EMJ DIABETES

European Edition — Vol. 8.1 November 2020 emjreviews.com

+ EASD VIRTUAL MEETING 2020

Reviewed

+ INTERVIEWS

A rousing look into the education, career, goals, and roles at EASD 2020 of three inspiring females in field of diabetes: Chantal Mathieu, Beatriz Merino Antolín, and Rodica Pop-Busui.

+ ABSTRACT REVIEWS

Summaries authored by abstract presenters from EASD 2020.

+ EDITOR'S PICK

Continuing Challenges in The Medical Management of Gestational Diabetes Mellitus

Contents

"Focussing on precision medicine, guided nutrition, digital health, and the crossover between the speciality with cardiology, nephrology, and urology, the educational content of the congress was second to none, and can be found in our exclusive Congress Review."

Spencer Gore, CEO

Editorial Board

VIEW IN FULL ←

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This Publication

ISSN 2054-6181

EMJ Diabetes is published once a year. For subscription details please visit: www.emjreviews.com

Front cover and contents photograph: Vienna, Austria.

EMJ Diabetes 8.1

Welcome

Dear Readers,

An estimated 415 million people globally are living with diabetes, of whom 46% are thought to be undiagnosed. As this epidemic is projected to affect 642 million people by 2040, there is no time left to lose in fuelling research in this vital medical specialty. Herein, we present *EMJ Diabetes 8.1*, an eJournal dedicated to educating healthcare professionals on this prevalent condition, to aid the future of guidelines and treatment.

The year 2020 has seen increased pressure on diabetes healthcare networks, as healthcare providers fight a battle on two fronts: coronavirus disease (COVID-19) and continuing diabetes patient care. It has highlighted the importance of events such as the virtual 56th European Association for the Study of Diabetes (EASD) Annual Meeting, which saw >20,000 delegates attend over the 4-day event. Focussing on precision medicine, guided nutrition, digital health, and the crossover between the speciality with cardiology, nephrology, and urology, the educational content of the congress was second to none, and can be found in our comprehensive Congress Review.

COVID-19 was also given a great deal of attention in the scientific programme, and our review of the congress session 'Navigating Through the COVID-19 Pandemic: New Lessons on Diabetes and the Cardiovascular System' is a must read for the endocrinologists and cardiologists amongst you. Also included in this year's issue is our review of the Exercise and Physical Activity Study Group (ExPAS) Session, providing the latest recommendations for nutrition and exercise in Type 2 diabetes mellitus.

Of course, *EMJ Diabetes 8.1* is also host to other stimulating content, including our EASD congress interviews with three inspiring females in field of diabetes: Prof Chantal Mathieu, Ms Beatriz Merino Antolín, and Prof Rodica Pop-Busui. We have also included abstract summaries from EASD, covering topics such as intermittent fasting and diabetic kidney disease.

As always, a selection of peer-reviewed articles also make their debut in this issue, with topics ranging from the continuing challenges in the medical management of gestational diabetes mellitus, to the psychological aspects of diabetes.

I would like to thank all of our contributors to this issue, and I hope that you find value in the following pages.

Spencer Gore

Chief Executive Officer, EMG-Health

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Foreword

Dear Colleagues and Readers,

It is my pleasure to welcome you to *EMJ Diabetes 8.1*, which is dedicated to the 56th European Association for the Study of Diabetes (EASD) Virtual Meeting 2020. Although the coronavirus disease (COVID-19) pandemic led to the challenge of organising a virtual meeting, the organisers did a great job of using live-stream symposia, oral presentations, and poster sessions to present the latest news in diabetes.* They also organised a Virtual Plaza and Virtual Exhibitor Space to enable networking, which worked exceptionally well, and impressive scientific progress was reported. The availability of GLP-1 agonists and SGLT-2 inhibitors has led to a paradigm shift. These agents reduce hyperglycaemia as well as the risk of cardiovascular events, heart failure, and chronic kidney disease, only partly explained by the reduction of hyperglycaemia. Importantly, they do not increase risk of hypoglycaemia and encourage weight loss rather than weight gain. I was impressed by a number of contributions to the meeting: sessions on precision medicine in diabetes (we are not quite there yet!); whether or not we should screen for nonalcoholic liver disease, which we probably should, but it is a formidable task; the use of semaglutide as a weight loss enhancer, which looks very promising; and the use of continuous glucose monitoring, which is rapidly gaining ground not only in Type 1 but also in Type 2 diabetes mellitus.

This issue features a wide variety of topics discussed at the congress. I'd like to draw your attention in particular to contributions on diabetes and COVID-19, and on a review of the Exercise and Physical Activity Study (ExPAS) symposium.

I wish to thank my predecessor, Prof Jörg Huber, from whom I will be taking over as Editor-in-Chief. From 2015, he and his team have developed the journal to where it now stands. Thank you for all your hard work!

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

*Disclosure: Prof Stehouwer has been elected to the EASD Board for 2021.

Coen Stehouwer

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

Editor-in-Chief, *EMJ Diabetes*

Congress Review

Review of the European Association for the Study of Diabetes (EASD) Virtual Meeting 2020

Location: EASD Virtual Meeting

Date: 21st–25th September 2020

Citation: EMJ Diabet. 2020;8[1]:10-22. Congress Review.

VIENNA, Austria's cultural, economic, and political centre is rich in architectural ensembles, including Baroque palaces and gardens, casting a spell on all its visitors with its majestic charm. More famous composers have lived here than in any other city in the world, including the likes of Wolfgang Amadeus Mozart, Ludwig van Beethoven, Joseph Haydn, Franz Schubert, and Johann Straus, earning the city the prestigious title of the 'World's Capital of Music'. Vienna is also known as the 'City of Dreams', serving as the home to the world's first psychoanalyst, Sigmund Freud. Accommodating over 1,000 research facilities and 35% of Austria's research and development expenses, the city is a major hotpot for science and research. Annually, over 2,000 large-scale meetings and events are hosted here, and between 2005 and 2013 Vienna was the world's primary destination for international congresses and conventions. It should come as no surprise that the European Association for the Study of Diabetes (EASD) chose Vienna as the host city for their 56th annual meeting.

Like many recent congresses, the physical meeting was cancelled and replaced virtually as a result of the coronavirus disease (COVID-19) pandemic. The EASD Virtual Meeting 2020 prevailed over other congresses by providing a truly three-dimensional virtual reality experience, demonstrated by Prof Stefano Del Prato, EASD President, in the Opening Ceremony. The platform provided each attendee with an avatar, capable of moving throughout the entire venue to chat, exchange information, and attend sessions and incorporated 35 symposia, 264 oral presentations, 712 poster sessions, 114 invited speakers, and 190 chairs. "It is really a new opportunity. I understand it is not like meeting people in person, but we did as much as possible to encourage you to have a real meeting," Prof Del Prato conveyed.

After the initial COVID-19 outbreak, the disease spread throughout the globe,

undermining the health of millions of people, including patients with chronic conditions such as diabetes; it is estimated that 10% of the patients with COVID-19 have diabetes. Prof Del Prato exclaimed: "It has been a tough and terrible fight, one requiring long hours, days, and weeks of generous dedication until exhaustion, but a fight that has allowed us to reduce and limit the number of our losses. To all of you, to all who have been assisting the patients with or without diabetes at the time of COVID-19, we would like to say a big thank you." The ceremony continued with a special 1 minute of silence to commemorate the victims of the COVID-19 pandemic and individuals of the EASD community, including Profs John Fuller, Angelo Gnudi, Arnold Gries, Robert Henry, Lelio Orci, and Roger Unger.

"To all of you, to all who have been assisting the patients with or without diabetes at the time of COVID-19, we would like to say a big thank you."

"Knowledge is key. The scientific method is the tool and generating and fostering research in science in diabetes is at the core of EASD," Prof Del Prato noted while explaining the aims of the EASD and presenting the award winners of this year. The scientific content presented at the EASD Virtual Meeting 2020 was tremendous, and so were the awards bestowed to recognise excellence in research and science in the field of diabetes and related disorders. Awards were presented to the winners of the 55th Minkoswki Lecture, 52nd Claude Bernard Lecture, 35th Camillo Golgi Lecture, and the 14th Albert Renold Lecture, to Prof Gian Paolo Fadini, Prof Takashi Kadowaki, Prof Naveed Scattar, and Prof Guy A. Rutter, respectively. The winner of the 6th EASD/Novo Nordisk Foundation Diabetes Prize for Excellence Lecture was Prof Jens C. Brüning and the winners of the EFSD/Novo Nordisk Rising Star Fellowship programme and Symposium were Ms Beatriz Merino Antolín, Dr Pierre Larraufie, Dr Lucille Dollet, and Dr Alexandra Smink. Lastly, for the first time presented at EASD, the Morgagni Prize was bestowed to Drs Olga Ramich and Giuseppe Daniele.

Concluding the opening ceremony, Prof Del Prato stated: "This is a virtual meeting, but a meeting to be remembered in the years to come because together we want EASD to continue representing **E**xcellence in science, to provide an **A**dvanced virtual experience, to be **S**uperior to any other virtual meeting, and remain **D**edicated to reach a worldwide audience." Next year, EASD will celebrate the 100-year anniversary of the discovery of insulin, a landmark achievement for humankind and the beginning of modern diabetology, which brought hope to many patients with diabetes. As the EASD looks forward to welcoming you to next year's congress in Stockholm, Sweden, Prof Del Prato proudly concluded: "EASD will continue working to provide hope and to provide solutions."

EASD 2020 REVIEWED →

What is the Difference in Life Expectancy with Diabetes?

IMPACT on lifespan of Type 1 and Type 2 diabetes mellitus (T1DM, T2DM) has been assessed in large-scale modelling studies. The shortened life expectancy in both groups was revealed in a study presented at the EASD Virtual Meeting 2020 and in a press release dated 21st September 2020.

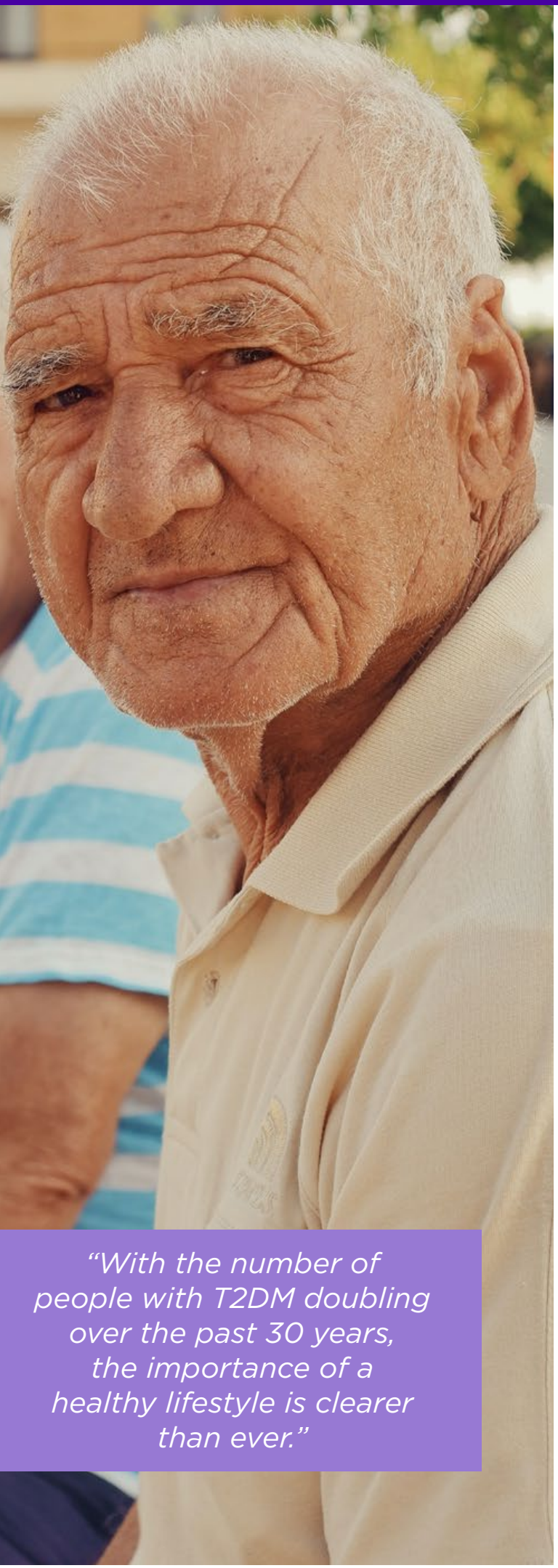
The study utilised data from the UK National Diabetes Audit (NDA) and the Office for National Statistics (ONS) to calculate future life expectancy for T1DM, T2DM, and nondiabetic populations, for subgroups of age and sex. 'Lost life years' (LLY) were calculated as the difference between total life expectancy with and without diabetes. Data from 41.3 million individuals (217,000 with T1DM, 2.5 million with T2DM) from 6,165 general practices were used in the modelling analysis.

Analysis compared an 'average' person with T1DM (age 42.8 years) to an equivalent without T1DM; the person with T1DM had a life expectancy of 32.6 years (living to 75.4 years), compared with a life expectancy of 40.2 years (living to 83 years) without T1DM. The mean LLY with T1DM were 7.6 years. In a similar comparison, the average person with T2DM (age 65.4 years) life expectancy (18.6 years; living to 84.0 years) was also less than those without T2DM (life expectancy: 20.3 years, living to 85.7 years), a mean LLY of 1.7 years.

LLY were 21% greater for females with T1DM and 45% greater for females with T2DM, compared with males in each group. For both T1DM and T2DM, life expectancy may be shortened by 100 days for each year that an individual spends with their HBA1c >58 mmol/mol. The authors of the study highlighted: "Knowledge of this may act as an incentive for clinicians to ensure that all people are on the best therapy to keep their blood sugar in the target range, and for those people to engage more strongly with their therapy and lifestyle recommendations."

Other factors likely contribute to the difference in life expectancy, including smoking, physical activity, weight, hypertension, and use of statin therapy. However, the authors believe that HbA1c will remain a strong independent determinant of mortality in their planned follow-up study using general practice-level data.

"Knowledge of this may act as an incentive for clinicians to ensure that all people are on the best therapy to keep their blood sugar in the target range..."



"With the number of people with T2DM doubling over the past 30 years, the importance of a healthy lifestyle is clearer than ever."

Type 2 Diabetes Mellitus Linked to Vascular Dementia, But Not Alzheimer's Disease

OVER 37,000 adults with Type 2 diabetes mellitus (T2DM) have been involved in an observational study that compared their risk of various dementia types with that of nearly 2 million matched controls. The results of this study were presented at the EASD Virtual Meeting 2020 and reported in a press release dated 21st September 2020.

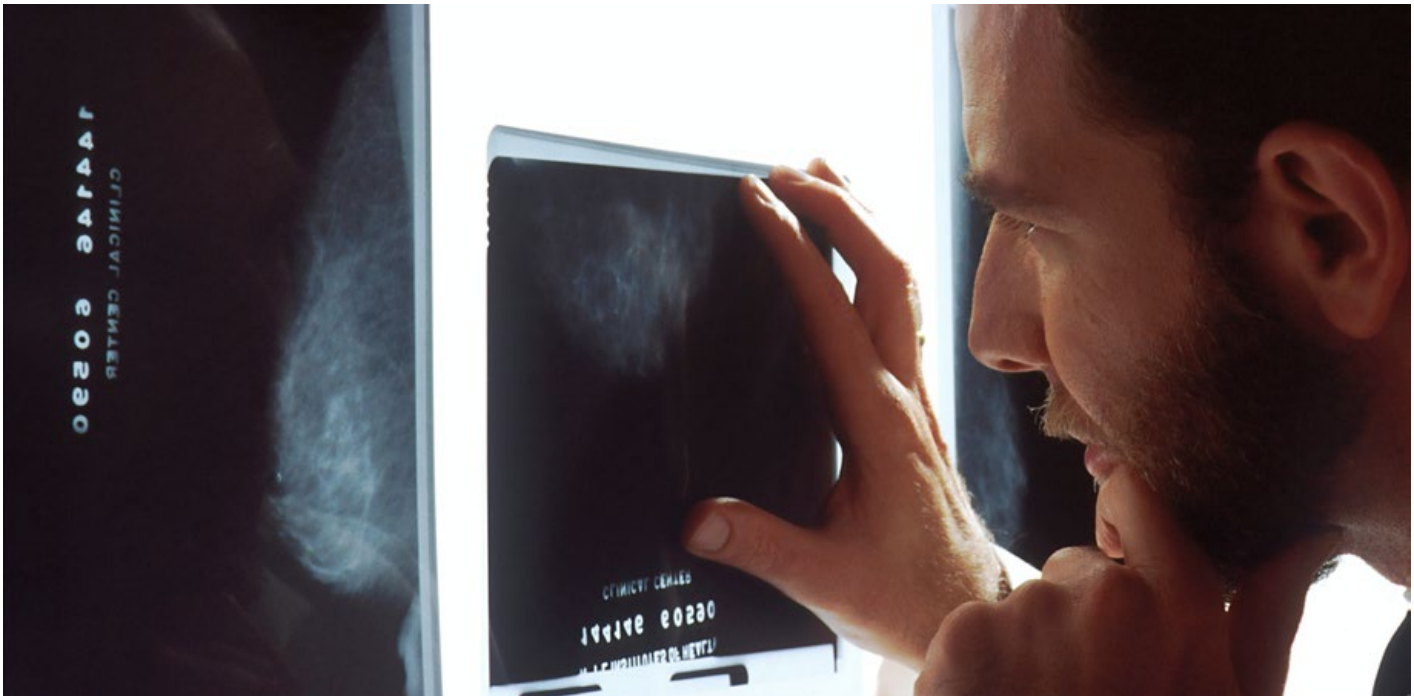
Dementia has long been linked to poor blood sugar control, but results of the observational study, led by researchers from the University of Glasgow, Glasgow, UK, and the University of Gothenburg, Gothenburg, Sweden, have conveyed that individuals with T2DM were 36% more likely to develop vascular dementia and 9% more likely to develop nonvascular dementia, though no more likely to develop Alzheimer's disease, than their matched counterparts.

Prof Naveed Sattar, coleader of the study and from the University of Glasgow, commented on the findings: "A 36% higher risk is in itself an argument for preventive measures such as healthier lifestyle. The importance of prevention is underscored by the fact that, for the majority of dementia diseases, there is no good treatment."

Though the findings do not suggest that most patients with T2DM will go onto develop vascular dementia, they do suggest that a healthy lifestyle, absent of obesity, smoking, and lack of physical activity, can reduce the risk of developing vascular or nonvascular dementia.

Coauthor Dr Carlos Celis, University of Glasgow, summarised the importance of the results: "With the number of people with T2DM doubling over the past 30 years, the importance of a healthy lifestyle is clearer than ever."

The authors did point out that although their study was large, it was observational, and therefore no conclusions can be drawn about direct cause and effect.



Residual Nonfunctioning β Cells in Patients with Longstanding Type 1 Diabetes Mellitus

RESTORING insulin-producing cells that are lost in Type 1 diabetes mellitus (T1DM) is now one step closer, as researchers have developed a noninvasive imaging technique to detect residual, nonfunctioning β cells in patients with longstanding T1DM. This breakthrough in β-cell regeneration research was presented at the EASD Virtual Meeting 2020 and reported in a press release dated 21st September 2020.

Scientists have struggled up until now to provide evidence for the existence of small numbers of nonfunctioning residual β cells, as it was widely believed that within years after T1DM diagnosis a complete destruction of the insulin-producing cells would occur. Now, single photon emission CT (SPECT) medical imaging, which has been used on a cohort of 10 adults aged 21–54 years with T1DM, has been able to confirm that most individuals with T1DM maintain a low level of residual β cells for years after diagnosis.

"The presence of a residual pool of dysfunctional β cells has important implications for treatment of Type 1 diabetes mellitus, since these cells could help people maintain some ability to make their own insulin."

