDs, particularly depression and anxiety, often go undetected, and systematic screening, even in high-income countries, is not satisfactory.[9] Thus, the screening of CMDs in primary care by using a brief instrument

should be made mandatory in routine clinical encounters. This integration has also been reported as an evidence-based approach for collaborative care.[16]

Addressing the overlapping risk factors and integrating the management of CMDs and NCDs can improve clinical outcomes.[56] Management of NCDs and CMDs can be made by adopting existing integrated models of care. The inter-related causal mechanism of CMD and NCD argue for an integrated approach to care.[16] The management of T2D and depression in the primary setting has been effective using the educative model, where healthcare professionals are trained to identify, refer, and communicate with the patient about the symptoms of CMD.[57] The efficiencies of integrated care have proven beneficial for both high-income and low- and middle-income countries.[16]

Several policies and programmes have been adopted in India to tackle the rising burden of NCDs and mental illnesses.[58] These include the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) and District Mental Health Programme (DMHP). It has been reported that the major challenges are in terms of inadequate resources and ineffective implementation of the programmes.[58] To overcome these challenges, health and wellness centres have been envisaged under the Ayushman Bharat programme of the Government of India, encompassing a range of services for NCDs and mental health closer to the community.[59] Health and wellness centres focus on wellness and lifestyle modification through various activities such as yoga, local sports, and other activities. The screening of NCDs is done by accredited social health activists or auxiliary nurse midwifes through the Community Based Assessment Checklist (CBAC). Identified individuals are then referred for necessary treatment. According to the recent statistics, approximately 9.1 crore screenings for hypertension, and 7.4 crore screenings for diabetes have been carried out.[60]

In addition, for effective management, social workers, accredited social health activists, auxiliary nurse midwifes, and NCD counsellors can be trained for population-based screening of CMDs in NCDs and vice versa, basic counselling skills, brief intervention for lifestyle modification, and behavioural activation.

STRENGTHS AND LIMITATIONS

The search strategy adopted was extensive and comprehensive in nature. The studies were limited to those conducted in India. This review included only the prevalence of anxiety and depression in NCDs and excluded other CMDs (somatisation) and substance use disorders. The pooled prevalence of anxiety and depression has not been provided because meta-analysis was not conducted. Small sample sizes in some of the studies may have contributed to sampling errors. All the studies were hospital-based and, therefore, the findings are not generalisable to the community. There were insufficient data to draw firm conclusions about the prevalence of anxiety and depression in hypertension and CVD, as only three studies evaluated the prevalence of depression in CVD and only one study examined the prevalence of CMD in hypertension. The broad range of prevalence can be explained by the following four factors: use of different tools to screen and assess anxiety and/or depression; the studies were conducted in geographic or cultural settings; sample sizes were disparate; and true variation across the different conditions that have been included as NCDs.

CONCLUSIONS

In summary, the authors found that NCDs and CMDs are underdiagnosed in India. The data related to the prevalence rates of both NCDs and CMDs is limited. Based on studies carried out in India, the prevalence of anxiety disorder and depression in individuals with NCD was 3.9–44.0% and 8.0–46.0%, respectively. The results of the included studies point to disadvantages for people with CMDs and NCDs with respect to risk factors and outcome. Depressive and anxiety symptoms have been strongly associated with poor QoL, health status, and physical function. Thus, future efforts should focus on integrated healthcare, which may help improve screening and identification of NCDs and CMDs; this in turn can improve outcomes.

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Chronic Complications of Diabetes

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Abstract

Diabetes is a chronic condition that afflicts over 450 million people worldwide. Diabetes can lead to the development of multiple chronic comorbidities, such as microvascular, macrovascular, and neuropathic complications. Furthermore, diabetes is the leading cause for many of these complications, such as blindness, peripheral arterial disease, and kidney disease. Many of these conditions can go unnoticed for many years until they become more severe and are no longer reversible. This article will provide an evidence-based review of the background, prevention, and screening for many of the complications of diabetes.

Key Points

1. Diabetes mellitus is a chronic condition affecting more than 450 million people globally and the incidence is rising. By 2045, it is anticipated that 783 million people will have a diagnosis of diabetes, according to the International Diabetes Federation. The burden of disease associated with diabetes is significant to both patients and healthcare systems.

2. In addition to altered glucose homeostasis, diabetes mellitus can lead to chronic microvascular, macrovascular, and neuropathic complications. These complications include diabetic neuropathy, retinopathy, and kidney disease as well as peripheral arterial disease, coronary heart disease, and cerebrovascular disease.

3. The most effective method of reducing the morbidity and mortality associated with the secondary complications of diabetes mellitus is prevention, aided through screening programmes that enable early detection and intervention. However, the currently available screening methods have limitations and further research identifying sensitive biomarkers for both microvascular and macrovascular complication screening are required.

INTRODUCTION

Diabetes is a condition characterised by either defects in insulin secretion, insulin sensitivity/action, or both. These include Type 1 diabetes (T1D), Type 2 diabetes (T2D), gestational diabetes, and diabetes secondary to other medical conditions. Diabetes is one of the fastest

growing global emergencies of the 21st century. Based on the International Diabetes Federation (IDF) Diabetes Atlas 2021,[1] it is estimated that 537 million people have diabetes; this number is expected to reach 643 million by 2030 and 783 million by 2045. In addition, at the time of writing, 541 million people are estimated to have impaired glucose tolerance in 2021. It is also estimated that over 6.7 million people aged 20–79 years will have died from diabetes-related causes in 2021. Early diagnosis is important to prevent the complications associated with diabetes. In one study of 200 newly diagnosed patients, 52%, 10%, and 6% of patients were found to already have signs of neuropathy, nephropathy, and retinopathy, respectively.[2] In another study, patients with insulin-dependent diabetes had a 27.2% and 53.5% prevalence of macro- and microvascular complications, respectively.[3] This review discusses many of the complications associated with diabetes, as well as the approach to screening.

MACROVASCULAR DISEASE

Macrovascular disease in diabetes is due to atherosclerosis, which leads to myocardial infarction, stroke, and peripheral arterial disease. Macrovascular disease is the leading cause of death for adults with T2D. Diabetes is a proinflammatory and thrombotic state that is associated with endothelial damage. High glucose also leads to an imbalance of nitric oxide bioavailability and reactive oxygen species, which leads to endothelial dysfunction. This is further compounded by the elevated low-density lipoprotein particles that accumulate in the endothelial walls. The American Heart Association (AHA) and the American Diabetes Association (ADA) have recommendations for primary prevention of cardiovascular disease (CVD) in patients with diabetes (Table 1),[4] yet only half of adults with T2D are adhering to some of these recommended guidelines, such as management of dyslipidaemia.[5] Furthermore, atherosclerotic disease is responsible for 42% of mortality in diabetes.[6] It is important to understand the risks for these conditions,

Table 1: The American Heart Association (AHA)/American Diabetes Association (ADA) guidelines for cardiovascular disease risk factor.

Nutrition	Reduction of energy intake for patients who are overweight or obese and limit sodium to <2,300 mg/dL Mediterranean-style dietary pattern may improve glycaemic control and CVD risk factors. Diet rich in fruits and vegetables
Weight management	For patients who are overweight or obese, a reduction of 3–5% of weight can be associated with clinically meaningful benefits For patients with BMI >40 kg/m^2 or >35 kg/m^2 with an obesity-related comorbidity and who want to lose weight but have not responded to treatment, bariatric surgery might improve health
Haemoglobin A1C	Lower A1C to ≤7% in most patients to reduce the incidence of microvascular disease. Ideally, fasting glucose should be maintained at <130 mg/dL and postprandial glucose at <180 mg/dL Less stringent A1C goals are appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced complications, cognitive impairment, and extensive comorbid conditions
Blood pressure	Most individuals with diabetes should have a goal of <140/90 mmHg. Lower targets might be appropriate for some individuals
Lipids	Moderate-intensity statins should be initiated for patients aged 40–75 years, with LDL of 70–189 mg/dL. A high-intensity statin should be used if ASCVD risk is ≥7.5% Evaluate and treat patients with fasting triglycerides >500 mg/dL

ASCVD: atherosclerotic cardiovascular disease; A1C: glycated haemoglobin; CVD: cardiovascular disease; LDL: low-density lipoprotein.

appropriately test and screen for them, and initiate primary and secondary prevention.

Peripheral Arterial Disease

Background

Peripheral arterial disease (PAD) is present in approximately 29% of patients with diabetes and may be underdiagnosed due to confounders, such as a lack of sensation from neuropathy to identify pain.[7] However, patients with PAD and diabetes are more likely to have symptoms of claudication, and more likely to present with ulcers, increasing the risk for limb amputation.[8]

Screening and prevention

It is recommended that as part of a thorough history, patients with diabetes are asked about limb claudication as well as foot ulceration. Furthermore, all patients should have inspection of feet and lower extremity vasculature, including femoral, popliteal, posterior tibialis, and dorsalis pedis pulses. The ADA recommends screening all patients with diabetes over the age of 50 years with Ankle Brachial Index (ABI) measurements and, if normal, repeating in 5 years.[9]

Coronary Heart Disease

Background

T2D is considered a coronary heart disease (CHD) equivalent, since patients with T2D without known CHD have the same risk of myocardial infarction and death from CHD as those with a prior history of myocardial infarction.[10] Almost 75% of patients with diabetes are found to have obstructive or non-obstructive coronary artery disease on a CT angiogram.[11]

Screening and prevention

While diabetes does lead to a significantly elevated risk, it is not recommended to screen patients without symptoms, as the evidence has failed to show improved outcomes with this approach. It is recommended that patients have risk factors aggressively treated as those with a previous history of known coronary artery disease. Patients should be screened annually for being overweight or obese, hypertension, dyslipidaemia, tobacco use, chronic kidney disease (CKD) or albuminuria, and family history of CHD. If any are present, then they should be managed appropriately.[12]

Hypertension

In addition to lifestyle modification, intensive treatment of hypertension with a goal blood pressure of <140/90 mmHg for those with lower cardiovascular (CV) risks, and <130/80 for those with higher CV risks (10-year atherosclerotic CVD [ASCVD] risk of ≥15%) should be initiated. Initial treatment should be with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) if albuminuria is present.

Lipid management

In addition to lifestyle modification, patients aged 40–75 years should be started on a statin. General recommendations are that in those without CVD, use of a moderate-intensity statin is indicated. For those with multiple risk factors, known CVD, or aged 50–70 years, a high-intensity statin is indicated. In those with ASCVD risk of ≥20%, it would be reasonable to add ezetimibe to statin therapy.

Stroke

Background

Just as diabetes increases the risk of CHD, the risk for stroke is also increased, with a relative risk of 2.0–5.8, with risks being higher in females than males. In addition, patients with T2D have a higher proportion of ischaemic stroke versus haemorrhagic stroke compared with the general population.[13]

Screening and prevention

There are no current guidelines for screening for carotid atherosclerosis in patients with diabetes. However, in patients with other occlusive disease or CV risk factors, there may be benefits.[14] In regard to prevention, the recommendations follow the same listed above for managing other CV risk factors, such as hypertension and lipid management. Patients should also have tight glucose control, although the evidence is not as robust as for microvascular complications.

Aspirin in Diabetes

For primary prevention of CVD, the ADA recommends that patients with diabetes and an ASCVD risk of >10% or with known CHD should

be placed on aspirin 75–162 mg daily, after discussing the risks of increased bleeding with the benefit of reduction in CVD. For patients with ASCVD risk of <5%, the increased risk of bleeding likely outweighs the benefits. For patients with ASCVD risk of 5–10%, shared decision making can help decide whether aspirin would be indicated.[12]

MICROVASCULAR COMPLICATIONS

Microvascular complications in diabetes include neuropathy, retinopathy, and nephropathy. Below is a review of each of these complications.

Neuropathy

In addition to vascular disease, patients with diabetes are also afflicted by neuropathies. The two most common neuropathies include distal symmetric polyneuropathy (DSPN) and CV autonomic neuropathy (CAN), affecting 19% and >50% of Americans with diabetes, respectively.[15,16] Guidelines for prevention of all neuropathies include optimising blood glucose levels as early as possible to prevent or slow the development of both DSPN and CAN.[17]

Distal symmetric polyneuropathy

DSPN is defined as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes."[17] This is thought to be caused by oxidative and inflammatory stress, which leads to damage of the nerve cells. It is recommended that all patients with T2D be screened annually for DSPN, and those patients with T1D should be screened annually 5 years after initial diagnosis. Screening is performed by taking a thorough history and examination. The history may indicate a feeling of pressure or feeling off-balance. Patients may also describe numbness and tingling, and occasionally pain. The physical exam should include assessment of either temperature or pin prick sensation, and vibration sense using a 128 Hz tuning fork. In addition to these assessments, patients should have a 10 g monofilament test to assess for the risk of ulceration. Patients should be educated on the risks of neuropathy and PAD and check their feet regularly. If patients do have DSPN, approved medications include pregabalin and duloxetine. However, other medications such as tricyclic antidepressants and some opioids can also be used.[17]

Cardiovascular autonomic neuropathy

CAN leads to symptoms of hypoglycaemia unawareness, orthostatic hypotension, gastroparesis, bowel changes including faecal incontinence, erectile dysfunction, and other autonomic dysregulations. While CAN is not prevalent in early diabetes, its prevalence increases with time, with 60% of patients with T2D having symptoms consistent with CAN after 15 years.[17] Furthermore, CAN is an independent risk factor for increased mortality.[18,19] The most common symptoms patients have are light-headedness, faintness, palpitations, or syncope. These questions should be asked in patients with microvascular and neuropathic complications. In this setting, other causes of those symptoms should be assessed, such as drug interactions.

Variability in heart rate when standing can be indicative of CAN. However, it is typically not identified until later, when symptoms of orthostasis and resting tachycardia present. As above, treatment is with glycaemic control. Symptoms of orthostasis can be treated with midodrine.[17]

Other neuropathies

Patients with neuropathy should also be screened for gastroparesis by asking about nausea, early satiety, or unexpected glycaemic variability. Both males and females with other forms of neuropathy should be checked for lower urinary tract symptoms such as incontinence and bladder dysfunction. Female sexual dysfunction, including decreased libido, dyspareunia, and inadequate lubrication, should also be screened. Lastly, patients should be screened for erectile dysfunction, including libido and ability to reach and maintain erection.[17]

Diabetic Retinopathy

Background

Diabetic retinopathy (DR) is one of the main causes of vision loss worldwide and is the main cause of blindness in working age adults in the USA. Over 25% of patients with diabetes will have some form of DR.[20] The majority of patients who develop DR have no symptoms until the extremely late stages, making screening

asymptomatic patients critical to preserving their vision. The primary risk factors for development and progression of DR are duration and intensity of glycaemic control.[21] Uncontrolled hypertension, hyperlipidaemia, and presence of other microvascular complications such as diabetic nephropathy and neuropathy also aid in the worsening of underlying DR.[22-24] Controlling these risk factors is important for the prevention of DR.

Screening

Patients with T1D should have their first ophthalmologic examination within 5 years of diagnosis, and those with T2D should have their first examination shortly after diagnosis. If there is no evidence of retinopathy during the screening examination, then ophthalmologic examination should be performed every 2 years. If there are any abnormalities, then the frequency of the exam will need to be yearly or more often, depending on findings.[25]

Prevention

In patients with diabetes, enhancing glycaemic control and treatment of systemic conditions like hypertension and hyperlipidaemia is essential to prevent vision loss. Because DR occurs exclusively in the setting of hyperglycaemia, good glycaemic control is the key to prevention. Multiple studies have proven that lowering glycated haemoglobin (A1C) reduces the rate and progression of DR.[26-28]

Blood pressure control

Blood pressure control decreases the incidence of DR and, in some trials, also slows the rate of progression of DR.[29] There are not enough data to recommend a specific antihypertensive agent based upon retinopathy endpoints.