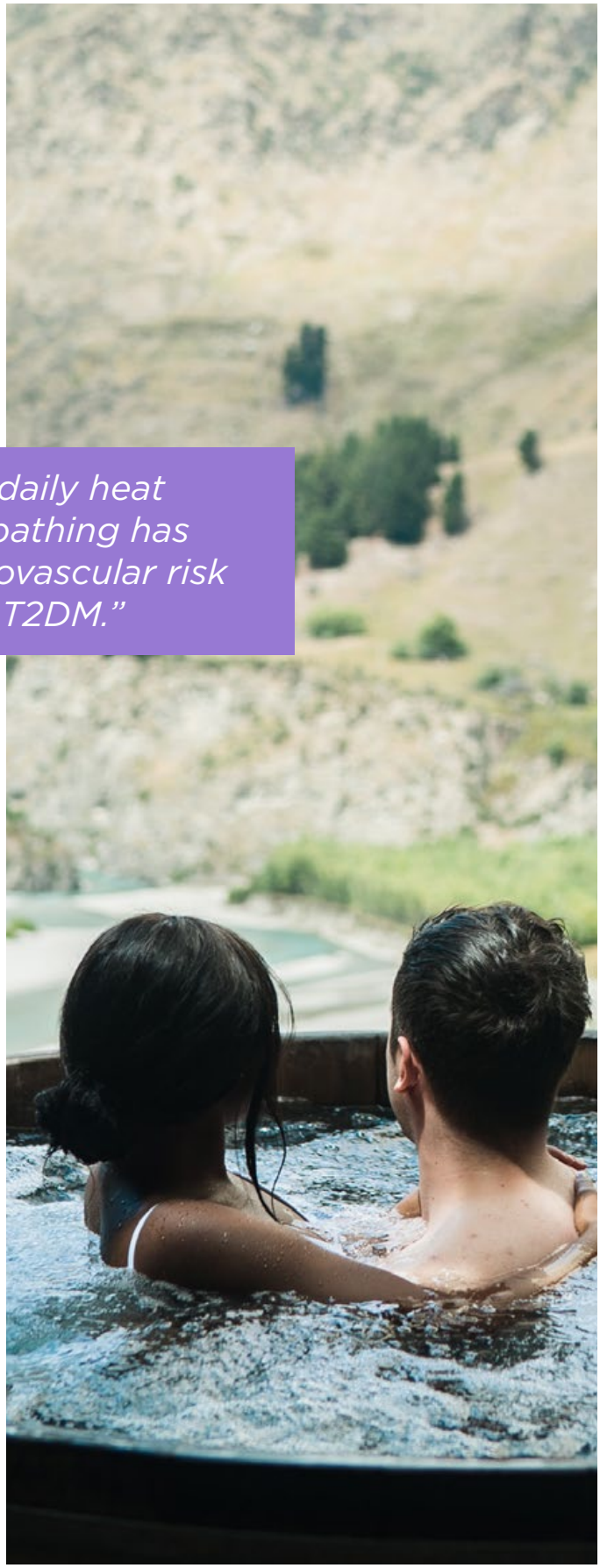
Using ^{111}In-exendin to measure pancreatic tracer uptake, six out of 10 patients were shown to have measurable pancreatic uptake after an average of 11 years post-T1DM diagnosis. Additionally, five out of the 10 displayed uptake similar to the lower levels observed in healthy controls; the indication is therefore that, despite years of T1DM, these β cells could have their function restored, if the right treatments become available.

Prof Martin Gotthardt, Radboud University Medical Center, Nijmegen, the Netherlands, who co-led the study, concluded the findings: "The presence of a residual pool of dysfunctional β cells has important implications for treatment of Type 1 diabetes mellitus, since these cells could help people maintain some ability to make their own insulin." He did, however, issue some caution: "These results are hugely encouraging, but we need to do more studies."

Hot Baths as A Therapeutic Tool for Type 2 Diabetes Mellitus

HOT baths have been associated with beneficial effects on Type 2 diabetes mellitus (T2DM) on account of regular heat exposure. This new research was presented at the EASD Virtual Meeting 2020 on 21st September.

Heat therapy, in the form of saunas and hot-tub bathing, has been proven to positively impact glycaemic control and body fat percentage. There are, however, no large studies that have examined this form of heat therapy and the effects on metabolic parameters of patients with T2DM in a real-world setting to date.



"Our results indicate that daily heat exposure through hot-tub bathing has beneficial influences on cardiovascular risk factors in patients with T2DM."

In this study led by Dr Hisayuki Katsuyama, Kohnodai Hospital, Ichikawa, Chiba, Japan, researchers investigated the effect of bathing in Japanese patients with T2DM, since bathing in a bath or hot tub is common practice in Japanese households. Dr Katsuyama and colleagues executed a questionnaire with 1,297 patients with T2DM between October 2018 and March 2019 and investigated the frequency of bathing with anthropometric measurements and blood test results.

The results from the study showed that increased bathing frequency was associated with decreased body weight, BMI, waist circumference, diastolic blood pressure, and HbA1c. After adjusting for age, sex, BMI, and drug therapy, analysis also showed that the patients who had the highest frequency of bathing had reduced HbA1c and diastolic blood pressure.

The authors commented on the positive results of their study: "Our results indicate that daily heat exposure through hot-tub bathing has beneficial influences on cardiovascular risk factors in patients with T2DM."

Restoration of Pancreas Size in Landmark Diabetes Remission Clinical Trial (DiRECT)

SHRUNKEN and small pancreas could result from Type 2 diabetes mellitus (T2DM), rather than lead to it, and reversal of T2DM can restore the pancreas to a normal size and shape. Smaller sized and abnormally shaped pancreases in people with T2DM have been evidenced but whether they are a consequence or cause of the metabolic disease was unknown until now. New research in this field from a team at Newcastle University, Newcastle, UK, was presented at the EASD Virtual Meeting 2020 on 21st September.

Increased postprandial insulin levels cause tissues to grow or at least maintain size. Imaging studies and past research have shown that achieving remission of T2DM through intensive weight loss regimes can restore the insulin-producing capacity of the pancreas to levels similar to those in people who have never been diagnosed with the disease. "This new study suggests that achieving remission of T2DM restores this healthy, direct effect of insulin on the pancreas," commented Prof Roy Taylor, lead researcher.

Over the course of 2 years, 64 participants from the landmark Diabetes Remission Clinical Trial (DiRECT), and 64 age-, sex-, and weight-matched controls without T2DM, were measured for β cell function, pancreas volume and fat levels, and irregularity of pancreas borders using MRI. Individuals in remission, or responders, were those classified as achieving an HbA1c level <6.5%, fasting blood glucose <7.0 mmol/L, and taking no medications.

At the beginning of the investigation, average pancreas volume was smaller, and the pancreas borders were more irregular in individuals with diabetes compared to the matched control group. Over a period of 5 months of weight loss, pancreas volume was unchanged in both groups. After 2 years, the pancreas had grown on average by one-fifth in size in responders compared with one-twelfth increase in size in those who were not in remission. Responders lost a significant amount of fat from their pancreas compared with nonresponders over the 2 years and achieved normal pancreas borders. They alone also showed early and sustained improvement in β cell function. After 5 months of weight loss, the amount of insulin being made by responders increased and was maintained at 2 years, but there was no change in nonresponders. Limitations of the study included the short follow-up time of 2 years and retrospective observations.

Prof Taylor commented on possiblities created with this new discovery: "Our findings provide proof of the link between the main tissue of the pancreas which makes digestive juices and the much smaller tissue which makes insulin, and open up possibilities of being able to predict future onset of T2DM by scanning the pancreas."

Exercise Capacity and All-Cause Mortality Risk in People with Diabetes

EXERCISE capacity may be positively correlated with a decreased all-cause mortality risk, according to results from a study presented at the EASD 2020 Virtual Meeting on 21st September.

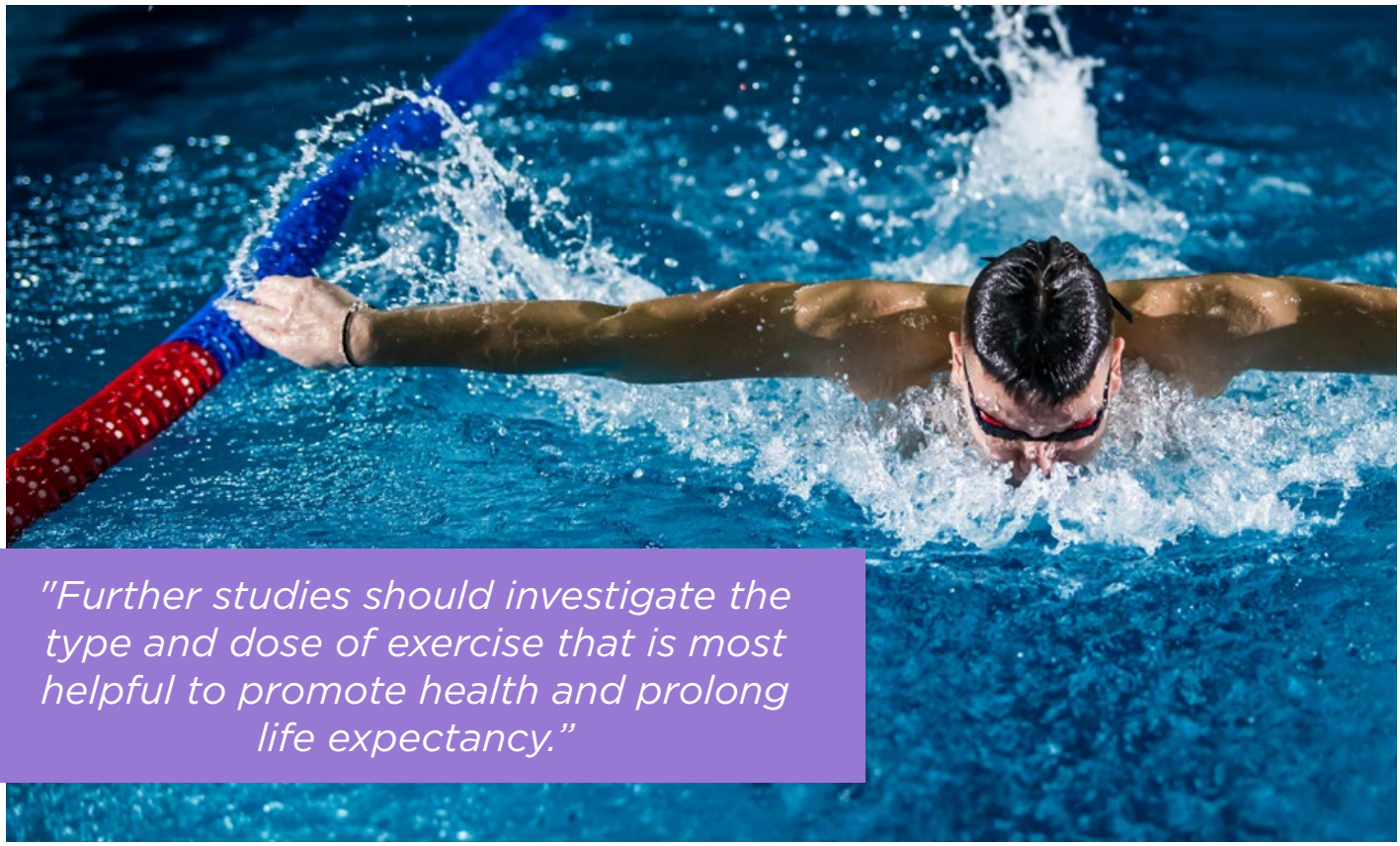
Physical activity has been shown to inhibit inflammatory cytokines, increased chronic production of which can largely contribute to inflammatory diseases such as diabetes. Thus far, investigations into the effect of exercise on all-cause mortality in people with Type 2 diabetes mellitus had not been fully explored. The new study by Dr Yun-Ju Lai and colleagues, at Puli Branch, Taichung Veterans General Hospital, Nantou, Taiwan, used data from the National Health Interview Survey (NHIS) and the National Health Insurance Research Database (NHIRD) in Taiwan to explore the link between higher levels of exercise and all-cause mortality risk.

Surveys performed between 2001 and 2013 used information about the characteristics of each participant, including their socioeconomic status, health behaviours, and exercise habits, and health status was followed-up until 31st December 2016.

A statistical analysis to evaluate the relationship between exercise capacity and all-cause mortality was also carried out.

The study enrolled, and obtained survey results for, 4,859 adult patients with Type 2 diabetes mellitus and a mean age of 59.5 years. Those with a higher exercise capacity were found to have a significantly lower risk of all-cause mortality compared with those who reported no physical activity or exercise. Participants who performed a moderate amount of exercise had a 25% lower all-cause mortality rate and individuals who were classed as having a high exercise level had a 32% lower all-cause mortality risk.

The team of researchers concluded: "Among people with Type 2 diabetes [mellitus], those with increased exercise capacity had a significantly decreased risk of all-cause mortality. Further studies should investigate the type and dose of exercise that is most helpful to promote health and prolong life expectancy."

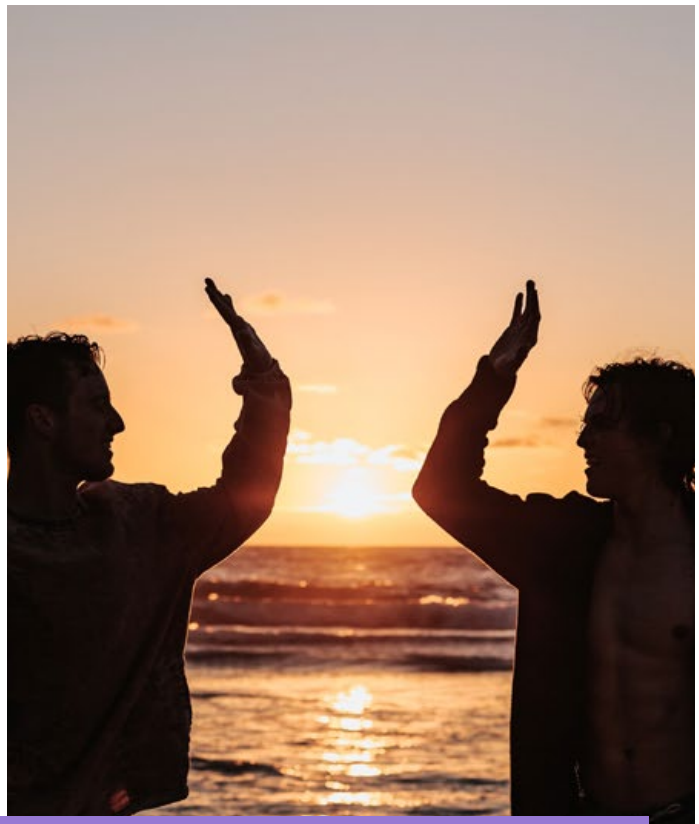


"Further studies should investigate the type and dose of exercise that is most helpful to promote health and prolong life expectancy."

Should Individuals with Rheumatoid Arthritis Be Screened for Diabetes Risk Factors?

RESEARCH from a new study presented at the EASD Virtual Meeting 2020 on Monday 21st September revealed that rheumatoid arthritis is linked with a 23% increased risk of Type 2 diabetes mellitus (T2DM), and may indicate that both conditions are associated with the body's inflammatory response. Inflammation is considered a key factor in disease progression of T2DM and it has been established that rheumatoid arthritis is an autoimmune and inflammatory disease.

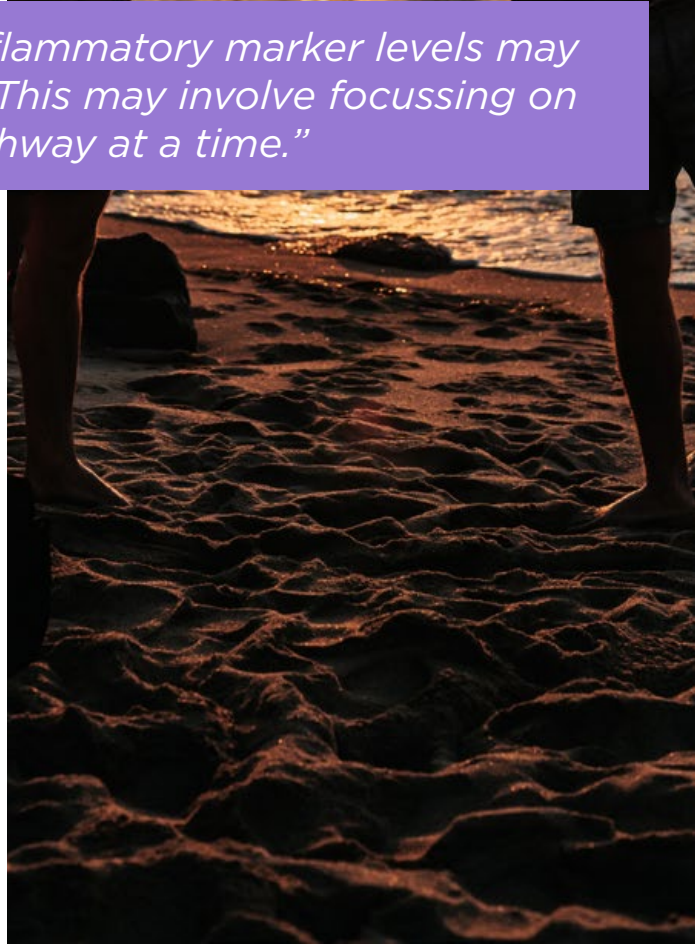
A team of researchers, led by Drs Zixing Tian and Adrian Heald from University of Manchester, Manchester, UK, suggested that the systemic inflammation associated with rheumatoid arthritis may increase the risk of an individual developing diabetes.



"Agents that reduce systemic inflammatory marker levels may have a role in preventing T2DM. This may involve focussing on more than one pathway at a time."

A comprehensive search of a range of medical and scientific databases, and statistical analyses for relative risk and publication bias, were carried out, comparing the incidence of T2DM among people with rheumatoid arthritis to the diabetes risk within the general population. After identifying the eligible studies, which comprised 1,629,854 participants, the authors found that patients with rheumatoid arthritis had a 23% higher chance of developing T2DM compared to the risk of being diagnosed with T2DM within the general population. The findings support the hypothesis of the team that inflammatory pathways are indicated in the pathogenesis of diabetes.

The researchers shared their ideas for future research and management: "We suggest that more intensive screening and management of diabetes risk factors should be considered in people with rheumatoid arthritis. Agents that reduce systemic inflammatory marker levels may have a role in preventing T2DM. This may involve focussing on more than one pathway at a time."



Undiagnosed Diabetes Could be Identified Earlier Through Population Screening

"Our study shows that population-level screening could identify cases of T2DM far earlier and potentially reduce complications."

SCREENING for Type 2 diabetes mellitus (T2DM) through population databases, such as the UK Biobank, using HbA1c levels could identify those with undiagnosed T2DM, according to a study presented at EASD Virtual Meeting 2020 and in a press release dated 21st September.

In the UK, diagnosis of T2DM is commonly established through HbA1c testing at a general practitioner practice when a patient is symptomatic. To reduce this potential delay in diabetes onset and initiation of treatment, researchers from the UK used the UK Biobank to test if population screening using the HbA1c levels measured at recruitment could identify those with undiagnosed T2DM.

The UK Biobank comprises approximately 500,000 participants between the ages 40 and 70 years (at time of recruitment), for whom primary care records are available for around one-half. Patients without diabetes (n=201,465) were defined as those who did not self-report diabetes and had no evidence in their primary care records of diabetes prior to recruitment. The authors retrieved data on the time it took for participants who had undiagnosed diabetes at recruitment (Hb1Ac of ≥48 mmol/mol) to be clinically diagnosed, finding that the median time was 2.3 years, with 23% having not received a diagnosis at the 5 years follow-up.

Using the UK Biobank, the authors found that 1.0% (n=2,022) of participants had an HbA1c measurement of ≥48 mmol/mol and therefore had undiagnosed diabetes. Resultant diagnosis of diabetes from this screening was predicted to be approximately 2 years earlier than a clinical diagnosis, potentially shortening the time to receiving treatment. Compared to those with an HbA1c of <48 mmol/mol at screening, these participants were older (median age: 61 years), had a higher BMI (median: 31), and were more likely to be male (60%).

Dr Katherine Young, University of Exeter, Exeter, UK, concluded: "Our study shows that population-level screening could identify cases of T2DM far earlier and potentially reduce complications." She acknowledged that the implications of the delays in diabetes diagnosis seen here are unclear but advocated for further research to illuminate this and the potential of screening for diabetes.

Increased Risk of Falls Seen in People with Diabetes

FALLS can occur for a multitude of reasons and potentially lead to fall-related injuries. The results from a study presented at EASD Virtual Meeting 2020 and in a press release dated 21st September showed that those with Type 1 diabetes mellitus (T1DM) were at a 33% increased risk of having a fall, and those with Type 2 diabetes mellitus (T2DM) were at a 19% increased risk, compared to the general population.