Lipid-lowering therapy

The benefit of cholesterol-lowering therapy for the prevention of DR has not been well established. Most patients with T2D will require treatment with statins to control hyperlipidaemia and prevent ASCVD. Lowering triglyceride levels with fenofibrates may have a beneficial effect. As an example, in the ACCORD Eye Study, there was a reduction in progression of retinopathy in patients taking fenofibrate.[30]

Exercise

Regular exercise and increased physical activity may lead to a reduction in retinopathy.[31,32]

Diabetic Kidney Disease

CKD is common in patients with both T1D and T2D, occurring in 20–40% of patients with diabetes. Diabetic kidney disease (DKD) is defined by the presence of reduced glomerular filtration rate (GFR) and/or increased urinary albumin excretion for at least 3 months in a patient with diabetes. Globally, DKD is a major cause of CKD, and is the most common cause of end-stage kidney disease.[33] In the USA, 48% of patients with diabetes will have microalbuminuria and 8% will have overt macroalbuminuria.[34]

Background

DKD is a complex and heterogeneous disease, with many overlapping aetiologic pathways, leading to changes in glomerular haemodynamics, oxidative stress, inflammation, interstitial fibrosis, and tubular atrophy. These pathways include activation of the renin–angiotensin system as well as hyperglycaemia.[35] While hyperglycaemia undoubtedly plays a leading role, hyperinsulinemia and insulin resistance also may instigate pathogenic mechanisms, possibly explaining the variation in histopathology between T1D and T2D.

Screening

Screening for microalbuminuria (spot urinary albumin-to-creatinine ratio: >30 mg/g creatinine) should be performed annually in patients with T1D of more than 5 years, and in patients with T2D at the time of diagnosis.[36] If microalbuminuria is present, non-diabetic conditions causing albuminuria like urinary tract infections, haematuria, heart failure, febrile illnesses, severe hyperglycaemia, and vigorous exercises should be ruled out. Urine tests for albuminuria should be repeated within 3–6 months and treatment should be considered if two of three albuminuria tests are positive.[34]

Prevention and treatment

Lifestyle modifications like healthy eating, regular exercise, weight loss, and smoking cessation have been recommended to all patients with diabetes, with or without underlying DKD. In addition, because of the increased risk of CVD, patients should also be on statins.

Blood pressure control

Intensive blood pressure lowering has been recommended in patients with DKD as it reduces mortality, prevents CV morbidity, and it may

prevent end-stage kidney disease with severely increased albuminuria (urine albumin excretion: ≥300 mg/day).[37] Initial antihypertensive therapy in patients with DKD usually consists of ACE inhibitors or ARBs, but not both concurrently.[36] It is important to not discontinue use of ACE or ARB if the rise in serum creatinine is less than 30% upon initiation. In patients who will need combination antihypertensive therapy, a calcium channel blocker may be preferred rather than a thiazide diuretic.[38]

Glycaemic control

Intensive blood glucose control has been known to prevent the development of DKD.[39-41] The glycaemic control target in patients with diabetes and DKD is ideally an A1C of 7% or less. The approach to target an A1C of 7% is clear for T1D, but less so in patients with T2D.[36] Glycaemic goal should be tailored to achieve a balance of improvement in microvascular complications with the risk of hypoglycaemia.

Sodium–glucose cotransporter-2 inhibitors

Sodium–glucose cotransporter-2 inhibitors reduce the risk of kidney disease progression among patients with DKD who are already taking ACE inhibitors (or ARBs), as well as the incidence of CVD.[42] These drugs should be used with caution in patients with a history of lower extremity amputation, ulcers, or peripheral vascular disease who are at risk of future amputation, or in patients with GFR <30 mL/min/1.73 m^2.

Monitoring

Patients with DKD should have blood pressure, volume status, GFR, potassium, and A1C evaluated every 3–6 months. In addition, it is important to assess the serum creatinine and potassium within 1–2 weeks of starting or intensifying renin–angiotensin system inhibitor. Patients with advanced CKD (estimated GFR: <30 mL/min/1.73 m^2), heavy albuminuria, rapid loss of kidney function, resistant hypertension, or evidence of an inflammatory kidney disease should be referred to a nephrologist.[35,36]

SUMMARY

Patients with diabetes are at increased risks of macrovascular, microvascular, and neuropathic complications. Based on the DCCT results, patients with T1D who managed to keep their blood glucose levels close to normal with intensive diabetes treatment as early as possible in their disease had fewer diabetes-related health problems after 6.5 years, compared with people who used the conventional treatment. This study also showed that people who used intensive treatment lowered their risk of diabetic eye disease by 76%, DKD by 50%, and diabetic neuropathy by 60%. Participants who used intensive treatment had an average A1C of 7%, while participants who used the conventional treatment had an average A1C of 9%.

Prevention is the most effective way to reduce morbidity and mortality, but screening for these in asymptomatic patients can lead to earlier detection and treatment (Table 2). These guidelines will likely continue to evolve as additional research and studies reveal more effective ways of screening. There are no good

Table 2: Summary of prevention, screening, and management.

Condition	Prevention	Screening	Management
Macrovascular			
CHD and stroke	Manage risk factors such as blood pressure, using statins if ASCVD is <10% and aspirin for ASCVD <10%; glycaemic control	No screening in asymptomatic patients	Manage risk factors and treat underlying vascular disease with goal-directed medical therapy or intervention, if appropriate
PAD	Manage risk factors (as above)	Screen by history and physical examination. All patients >50 years old should have ABIs every 5 years	Manage risk factors (as above) and consultations with vascular surgeon

Table 2 (continued)

Neuropathy			
CAN	Aggressive glycaemic control	Screen for symptoms related to CAN, gastroparesis, erectile dysfunction, and female sexual dysfunction by history	Use of midodrine can improve symptoms of autonomic dysfunction
DSPN	Aggressive glycaemic control	Patients should have an annual foot exam, including monofilament, vibration, and reflex tests	If present, can be treated with gabapentin or duloxetine. Another option is tricyclic antidepressants
Microvascular			
Retinopathy	Aggressive glycaemic control and BP management (BP: <140/90 mmHg)	Patients should have an ophthalmologic exam annually	Regular testing to look for progression
Nephropathy	Aggressive glycaemic control, BP control, and lifestyle measures	Patients should have annual assessments of GFR, creatinine, potassium, and spot urinary albumin-to-creatinine ratio	Use of ACE or ARB for persistent microalbuminuria and the addition of a calcium channel blocker for additional BP management

ABI: Ankle Brachial Index; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blockers; ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; CAN: cardiovascular autonomic neuropathy; CHD: coronary heart disease; DSPN: distal symmetric polyneuropathy; GFR: glomerular filtration rate.

screening tests for macrovascular complications of stroke and CHD, and clinicians look at other markers through blood pressure and lipids. While screening for microvascular disease in the form of DR and nephropathy are fairly effective, they have their limitations. Future studies looking into other tests for screening macrovascular complications, as well as more sensitive biomarkers for microvascular complications such as nephropathy, will be advantageous to preventing morbidity in the future.

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An Unexpected Post-ocrelizumab Improvement in Glycaemic Control in a Patient with Multiple Sclerosis

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Abstract

Ocrelizumab, a novel member of disease-modifying therapies for multiple sclerosis (MS), is a humanised monoclonal antibody against the CD20 molecule on the surface of B cells. Reports on possible effects of this molecule in MS therapy have attracted a lot attention since its approval in 2017.

The authors present a 31-year-old female patient who was diagnosed with MS in 2008, with a concomitant disease of Type 1 diabetes (T1D). The patient's MS treatment included interferon-β1a and fingolimod prior to ocrelizumab initiation in 2019. In regard to the patient's T1D course, they had poor glycaemic control despite regular follow-ups and strict treatment plans. Subsequent to the commencement of ocrelizumab therapy, a significant improvement was observed in their glycaemic control.

The authors' case study aims to raise motivation for further investigation and studies to evaluate this unexpected potential impact of ocrelizumab on T1D control.

Key Points

1. The co-occurance of multiple sclerosis and Type 1 diabetes (T1D) is not uncommon. The former leads to demyelination and neurodegeneration of the central nervous system, while the latter causes the destruction of insulin-secreting β cells in the islets of Langerhans of the pancreas.

2. This case study of a 31-year-old female diagnosed with T1D and multiple sclerosis showed that the initiation of ocrelizumab was associated with a significant improvement in glycaemic control within 3 months.

3. As no other studies to date have analysed the mechanism and impact of ocrelizumab in glycaemic control, further studies are needed to further understand its effects on T1D.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system, causing a plethora of neurological manifestations and a leading cause of non-traumatic disability among young adults. According to MS International Federation data, global MS incidence in 2020 is 75 cases per 100,000.[1]

MS was initially considered a T lymphocyte-mediated disease. Hence, over the past couple of decades, B lymphocyte involvement has been implicated in MS pathophysiology.[2] Therefore, therapies leading to B lymphocyte depletion have been increasingly popular in the treatment of MS. Ocrelizumab is an intravenously administered humanised monoclonal antibody that targets the CD20 marker on B lymphocytes and is approved for the treatment of relapsing–remitting MS and primary progressive MS (PPMS).[2] The mechanism by which ocrelizumab works in MS is presumed to involve binding to CD20, a cell surface antigen present on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ocrelizumab results in antibody-dependent cellular cytolysis and complement-mediated lysis.[2]

Similar to MS, Type 1 diabetes (T1D) is an organ-specific autoimmune disorder with an inflammatory component, but with marked differences in pathogenesis and clinical manifestations. While MS is associated with demyelination and neurodegeneration of the central nervous system, T1D is responsible for the inflammatory autoimmune destruction of insulin-secreting β cells in islets of Langerhans of the pancreas, which ultimately results in the failure of insulin-mediated regulation of glucose levels. HbA1c can be used as a diagnostic test for T1D. Furthermore, HbA1c concentration is a reliable and commonly used tool for monitoring long-term glycaemic control as well as defining specific treatment targets.[3]

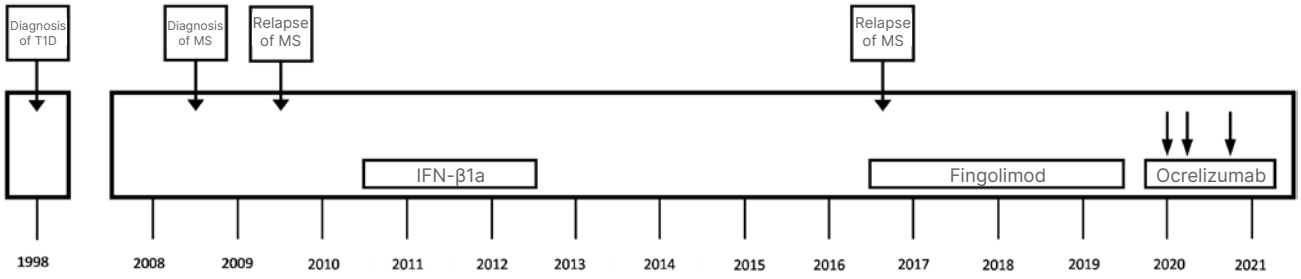
The authors performed a literature review in databases such as Wiley and PubMed, using the following keywords: "ocrelizumab," "multiple sclerosis," and "Type 1 diabetes." They found no reported data associated with T1D and ocrelizumab when searching for “ocrelizumab” and “Type 1 diabetes.” Herein, the authors present a patient with MS who was diagnosed with T1D at the age of 8, whose HbA1c levels decreased with the initiation of ocrelizumab.

CASE REPORT

A 31-year-old female, diagnosed with T1D at the age of 8, was diagnosed with MS in October 2008 based on clinical presentations and results of further examinations, according to the 2005 McDonald criteria. Even though their only presenting symptom was diplopia, they experienced other symptoms, including right extremity dominant muscle weakness of limbs, unsteady gait, and difficulty speaking during the course their disease. The patient started treatment with interferon-β1a for 2 years and, due to the lack of efficacy, treatment was switched to fingolimod in 2011. As a result of persistent radiological activity and clinical progression, the patient’s treatment was changed to ocrelizumab in 2019 (Figure 1). They had an Expanded Disability Status Scale (EDSS) score of 4.5. They received standard dosing with two 300 mg infusions separated by 2 weeks, followed by 600 mg every 6 months thereafter.

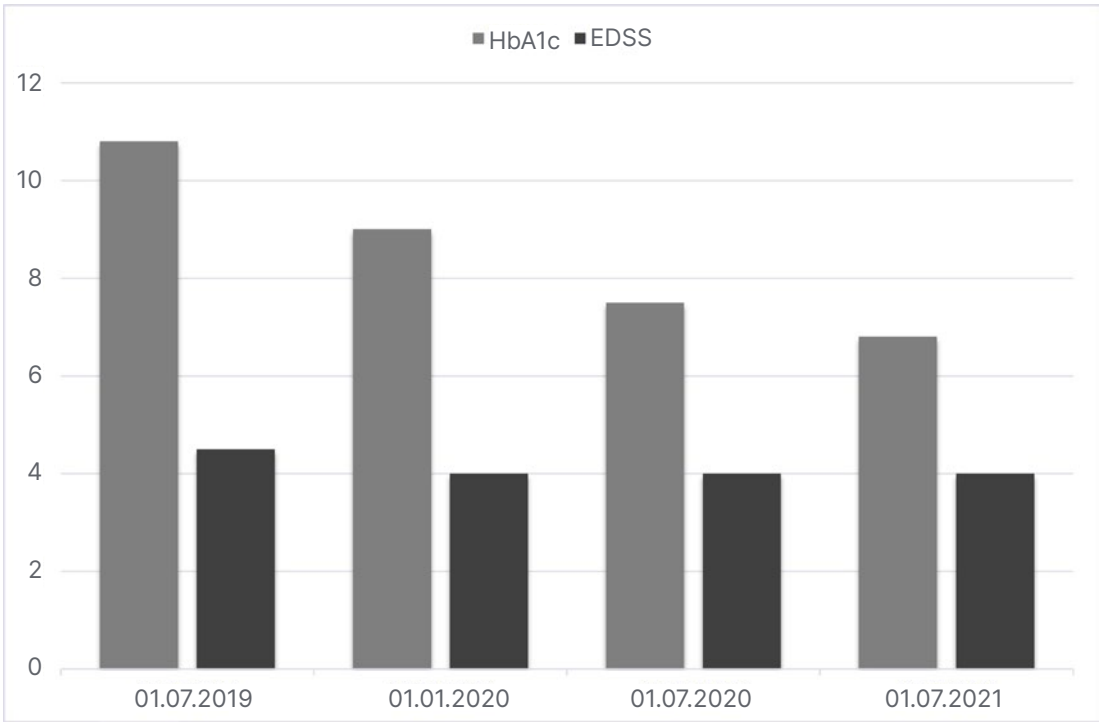
The patient’s T1D course, on the other hand, had shown a fluctuating pattern throughout the 21 years since their primary diagnosis. Prior to the ocrelizumab therapy, their T1D was being treated with 62 IU/day of insulin (neutral protamine Hagedorn insulin and insulin glargine) on four injection regimens. The patient had also followed their diabetic dietary regime and individualised exercise programmes. Despite the patient’s strict treatment plan, their HbA1c levels were high in comparison to the target levels. Figure 2 illustrates a brief catch-up on the patient’s HbA1c levels and EDSS scores prior and after their ocrelizumab therapy. Within 3 months of initiating ocrelizumab therapy, a significant decrease was observed in the patient’s HbA1c levels. Besides their ocrelizumab therapy, no other potential factors (changes in T1D treatment protocols and lifestyle) could have been responsible for this decrease. Accordingly, a gradual 70% reduction was applied to their insulin doses. They are currently on 18 IU/day of a combination of insulin degludec/insulin aspart and insulin aspart on three injection regimens. The patient is currently stable on the course of both T1D and MS.

Figure 1: Treatment history of a 31-year-old female with Type 1 diabetes who was diagnosed with multiple sclerosis in 2008.



IFN-β1a: interferon-β1a; MS: multiple sclerosis; T1D: Type 1 diabetes.

Figure 2: The HbA1c results of a 31-year-old female patient and their Expanded Disability State Scale score before and after treatment with ocrelizumab.



EDSS: Expanded Disability Status Scale.

DISCUSSION

The current data on the concurrence of MS and T1D has shown that the co-occurrence of the two diseases is not uncommon. Nielsen et al.[4] demonstrated a relative risk of 3.26 (95% confidence interval: 1.80–5.88) for MS in thousands of patients with T1D in the Danish population. In this report, the authors presented a 31-year-old female patient with MS and a history of T1DM, whose initiation of ocrelizumab was sheerly due to their MS progression and

independent of their T1D history. A noticeable improvement in the patient's glycaemic control was observed within 3 months after ocrelizumab initiation. Ruling out other possible factors, the authors speculate that ocrelizumab could be responsible for the patient's T1D course improvement.