The study investigated the risk factors associated with increased falls in both those with diabetes and the general population using data from the Danish National Patient Register. Patients with T1DM (n=12,975) or T2DM (n=407,099) were matched for sex and age (1:1) with those from the general population, which formed the control group. Computer modelling was used to analyse the fall-related hospitalisations from 1996 to 2017.

The results for the adjusted analyses, which included risk factors such as age, sex, diabetic complications, history of alcohol abuse, and medication history, showed that there was a 33% increased risk of having a fall in those with T1DM, and a 19% increased risk in those with T1DM. Other risk factors that had a profound impact on the risk of fall in T1DM and T2DM were female sex, age (>65 years), selective serotonin receptor inhibitor use, opioid use, and history of alcohol abuse.

When analysing the differences in risk of bone fracture compared to the general population, those with T2DM were at increased risk of fractures to the hip and femur, humerus, radius, and skull or face; those with T1DM were at an increased risk of fractures of the hip or femur. "Gaining further information on risk factors for falls could guide the management of diabetes treatment such as the choice of medication, which enables us to improve treatment, particularly in people with a high risk of falls and fractures associated with high mortality," the authors concluded.

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Spousal Concordance Can Influence Type 2 Diabetes Mellitus Risk Factors

BEHAVIOURS, such as those relating to diet and exercise, can reduce the likelihood of developing Type 2 diabetes mellitus (T2DM). According to a study presented at EASD Virtual Meeting 2020 and summarised in a press release dated 21st September, if one partner in a relationship displays high levels of behaviours that positively influence the risk of T2DM, then the other partner is also likely to do so.

In this cross-sectional study, the similarity in the pathophysiology mechanisms, including β cell function and insulin sensitivity, of T2DM and risk factors, such as BMI, percentage body fat, physical activity levels, and diet indicators, were analysed in 172 couples using data from the Maastricht Study. Glucose metabolism status was also assessed through fasting and 2-hour plasma glucose testing and HbA1c.

The Dutch Healthy Diet Index (DHDI) showed the strongest spousal concordance, with a 1-unit increase in the female partner's DHDI correlated with a 0.53-unit increase in the male's DHDI. A similar association was seen with time spent in high intensity physical activity (HPA), for which a 1-unit increase in the male's time spent in HPA corresponded with a 0.36-unit increase in the female partner's time spent in HPA. The strong spousal concordances seen in the behavioural risk factors were not observed in the pathophysiological factors, with the weakest spousal concordance observed in β cell function measurements.

The authors concluded: "From a practical point of view, public health prevention strategies to mitigate diabetes risk may benefit from spousal similarities in health-related behaviours and diabetes risk factors to design innovative and potentially more effective couple-based interventions."

Exercise and Physical Activity Study Group (ExPAS) Session

Anaya Malik
Editorial Assistant

Citation: EMJ Diabet. 2020;8[1]:23-25.

THE EXERCISE and Physical Activity Study Group (ExPAS) Symposium took place at the European Association for the Study of Diabetes (EASD) Virtual Meeting 2020 on Thursday 24th September. The session was chaired by Dr Dominik Pesta, German Diabetes Center, Düsseldorf, Germany, together with Dr Richard Bracken, Swansea University, Swansea, UK. The talks discussed Type 2 diabetes mellitus (T2DM) and the interaction of this chronic condition with nutrition and exercise. ExPAS is an EASD study group with the overall goal of improving communication, collaboration, and clinical education in the areas that link exercise science to diabetes.

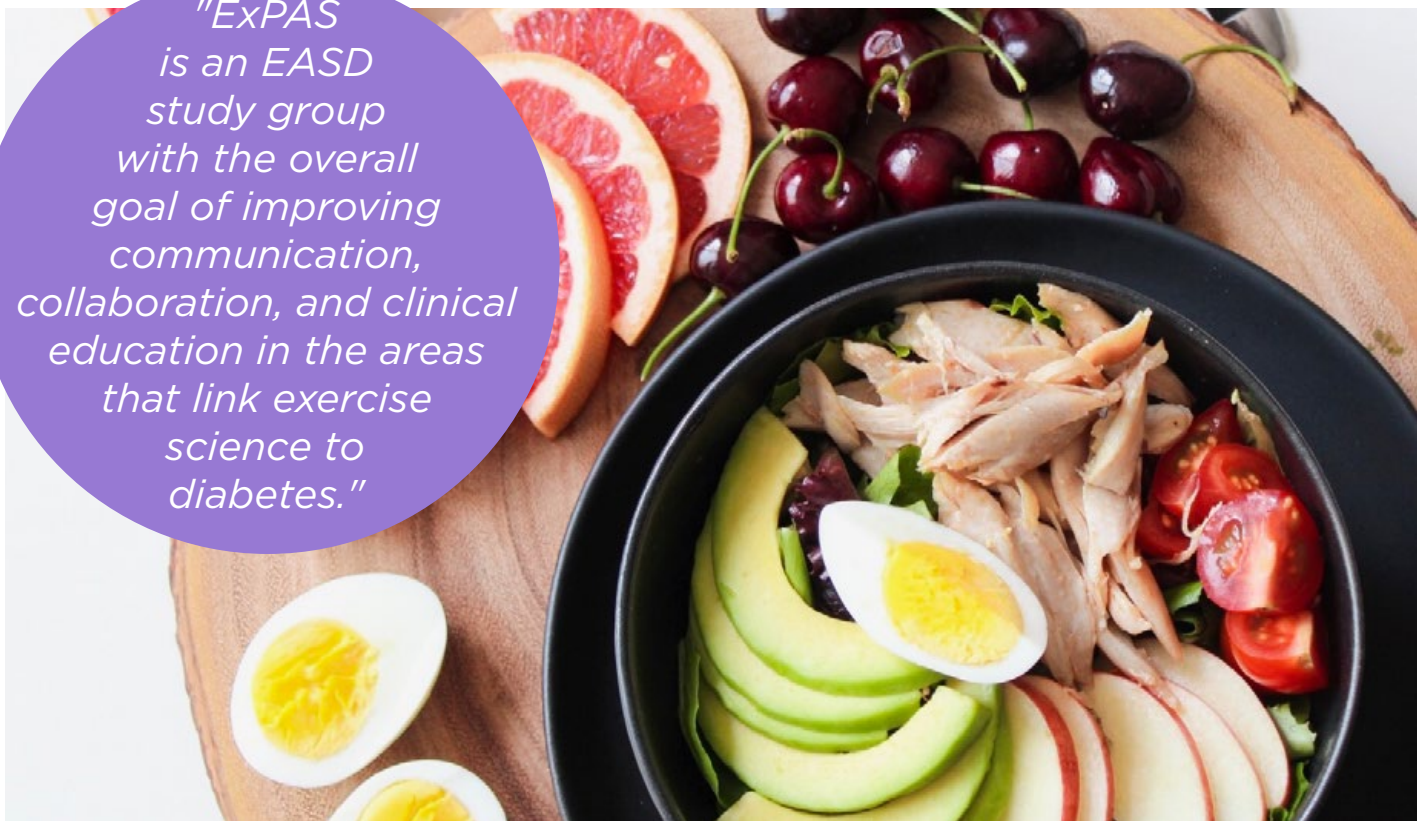
REDUCTIONS IN DIETARY CARBOHYDRATE CONTENT IN TYPE 2 DIABETES MELLITUS

The first presentation, and keynote lecture, was delivered by Dr Brendan Egan, Associate Professor of Sport and Exercise Physiology, Dublin City University, Dublin, Republic of Ireland.

The session focussed on dietary carbohydrate content in T2DM and the emerging evidence for the potential therapeutic reduction of dietary carbohydrates. A very low-carbohydrate ketogenic diet is an intake of <10% of daily calories (kcal) from carbohydrates, the low-carbohydrate diet is <26% of total kcal from carbohydrates, the moderate-carbohydrate range is 26–45% of daily kcal, and >45% of daily kcal intake from carbohydrates is considered a high-carbohydrate diet. Dr Egan introduced the ketogenic diet, for which recent interest has spiked because of the potential metabolic signalling effects of ketone bodies, as a method of reducing carbohydrates to the extent that the absence of low concentrations of insulin and higher concentrations of glucagon drive metabolic parameters, activating ketogenesis in the liver.

Physical inactivity does indeed contribute to T2DM and Dr Egan deliberated the effect of combining exercise with a low-carbohydrate diet in T2DM. He explained that studies of this nature have not been carried out, but did share data from previous studies of these combinations in patients without T2DM, emphasising that it is difficult to confirm whether exercise has additive benefits to low-carbohydrate diets. Dr Egan highlighted that all low-carbohydrate diets do not necessarily equate to a high-quality diet.

"ExPAS is an EASD study group with the overall goal of improving communication, collaboration, and clinical education in the areas that link exercise science to diabetes."



UNDERLYING MECHANISMS OF DIABETES REMISSION: 1-YEAR INTENSIVE LIFESTYLE INTERVENTION

The 2019 study, "The underlying mechanisms of Type 2 diabetes remission: 1 year after an intensive lifestyle intervention," was presented by Ms Mette Yun Johansen, University of Copenhagen, Copenhagen, Denmark.

Participants with T2DM were randomised to standard care (n=34), or standard care and intensive lifestyle intervention, with a high volume of exercise (n=64), groups. During a 1-year intervention period, baseline, 12-month, and 24-month follow-up measurements were taken, and partial or complete remission, defined as glycaemic control with no glucose-lowering medications at 12- and 24-months follow-up, was investigated.

In the intensive lifestyle group, 23% achieved some remission compared to 7% in the standard care group. Follow-up investigations allowed the authors to conclude that remission is characterised by changes in some underlying pathophysiological characteristics of T2DM.

INTERACTION BETWEEN METFORMIN AND PHYSICAL ACTIVITY

The next presentation was delivered by Ms Nanna Pilmark, Centre for Cancer and Organ Diseases, Rigshospitalet, Copenhagen, Denmark, who spoke about a new study that investigated the combined effect of physical activity and metformin to improve glycaemic control. The study evaluated whether a 12-week exercise training programme would improve postprandial glucose and whether potential improvements were affected by metformin treatment.

The authors tested individuals at baseline, 3 weeks after randomisation for metformin or placebo treatment, and after 12 weeks, during which time an intensive training intervention was executed alongside metformin or placebo. There was a reduction in postprandial glucose from baseline to the study end, with no difference between the placebo and metformin groups, but reduction occurred at different timepoints between groups. In the placebo group, reduction was seen during the exercise period, suggesting that the intervention was effective at managing postprandial glycaemia. In the metformin treatment group, the reduction was seen before the exercise period.

"This has important implications for public health and emphasises the need for preventive programmes promoting a healthy lifestyle to reduce the diabetes burden."

The authors were left with the question of whether further reduction through exercise was not possible after metformin had acted in full, or if the two therapy options, metformin and physical activity, inhibited each other.

COMBINED LIFESTYLE FACTORS AND THE RISK OF LATENT AUTOIMMUNE DIABETES IN ADULTS

Dr Katharina Herzog, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, presented the results of the review "Combined lifestyle factors and the risk of latent autoimmune diabetes in adults." The authors investigated the risks of latent autoimmune diabetes in adults (LADA) and in association with the characteristics of a healthy lifestyle.

Participants completed questionnaires for low-risk lifestyle components, including physical activity, healthy diet, BMI <25, no smoking, and moderate alcohol consumption; the combination of components gave information on whether they led a poor, moderate, or healthy lifestyle. BMI <25 was associated with the largest risk reduction for LADA and combined characteristics showed a reduced risk of LADA in those who led a moderate lifestyle.

Healthy lifestyle adherence was associated with a 60% reduced risk of LADA. A moderate lifestyle was associated with a decreased risk of LADA, so even partial lifestyle modifications may reduce the risks of the autoimmune disease and a healthy lifestyle leads to even further reductions. "This has important implications for public health and emphasises the need for preventive programmes promoting a healthy lifestyle to reduce the diabetes burden," concluded Dr Herzog.

HIGHER CAPACITY FOR MUSCLE CARNOSINE IN METABOLIC DISEASE IMPROVEMENT

Dr Martin Schön, German Diabetes Center, presented a pilot study that investigated capacity for muscle carnosine loading by implementing a double-blind, randomised 12-week carnosine supplementation programme in sedentary middle-aged adults who were overweight or obese.

Carnosine, primarily found in skeletal muscle, enhances exercise by lowering chronic inflammation and oxidative stress, and has been shown to normalise impaired glucose tolerance. The authors measured skeletal muscle carnosine content, muscle metabolism, body composition, and blood glucose, among other parameters.

The results showed that carnosine supplementation induced distinct responses in muscle carnosine accumulation and one-half of participants showed an increase in carnosine muscle loading. Regular exercise and BMI were identified as predictors of carnosine accumulation capacity in skeletal muscle and higher loading capacity was associated with reduced protein glycation and increased postexercise phosphocreatine recovery.

The outcomes of the study suggest that carnosine is a favourable food additive with positive effects on glucose metabolism and the potential to reduce the risk of metabolic diseases such as T2DM.

CONCLUDING REMARKS

Since 2014, ExPAS has organised sessions on diabetes, as seen in previous EASD Annual Meetings, and has brought scientists and leaders together to exchange ideas. With increasing interest in this discipline, global experts continue to propel research to fill knowledge gaps and reveal the positive impact of physical activity on chronic diseases such as diabetes, with potential implications on national and global guidelines.

Navigating Through the COVID-19 Pandemic: New Lessons on Diabetes and the Cardiovascular System

Rachel Donnison
Editorial Assistant

Citation: EMJ Diabet. 2020;8[1]:26-28.

MULTIDISCIPLINARY care is the future of medicine, as it becomes increasingly apparent that a single patient treated by a single doctor is an old-fashioned and restrictive approach. This year's European Association for the Study of Diabetes (EASD) Virtual Meeting showcased the importance of such cross-disciplinary care by timetabling multiple cross-curricular sessions, including 'Navigating Through the COVID-19 Pandemic and New Lessons from Cardiovascular Outcome Trials', which served to update clinicians across the endocrinology and cardiology therapeutic areas on coronavirus disease (COVID-19) patient management.

CARDIOVASCULAR RISK MANAGEMENT IN PATIENTS WITH DIABETES AND COVID-19

"There is no doubt that diabetes is one of the most important contributors to the worst prognosis in COVID-19," began Prof Antonio Ceriello, Head of the Diabetes Department, IRCCS MultiMedica, Milan, Italy. However, he was quick to interject that we have already learnt many valuable lessons about patient care in diabetes and COVID-19 since the start of the pandemic, including the control of hyperglycaemia, and the prescribing of antidiabetic drugs, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), corticosteroids, and hydroxychloroquine.

Hyperglycaemia

A recent study has analysed the mortality rate among 7,300 patients with COVID-19 and Type 2 diabetes mellitus; those with well-controlled blood glucose (upper limit: ⩽10 mM), as opposed to those with poorly-controlled blood glucose (upper limit: >10 mM), showed a strong association to a lower death rate. Looking further into this relationship, Prof Ceriello reported on another study's findings: "What appeared to be most important was the level of the hyperglycaemia at admission, more than previous glycaemic control." There are several other

studies that have since confirmed this evidence, suggesting that the level of HbA1c before admission to hospital does not have a negative effect on the prognosis of these patients with COVID-19 and diabetes.

The link between hyperglycaemia at hospital admission and severity of COVID-19 has also been observed in other studies, though Prof Ceriello noted: "Hyperglycaemia worsened the prognosis, but this was particularly in people without previous history of diabetes." Hyperglycaemia therefore appears to be a very good predictor of the prognosis, but it does appear to be more dangerous in people without diabetes. Other study findings discussed by Prof Ceriello included the recent observations that admission hyperglycaemia is an independent risk factor for poorer outcomes in people with lung disease, sepsis, and in those who experience a cardiac event.

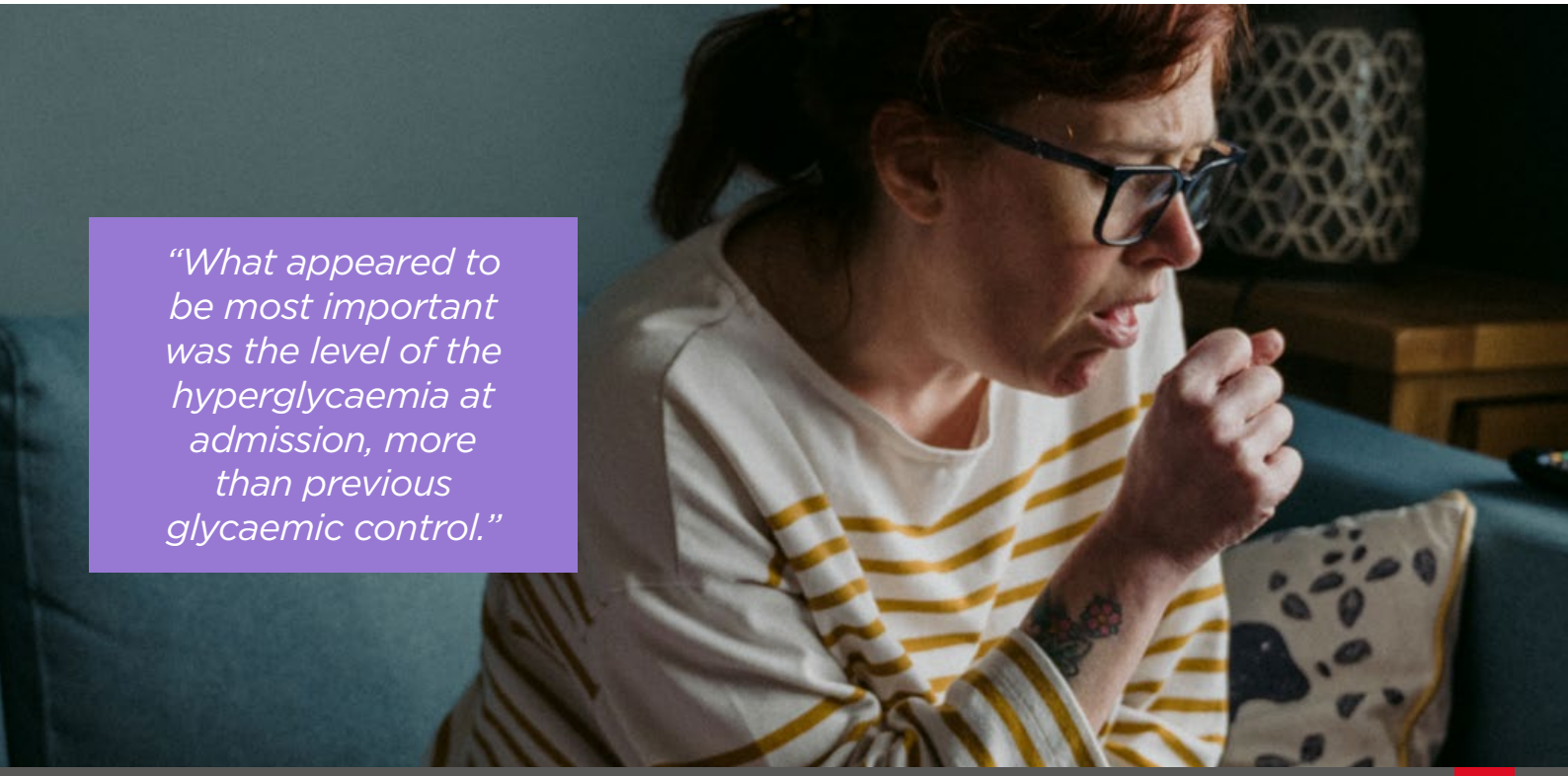
"The control of hyperglycaemia should be considered a key action for the management of this disease," concluded Prof Ceriello.

Antidiabetic Drugs

The mechanisms of antihyperglycaemic drugs must be considered in the management of COVID-19 and diabetes, stressed Prof Ceriello. For example, the effect of lowering inflammatory stress and peripheral insulin resistance by reducing the infiltrate with macrophages, via glucagon-like peptide 1 (GLP-1)-dependant signalling by regulating M1/M2 macrophage polarisation, have been described with dipeptidyl peptidase (DPP4) inhibition and GLP-1 receptor activation. Given the significance of preserving the cardiovascular system and kidney function in this pandemic, alongside the known benefits of drugs such as GLP-1 receptor agonists and SGLT-2 and DPP4 inhibitors in achieving this, Prof Ceriello resolved that: "These drugs have a very strong anti-inflammatory activity which can probably help patients with COVID-19."