Due to the important role of B cells in the pathogenesis of MS through antibody and cytokine production and antigen presentation, B cell depleting monoclonal antibodies against CD20 cell surface marker of B cells such as rituximab, ocrelizumab, and ofatumumab have revolutionised the treatment of MS.[5] The mechanism of action of ocrelizumab, the first anti-CD20 monoclonal antibody approved for relapsing MS and first ever pharmacotherapy approved for PPMS, is thought to involve immunomodulation through a reduction in the number and function of CD20 expressing B cells.[2]

The use of disease modifying therapies in patients with MS has remarkably changed the management of the disease and has shown promising results for reducing the disease associated morbidity. Regarding the recent European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)/ European Academy of Neurology (EAN) guidelines, ocrelizumab has shown a high quality of evidence for annual relapse rate reduction in patients with relapsing–remitting MS and for ≥24-week confirmed disability progression risk reduction in those with PPMS.[6]

The pathogenic destruction of insulin-secreting pancreatic β cells in T1D occurs via direct interaction with autoreactive T cells. The role of autoreactive T cells in T1D pathogenesis was defined long ago; therefore, autoreactive T cell targeting immunotherapy trials in T1D started to be conducted over 30 years ago.[7] On the other hand, the role of B cells in T1D has been evidenced by different studies more recently, among which is the success of rituximab. It is a B cell targeting anti-CD20 monoclonal antibody that is used in patients with various CD20-expressing lymphoid malignancies, which delays T1D progression in both non-obese diabetic mice and patients with new-onset disease.[8] In randomised controlled trials, several biological agents targeting T cells (cluster of differentiation 3 antibodies, lymphocyte function-associated antigen 3 antibodies, and anti-lymphocyte serum), B cells (rituximab), and T cell-associated co-stimulation pathways improved β cell functions in different magnitudes and durations.[9] To the authors' best knowledge, no study has yet been conducted to measure the effects of ocrelizumab on T1D.

In order to draw definite conclusions on this possible effect of ocrelizumab, clinicians managing patients with MS should be aware of the effects in glycaemic control while using this drug on patients with MS and T1D.

The authors report, to the best of their knowledge, the first case of a patient with concomitant MS and T1D whose glycaemic control was improved after the initiation of ocrelizumab for MS treatment. Further studies may be of interest to evaluate the mechanism and impact of ocrelizumab in glycaemic control.

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Tropical Diabetic Hand Syndrome: A Case Report and Literature Review

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Abstract

Tropical diabetic hand syndrome (THDS) is an acute complication that mainly affects patients with diabetes living in the tropics. The cause is usually unknown, but it is often preceded by minor trauma to the hand. Other risk factors for TDHS are poor glycaemic control, poorly treated wounds, malnutrition, and diabetic neuropathy. Early signs include swelling and ulceration of the hand. It can rapidly progress to sepsis and may further worsen, leading to deformity, disability, and amputation. If not treated promptly, death may occur. Unlike diabetic foot ulcer, TDHS often goes unreported. Here is a case of a 39-year-old female and a known patient with diabetes who presented to the outpatient department with swelling and tenderness of the left hand, along with foul-smelling purulent discharge. It began after the patient peeled off a patch of scaly, thickened skin over the distal part of their middle finger. Investigations showed high blood sugar and slightly increased leukocyte count. The patient was started on antihyperglycaemic medications and intravenous antibiotics. Urgent surgical debridement was done, which led to amputation of the middle finger. Thereafter, the patient showed significant improvement and was discharged with follow-up instructions. This case report emphasises the importance of timely intervention in cases of tropical diabetic hand syndrome, and the need for adequate patient education on this issue.

Key Points

1. Tropical diabetic hand syndrome, which manifests in swelling and ulceration of the hand and can lead to deformity, disability, amputation, and death, mainly affects patients with diabetes living in the tropics.

2. Treatment includes antihyperglycaemic medications, antibiotics, and surgical debridement.

3. Timely intervention and adequate patient education are imperative to treat this condition, and measures to increase awareness of the condition should be taken.

INTRODUCTION

Diabetes is a public health burden and a leading cause of morbidity and mortality globally.[1] Microvascular and macrovascular complications of diabetes include retinopathy, nephropathy, neuropathy, cardiovascular disease, and diabetic foot syndrome. Diabetes constitutes an important cause of ischaemic heart disease, stroke, end-stage renal disease, blindness, and nontraumatic limb amputations.[2] A less frequently reported complication, prevalent in the tropics, is tropical diabetic hand syndrome (TDHS). TDHS is characterised by variable hand symptoms ranging from a localised cellulitis, ulcer, or abscess, to a rapidly progressive gangrene and attendant overwhelming sepsis, which may result in permanent disability and fatality.[3,4] Poor glycaemic control, poor nutrition, peripheral neuropathy, and low socioeconomic status are major risk factors contributing to the development of TDHS, usually in the setting of a preceding minor hand trauma.[4,5] Management of TDHS involves broad-spectrum antibiotic therapy as well as surgical interventions, including incision and drainage of wounds, debridement, amputation, and rehabilitation of the affected limb.[4-6] Lack of awareness about this condition and poor health-seeking behaviours in the low-resource settings pose a challenge, and contribute to increased risks of morbidity and mortality. Hence, proper education of patients about this syndrome and its precipitating factors, early recognition and presentation, and prompt management of TDHS is of the utmost importance. Below is a more detailed outline of notable risk factors, proposed classification, and treatment options pertaining to TDHS.

Common identifiable risk factors include poor glycaemic control; low socioeconomic status and limited access to healthcare; hand trauma, including minor trauma; poor hand care; neglect or inadequately treated hand wounds; lack of patient education on the subject matter and the need to seek urgent care when need arises; lack of proper follow-up at office visits for regular evaluation; and peripheral neuropathy.

According to the proposed Lawal classification, Grade I TDHS is characterised by infections involving the skin, subcutaneous tissue, muscular layer, and metacarpal web spaces; Grade II TDHS involves infections extending to deeper tendons, bones, and joints without gangrene of the affected hand; and Grade III TDHS is associated with infections extending down to deeper structures with gangrenous elements noted.

The recommended treatment strategy includes adequate glycaemic control; early initiation of broad-spectrum antibiotics and subsequent adjustment based on culture and sensitivity results when necessary; and urgent surgical debridement with or without amputation (if need arises) and aggressive wound care.

It is pertinent to note that lack of patient education on the subject matter, late presentation for care, delay in initiation of broad-spectrum antibiotics (preferably intravenous antibiotics), poor glycaemic control, and inadequate wound care can significantly affect the patient's prognosis.[5-8]

CASE PRESENTATION

A 39-year-old African female presented to the medical outpatient department with complaints of progressive left hand swelling with continuous discharge of pus from the base of the index finger, which began 10 days prior to presentation. The patient had noticed scaly and thickened skin over the distal phalanges of the left middle finger, which was peeled off by the patient. The lesion became pustular, erythematous, and painful, with discharge of purulent fluid from the primary site. The swelling and erythema extended over the full length of the left middle finger and up to the distal forearm, with a blister noted over the dorsum of the patient's left hand. Prior to the hospital visit, the patient resorted to herbal treatment with the application of vegetable-based herbs. The patient also presented to a traditional practitioner who aspirated pus from the lesions using a syringe. Fever was noticed a day before the presentation. No history of numbness in the upper or lower extremities was reported. A 2-year history of Type 2 diabetes with poor compliance to oral antihyperglycaemic medications was stated at presentation. There was no history of hypertension or other medical comorbidities. No family history of diabetes was reported, and the patient had no previous history of smoking or alcohol use.

Physical examination revealed an acutely ill-looking patient, febrile (100.8 °F), with a BMI of 18.5 kg/m^2, not pale or dehydrated. Blood pressure at presentation was 130/70 mmHg. The left hand was swollen, warm, fluctuant, and tender. There were areas of ulceration over the dorsum of the hand, also involving the middle finger (Figure 1). Copious discharge of foul-smelling purulent fluid from multiple sites and surrounding tissue cellulitis were also noted. Sensations were preserved in both extremities. The radial and brachial pulses were palpated with normal intensity on both upper limbs.

Investigations carried out at admission included random blood glucose of 13.3 mmol/L, full blood count with haemoglobin of 12 g/dL, and a high normal leukocyte count of 11.9×10^9 cells/L. The patient was placed on intravenous antibiotics, analgesics, antioxidants, as well as oral antihyperglycaemic medications, including metformin and glimepiride at presentation. Intravenous ciprofloxacin, metronidazole, and ceftriaxone plus sulbactam were commenced empirically while awaiting the wound swab culture and sensitivity result. The wound swab culture and sensitivity yielded *Escherichia coli*, which was sensitive to ciprofloxacin, ofloxacin, gentamicin, and chloramphenicol. X-ray of the affected limb revealed no findings suggestive of bone involvement (Figure 2). The patient was counselled on the need for urgent surgical

Figure 1: Tropical diabetic hand syndrome at presentation.

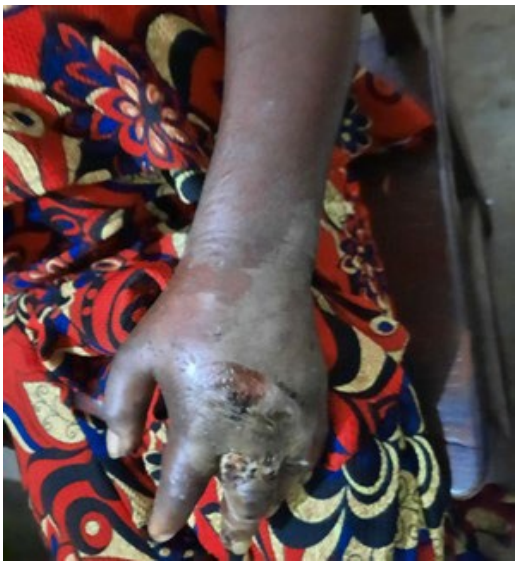


Figure 2: X-ray of the affected limb (left forearm and hand) with no bone involvement.

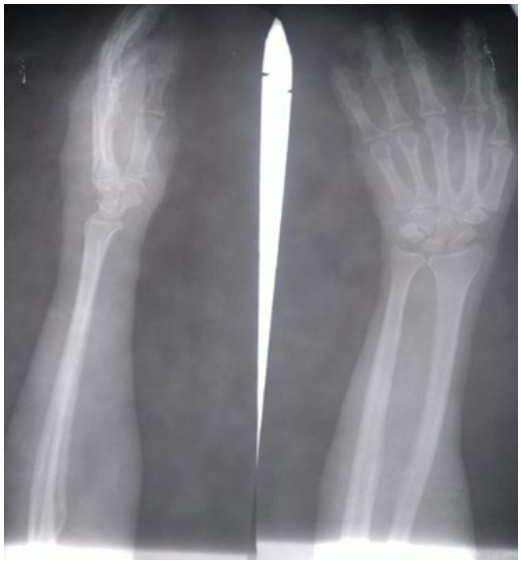
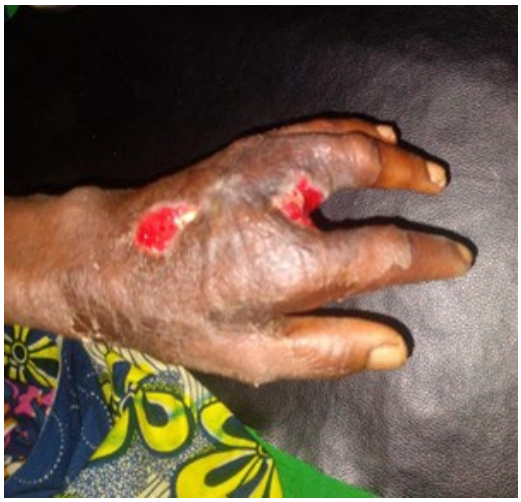


Figure 3: Wound condition 2 weeks after surgical intervention.



debridement. Surgical debridement was done on the sixth day of admission. Intraoperative findings revealed significant gangrene of the soft tissues of the left middle finger extending into deeper structures with copious purulent effluence. This prompted the amputation of the middle finger. Thereafter, daily wound dressing was done. Intravenous antibiotics were continued postoperatively with other medications including analgesics, oral vitamins, and antihyperglycaemic agents. Significant wound healing was noted postoperatively (Figure 3). Daily fasting blood sugar was done to monitor sugar control.

Subsequently, intravenous antibiotics were switched to oral cefixime and flagyl. The dosage of oral antihyperglycaemic agents was adjusted in order to achieve adequate sugar control. The patient was discharged 4 weeks after surgery and asked to return for alternate day wound dressing on an outpatient basis. The patient was strongly counselled on the need to adhere to prescribed medications and comply with follow-up visits.

DISCUSSION

TDHS is a rare but debilitating cause of morbidity, hospital admissions, and mortality amongst patients with diabetes, especially for patients in the tropics.[7,8] Compared with diabetic foot infection, TDHS seems to be less prevalent.[7-9] Some notable risk factors for TDHS include trauma, poor glycaemic control, and malnutrition.[7-9] Complications can range from sepsis, limb deformity, amputation, and death.[7-9] Therefore, the authors strongly feel that timing of presentation and intervention strongly affects the prognosis of patients with this condition. Some causes for delayed presentation include downplay of disease severity by patients; limited healthcare access; socioeconomic factors (in low- and middle-income countries); and improper health-seeking behaviours, such as initially resorting to traditional healers.[8,9] In some studies, improper health-seeking behaviour was found to correlate with low-income earners, poor education, rural dwelling, and lack of health insurance.[8-11] As in this case, the patient had initially attempted self-care by applying herbal mixtures to the wound, and subsequently visited a traditional healer who aspirated a purulent effluence from the wound site under questionable sanitary conditions. Likewise, due to the patient's poor financial state and lack of insurance coverage, certain pertinent investigations such as lipid profile, extremity doppler ultrasound, serum electrolyte, urea, and creatinine tests could not be carried out while the patient was admitted. Early diagnosis and immediate treatment of TDHS favours better outcomes, as shown in several reports.[8-11] It is important to carry out prompt surgical debridement when necessary to prevent promulgation of soft tissue infection and gangrene. Studies have shown that timely glycaemic control, antibiotic therapy, adequate wound care, and aggressive surgical intervention reduces morbidity and mortality associated with TDHS.[8-11] There is a need to create better awareness of the potential severity of TDHS for patients and health workers, as well as to make available a well-structured health insurance system with adequate health coverage for patients, especially in low- and middle-income countries, or for patients of low socioeconomic status. Such incentives would help to shorten the interval between appearance of symptoms and presentation to the hospital, which may ultimately improve medical outcomes for patients with these conditions.

CONCLUSION

From the in-depth analysis of this case and recently published reports, it is evident that prompt presentation for appropriate care, adequate sugar control, urgent medical and surgical intervention, as well as proper wound care is highly recommended for patients with TDHS. It is imperative that patients with diabetes should be counselled and duly educated by their healthcare providers on precautionary measures to take to prevent this condition. Patients with diabetes should also be encouraged to adhere to their medications and follow-up visits, as this may help to prevent and quickly identify such complications. As diabetes is a disease of public health significance, measures should be taken to increase awareness of TDHS among the general population, which would further aid early recognition and presentation to the hospital, and reduce overall morbidity and mortality. The authors encourage more research on this topic to add to the available body of data, to further broaden the knowledge on this condition, and positively influence management practices.

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Acute Worsening of Glycaemic Control in a Patient with Latent Autoimmune Diabetes of Adulthood After Receiving the COVID-19 Vaccine

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Abstract

Patients with diabetes who are infected with severe acute respiratory syndrome coronavirus 2 experience a worsening of glycaemic control and are at increased risk for severe outcomes. Little is known regarding the impact of COVID-19 vaccinations on glycaemic control. This case report explores a patient with diabetes who experienced an acute worsening of glucose control in the week following the second dose of the Pfizer-BioNTech COVID-19 vaccine.

Key Points

1. Patients with diabetes are at risk of experiencing a worsening of glycaemic control and severe outcomes if they are infected with severe acute respiratory syndrome coronavirus 2; however, little is known regarding the impact of COVID-19 vaccination.