Angiotensin-Converting-Enzyme Inhibitors and Angiotensin II Receptor Blockers

Given the ACE2 receptor is the entry point for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) into cells, it was hypothesised that patients with cardiac diseases, hypertension, or diabetes who were treated with ACE2-increasing drugs, were at higher risk of severe COVID-19 infection. However, Prof Ceriello then presented the findings of several further studies which found no such link between ACEi or ARB with in-hospital death. Prof Ceriello believes this first report of ACEi and severe COVID-19 could have been very damaging: "Nobody knows how many people stopped using ACEi and ARB, or how many cardiovascular deaths or vascular deaths there were because people stopped use of these drugs."



"What appeared to be most important was the level of the hyperglycaemia at admission, more than previous glycaemic control."

Corticosteroids

"At the beginning, the guidelines were suggesting that corticosteroids must be avoided for the treatment of COVID-19," began Prof Ceriello. Now, we have evidence that, in patients hospitalised with COVID-19, dexamethasone can be life-saving; one study concluded that the drug resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone, but not among those receiving no respiratory support. However, corticosteroids are known to increase glycaemia; "When they are used in diabetes, we must pay attention to the balance between the benefits of use and the damage caused by high glucose," emphasised Prof Ceriello.

Hydroxychloroquine

At the beginning of the pandemic, hydroxychloroquine was suggested to be very beneficial for the treatment of COVID-19; however, the articles which advocated its use were subsequently retracted on the grounds of serious methodological issues. "It is well known that this compound can cause some heart damage, as well as increasing the risk of hyperglycaemia in diabetes," warned Prof Ceriello. Unfortunately, the benefits of this treatment are still unclear and under research.

LESSONS LEARNT

There has been much controversy amongst study authors so far in this pandemic, which has led to consequences such as hyperglycaemia (in diabetes and nondiabetes) not being identified as an issue in COVID-19 treatment earlier; "The communications between different specialists has failed," said Prof Ceriello. Purely scientific hypotheses have been considered as true evidence without significant proof, and preliminary therapeutic data were not interpreted with enough caution. However, he did provide some possible solutions to these global challenges: he suggested collaboration between healthcare professionals, patients, professional bodies and organisations, government decision makers, and the mass media, in order to share both best and worst practices.

Prof Ceriello then ended the session with the words: "Effective communication, collaboration, and trust, leading to evidence-based science and decisions, are essential between all 'players' involved in the pandemic of COVID-19."

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Kidney Disease: Improving Global Outcomes (KDIGO) New Guideline for Diabetes Management in Chronic Kidney Disease: A Meet-the-Expert Session

This symposium took place on 22nd September 2020, as part of the Virtual European Association for the Study of Diabetes (EASD) Annual Meeting 2020

Chairperson: Ian de Boer[1]

Speakers: Peter Rossing,[2,3] Tami Sadusky[1]

1. Kidney Research Institute, Seattle, Washington, USA
2. Steno Diabetes Center Copenhagen, Copenhagen, Denmark
3. Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Disclosure: Prof de Boer has received consulting fees from Boehringer Ingelheim, George Clinical, Goldfinch Bio, and Ironwood Pharmaceuticals; and research equipment and supplies from Medtronic and Abbott. Prof Rossing has received consultancy and/or speaking fees (to his institution) from Astellas Pharma, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly and Company, Gilead, MSD, Novo Nordisk, Sanofi Aventis, and Vifor; and has received research grants from AstraZeneca and Novo Nordisk. Ms Sadusky has declared no conflicts of interest.

Acknowledgements: Writing assistance was provided by Stefan Amisten, Amisten Consulting Limited, Epsom, UK.

Support: The symposium and publication of this article were funded by Boehringer Ingelheim and Eli Lilly and Company.

Citation: EMJ Diabet. 2020;DOI/10.33590/emjdiabet/201014

Meeting Summary

Prof de Boer opened this virtual seminar on the new Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on diabetes management in chronic kidney disease (CKD), which is the first set of KDIGO guidance on this topic. Prof de Boer emphasised that the aim of the guideline was to generate a useful resource for clinicians and patients, to address relevant questions with actionable recommendations supplemented by practice points, to take on controversial topics when sufficient evidence was available, and to communicate findings clearly and concisely. The scope of the new guideline includes patients with Type 1 diabetes mellitus, Type 2 diabetes mellitus, and all severities of CKD, including patients treated with dialysis or kidney transplantation. The new guideline also includes recommendations related to lifestyle, pharmacotherapy, and the organisation of healthcare systems, addressed using systematically identified data from randomised controlled trials. Topics such as blood pressure control and lipid management and prevention of and screening for diabetes are not covered by the new KDIGO guideline and have been addressed either in prior KDIGO publications or in other international guidelines.

After his introduction, Prof de Boer handed over to Prof Rossing, who offered a detailed overview of the new guidelines, and Ms Sadusky, who highlighted the contribution of patients in the

development of the guidelines. Prof Rossing and Ms Sadusky concluded the seminar by emphasising the importance of shared decision-making, where the patient is involved in defining individualised treatment goals, and the critical need for a team-based approach in the care of patients with diabetes and CKD.

Management of and Living with Diabetes and Chronic Kidney Disease

Professor Peter Rossing and Miss Tami Sadusky

Diabetes is a chronic, metabolic disease characterised by elevated blood glucose levels, which over time leads to serious damage to the heart, blood vessels, eyes, kidneys, and nerves. The most common form of diabetes are Type 2 diabetes mellitus, characterised by insulin resistance or insufficient production of insulin; followed by Type 1 diabetes mellitus, which is caused by the loss of endogenous insulin production.[1] CKD develops in approximately 40% of patients with diabetes and is the leading cause of CKD worldwide.[2]

KDIGO is a global nonprofit organisation that develops and implements evidence-based clinical practice guidelines for kidney disease.[3] The first KDIGO guideline on diabetes management in CKD has recently been developed and its guidance and recommendations on comprehensive care in patients with diabetes and CKD includes glycaemic monitoring and targets, lifestyle, and pharmacologic interventions.[4] It emphasises that patients should be treated with a comprehensive strategy beyond lowering glycaemia to reduce risks of kidney disease progression and cardiovascular disease by highlighting the importance of screening for and management of the complications of diabetes.

The Importance of Patient Perspectives for Treatment Guidelines

A new evolution in the development of the KDIGO guidelines is the explicit inclusion of patient perspectives. This new concept was implemented by the involvement of patients as members of the KDIGO Work Group. Ms Sadusky, community and patient advocate and KDIGO Diabetes Guideline Work Group Member, demonstrated the value of including a patient in the guideline development process by sharing her perspective on patient care, with an emphasis on the importance of early testing and diagnosis of diabetes and its complications, such as CKD. She also highlighted the importance of including the patient in the decision-making process for their care (i.e., shared decision-making between patient and healthcare provider) and ensuring that a healthy lifestyle (e.g., diet and exercise), individualised to each patient, is a priority in the care of patients with diabetes and CKD. Ms Sadusky also stressed that adding lifestyle considerations to the decision-making process reduces the risk of future complications, and that there is a critical need for a team-based approach by healthcare providers in the care of patients with diabetes and CKD.

Glucose Monitoring

Monitoring of glycaemic status by either the patients or healthcare providers helps to guide treatments to achieve the best possible glycaemic control.[5] Long-term glycaemia may be monitored through HbA1c, glycated albumin, fructosamine, or 1,5-anhydroglucitol,[6] but it has not been clear which method is best suited for monitoring long-term glycaemia in patients with diabetes and CKD. In the new guideline, KDIGO recommends HbA1c to monitor glycaemic control, as HbA1c is a long-term glycaemic marker with a thoroughly studied performance as both a marker and a prognostic indicator, with standardised assays being readily available.[4]

Daily glycaemic monitoring with continuous glucose monitoring or self-monitoring of blood glucose may help to prevent hypoglycaemia and improve glycaemic control when antihyperglycaemic therapies associated with risk of hypoglycaemia, such as insulin, sulfonylureas, and meglitinides, are used.[4] Prof Rossing also pointed out that monitoring for hypoglycaemia is less necessary for antihyperglycaemics such as metformin, sodium–glucose co-transporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide 1 receptor agonists (GLP1RA).

Individual Treatment Targets

The new KDIGO guideline emphasises balancing risks and benefits for personalised treatment goals and recommends an individualised HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not receiving dialysis. The individualised HbA1c target most suitable for each individual patient depends on a variety of factors, including CKD severity, macrovascular complications, comorbidities, life expectancy, hypoglycaemia awareness, resources for hypoglycaemia management, and the propensity of treatments to cause hypoglycaemia (Figure 1).[4] Despite controversy about the goals for 'many' or 'most' patients, there is general agreement that glycaemic targets should be individualised based on consideration of specific factors (Figure 2). More stringent control may be recommended if it can be achieved safely and with an acceptable burden of therapy and if life expectancy is sufficient to reap benefits of tight control, whereas less stringent control may be recommended if the life expectancy of the patient is such that the benefits of an intensive goal may not be realised, or if the risks and burdens outweigh the potential benefits.[4]

Lifestyle Interventions

The new KDIGO guideline recommends that patients with diabetes and CKD should consume an individualised diet high in vegetables, fruits, whole grains, fibre, legumes, plant-based proteins, unsaturated fats, and nuts, but lower in processed meats, refined carbohydrates, and sweetened beverages. KDIGO advocates a plate model, which can easily be adapted to different cultural contexts by substituting the visualisation of a plate for that of a rice bowl, injera, tortilla, or banana leaf. Regardless of the shape of the plate or its equivalent, the proportion of major food groups remains the same: 50% fruit and vegetables, 25% plant or animal protein, and 25% whole grain or starchy vegetables.[4] The new KDIGO guideline suggests that sodium intake be limited to <2 g per day (or <5 g sodium chloride), consistent with the KDIGO guideline on blood pressure management and international guidelines on the prevention and treatment of CVD.[7,8]

The new guideline also recommends that patients with diabetes and CKD should be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance. Patients should be advised to avoid sedentary behaviour, and physicians should consider advising and encouraging patients with obesity, diabetes, and CKD to lose weight, particularly patients with an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2.[4]

Pharmacologic Treatment for Glycaemic Control and Kidney Protection

After lifestyle intervention therapy centred on increased physical activity, improved nutrition, and weight loss, first-line therapy with metformin and a SGLT-2 inhibitor is recommended for patients with diabetes and CKD, and those with an eGFR ≥30 mL/min/1.73 m^2. This guidance is based on findings reported from the recent CREDENCE study.[9]

For metformin, a reduced dose is recommended for eGFR <45 mL/min/1.73 m^2, with discontinuation at eGFR <30 mL/min/1.73 m^2. For patients with eGFR ≥45 mL/min/1.73 m^2, both immediate-release and extended-release formulations of metformin are recommended, with extended-release metformin recommended for patients experiencing gastrointestinal side effects by the immediate-release formulation. Dose uptitration over 7 days until the maximum dose has been reached is recommended for both formulations. Monitoring of vitamin B12 deficiency is recommended for patients who are either at risk of deficiency, or for patients who have been taking metformin for >4 years, regardless of kidney function. Annual kidney function monitoring is recommended for patients with eGFR ≥60 mL/min/1.73 m^2, whereas kidney function monitoring is recommended at least every 3–6 months for patients with eGFR 30–59 mL/min/1.73 m^2. Dose adjustments may also be required for patients with eGFR 30–44 mL/min/1.73 m^2. KDIGO also recommends that SGLT-2 inhibitor therapy should not be initiated in patients with eGFR <30 mL/min/1.73 m^2, and that SGLT-2 inhibitor therapy should be discontinued in patients starting dialysis (Figure 3).[4] For patients with eGFR <45 mL/min/1.73 m^2, the primary treatment goal is not lowering glycaemia *per se*, but cardiovascular and kidney protection.

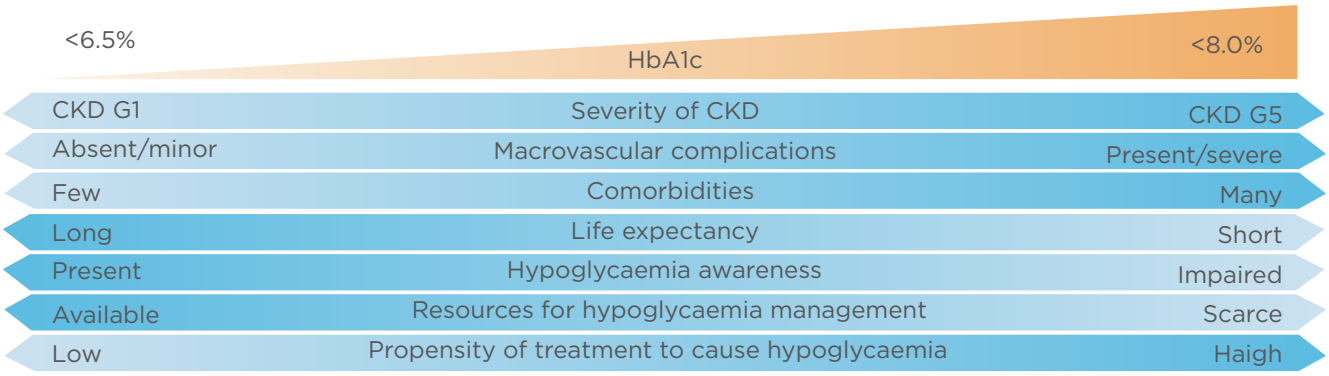

Figure 1: Factors influencing individualised HbA1c targets for patients with diabetes and chronic kidney disease.
CKD: chronic kidney disease; G: glomerular filtration rate category.

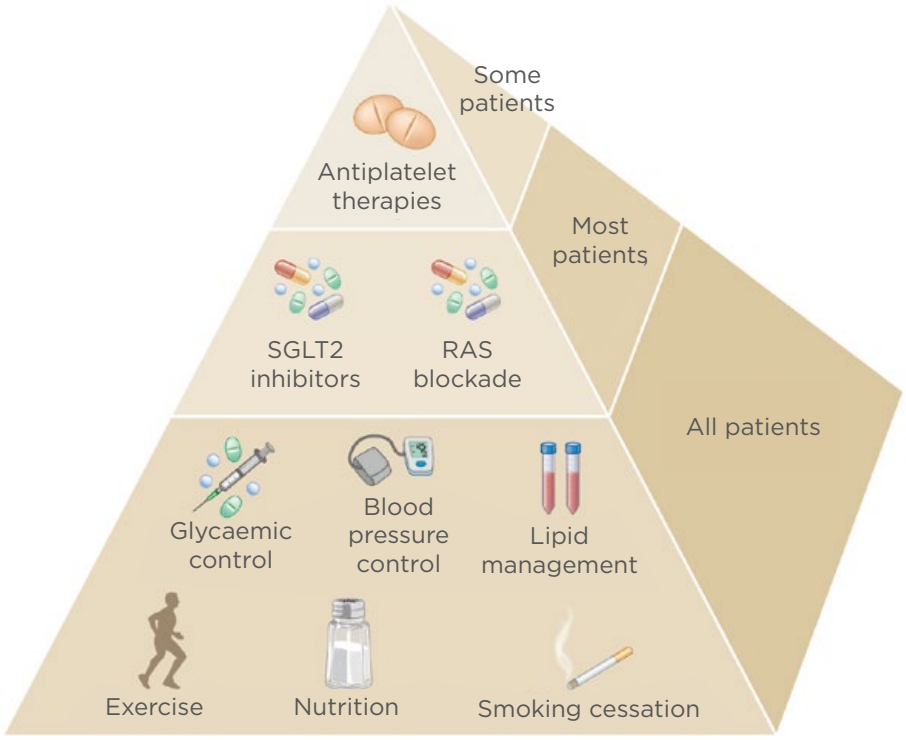

Figure 2: Specific factors influencing individualised glycaemic targets for patients with diabetes and chronic kidney disease.
RAS: renin–angiotensin system; SGLT-2: sodium–glucose co-transporter-2.

Additional glucose-lowering therapies should be selected as needed for glycaemic control. These include GLP1RA (preferred), dipeptidyl peptidase-4 inhibitors, insulin, sulfonylureas, thiazolidinediones, or alpha-glucosidase inhibitors (Figure 3). Considerations for adding these therapies include patient preferences, comorbidities such as heart failure, high-risk atherosclerotic cardiovascular disease risk markers, need for potent glucose-lowering or reduced risk of hypoglycaemia, eGFR, cost, and other factors such as avoidance of injections, weight loss, renin–angiotensin system inhibitors (RAASi), and antiplatelet therapy.

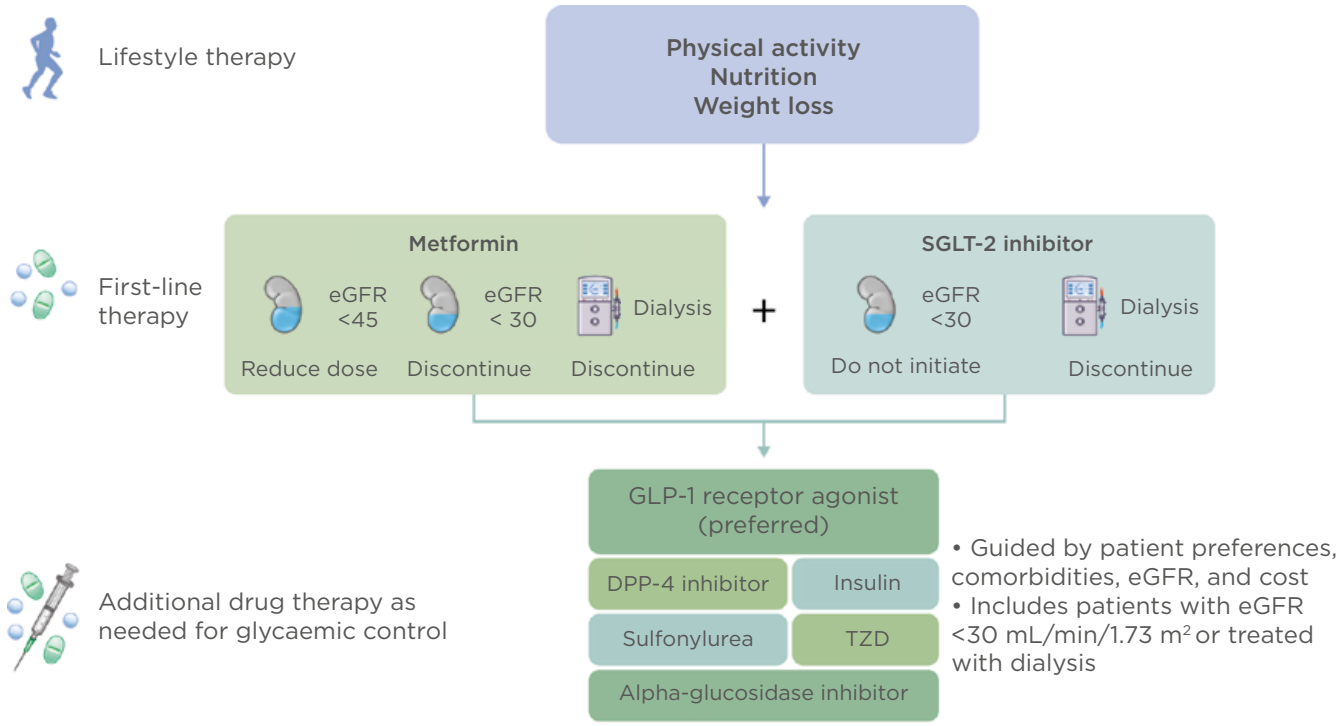

Figure 3: Overview of therapy options for patients with diabetes and chronic kidney disease.

eGFR: estimated glomerular filtration rate; SGLT-2: sodium–glucose co-transporter-2; GLP-1: glucagon-like peptide 1; DPP-4: dipeptidyl peptidase-4; TZD: thiazolidinediones.

Patient Education

As a preferred approach to the management of patients with diabetes and CKD, KDIGO recommends that a structured self-management educational programme be implemented for the care of individuals with diabetes and CKD.