2. This case report presents a 66-year-old male who experienced an acute worsening of glucose control in the week following the second dose of COVID-19 vaccine.

3. More research is needed to clarify the pathophysiologic mechanism of hyperglycaemia caused by the COVID-19 vaccine, as patients may require closer follow-up or self-monitoring following vaccination.

INTRODUCTION

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide since December 2019.[1] Though SARS-CoV-2 is spread primarily via respiratory droplets, the virus can produce a wide range of systemic signs and symptoms.[2-4] In addition to adverse effects on the lungs, kidneys, nervous system, and cardiovascular system, COVID-19 affects the endocrine system, including causing hyperglycaemia in patients with and without diabetes.[5] Several mechanisms have been proposed by which COVID-19 leads to hyperglycaemia. First, a large burden of inflammatory cells and markers such as IL-6, ferritin, D-dimer, erythrocyte sedimentation rate, and C-reactive protein affect the functions of skeletal muscle and the liver, the major insulin-responsive organs that are responsible for the bulk of insulin-mediated glucose uptake.[6-8] Furthermore, as shown by Yang et al.,[9] the SARS-CoV-2 virus can enter and destroy the islet cells of the pancreas via the angiotensin-converting enzyme 2 (ACE2) receptor, leading to decreased insulin production. Additional research by Hoffman et al.[10] proved that the SARS-CoV-2 virus also uses the same ACE2 receptor.

As of 16th January 2022, over 63 million people in the USA have been infected by the SARS-CoV-2 virus and over 838,000 have died because of the COVID-19 disease.[11,12] In December 2020, vaccines produced by Pfizer (Mainz, Germany) and Moderna (Cambridge, Massachusetts, USA) against SARS-CoV-2 received emergency use authorisation by the U.S. Food and Drug Administration (FDA) for the prevention of COVID-19.[13] According to data from the Phase III clinical trials that led to approval, the most common side effects of the vaccines include fever, fatigue, headache, chills, and injection site pain. Neither Phase III trial reported hyperglycaemia as an adverse event.[14,15] The Vaccine Adverse Events Recording System (VAERS), a collection of unconfirmed vaccine adverse events submitted by healthcare providers, manufacturers, and the public, reports 438 cases of hyperglycaemia following vaccines. According to VAERS, there have been 105 cases of reported hyperglycaemia following COVID-19 vaccination with any brand of vaccine, 58 of which occurred following the Pfizer-BioNTech vaccine and 46 after the Moderna vaccine.[16]

The authors conducted a literature search regarding the impact of vaccines, particularly for COVID-19, on glucose control in patients with diabetes. The only report in the literature regarding post-vaccine hyperglycaemia was a patient with well-controlled diabetes who experienced self-limited hyperglycaemia for 72 hours following the influenza vaccine.[17] There is no published literature regarding hyperglycaemia in latent autoimmune diabetes of adulthood or Type 1 diabetes following the COVID-19 vaccine. In this case, the authors describe a patient with diabetes who experienced worsened glycaemic control in the first 7 days after they received their second dose of the Pfizer-BioNTech COVID-19 vaccine in February 2021.

CASE DESCRIPTION

This case is a 66-year-old Indian-American male with latent autoimmune diabetes of adulthood in the setting of diabetic ketoacidosis. They have no history of macrovascular or microvascular complications of diabetes, and their most recent glycated haemoglobin tests were 6.3% (45 mmol/mol) on 9th November 2020, and 7.0% (53 mmol/mol) on 4th March 2021. Prior to receiving the Pfizer-BioNTech COVID-19 vaccine in February 2021, the patient was using insulin degludec 20 units at night; insulin aspart with an insulin to carbohydrate ratio of 1 unit: 8 g with breakfast and 1 unit: 10 g with lunch and dinner; insulin aspart with a correction of 1 unit for every 40 mg/dL over 140 mg/dL; and metformin 500 mg twice daily. These medications and doses had not changed in over 3 months. The patient monitors their glucose with a Dexcom (San Diego, California, USA) continuous glucose monitor.

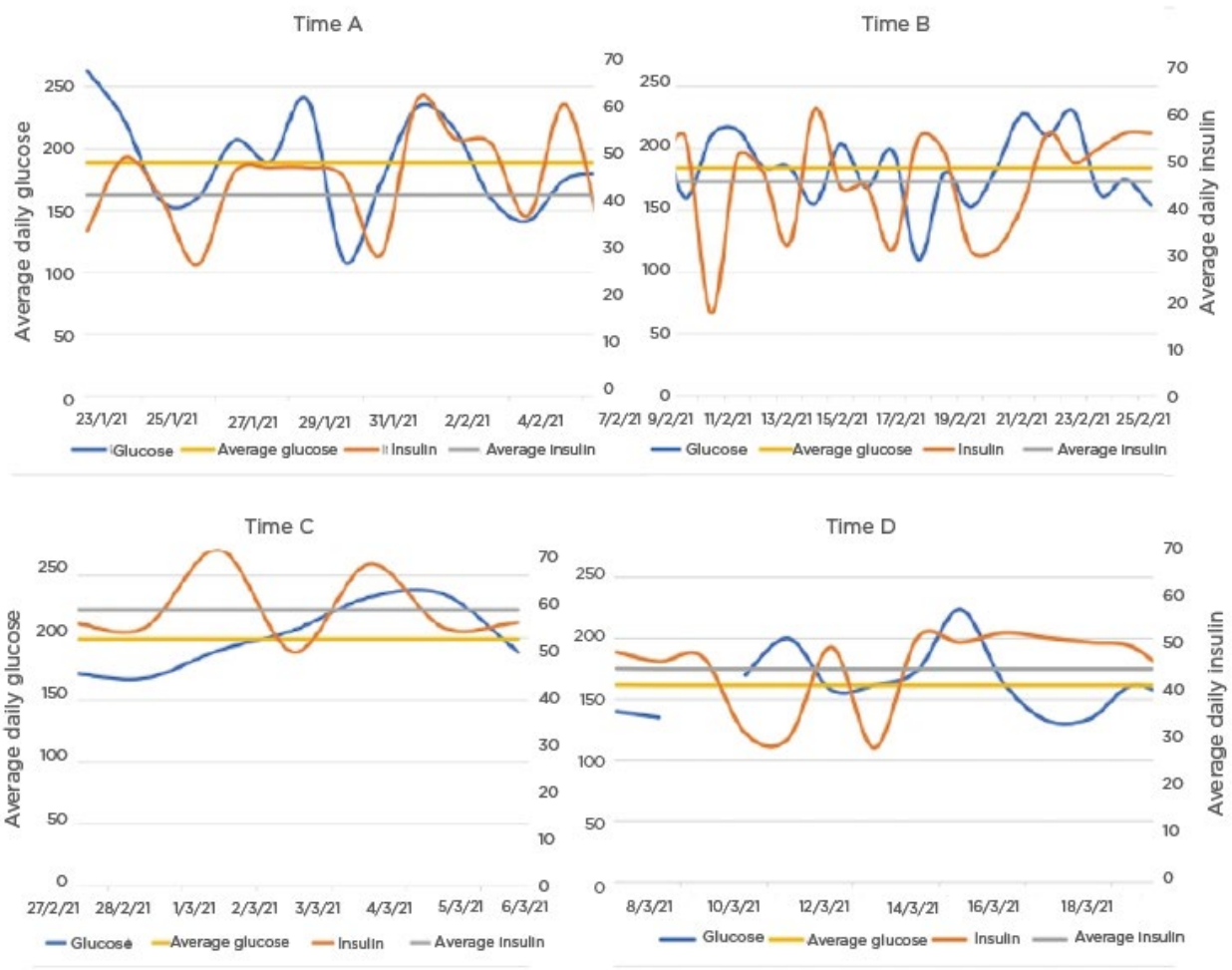
The patient received the first dose of the vaccine on 6th February 2021. In the two weeks leading up to this (23rd January–6th February: Time A), their average daily glucose was 188.7 mg/dL, and their average total insulin use was 44.1 units. They received the second dose of the vaccine on the 26th February. In the time

between the two doses (7th February–26th February: Time B), their average daily glucose was 184.3 mg/dL and their average total insulin use was 44.1 units. In the 7 days following the second dose (27th February–5th March: Time C), their average daily glucose increased to 198.8 mg/dL, despite an increase in the average total insulin use of 56.7 units. From 5th March–19th March (Time D), their average daily glucose decreased to 160.6 mg/dL and average total insulin use to 44.5 units (Figure 1). According to the patient's continuous glucose monitor, they were in target glucose range 49% of the time during Time A, 61% of the time during Time B, 50% of the time during Time C, and 70% of the time during Time D.

RESULTS

Student's T-tests were used to compare the patient's total daily insulin use among the four time periods (A–D). There was no difference in total daily insulin use between Time A and B (p=0.992). However, the authors found a significant difference Time B and C (p=0.004) and between Time C and D (p=0.005). The patient's average daily glucose was also analysed: there were no significant differences found between Time A and B and between Time B and C (p=0.737 and p=0.262, respectively), but there were significant differences between Time C and D (p=0.019). The patient's daily carbohydrate intake was also analysed, and there was only a significant increase found between Time C and D (p=0.006 [Table 1]).

Figure 1: The patient's average daily glucose levels and total daily insulin use across Times A, B, C, and D, as well as average glucose and average daily insulin during each time period.



DISCUSSION

The authors report a case of a patient with well-controlled latent autoimmune diabetes of adulthood that experienced an acute worsening of glucose control in the week following the second dose of the Pfizer-BioNTech COVID-19 vaccine. They analysed the average total daily insulin used by the patient and average glucose levels before receiving the first vaccine dose, in between the two vaccines doses, the week following the second vaccine dose, and after the second dose. The statistics show that glucose levels peaked in the week following the second dose of the vaccine compared to the time immediately before and immediately after receipt of the vaccine, despite a statistically significant increase in insulin use. Though the average daily glucose was statistically higher only when comparing the levels during the first week following the second dose (Time C) with the levels beyond that time (Time D), the levels immediately following the second dose showed a clear trend towards statistical significance when compared with earlier levels (Times A and B). However, during this time, the patient was using significantly increased levels of insulin to keep their glucose levels in a similar range. This further supports the use of average daily insulin as a surrogate for glucose control. There were no other changes reported by the patient that might explain the acute worsening of glycaemic control, including dietary changes, infection, stress, or medication use. The patient's daily carbohydrate intake during these time periods showed no significant changes. This helps eliminate any doubt that the increase in total daily insulin requirement following the vaccine was due to changes in dietary habits.

A possible cause of the patient's acute worsening of glycaemic control could be due to the fact that the Pfizer-BioNTech is an mRNA vaccine. Compared with DNA vaccines, mRNA vaccines work through inflammatory pathways such as toll-like receptors 3, 7, and 8, leading to greater systemic inflammation.[18] It is possible that the inflammatory effects of the vaccine impacted this patient's glucose regulation. Given that the patient has latent autoimmune diabetes of adulthood, the authors can presume that it is an increase in insulin resistance, rather than a decrease in beta cell function and insulin production, that caused the increase in insulin requirements.

A weakness of this study is that the carbohydrate intake described was inputted into the continuous glucose monitor and, therefore, self-reported by the patient. This leaves room for the possibility of error in reporting that could have an impact on the results. However, the patient has demonstrated extensive knowledge in the past about their disease; all meals are

Table 1: The total daily insulin use, carbohydrate intake, average daily glucose, and homeostatic model assessment of insulin resistance for the time periods of interest.

	Time A	Time B	p	Time B	Time C	p	Time C	Time D	p
Total daily insulin use (units)	44.13	44.10	0.992	44.10	56.70	0.004*	56.70	38.90	0.005*
Daily carbohydrate intake (g)	211.60	203.0	0.537	203.0	215.10	0.242	215.10	229.50	0.006*
Average daily glucose (mg/dL)	188.70	184.30	0.737	184.30	198.80	0.262	198.80	166.90	0.019*

Significant differences were found in total daily insulin usage between Time B and Time C, as well as when comparing Time C with Time D. Average daily glucose between Times C and D were also significant. There was also a significant increase in daily carbohydrate intake between Time C and D (p=<0.05*).

cooked and eaten at home; and they have a history of properly taking their medications and documenting their carbohydrate intake. Another weakness is that the authors cannot be completely certain that the patient's acute hyperglycaemia was due to the vaccine. The patient was in the hospital from the 4th January to 11th January 2021 for post-infection vertigo, following a left ear infection. It is possible, but very unlikely, that the stress from this hospitalisation had an impact on the patient's glucose control. Before their hospital stay, the patient was treated with levofloxacin, an antibiotic that has been shown to cause issues with glucose control.[19] However, this is less likely because statistically significant change in their glucose control occurred over 1 month after this hospitalisation and use of the medication.

While acute hyperglycaemia is known to occur following infection with the SARS-CoV-2 virus, it is not clear if this is due to pancreatic β-cell dysfunction or increased insulin resistance. The COVID-19 virus interacts with the ACE2 receptor, potentially causing pancreatic islet cell destruction, leading to decreased insulin release and hyperglycaemia. Given that the mRNA vaccines encode the SARS-CoV-2 full-length spike rather than an attenuated version of the virus, the authors would not expect that the mechanism hyperglycaemia following the Pfizer-BioNTech COVID-19 vaccine is the same for the virus and the mRNA vaccine.[9,10] However, there is no currently available literature about how and if the vaccine's SARS-CoV-2 full-length spike interacts with the ACE2 receptor. This case, as well as the unconfirmed cases reported by VAERS, illustrate that hyperglycaemia is an adverse event that can be seen following COVID-19 vaccination. This finding is important because hyperglycaemia can lead to the life-threatening complications of diabetic ketoacidosis and hyperosmolar hyperosmotic state in patients with diabetes. As a result of poorer clinical outcomes following infection with the SARS-CoV-2 virus, patients with diabetes are considered to be at a high-risk for severe disease.[20,21] Studies show that patients with new-onset or pre-existing diabetes who are infected with COVID-19 are more likely to be admitted to the intensive care unit and have increased disease severity and mortality, making primary prevention of infection in this population essential.[22,23] Subsequently, there is a greater push for this population to receive a COVID-19 vaccination.[20-23] In fact, as of 2nd April 2022, there were over 114 million people in the USA who were not yet completely vaccinated.[24,25] With an estimated 10.5% of the USA's population having diabetes, and 34.5% having pre-diabetes, this meant that there were 120.4 million Americans who may have been at risk of poor glycaemic control following COVID-19 vaccination.[26]

With the knowledge that hyperglycaemia can occur following the Pfizer-BioNTech COVID-19 vaccine, clinicians should have close follow-up with patients with diabetes and monitor glucose and insulin levels. Additionally, patients with diabetes and their physicians should be educated about this possible side effect. There must be awareness amongst this population so the proper steps can be taken if a patient experiences hyperglycaemia or a worse sequela following vaccination.

Ultimately, there is still much to learn about the relationship between worsening glucose control and the COVID-19 vaccine. Continued reporting of this side effect will help with this effort so the patient population can be better understood. Additional studies to elucidate the mechanism by which the Pfizer-BioNTech effects glucose metabolism will also be useful. Greater understanding of how this vaccine can induce worsening of hyperglycaemia may help us further understand how COVID-19 induces hyperglycaemia, why hyperglycaemia is associated with poorer outcomes from COVID-19, and how this and future mRNA vaccines can be used safely.

SUMMARY

While VAERS reports cases of hyperglycaemia following COVID-19 vaccination, this is among the first cases reported in scientific literature. Fortunately, the authors' patient closely monitors their glucose levels and adjusts their insulin appropriately. Other patients with diabetes who are not as attentive may have poor outcomes because of Pfizer-BioNTech COVID-19 vaccine-induced hyperglycaemia. Given the novelty of the COVID-19 virus and the mRNA vaccines, it is essential that these cases are reported to add to the growing body of literature. More research must be undertaken to

elucidate the pathophysiologic mechanism of hyperglycaemia caused by the Pfizer-BioNTech COVID-19 vaccine. Cases such as this will also show which patients may require closer follow-up or self-monitoring following vaccination. This also allows patients and physicians to better understand the risks and possible side effects of vaccination given specific comorbidities.

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