The key objectives of such programmes are to improve diabetes-related knowledge, beliefs, and skills; improve self-management and self-motivation; encourage adoption and maintenance of healthy lifestyles; improve vascular risk factors; increase engagement with medication, glucose-monitoring, and complication screening programmes; reduce risk to prevent (or better manage) diabetes-related complications; and to improve emotional wellbeing, treatment satisfaction, and quality of life.[4]

The Importance of a Team-Based Approach

The new KDIGO guideline also recommends that patients with diabetes and CKD should be treated using an integrated care approach to improve outcomes, self-management, and patient–provider communication. This approach consists of physician and other allied health professional care, supported by information technology to promote communication and feedback between specialists and other care providers.[4] The aim of this care model is to achieve structured patient education and empowerment by improving self-management and providing regular feedback to engage both patients and physicians.

In order to achieve this, KDIGO suggests that policymakers and institutional decision-makers should implement team-based, integrated care focussed on risk evaluation and patient empowerment to provide comprehensive care in patients with diabetes and CKD.[4] The overarching goals are multi-target treatment for patients with diabetes and CKD (e.g., glycaemia, blood pressure, lipids), use of organ-protective drugs (e.g., RAASi, SGLT-2 inhibitors, GLP1RA, statins), and ongoing patient support to promote self-care.[4]

Summary

In summary, the new KDIGO guideline on the treatment of patients with diabetes and CKD provides recommendations and practice points on comprehensive care, with an emphasis on shared decision-making, in which the patient is involved in defining treatment goals best suited for them. It also provides guidance on lifestyle and antihyperglycaemic therapies for glycaemic control, the use of therapies such as SGLT-2 inhibitors to reduce the risk of cardiovascular and kidney complications, and the critical need for a team-based approach for the care of patients with Type 1 diabetes mellitus, Type 2 diabetes mellitus, and all severities of CKD, including patients treated with dialysis or kidney transplantation.

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Abstract Reviews

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Fatty Liver, Irrespective of Ethnicity, is Associated with Reduced Insulin Clearance and Hepatic Insulin Resistance in Obese Youth

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Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: The authors are grateful to the patients and their families, as well as to the personnel of the Yale Center for Clinical Investigation and Hospital Research Unit. This study was supported by the National Institutes of Health (NIH), Eunice Kennedy Shriver National Institute of Child Health and Human Development (grants R01-HD-40787, R01-HD-28016, and K24-HD-01464 to Dr Caprio), the National Institute of Diabetes and Digestive and Kidney Diseases (grant R01-DK-111038 to Dr Caprio; grant R01DK114504 to Dr Santoro), the National Center for Research Resources (Clinical and Translational Science Award [grant UL1-RR-0249139] to Dr Caprio), the American Diabetes Association (AAD) (Distinguished Clinical Scientist Award to Dr Caprio), the European Foundation for the Study of Diabetes (EFSD) (Future Leaders Mentorship Programme for Clinical Diabetologists to Dr Tricò; Rising Star Fellowship to Dr Tricò), and the International Society for Pediatric and Adolescent Diabetes (IPSAD), and the Robert E. Leet Patterson and Clara Guthrie Patterson Trust Mentored Research Award (to Dr Galderisi).

Keywords: Ethnicity, hepatic insulin resistance, insulin clearance, insulin secretion, nonalcoholic fatty liver disease (NAFLD), paediatric disease.

Citation: EMJ Diabet. 2020;8[1]:36-38. Abstract Review No: AR1.

BACKGROUND AND AIMS

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in Western countries[1] and a frequent complication of childhood obesity, with a prevalence

of approximately 30% in obese youth.[2,3] Accumulation of intrahepatic fat has been associated with metabolic abnormalities within the liver that may directly contribute to the aetiology of Type 2 diabetes mellitus, such as reduced endogenous insulin clearance (EIC) and hepatic insulin resistance (HIRI).[4-9] Differences between ethnicities in the prevalence of NAFLD, and its associated metabolic alterations, are well-documented. Compared with Caucasian backgrounds, African American people typically show reduced intrahepatic fat content (HFF).[3,9] Nonetheless, African American patients are also documented to have a greater prevalence of diabetes, impaired EIC, and increased HIRI.[3] This paradox has led to the hypothesis of a dissociation between HFF% and liver metabolic abnormalities in populations of African ancestry.[9] In this study, the authors evaluated whether, and to what extent, the HFF% contributes to impair insulin clearance and insulin sensitivity in the three most prevalent racial and ethnic groups in the USA: Caucasian, African American, and Hispanic.

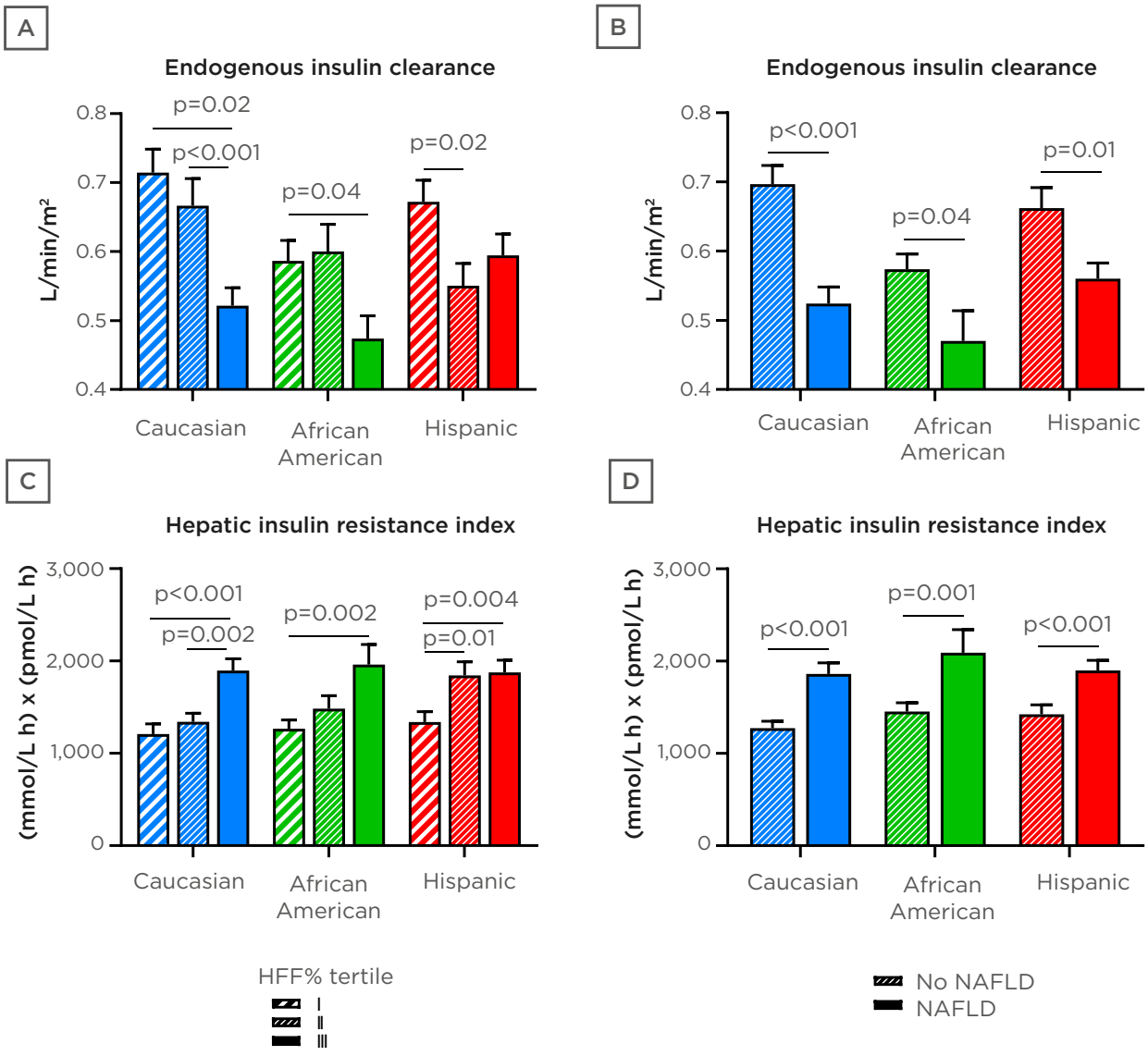

Figure 1: Hepatic fat content.

Endogenous insulin clearance by **A)** group-specific tertile of HFF% and **B)** presence of NAFLD, in obese adolescents from the Yale Pediatric NAFLD cohort. Hepatic insulin resistance index by **C)** group-specific HFF% tertile and **D)** NAFLD, in the same cohort. Data are mean ±SEM. Differences were tested by Kruskall–Wallis test followed by post hoc pairwise comparisons.

h: hour; HFF: intrahepatic fat content; NAFLD: nonalcoholic fatty liver disease; SEM: standard error of the mean.

MATERIALS AND METHODS

The authors analysed cross-sectional and longitudinal data from the Yale Pediatric NAFLD study,[3] providing a large and well-characterised multiethnic cohort of nondiabetic adolescents who were overweight or obese (n=632). The HFF% was quantified using a validated magnitude-based MRI method.[10] Insulin secretion rate, EIC, and HIRI were estimated by modelling glucose, insulin, and C-peptide data during 9-point oral glucose tolerance tests. A subgroup of subjects had repeated metabolic assessments after a median follow-up of 2 years (n=89).

RESULTS

African American individuals (27.2%; n=172) exhibited the lowest HFF% and a prevalence of NAFLD less than one-half of Caucasian individuals (36.2%; n=229) and one-third of Hispanic individuals (36.6%; n=231) ($p<0.0001$ for all comparisons). Furthermore, African American individuals had lower EIC (Figure 1A and 1B) and glucose stimulated ISR, but similar HIRI (Figure 1C and 1D) and plasma insulin levels. The HFF% correlated with EIC (standardised β coefficient [std. β]: -0.13, $p=0.0003$) and HIRI (std. β: 0.17, $p<0.0001$), irrespective of the ethnic background, after adjustment for age, sex, ethnicity, BMI, pubertal status, and plasma glucose levels. Consistently, EIC and HIRI declined across group-specific HFF% tertiles (Figure 1A and 1C) and were markedly lower in individuals with NAFLD (Figure 1B and 1D) in all ethnic groups. EIC and HIRI showed a negative correlation (r: -0.68, $p<0.0001$) that was not modulated by the ethnicity (interaction factor, $p=0.69$) and remained significant in adjusted models (std. β= -0.42, $p<0.0001$). After a 2-year observational follow up, the prevalence of adolescents whose HFF% remained stable (HFF% change ±1% or lower) was 2-fold higher in the African American group (52%) than in Caucasian (28%) and Hispanic (20%; $p=0.036$) individuals. Nevertheless, changes in HFF% over time were associated with changes in EIC (r: -0.25, $p=0.02$) and HIRI (r: 0.22, $p=0.04$) across all groups, without differences between ethnicities.

CONCLUSION

The authors demonstrated that intrahepatic lipid accumulation is associated with reduced EIC and HIRI in obese youth, irrespective of their racial background, in cross-sectional and longitudinal analyses adjusted for multiple confounding factors. These findings support the role of fatty liver in the pathogenesis of Type 2 diabetes mellitus across different ethnicities.

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Long-Term Mortality among Kidney Transplant Recipients with and Without Diabetes: A Nationwide Cohort Study in the USA

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Disclosure: The authors have declared no conflicts of interest.

Keywords: End-stage kidney disease (ESKD), epidemiology, kidney transplant, Type 1 diabetes (T1DM), Type 2 diabetes mellitus (T2DM).

Citation: EMJ Diabet. 2020;8[1]:39-41. Abstract Review No: AR2.

BACKGROUND AND AIMS

Diabetes is the leading cause of end-stage kidney disease (ESKD) accounting for 47% of all new ESKD cases in the USA in 2016.[1] Once diagnosed with ESKD, the preferred treatment is kidney transplantation.[2,3] However, mortality remains approximately two- to three-times higher in diabetic versus nondiabetic transplant patients.[4-6] Reasons for this difference remain an understudied area of research. Further, few studies have considered the roles the two main types of diabetes (Type 1 and Type 2 diabetes mellitus [T1DM and T2DM]) play in modifying prognosis, despite the different disease aetiologies, age distributions, and comorbidities in T1DM versus T2DM.[7,8]

Using the United States Renal Data System (USRDS), a national registry of people being treated for ESKD, the authors aimed to: 1) provide contemporary survival estimates among USA adult kidney transplant recipients with T1DM or T2DM, compared to those with nondiabetic causes of ESKD; and 2) determine trends in mortality rates over time compared with the USA general population.

METHODS

Between January 2000 and August 2018, the authors identified 254,188 first-time kidney transplant recipients aged ≥18 years from the USRDS. Diabetes status, as primary cause of ESKD, was defined using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM codes, as indicated on the Centers for Medicare Services (CMS) 2728 medical evidence form. Data on recipient and donor characteristics, and mortality were obtained from CMS and Organ Procurement and Transplantation Network (OPTN) data. Transplant recipients were followed from their transplant date until 10th Aug 2018 or until their death date, whichever occurred first. Cox proportional hazards regression was used to perform multivariable modelling of survival probabilities and adjusted for recipient (age, sex, race/ethnicity, insurance status, ESKD duration prior to transplant, BMI, history of smoking, comorbidities, organ type, and graft failure) and donor (age, sex, race/ethnicity, donor risk level, and cold ischaemic time) characteristics. Standardised mortality ratios (SMR) compared mortality between the transplant population (by diabetes status) and the year (2000–2017) to the age-matched USA general population. Trends in SMR were assessed using Joinpoint regression, with annual percent change reported.

RESULTS

A total of 72,175 (28.4%) deaths occurred over a median follow-up of 6.3 (interquartile range [IQR]: 2.9–10.5) years. In fully adjusted models, relative mortality risk was highest among people with T1DM (hazard ratio [HR]: 1.94; 95% confidence interval [CI]: 1.87–2.02) and then T2DM (HR: 1.64 (95% CI: 1.61–1.68), compared to nondiabetes. From 2000 to 2017, SMR declined in T1DM, T2DM, and nondiabetes, (Figure 1) but in 2017, SMR remained at 2.4 (95% CI: 2.3–2.5), 6.6 (6.1–7.1), 3.8 (3.7–4.0) for nondiabetes, T1DM, and T2DM, respectively.

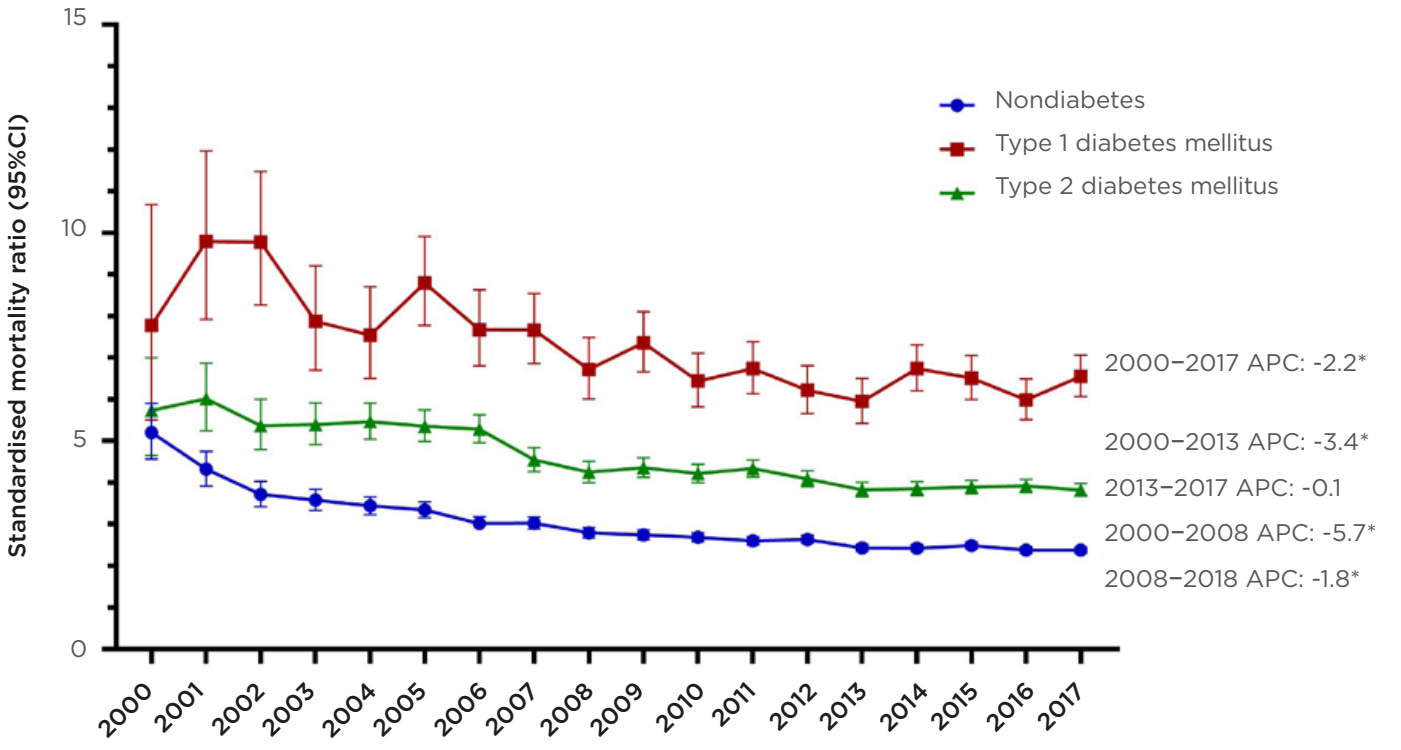

Figure 1: Standardised mortality ratios comparing year and age-matched mortality rates in the transplant versus general USA population, by diabetes status, in the years 2000–2017.

*ptrend<0.05

APC: annual percent change; CI: confidence interval.

CONCLUSIONS

In this study, it has been shown that people with T1DM- and T2DM-related ESKD have a 94% and 64% increased risk of mortality, respectively, compared with nondiabetes-related ESKD. This excess risk was not explained by differences in age, graft failure, comorbidities, or donor characteristics. In addition, age-standardised mortality rates among transplant recipients was evidenced to have declined since 2000 but remains approximately 2- to 7-fold higher compared to the USA general population, with highest rates among T1DM.

Additional research is needed to identify effective interventions to reduce excess mortality in transplant recipients with diabetes. In the interim, adequate management of glycaemia,[9] in parallel with blood pressure control and anticipation of cardiovascular effects of immunosuppression,[10] may be effective in reducing mortality in T1DM and T2DM kidney transplant recipients.

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Acute Metabolic Effects of Intermittent Fasting in the Morning Compared to Two Different Breakfasts Among Lean Individuals

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Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: The authors would like to thank all study participants for voluntarily contributing their time to this study

Keywords: β-Hydroxybutyrate, intermittent fasting, Mediterranean breakfast, zero carbohydrate breakfast.

Citation: EMJ Diabet. 2020;8[1]:41-42. Abstract Review No: AR3.

BACKGROUND AND AIMS

It has been hypothesised that prolongation of the nocturnal low insulin state that is achieved through early day fasting[1] or a zero carbohydrate breakfast[2] results in greater mobilisation of adipose tissue stores. The aim of this study was to investigate this hypothesis further in comparison to two different approaches of early day nutritional strategies.

MATERIALS AND METHODS

In this cross-over study, 10 lean, healthy volunteers (females: 7; males: 3) aged 28.6±4.3 years with a mean BMI of 22.9±1.4 kg/m^2 underwent three 6-hour morning sessions after an overnight fast: A: fasting; B: 500 kilocalorie (kcal) zero carbohydrate breakfast;[3] and C: 500 kcal Mediterranean-type breakfast. Fasting duration before the experiments was reported. Insulin resistance (Homeostatic Model Assessment of Insulin Resistance [HOMA-IR]) was measured at baseline. Plasma glucose and insulin measurements, as well as Visual Analogue Scales (VAS) for hunger, were obtained every 30 minutes during the study. Plasma β-hydroxybutyric acid (bHB) concentrations were used as an index of adipose tissue mobilisation,[2] and were measured via a colorimetric assay on an hourly basis. The trapezoidal rule was used to calculate the area under the curves (AUC) during the study for all obtained parameters.

RESULTS

The unadjusted AUC [bHB] was not significantly different between the three sessions (p=0.089). After controlling for session type, linear regression analysis demonstrated that the AUC [bHB] correlated positively with fasting duration (β=0.416; p=0.018) and negatively with HOMA-IR (β=-0.398; p=0.024). The AUC [bHB], after adjustment for fasting duration

and HOMA-IR, was significantly higher after session A versus B (p=0.021) and A versus C (p=0.008), but it did not differ (p>0.05) between session B versus C (6.08±0.55 versus 4.14±0.55 versus 3.76±0.60 mmol/hour/L, for sessions A, B, and C, respectively). The AUC [insulin] was significantly lower for session A versus C (p=0.001), session A trended lower than B (p=0.067), and session B trended lower than C (p=0.081), while the AUC [glucose] was similar among the three sessions (p=0.907). The AUC [VAS-hunger] was significantly higher in session A compared with either B or C (p<0.01) and similar between B and C. AUC [VAS-hunger] in the second half of each session was significantly higher in session C compared with session B (p<0.01).

CONCLUSION

Greater mobilisation of adipose stores, as indexed by increased [bHB], may be achieved through intermittent fasting in the morning compared with either a zero carbohydrate or a Mediterranean-type breakfast eaten by lean individuals. Carbohydrate restriction in the morning and a Mediterranean-type breakfast constitute equal choices in terms of adipose tissue mobilisation, while a zero-carbohydrate breakfast provides a more prolonged hunger suppression. Further studies are needed to examine the long-term metabolic effects of fasting in the morning.

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Machine Learning-Based Glucose Prediction with Use of Continuous Glucose and Physical Activity Data: The Maastricht Study

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Disclosure: The authors have declared no conflicts of interest. The Maastricht Study was supported by the European Regional Development Fund (ERDF) via OP-Zuid, the Province of Limburg; the Dutch Ministry of Economic Affairs (grant 310.041), Stichting De Weijerhorst (Maastricht, the Netherlands); the Pearl String Initiative Diabetes (Amsterdam, the Netherlands); School for Cardiovascular Diseases (CARIM, Maastricht, the Netherlands); School for Public Health and Primary Care (CAPHRI, Maastricht, the Netherlands); School for Nutrition and Translational Research in Metabolism (NUTRIM, Maastricht, the Netherlands); Stichting Annadal (Maastricht, the Netherlands); Health Foundation Limburg (Maastricht, the Netherlands); and by unrestricted grants from Janssen-Cilag B.V., Novo

Nordisk Farma B.V., Sanofi-Aventis Netherlands B.V., and Medtronic.

Acknowledgements: Mr Foreman, Mr van Doorn, Dr Meex, and Prof Brouwers equally contributed to the manuscript. The first authors contributed equally and the last authors contributed equally.

Keywords: Accelerometry, clinical error grids, continuous glucose monitoring (CGM), glucose prediction, machine learning.

Citation: EMJ Diabet. 2020;8[1]:42-44. Abstract Review No: AR4.

BACKGROUND AND AIMS

The closed-loop insulin delivery system is one of the most promising developments for individuals who require insulin treatment. Such a system combines continuous glucose monitoring (CGM), insulin (with or without glucagon) delivery, and a control algorithm to continuously regulate blood glucose levels.[1,2] The merit of incorporating closed-loop insulin delivery systems into clinical care has been shown in individuals with Type 1 and Type 2 diabetes.[3,4] Nevertheless, these devices may be further optimised by the ability to predict future glucose values, as it can be used to overcome both sensor delay (i.e., the inherent approximately 10-minute discrepancy between interstitially measured and actual plasma glucose values) and sensor malfunctions (i.e., periods during which no glucose values are recorded). The use of machine learning has yielded encouraging glucose prediction results in relatively small study populations or *in silico* studies.[5] Large, human-based studies are now needed to reliably investigate whether and within what time interval glucose values can be accurately predicted by using machine learning. In this proof-of-principle study, the authors assessed to what extent machine learning models can predict glucose values based on historical continuous glucose measurements and physical activity data.

MATERIALS AND METHODS

Data from The Maastricht Study,[6] an observational population-based cohort that comprises individuals with normal glucose metabolism, prediabetes, or Type 2 diabetes, was used. Included were individuals who underwent at least 48 hours of CGM (n=851), most of whom simultaneously wore a physical activity tracker. A random subset of individuals (70%) were used to train models at predicting glucose levels at 15- and 60-minute intervals based on 30 minutes of previous CGM data only, or combined CGM and physical activity data. In the remainder of the participants, predicted values were compared to actual glucose values and evaluated with root-mean-square error (RMSE), Spearman's correlation coefficient (rho), and surveillance and Parkes error grids.[7,8]

RESULTS

Models trained with CGM data were able to accurately predict glucose values at 15 (RMSE: 0.19 mmol/L, rho: 0.96) and 60 minutes (RMSE: 0.59 mmol/L, rho: 0.72). Performance at 15 (RMSE: 0.29 mmol/L, rho: 0.99) and 60 minutes (RMSE: 0.70 mmol/L, rho: 0.78) was comparable in individuals with Type 2 diabetes. Incorporation of physical activity data only slightly improved glucose prediction in both the total study population (15-minute RMSE: 0.18 mmol/L, rho: 0.97; 60-minute RMSE: 0.58 mmol/L; rho: 0.73) and Type 2 diabetes population (15-minute RMSE: 0.27mmol/L, rho: 0.99; 60-minute RMSE: 0.70 mmol/L, rho: 0.79). According to surveillance error grids, glucose prediction was clinically safe at both 15 (>99%) and 60 minutes (>98%). In general, the models tended to underestimate rather than overestimate the actual glucose values.

CONCLUSION

In this proof-of-principle study, the authors showed that machine learning-based models are capable of accurately and safely predicting glucose values at 15- and 60-minute intervals. As such, the prediction models can be used to improve closed-loop dosing systems by overcoming sensor delay and bridging periods of sensor malfunction. Future research should extend and validate these results in individuals with Type 1 diabetes.

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Offspring of Mothers with Gestational Diabetes: A 5-Year Follow-Up

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Disclosure: The authors report grants from the Ministry of Health of the Czech Republic during the conduct of the study.

Acknowledgements: The authors would like to thank Dr Jana Belobradkova for her co-operation in the recruitment of patients with diabetes. The study was supported by the Ministry of Health of the Czech Republic (Grant number: NV18-01-00046).

Keywords: Gestational diabetes mellitus, obesity, offspring, pregnancy, prospective study.

Citation: EMJ Diabet. 2020;8[1]:44-46. Abstract Review No: AR5.

BACKGROUND AND AIMS

Females with gestational diabetes mellitus (GDM) are at an increased risk of complication during delivery (adverse perinatal outcomes) and having abnormalities in glucose metabolism postpartum. They are also seven times more likely to develop prediabetes or Type 2 diabetes mellitus.[1,2] At the same time, GDM represents a risk for the offspring as children of mothers with GDM are more prone to develop childhood obesity, cardiovascular diseases, or Type 2 diabetes mellitus.[3]

The aims of this study were to ascertain possible anthropometric and psychomotor development abnormalities and/or morbidity in the offspring of GDM mothers versus controls in a 5-year follow-up; and to describe the consequences of perinatal morbidity (adverse perinatal outcomes) with childhood morbidity or psychomotor development in a cohort of offspring of GDM mothers versus controls. The secondary aim was to investigate whether the mother's obesity plays a role in the development of the offspring independent of GDM.

MATERIALS AND METHODS

The baseline study population comprised a total of 432 participants. Of those, 68 had a physiological pregnancy without GDM and 364 had GDM, previously described in another study.[4] All follow-up participants were contacted electronically through a questionnaire designed according to the 'child health card', which is available to all children in the Czech Republic healthcare system. The evaluated parameters can be seen in Table 1.

A subset of n=89 (20.6% of females at baseline; 26 with GDM and 63 controls) participated in the prospective study.

Table 1: Offspring data.

Parameter	GDM (n=26)	Control (n=63)	p value	Obese mothers (n=11)	Nonobese mothers (n=78)	p value
Birth weight (g)	3,405 (3,010–3,585)	3,240 (3,020–3,600)	NS	3,350 (3,050–3,540)	3,270 (3,000–3,630)	NS
Newborn jaundice	12.5%	13.5%	NS	18.2%	10.3%	NS
First word (abnormities)*	16.7%	1.9%	**0.015**	0.0%	6.4%	NS
Linking words (abnormities)†	45.8%	17.3%	**0.009**	45.5%	19.2%	**0.034**
Walking alone (abnormities)†	8.7%	3.8%	NS	0.0%	5.1%	NS
Breastfeeding	87.5%	92.3%	NS	81.8%	76.9%	NS
Vaccination (abnormities)	12.5%	13.5%	NS	0.0%	12.8%	NS
Need for regular specialist observation	44.0%	47.5%	NS	36.4%	46.2%	NS
Percentile weight-for-height‡	54.0 (33–63)	45.0 (23–65)	NS	56.5 (33–75)	46.0 (22–63)	NS
Percentile weight-for-height§	57.0 (35–69)	37.0 (22–67)	NS	69.0 (62–85)	37.0 (22–65)	**0.04**
Systolic blood pressure (mmHg)§	95.0 (92–103)	100.0 (94–110)	NS	105.0 (95–110)	99.0 (92–105)	NS
Diastolic blood pressure (mmHg)§	52.0 (48–61)	58.0 (50–60)	NS	53.0 (51–58)	57.5 (50–60)	NS
Heart rate (min)§	91.0 (80–98)	90.0 (81–103)	NS	69.0 (59–79)	91.0 (85–105)	NS
Psychomotor development (abnormities)§	8.3%	0.0%	**0.048**	0.0%	1.3%	NS
Nutritional status (abnormities)§	0.0%	2.0%	NS	0.0%	1.3%	NS
Vision (abnormities)§	0.0%	2.0%	NS	0.0%	9.0%	NS
Hearing (abnormities)§	0.0%	0.0%	NS	0.0%	0.0%	NS
Speech (abnormities)§	30.8%	23.5%	NS	9.1%	19.2%	NS
School Readiness Test (abnormities)§	8.3%	0.0%	**0.048**	0.0%	1.3%	NS
Any illness/hospitalisation	62.5%	23.9%	**0.022**	36.4%	29.5%	NS
Need for regular drug therapy	37.5%	16.4%	NS	18.1%	19.2%	NS

Data expressed as median interquartile range, Mann-Whitney test or frequency (%), and Chi-square test. Bold number indicate statistically significant results.

*evaluated at 12 months of age.

†evaluated at 18 months of age.

‡evaluated at 3 years of age.

§evaluated at 5 years of age.

GDM: gestational diabetes mellitus; NS: nonsignificant.

RESULTS

Mothers with GDM in the second trimester of pregnancy had a significantly higher BMI (p=0.019, Mann-Whitney test); obesity was also higher in the GDM group, but this was not statistically significant. Those with GDM also smoked actively or were former smokers (p=0.012, Chi-square test). Offspring in the control group were breast-fed for longer periods (12 months; interquartile range: 8–17) compared those in the GDM group (6 months; interquartile range: 3–22), but the difference was not statistically significant.

Perinatal parameters of both groups (GDM versus controls) were comparable. Adverse perinatal outcomes (macrosomia, length of delivery, and necessity of instrumental delivery) had no significant influence on the psychomotor development or morbidity of the offspring ≤5 years, in both groups.

Offspring data were compared at 3 years and 5 years. At the age of 12 and 18 months, offspring of GDM mothers had significantly worse speech abilities: they did not say any words at 12 months of age and did not link words at 18 months of age (p=0.015 and p=0.009, respectively, Chi-square test). The speech abilities at the age of 5 years were better in the control group, but the difference was not statistically significant. The Psychomotor Development Screening Test and School Readiness Test (SRT) were borderline worse in the GDM group at 5 years of age (p=0.048 for both, Chi-square test). Offspring of GDM mothers were ill more in their first 5 years of life and required hospitalisation (p=0.022, Chi-square test), with upper respiratory tract illnesses and allergies arising most frequently (Table 1).

CONCLUSION

The authors presented a unique prospective study focussing on the children of mothers with GDM ≤5 years of age and found several differences in selected parameters in the offspring, primarily in their speech abilities and total morbidity. Moreover, a significant link to the mother's obesity and the offspring's increased adiposity was noted, independent of GDM.

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Diabetic Kidney Disease Phenotypes, Mortality, and Incidence of Vascular Outcomes in a Single-Centre Cohort with Type 2 Diabetes: A 13-year Follow-up Observational Study

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Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: The authors wish to thank the patients attending the outpatients' diabetic clinic, and

the staff of the Renzo Navalesi Diabetes Centre in Pisa, particularly in the clinical laboratory and the medical records unit. Giuseppe Penno and Monia Garofolo contributed equally to the study.

Keywords: Albuminuria, all-cause mortality, cardiovascular outcomes, diabetic kidney disease (DKD), end-stage renal disease (ESRD), heart failure, Type 2 diabetes mellitus (T2DM).

Citation: EMJ Diabet. 2020;8[1]:46-48. Abstract Review No: AR6.

BACKGROUND AND AIMS

Diabetes is an emerging public health problem because of the high mortality and morbidity rates associated with its serious complications. Among the most common microvascular complications, diabetic kidney disease (DKD) represents a leading cause of the development of end-stage renal disease (ESRD). Additionally, DKD is associated with a substantially increased burden of cardiovascular (CV) outcomes and all-cause mortality.[1] Along with temporal changes in diabetes care, and in spite of stable overall prevalence of DKD, the frequency of increased albuminuria has declined, while that of low estimated glomerular filtration rate (eGFR) has increased.[2] Thus, non-albuminuric DKD has become the prevailing phenotype (PH) in patients with Type 2 diabetes mellitus (T2DM);[3] however, it remains unclear whether its prognosis is different from that of the other DKD PH.[4] This study evaluated the relationship between different DKD PH and incidence of major vascular events and all-cause mortality in subjects with T2DM.

MATERIALS AND METHODS

This observational, prospective, single-centre, cohort study enrolled 986 adults with T2DM in 2002–2004; subjects were followed-up for a mean of 12.9±2.7 years. Based on albuminuria (Alb; measured by urine albumin-to-creatinine ratio) and eGFR (measured by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation), each subject was classified as: no-DKD (Alb-/eGFR-), albuminuria alone (urine albumin-to-creatinine ratio ≥30 mg/g; Alb+/eGFR-; DKD1–2), reduced eGFR alone (eGFR <60 mL/min/1.73 m^2; Alb-/eGFR+; Alb-DKD), or both albuminuria and reduced eGFR (Alb+/eGFR+; Alb+DKD). Vital status was retrieved for all individuals on 31st December 2017 by interrogating the Italian Health Card Database; data for major vascular events were available for 972 participants (98.6%) and were obtained, to the same date, in collaboration with the Tuscany Regional Health Agency through hospital discharge registers (International Classification of Diseases, Ninth Revision, Clinical Modification codes). Subsequent to Kaplan–Meier (K–M) analyses, hazard ratios (HR; 95% Confidence Interval [CI]) for different outcomes associated with each DKD PH were assessed by unadjusted and adjusted Cox regressions.

RESULTS

Of 986 patients with T2DM, 779 (79.0%) had no-DKD, 144 had DKD1–2 (14.6%), 33 (3.3%) had Alb-DKD, and 30 (3.0%) had Alb+DKD PH; thus, Alb-DKD accounts for 15.9% of all DKD and for 52.4% of all DKD Stages ≥3. A gradually heavier CV risk profile, in terms of traditional and nontraditional risk factors, was distributed through the DKD PH. Death from all causes occurred in 230 individuals (23.3%; 18.0 per 1,000 patient-years [PY]): 19.1% in the no-DKD group, 33.3% in DKD1–2, 36.4% in Alb-DKD, and 70.0% in Alb+DKD (K–M log-rank 77.97; p<0.0001). After adjustment for confounders, HR for death were 1.47 (95% CI: 1.04–2.07) for DKD1–2, 1.22 (95% CI: 0.66–2.25) for Alb-DKD, and 2.43 (95% CI: 1.46–4.06) for Alb+DKD. Major CV events occurred in 276 out of 972 subjects (28.4%; 25.2 per 1,000 PY): 25.3, 38.5, 43.8, and 43.3% through each DKD PH, respectively (K–M; p<0.0001). Adjusted HR for major CV events were 1.37 (95% CI: 1.00–1.89) in DKD1–2, 1.73 (95% CI: 0.98–3.03) in Alb-DKD, to decrease to 1.11 (95% CI: 0.61–2.03) in Alb+DKD, due to competition with all-cause mortality. Coronary events occurred in 184 subjects (18.9%; 16.0 per 1,000 PY): 16.7, 25.9, 31.3, and 30.0% through DKD PH, respectively (K–M; p<0.0001). Adjusted HR for coronary events were 1.41 (95% CI: 0.96–2.07) in DKD1–2, 2.18 (95% CI: 1.11–4.30) in Alb-DKD, to decrease to 1.31 (95% CI: 0.46–3.70) in Alb+DKD. Hospitalisation for heart failure occurred in 84 subjects (8.6%; 6.8 per 1,000 PY): 6.8, 14.7, 21.9, and 13.3% through DKD PH (p<0.0001). Adjusted HR for hospitalisation for heart failure were 1.91 (95% CI: 1.14–3.19) in DKD1–2, 2.40 (95% CI: 1.07–5.38) in Alb-DKD, and 1.31 (95% CI: 0.46–3.70)

in Alb+DKD. ESRD occurred in 71 individuals (7.3%; 5.7 per 1,000 PY): 5.7, 10.5, 9.4, and 30.0% through DKD PH (p<0.0001). Adjusted HR for ESRD were 1.79 (95% CI: 0.99–3.26) in DKD1–2, 1.28 (95% CI: 0.39–4.23) in Alb-DKD, and 5.37 (95% CI: 2.46–11.72) in Alb+DKD.

DISCUSSION

In the patient cohort of T2DM over a very long follow-up, the non-albuminuric DKD PH did not show a significantly greater risk of all-cause mortality; had a significant risk of CVD events, mainly coronary events; and had the highest risk of hospitalisation for heart failure, but a low risk of renal function decline to ESRD. Distribution of DKD PH and, in particular, the prevalence of the emerging Alb-DKD PH was similar to that reported in a larger Italian study, the RIACE multicentre study.[1,4] Similar findings have emerged from cross-sectional observations in cohorts of T2DM from several countries, as well as in subjects enrolled in multinational interventional studies, as summarised in a recent review.[3] A high prevalence of the Alb-DKD PH has also been observed in Type 1 diabetes mellitus.[5,6] At variance with the present study, RIACE showed that risk of all-cause death in Alb-DKD was significantly increased and similar to that of the albuminuria-alone PH (DKD1–2); these differences are likely due to the larger population of the RIACE study, but also to the longer follow-up of the present cohort. Incidence of major CV events and coronary events, and of hospitalisation for heart failure, were significantly higher in Alb-DKD; these observations are consistent with cross-sectional data from RIACE where coronary events correlated more strongly with the Alb-DKD PH than with the albuminuric forms. Finally, as reported by others,[7] the Alb-DKD PH was less prone to progress to ESRD.

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Macrophage Phenotype in Diabetic Wound Healing

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Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: The authors would like to thank Maria Maragkoula, Assoc Prof Konstantinos Evangelou, and Prof Vassilis G. Gorgoulis for their valuable help at the Laboratory of Histology-Embryology in Medical School, National and Kapodistrian University of Athens, Athens, Greece

Keywords: Diabetes, inflammation, macrophage phenotype, wound healing.

Citation: EMJ Diabet. 2020;8[1]:48-50. Abstract Review No: AR7.

BACKGROUND

Diabetic foot ulcers (DFU) are usually chronic wounds that present in the inflammatory phase of the wound healing process.[1] In the early inflammation phase, proinflammatory or classically activated (M1) macrophages secrete proinflammatory cytokines and 'clean' the ulcer by phagocytosing bacteria and debris. As the inflammation resides, macrophages undergo a transition to an anti-inflammatory and healing phenotype (M2 or alternatively activated macrophages).[1,2,3] Diabetic animal wound studies have shown a delayed macrophage phenotype transition and an increased M1/M2 macrophage ratio.[4,5,6]The aim of the current study was to examine the macrophage phenotype in the skin of patients with diabetes with and without DFU, and to look for potential differences in skin macrophages in the forearm and foot of patients with DFU.

METHOD

A total of 20 patients with diabetes (10 with chronic noninfected DFU and 10 without DFU) and 12 healthy controls were recruited. Forearm 3 mm skin punch biopsies were obtained from all participants. In addition, punch biopsies from the borders of the foot ulcers were obtained from patients with DFU. Skin biopsies were fixed in formaldehyde, embedded in paraffin, and sections were cut for immunohistochemistry. Cluster of differentiation (CD)64 was used as a marker for the identification of M1 macrophages and CD163 as a marker of M2 macrophages. The ankle–brachial index was measured and values ≤0.90 were considered indicative of peripheral arterial disease, while diabetic peripheral neuropathy diagnosis was based on neuropathy symptom score and neuropathy disability score.

Table 1: CD64 and CD163 positive cells in forearm biopsies.

	Group 1 DFU (n=10)	Group 2 DM without DFU (n=10)	Group 3 Control (n=12)	p value (All groups)	p value 1 vs 2	p value 1 vs 3	p value 2 vs 3
CD64+ cells	5.8 (5.3, 6.4)	3.9 (3.1, 4.4)	3.4 (3.1, 4.5)	0.001*	0.001†	<0.001†	0.872†
CD163+ cells	6.5 (5.2, 7.5)	7.0 (6.0, 7.6)	3.6 (2.7, 5.7)	0.003*	0.579†	0.006†	0.002†

*p values for comparisons between all three groups by Kruskal–Wallis H test.

†p values for comparisons between pairs of groups (1 vs 2, 1 vs 3, and 2 vs 3) by Mann–Whitney U test.

CD: cluster of differentiation; DFU: diabetic foot ulcers; DM: diabetes mellitus; vs: versus.

RESULTS

The three groups of participants did not differ in terms of age and sex. The two diabetic cohorts did not differ in terms of diabetes duration and glycaemic control. None of the participants had peripheral arterial disease, while all patients with DFU and nine patients (90%) with diabetes without DFU had diabetic peripheral neuropathy. The number of $CD64^+$ and $CD163^+$ cells from the forearm biopsies differed significantly between the three groups of participants (Table 1); subanalysis showed that patients with DFU had significantly higher numbers of $CD64^+$ cells when compared with patients without DFU and healthy participants. Participants with DFU and without DFU had significantly higher numbers of $CD163^+$ cells when compared with healthy individuals in the forearm biopsies. The number of $CD64^+$ and $CD163^+$ cells did not differ between the forearms and feet of patients with DFU: 5.8 (5.3, 6.4) versus 6.0 (5.5, 11.7), p=0.139; and 6.5 (5.2, 7.5) versus 7.0 (4.5, 8.3), p=1.000, respectively.

CONCLUSION

There was increased inflammation in the skin of patients with DFU when compared with patients with diabetes without DFU, and with healthy individuals. In the forearms and feet of individuals with DFU, similar macrophage phenotype, which is associated with a chronic proinflammatory state, was observed. This notion could suggest that increased inflammation in the skin of patients with diabetes either results in foot ulceration, or impairs normal wound healing. Further, larger clinical studies are needed to clarify whether inflammatory cytokine inhibition or modification of macrophage phenotype could be a promising therapeutic approach for chronic refractory DFU.

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Congress Interviews

This collection of interviews is a rousing look into the education, career, and goals of three inspiring females in field of diabetes. Prof Chantal Mathieu, Ms Beatriz Merino Antolín, and Prof Rodica Pop-Busui spoke to EMJ about their roles at the European Association for the Study of Diabetes (EASD) and how their work has been affected by the coronavirus (COVID-19).

Prof Chantal Mathieu

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

Q1 What led you to pursue a career in diabetes and endocrinology? And then focus your research on diabetes care, the effect of vitamin D on the immune system and diabetes, and the β cell?

As a child, I thought I would become a nurse. I like to take care of and help people. I decided to go for medical school, and in medical school I was interested in biochemistry and physiology and so I decided to become an internist. While specialising to become an internist I met, in a very strange but true story, two young people with Type 1 diabetes mellitus (T1DM). I was intrigued by this disease; I got the taste of wanting to become an endocrinologist and, more specifically, to work with people with diabetes. The two young people I met had quite complicated T1DM and one of them died while I knew him. I made it a goal that I wanted to understand: 'What is T1DM?' I wanted to study this disease to try and prevent or arrest it.

It is because I was interested in biochemistry and physiology that I became an internist, and then I became an endocrinologist mainly because of the profile of people with T1DM. That is also why I started to do my PhD thesis on immune

interventions in animal models of T1DM. I have a laboratory that is now run with two very experienced laboratory managers; [they] work with me and we do a lot of research on immune interventions in T1DM.

I also have the advantage of being a clinician and a basic researcher. This means that I can do research *in vitro* and also translate this research for people living with T1DM or at risk of T1DM. It is really every researcher's dream to be able to bridge from the laboratory to the patient. And [my interest in] vitamin D is a very strange story because the professor of endocrinology who accepted me to train for endocrinology is one of the leaders in vitamin D, bone, and calcium. In the 1980s, we had one of the first discoveries in receptors for vitamin D on immune cells. We, and then others, showed that immune cells can activate vitamin D. I used vitamin D as an immune modulator in models of T1DM, and so we studied the effects of vitamin D as an immune modulator in T1DM. I got into vitamin D through calcium, but I was never interested in calcium or bones. I was interested in T1DM and the immune system.

Q2 In 2013, your scientific merit was recognised with the InBev-Baillet Latour Prize for Clinical Research. Could you tell me a bit about the work you carried out when you were given this prestigious award?

This award, which is indeed a prestigious award here in Belgium, was given to me especially because of this 'bridging'. We did clinical research on T1DM *in vitro* and then in mice, and then were able to bridge that to humans, to do intervention trials in people at risk of T1DM and with newly diagnosed T1DM, really analysing why specific therapies worked or worked a little bit and why others didn't work. It was this translational aspect of my research where, from mice to men, the whole story was being bridged. As I said, it is really the dream of every researcher to be able to realise that. I do hope to live to see prevention or arrest of T1DM one day.

Q3 You currently have more than 350 international research publications in diabetes and endocrinology. What do you believe to be the current gaps in literature and which topics require greater attention?

I think different gaps are there when it comes to overall T1DM and Type 2 diabetes mellitus (T2DM). I also do a lot of research in T2DM, mainly clinical, and, to me, the major gaps are how to translate what we find in randomised controlled trials, what we advocate in consensus statements and in guidelines, and how to translate that to value for patients in the real world. We now have very strong evidence; for instance in T2DM, where we know that specific classes or specific agents of glucose-lowering potential have effects on the heart or the kidney and still, when we look at the real world and how much these agents are being used in the people who would be good candidates for these agents, it's only a minority. So how to translate trial findings to the real world and how do we organise our healthcare systems in such a way that this is all affordable? I think this should be a subject of research and it is not very sexy, it's not 'New England', but it's extremely relevant for day-to-day practice.

In T1DM, I believe the major gaps are still in finding who is at risk. We are getting better, and getting better, and [identifying] more precise biomarkers that can, again in a very affordable way, find people who are at high risk of getting T1DM so that we can intervene earlier than we're doing now, namely when glucose is elevated. This, to me, is an important gap. Studies are screening the whole population, but you need to screen tens of thousands of people to find a few who are at risk. That's fine for research and for publications, but it's not workable. The way I do my research, I always have a thought in the back of my head: "How can this be applied to the real world?" I believe important gaps are there in TD2M but also in T1DM; finding good and robust biomarkers will allow us to find people in such a way that we can study interventions in a cheaper and more efficacious way.

Q4 You are currently Vice President at the EASD and have chaired many sessions at the annual congresses. How important is it to continue to hold these meetings every year, even when it must be virtual?

The face-to-face meetings are still extremely important and I look forward to, hopefully next year, being able to have a face-to-face meeting for contacts and for liaising with other

researchers, other clinicians, and healthcare providers or organisers of our healthcare systems. This is extremely important; big conferences are where you meet to put together a consortium on an interesting research tool. The face-to-face meetings, to me, still have enormous value. This being said, I also believe that virtual sessions have an enormous value to bring scientific content because scientific content can be brought in as good a way in virtual setting as a face-to-face setting, whether you give your lecture to 5,000 people in a room or to a camera. It's a bit different: you don't have the stress, but you don't have the vibe. The way we do it now will be the kindergarten version of how we will do it in a couple of years. We, as researchers and clinicians, don't exploit the full possibilities of these virtual platforms. I think we could make our lectures so much more appealing with tools and interactivity and little movies. This is only the beginning. I'm a big proponent of hybrid meetings, where I hope EASD will go, and that's the direction I will push it in. Namely, to have on the one hand, face-to-face meetings with perhaps 6,000–7,000 people for those who need to be in contact and networking, and then on the other hand, have the virtual platform in parallel where you bring the research and where you allow people to discuss in fora.

I invite everybody to go to our virtual annual meeting this year because the platform we have designed with the vendour really is amazing. There will be the sessions, a big EASD plaza where people will create their avatar and will be able to walk around and, for example, visit the booth of postgraduate education, talk to people, and look at our e-learning programme. It will be quite amazing.

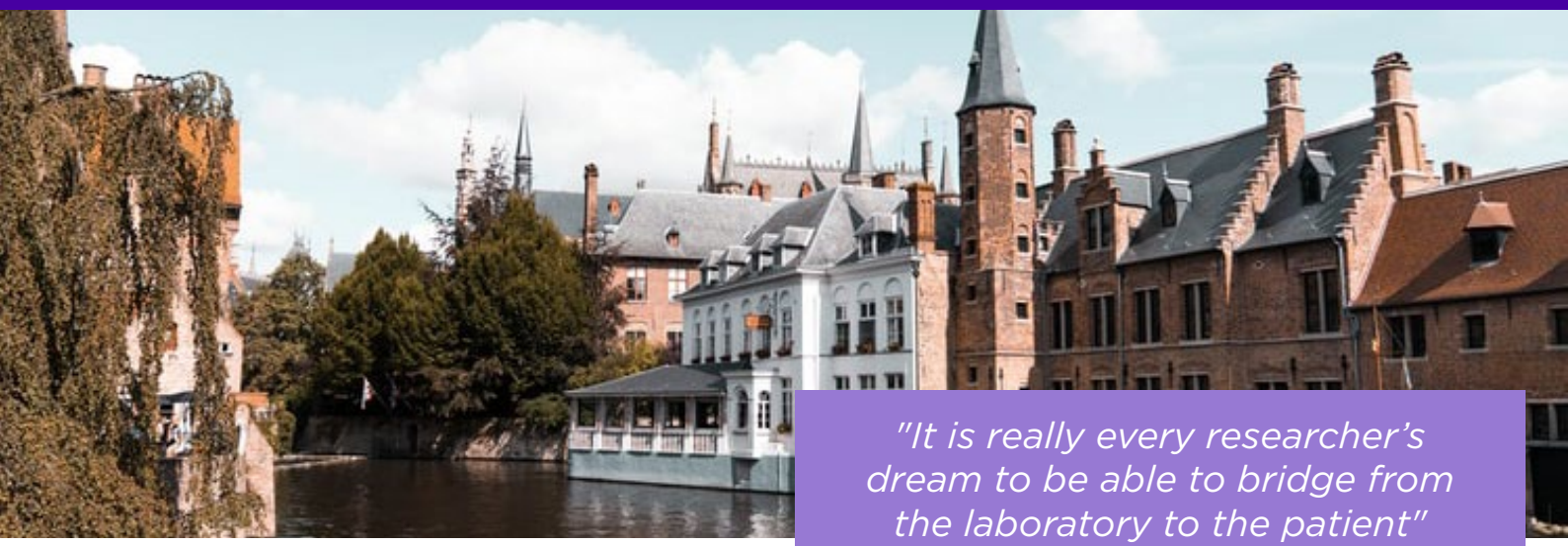
Four years ago, [EASD] launched the virtual annual meeting. Since then, EASD has had a platform where we streamed our sessions; this is open for everybody for 30 days after the annual meeting and this is free. We have had 14,000 people attending the live annual meeting. During the week of the meeting, we had another 14,000 accessing the virtual meeting. In the weeks and months after the annual meeting, we had another 60,000 people visiting our virtual platform. The reach you can have with virtual sessions is just a logarithm higher than what you can have face-to-face. We realised that we now reach the whole subcontinent of India, Africa, and South America. That's also why this year we wanted to keep our registration at a very democratic level: €70 for members and €150 for nonmembers, because we thought that we would be able to reach people for whom spending a registration fee, airfare, and a hotel is completely unreachable. We believe that we are now at a crossroads where we can become global. This is very important to us. The second thing that is also very important to us is that we do not only want to reach endocrinologists or diabetologists, but also primary care physicians, who are the ones who treat most people with T2DM.

Cardiologists and nephrologists paying €500–600 to pick a few sessions that are of interest to them is too high. Paying €150 is perhaps reachable for many cardiologists, nephrologists, or primary care physicians. I am a big believer of a hybrid formula once all of this is done; I do believe we will continue with the virtual version, absolutely, but we will also have the face-to-face.

Q5 In what ways does EASD aim to organise diabetes care, a particular area of interest of yours?

I am the chair of an initiative of EASD called the European Diabetes Forum (EUDF). EASD is not the same as the American Diabetes Association (ADA). ADA is the professional organisation where patients, educators, and specialist nurses all have a voice. EASD is about the study of diabetes. Prof Juleen Zierath, when she was president of EASD several years ago, had an idea to make a forum where everybody could come together; the researchers, EASD, patients, primary care, the companies making drugs, the companies making tools, all stakeholders in diabetes, could come together, have a voice, and advise on policy in diabetes and diabetes care. And so, when you ask, 'how does EASD see diabetes care?' it is in the realm of the EUDF.

In the EUDF, we have three big pillars where we see diabetes care going. The first pillar is the fact that we need data. In Europe, we don't have Centers for Disease Control and Prevention (CDC) like in the USA, so we have no clue on prevalence, evolution, or complications of diabetes, for example. Several countries have these registries or data but getting this on a European level would help us to organise care. We want to put effort into co-ordinating this. Second is that, as the COVID-19 epidemic has shown us, digital



"It is really every researcher's dream to be able to bridge from the laboratory to the patient"

health and novel technologies are very helpful in diabetes care. In EUDF, we also want to put emphasis on digital health, how this can help digital healthcare, and how this can help people with diabetes. We saw it with COVID-19; we had to switch to teleconsultations from Day 0, and so now we have data on how digital health has benefits in reaching patients, but also has limitations. At EASD 2020, the EUDF will have a symposium on the 24th September where we will discuss digital health as the hope for diabetes care. Thirdly, what we also want to put emphasis on in the EUDF is access to care. In different areas of Europe, access to diabetes care and prevention of diabetes is very different from area to area; having access to prevention and to care of complications is also where we in EUDF want to put a lot of emphasis. [These are] three big pillars where EASD, as one of the founding members of EUDF, will put a lot of emphasis.

Q6 As well as Vice President of EASD, you are also the Chair of Postgraduate Education. Could you please explain what this position entails, and how it contributes to the success of the organisation?

This is a project very dear to my heart. When I took over 3 years ago, we were face-to-face. All the postgraduate education efforts were in small, workshop-style, face-to-face meetings of 2–3 days in different areas of Europe. Then I introduced e-learning. We have created a whole e-learning platform, *easd-elearning.org*, where we offer free education for all those healthcare workers who work with people with diabetes. We have courses with different modules on diabetes in Ramadan, use of novel technologies, pathogenesis of T1DM, and how to apply the consensus statement to the real world. We have different courses, free and accessible from all over the world. This, for us, was very important to bring us from face-to-face to virtual. It is like what we are doing now with COVID-19 for our virtual annual meeting. We touch people working with people with diabetes in all countries of the world now; for instance, during the first COVID-19 epidemic we made little webinars on hot topics and some of them were reached by or were seen by 25,000 people. I absolutely believe in this virtual platform to reach the world. Again, the subcontinent of India, Africa, South America, but also in the USA for instance, we have a lot of people accessing e-learning.

Q7 What are the most exciting changes that have been made to the scientific programme for the EASD 2020 meeting compared to the meeting held last year in 2019?

Of course, the fact that it is virtual is a big change, but we have made the platform such that people can still create networks. For when you register, we have introduced artificial intelligence. You can choose to have specific keywords so the programme will propose an even more personalised programme than last year. Artificial intelligence has been introduced to make it even more personal; so if you attend a SGLT2-inhibitor symposium, you will get push messages saying: "Are you interested in more in-depth learning? Go to the e-learning platform." You will be able to become a member of a network of [your] choice. If you say, I am a clinician in Southwest London and I want to create an EASD meeting group with all the clinicians in the area, you can do that. We will have interesting concepts; we have discussion fora where you can have an inner circle

of those discussing and then an outer circle of those looking in, and people from the inner circle can invite people from the outer circle to join the discussion. These are all very new concepts. The avatar in the plaza can roam, you can touch people, talk to them, and give your address card. It will be a next-level virtual meeting.

As for the content, it will very much be like our previous years where we have the big prize lectures with leading researchers. We have the upcoming stars and the young investigators who are also invited. There is a lot of emphasis on our posters; we have the poster tours where we discuss poster sessions. A lot is new on the virtual side and on the technical side, but there is still the very high-level science of previous years.

It will be clever! Because we are a charity, we cannot mix the science with the industry. We have all science on the blue background of EASD, and all the industry will be on an orange background. And if you open the virtual door to the EASD plaza, the carpet will be blue; if you open the virtual door to the industry plaza, where all the industry booths are, the carpet is orange!

Q8 What is the mission hoping to be achieved by the INNODIA Project?

INNODIA is another of my pet projects and it was a unique project in that it comes from the Innovative Medicines Initiative (IMI) of the European Commission. Academic researchers are brought together with industry researchers because they want to accelerate [the process] to cure certain diseases or treatment of certain diseases. We brought together a simple consortium I was leading, called 'Name It', with our researchers in academia, together with clinical researchers. A big group of over 30 academic researchers came together with industry leaders in T1DM. Our mission was, as I said before, to find better biomarkers of T1DM. Also, true innovative clinical trial design accelerates what we know about T1DM, to come to prevention or a cure for T1DM. My big aspiration with INNODIA is to be able to find people with a risk of T1DM in an affordable and efficient way, and to be able to stop this horrible disease that is T1DM.

Q9 What have been the greatest challenges faced by diabetologists and endocrinologists during the COVID-19 pandemic? What have been your main concerns for the community?

My biggest concern is the fact that now all attention goes to COVID-19 and people forget that chronic diseases do not sleep. Diabetes doesn't sleep. Complications of diabetes continue, and what we have seen is a lot of anxiety in our patients, not daring to come to the hospital when they need help. We have seen progressed diabetic foot lesions [that we hadn't previously seen], or severe diabetic ketoacidosis. There is anxiety and fear in people whose condition doesn't sleep and who still need help. That is the negative side: the fact that all the attention goes to COVID-19 and it is like chronic diseases don't matter anymore. They still exist.

The positive is the resilience of our patients. They just get up again, and it is amazing. I'm in admiration. Another positive is the fact that we did accelerate the use of novel technologies and of digital healthcare. For example, we have an app in our hospital on smartphones where people can see their whole file, they can upload data, and we can send them questionnaires. Before COVID-19, 20% of our patients with T1DM had the app on their phone, now 80% have it because they realise it is a way of communication. It has been an accelerator. Centres and new tools have allowed us to look at glucose levels of our patients from a distance. Positives are seeing that people are so resilient, and also the boost it has given to digital health.

Q10 Where can we expect to see your focus lie in the coming years?

My focus will still be on trying to understand T1DM, trying to prevent, or arrest T1DM. My other focus will be on trying to do randomised controlled trials, but trying to translate the data we get from all these fantastic trials that have happened into the real world, and give people a handle on how to apply what we've learned in randomised controlled trials in an affordable way in the real world. I'm now in the second half of my 50s and I don't need another big publication. I really want to spend my time making a difference and bringing value to people living with diabetes. I'm getting a bit impatient with my colleagues who still want to publish: I'm a full professor, I don't need this anymore. I really want to make a difference and create value.

Ms Beatriz Merino Antolín

Winner of EASD Rising Star Symposium and European Foundation for the Study of Diabetes (EFSD) Research Fellowship, University of Valladolid, Valladolid, Spain

Q1 What was your biggest inspiration behind pursuing a career in diabetes research?

I have always loved research careers in biomedicine, in any field in which they can contribute, but, without a doubt, being married to a someone with Type 1 diabetes mellitus is my main driver to continue working to unravel the enigmas of this disease.

Q2 What first sparked your interest to carry out research in insulin resistance?

Insulin resistance is the most important factor in the development and establishment of Type 2 diabetes mellitus. Really, I came to this field by chance with thanks to the predoctoral fellowship associated with a research project by Dr Iván Quesada Moll, Miguel Hernández University of Elche, Elche, Spain, which focussed on the study of the adaptation of pancreatic α cells in the context of obesity and prediabetes. Iván Quesada group is part from the diabetes study group led by Prof Angel Nadal Navajas, Miguel Hernández University of Elche, in a benchmark study in endocrine disruption and diabetes research. Unravelling the mechanisms of insulin resistance and aetiology is key in the fight against this disease and poses a fascinating challenge in this field; my interest began in my postdoctoral stage thanks to everything I learned from my actual mentors: Irene Cózar-Castellano, University of Valladolid, Valladolid, Spain, and Germán Perdomo, CSIC, Valladolid, Spain.

Q3 What advice would you give to young people choosing to start a career as an academic researcher in diabetes?

My advice to any researcher in the field of medicine is to always think that you are doing work that the whole of society will benefit from. Sometimes this job is thankless and the research career is tough, but perseverance leads to achievements that are worth the effort. Knowing that your findings can help further research and improve people's lives is the best of the rewards.

Q4 Which sessions did you enjoy most at EASD Virtual Meeting 2020? Why?

The session I have enjoyed the most is the 14th Albert Renold lecture, given by the great researcher Prof Guy Rutter from Imperial Collage of London, London, UK. This talk was a fascinating review of the metabolic and functional specialisation of β cells and their relationship to the development of diabetes. It shed light on the genetic variants presented in patients with diabetes that would lead to the development of personalised medicine.

Q5 What difference do you think the virtual format of the congress made to the annual meeting?

The virtual format of the current edition has been a success in terms of organisation and dynamism to be able to attend different sessions. The organisers are to be congratulated for the great effort and resources used in this virtual edition. On the other hand, the personal presence and networking that this type of event allows you in its annual form is always missed. Let's hope that next year the presence form can be resumed; in the meantime, we have very much enjoyed the best way that the coronavirus disease (COVID-19) pandemic allowed.

"Sometimes this job is thankless, and the research career is tough, but perseverance leads to achievements that are worth the effort."

Q6 Congratulations on winning the EASD Rising Star Symposium & EFSD Research Fellowship! Could you explain a bit about the research carried out on insulin-degrading enzyme and the endocrine pancreas that led to you winning this award?

Thank you very much for the acknowledgment. It is a project that aims to elucidate the role of the protein insulin-degrading enzyme in the development of the endocrine pancreas and the pathology of diabetes. Our group has discovered that this protein plays a fundamental role in the physiology of the insulin and glucagon secreting pancreatic cells, which are the main pancreatic hormones that regulate glucose homeostasis. When there are functional problems or dysregulations in these cells, diabetic conditions develop. The novelty of this project is that we have data that suggest that the absence of insulin-degrading enzyme could be related to problems in the development of the endocrine pancreas and in the identity of the cells, causing an immature phenotype in these cell types and therefore dysfunctional hormonal secretion. The endocrine pancreas made up of immature cells could lead to the accelerated development of diabetes.

Q7 What did you enjoy most working as part of a team on this research project?

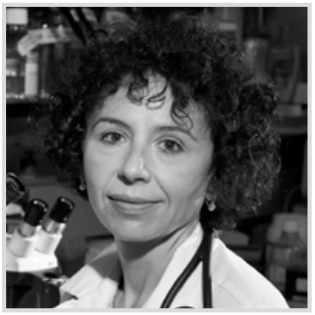
I always enjoy teamwork, each new finding shared with the members of the laboratory encourages further research. Seeing the predoctoral students grow and grow as a postdoctoral with them is one of the best things I have experienced in this project. This project has also allowed me to mature as a researcher thanks to my mentors in this postdoctoral stage, Irene Cózar-Castellano and Germán Perdomo.

Q8 What effect did COVID-19 have on this important project and the work you were able to carry out? What were some of the unique challenges?

COVID-19 affected us with the closure of the laboratory during confinement, this meant that we have had to delay some important experiments including the start of the Rising Star project funded by the EFSD. Fortunately, the EFSD has had no problem giving us the flexibility we needed in this special situation. We hope to begin developing our mouse model for studying endocrine pancreas development in the coming months.

Q9 What aspirations do you have for your future career? Where will your focusses lie in the coming years?

My aspirations are to be able to consolidate a career as an independent researcher in the field of diabetes and to promote the training of new researchers who can help to unravel the enigmas of this other major pandemic. In the years to come I hope to be able to prove myself and continue to help expand the state of the art in the physiology and pathophysiology of the endocrine pancreas.



Prof Rodica Pop-Busui

Chairperson at EASD; Professor of Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, Michigan, USA

Q1 Why is diabetic neuropathy such a prevalent complication in the USA?

Diabetic neuropathy is arguably the most prevalent chronic complication, not only in USA, but throughout the Western world. In addition, emerging data demonstrate very high prevalence rates worldwide. Although all reasons are still not well understood, many of us are actively working to unveil and understand what drives this high risk. An important point is the broad spectrum of diabetic neuropathy clinical manifestations, including peripheral and autonomic forms. In addition, the plethora of risk factors besides hyperglycaemia that contribute to nerve fibre damage and loss include other important players such as the underlying chronic inflammation in diabetes and prediabetes, obesity, insulin resistance, ageing, and lifestyle, as well as several recently described socioeconomic factors.

Q2 You have served as principal investigator on a number of landmark diabetes trials to study the mechanisms of diabetic complications, including diabetic cardiovascular autonomic and peripheral neuropathy. Have you ever experienced a particularly unusual or surprising case? What results did you find?

Indeed, I have had the privilege of leading several neuropathy evaluations and studies in a number of large cohorts of Type 1 and Type 2 diabetes mellitus. Several examples come to mind and I will enumerate just few: firstly, we have conclusively demonstrated in the >10,000 patients with Type 2 diabetes mellitus participating in the ACCORD trial that cardiovascular autonomic neuropathy at baseline independently predicted all-cause and cardiovascular mortality during the trial, doubling the mortality risk. Secondly, with my younger colleague and mentee Dr Kara Mizokami-Stout, by phenotyping the large Type 1 diabetes mellitus Exchange cohort (a contemporary cohort of patients with Type 1 diabetes mellitus reflecting the current standard of care practice in the entire USA and including >25,000 patients), we found that socioeconomic factors are driving a high risk for neuropathy, which has not been demonstrated before; our findings were published earlier this year (2020) and were then confirmed by our colleagues in Scotland, UK with the Scottish Type 1 Register. Thirdly, the differences in the risk-factor profiles between peripheral and autonomic neuropathy that we were able to unveil with complex analyses in the fully phenotyped Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort. This study was published earlier this year as well with my colleague Dr Barbara Braffett and the rest of the neuropathy team.

Q3 The coronavirus 2019 (COVID-19) pandemic has been extremely pressurising for healthcare professionals and you recently co-authored an article titled "COVID-19 and Diabetes: A Collision and Collusion of Two Diseases". What makes patients with diabetes highly susceptible to COVID-19 and how has the pandemic complicated the treatment of patients with diabetes this year? What were the take-home messages of this article?

Overall, there is a consensus from clinical studies and meta-analyses that diabetes is a risk factor for serious COVID-19 infection and mortality. Although research is ongoing, several common risk factors are contributing and include the fact that patients with diabetes frequently suffer from comorbidities such as obesity, hypertension, cardiovascular disease, and chronic kidney disease, and dyslipidaemia, which predispose them to poorer COVID-19 outcomes. In addition,

the low-grade inflammation and degree of glucose control and hyperglycaemia at infection time all promote more severe forms of infection and a higher release of inflammatory mediators.

Q4

You are set to present several sessions at the EASD Virtual Meeting 2020. How widespread has the knowledge of diabetic neuropathy become since the start of your career?

I was honoured to present a plenary lecture on the epidemiology of diabetic neuropathies and share all recent data on this important complication. It is our role to disseminate the knowledge on the actual magnitude of this complication, its risk factors, and the characteristics of patients who are more likely to develop the disease, as well as to provide guidance on the best way to screen, diagnose, and manage patients.

Q5

As co-director of the Neuropathy Centre at the University of Michigan, what are some of the projects that your research team work on?

We have several exciting projects, including a Phase II/III clinical trial designed to test a potential new disease-modifying treatment for diabetic neuropathy, which is funded by the National Institutes of Health (NIH). I am also involved in a couple of novel and complex phenotyping studies in patients with both Type 1 and Type 2 diabetes mellitus, which are funded by the NIH and the Juvenile Diabetes Research Foundation (JDRF). Additionally, we are very excited that we have received funding from the NIH to study longer-term effects of COVID-19 in patients with diabetes.

Q6

What was the long-term goal you set out to achieve when you began your career? Do you still regularly set yourself goals to achieve in your personal or academic development?

I have dedicated my entire career to research and clinical care, targeting new therapies and new technologies to fight against diabetes and its complications, including implementing optimal management of hyperglycaemia and all risk factors in these patients, and advocating for access to optimal care for all patients with diabetes. I am very fortunate to have succeeded in my career thus far, as I am a Professor with Tenure of Internal Medicine, Metabolism, Endocrinology ,and Diabetes, Vice Chair of clinical research for the entire department of Internal Medicine with a faculty of approximately 900 and I am also honoured with an endowed professorship by the University of Michigan. I have achieved national and international recognition, including chairing the American Diabetes Association (ADA) Position Statement on Diabetic Neuropathy. At this stage, my goals are to help our younger and early-career colleagues to succeed as well.

"Diabetic neuropathy is arguably the most prevalent chronic complication, not only in USA, but throughout the Western world"

Continuing Challenges in the Medical Management of Gestational Diabetes Mellitus

EDITOR'S PICK

Gestational diabetes mellitus (GDM) is an important risk factor for Type 2 diabetes mellitus as well as for adverse outcomes of pregnancy. As the title of the insightful review by Jiang et al. suggests, GDM remains a considerable challenge. The review discusses several areas of controversy: notably how to screen, diagnostic criteria, the use of metformin, how to distinguish GDM from other types of diabetes, and follow-up of individuals who have been diagnosed with GDM.

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Disclosure: Dr Rajagopal reports receiving honoraria for lectures from Novo Nordisk Pharmaceuticals outside the submitted work. The other authors have declared no conflicts of interest.

Received: 06.01.20

Accepted: 15.04.20

Keywords: Diabetes, fetal, gestational.

Citation: EMJ Diabet. 2020;DOI/10.33590/emjdiabet/20-00003

Abstract

The management of gestational diabetes mellitus (GDM) involves screening (or universal testing), a diagnostic oral glucose tolerance test, patient counselling/education, gestational weight management and medical nutrition therapy, and self-monitoring of blood glucose levels with regular glycaemia reviews. This is in addition to pharmacological treatment, often insulin therapy, if glycaemia is above target. Individuals with GDM receive more frequent ultrasound testing to assess fetal growth, and birth is planned and not usually allowed to go much past term. A range of challenges continue to arise in GDM management including screening approaches and diagnostic criteria, dealing with the increasing numbers of individuals diagnosed, weight and glycaemic targets, the long-term safety of oral antihyperglycaemic agents for the offspring, particularly metformin, and adjunct medication for complication prevention. GDM management involves additional complexities including differentiating between those with likely undiagnosed Type 2 diabetes mellitus (diabetes in pregnancy), how to manage patients with high glucose early in pregnancy less than diabetes in pregnancy, and identifying patients with rare causes, for example monogenic diabetes or new Type 1 diabetes mellitus in pregnancy. While the management of GDM has evolved from identifying individuals at high risk of progressing to Type 2 diabetes mellitus, to greater focus on improving pregnancy outcomes, those with prior GDM and their offspring have the highest need for follow-up and prevention strategies. To date, follow-up and intervention remains limited for this high-risk group for both diabetes and cardiovascular disease. Follow-up in these individuals is particularly important for the next pregnancy, especially as GDM prevention from the second trimester onwards remains another continuing challenge.

INTRODUCTION

Gestational diabetes mellitus (GDM) is hyperglycaemia first detected in pregnancy, short of overt diabetes in pregnancy (DIP).[1] While some females enter pregnancy with relative hyperglycaemia, worsening of glycaemic levels usually occurs in the third trimester following increased insulin resistance, secondary to changes in circulating hormones and cytokines that overcome the maximum insulin secretory capacity.[2] GDM-associated adverse pregnancy outcomes for the mother include pre-eclampsia, pregnancy-induced hypertension, increased rates of caesarean section as well as delivery complications associated with neonatal macrosomia.[3] Adverse neonatal outcomes include babies who are large for gestational age (LGA), birth trauma, shoulder dystocia, prematurity, and neonatal hypoglycaemia. The Pederson hypothesis[4] proposes that these complications are driven by maternal hyperglycaemia, with glucose crossing the placenta leading to fetal hyperglycaemia and hyperinsulinaemia. Optimal management of GDM decreases the risk of many of these adverse events.[5] In this article, the authors outline the latest recommendations for the diagnosis of GDM and its medical treatment, with discussion of the supporting evidence and remaining controversies. Prediagnostic GDM prevention is out of the scope of this review.

CHALLENGES IN GESTATIONAL DIABETES MELLITUS SCREENING AND DIAGNOSIS

Criteria for the diagnosis of GDM have evolved over decades from identifying individuals at long-term risk of developing Type 2 diabetes mellitus, to diagnostic criteria derived from observational studies on the risk of adverse pregnancy outcomes. The landmark Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study[6] heavily influenced the current internationally recommended GDM diagnostic criteria. HAPO was an international, prospective, blinded observational study of 23,316 participants examining the relationship between venous BG concentrations at three timepoints during a 75 g oral glucose tolerance test (OGTT) undertaken at 24–32 weeks gestation, and the risk of adverse pregnancy outcomes. Primary outcomes were LGA, primary caesarean section, neonatal hypoglycaemia, and high cord C-peptide above the 90th percentile as a surrogate marker for neonatal hyperinsulinaemia. A continuous linear positive relationship was shown between each of the three-timepoint BG concentrations and the primary outcomes. Using these study data, the International Association of Diabetes in Pregnancy Study Groups (IADPSG) formulated the GDM diagnostic thresholds (via consensus) based on an adjusted odds ratio of 1.75 for the primary study adverse pregnancy outcomes.[1]

The IADPSG diagnostic criteria have been adopted by the World Health Organization (WHO), the International Federation of Gynaecology and Obstetrics (FIGO),[7] the International Diabetes Federation (IDF),[8] and many countries internationally (e.g., the Australasian Diabetes in Pregnancy Society [ADIPS][9]). However, other approaches to the criteria include the HAPO adjusted odds ratio of 2 for adverse outcomes (used in Canada, for example)[10] and locally developed criteria (used in England),[11] while the American Diabetes Association (ADA)[12] accepts both the American College of Obstetricians and Gynecologists (ACOG)[13] and IADPSG diagnostic criteria. Moreover, there remains diversity in screening practice to identify those who require an OGTT (if not universal), including risk factor screening and the 50 g glucose challenge test which misses relative fasting hyperglycaemia, a better correlate of adverse pregnancy outcomes.[14] Table 1 shows the major criteria for GDM used internationally.

The major justification against the IADPSG criteria is the increase in individuals requiring treatment, putting strain on public health systems, and medicalising more pregnancies. Within Australia, GDM incidence has been reported to increase from a baseline of 9.6% to 13.0%,[18] with a conservative estimated workload increase of up to 31.0%,[19] while in high-risk populations, such as the United Arab Emirates, over a 4-fold increase in prevalence from 9.2% to 45.3% has been reported.[20]

Table 1: Major current diagnostic criteria for gestational diabetes mellitus.

Criteria	IADPSG/WHO[1,15]	*ADA/ACOG, USA[12]	NICE, UK[11]	*Canada[10]	NZSSD[16]	DIPSI[17]
Early testing: when, who, and test used (all repeat at 24–28 weeks if negative)	First antenatal visit if risk factors*: FBG, RBG, HbA1c	First antenatal visit if risk factors*: FBG, RBG, HbA1c	First antenatal visit if past GDM 75 g OGTT	First antenatal visit if risk factors*: HbA1c	Universal HbA1c <20 weeks GDM if HbA1c ≥50 mmol/mol	Universal, one step, 75 g nonfasting
Criteria for proceeding to OGTT	Usually one step only	50 g GCT 1HBG ≥7.2 mmol/L	Any of five risk factors: - BMI >30 kg/m^2 - Previous macrosomic baby - Past GDM - First-degree relative with diabetes - Ethnic minority with high prevalence to diabetes	50 g GCT 1HBG ≥7.8 mmol/L	50 g GCT 1HBG ≥7.8 mmol/L	Usually one step only
Glucose load	75 g fasting	100 g fasting	75 g fasting	75 g fasting	75 g fasting	75 g nonfasting
Fasting glucose†	≥5.1 mM	≥5.3 mM	≥5.6 mM	≥5.3 mM	≥5.5 mM	-
1-hour glucose†	≥10.0 mM	≥10.0 mM	-	≥10.6 mM	-	-
2-hour glucose†	≥8.5 mM	≥8.6 mM	≥7.8 mM	≥9.0 mM	≥9.0 mM	≥7.8mM
3-hour glucose†	-	≥7.8 mM	-	-	-	-
No. of abnormal tests required	1	2	1	1	1	1

*Also recommend early screening for diabetes in pregnancy in the presence of risk factors, e.g., previous elevated glucose levels, maternal age ≥40 years, females from high-risk ethnicity groups, family history of diabetes including GDM in a first-degree relative, prepregnancy BMI ≥30 kg/m^2, previous macrosomia, polycystic ovarian syndrome, and high-risk medication use (e.g., corticosteroids or antipsychotics). Criteria for (overt) diabetes in pregnancy (unless stated otherwise) are FBG: ≥7.0 mmol/L; HbA1c ≥6.5% (47 mmol/mol); RBG: ≥11.1 mmol/L.

†Thresholds for diagnosis

ACOG: The American College of Obstetricians and Gynecologists; ADA: The American Diabetes Association; DIPSI: The Diabetes in Pregnancy Study Group India; FBG: fasting blood glucose; GCT: glucose challenge test; GDM: gestational diabetes mellitus; IADPSG: International Association of Diabetes in Pregnancy Study Group; NICE: The National Institute for Health and Care Excellence; NZSSD: The New Zealand Society for the Study of Diabetes; OGTT: oral glucose tolerance test; RBG: random blood glucose; WHO: World Health Organization; 1HBG: 1-hour blood glucose.

These increases in incidence have been mainly through dropping nonevidence-based screening tests, adding early screening for DIP, only using one positive test for diagnosis (as opposed to the ACOG OGTT criteria requiring two readings above the diagnostic threshold),[13] a reduction in the fasting glucose cut-off, and including 1-hour glucose criteria. On the other

hand, the new criteria capture individuals at increased risk of adverse pregnancy outcomes otherwise missed by alternative OGTT diagnostic criteria,[21, 22] and can improve pregnancy outcomes on a population basis with associated health cost savings.[23] Essentially, work has moved from the delivery room, postnatal ward, and neonatal intensive care unit, to antenatal care including the input of diabetes services.

Further rationale limiting uptake of the new GDM criteria is that they are predominantly based on one observational study classified by the WHO as 'weak evidence'[15] and that there have been no randomised controlled trials (RCT) of treatment using these criteria (a criticism which can be applied to most GDM criteria). In the interim, new models of care are now being introduced to deal with the larger numbers of patients, for example use of a risk-based step-up or step-down approach to more intensive management.[24]

Up to 1.8% of individuals with GDM have undiagnosed monogenic diabetes, particularly with *glucokinase* mutations (maturity onset diabetes of the young [MODY 2]).[25] Individuals with MODY 2 have a high fasting glucose but often a normal postload glucose, hence are readily identified with an OGTT rather than GCT. If the baby also has the mutation for MODY 2, then managing maternal glycaemia to current maternal glucose targets can result in a baby who is small for gestational age (SGA). Approaches to systematically identify those with MODY 2, including risk calculators and clinical genetic assessment, are becoming increasingly widespread but still require clinical recognition to initiate the process.

The current issues with diagnosing GDM clearly remain an area of debate. There is a need to balance the overarching requirement or global consensus on a single set of criteria and the strength of evidence for the diagnostic threshold with the practicality of their implementation in large populations. A further complication is the impact of early GDM screening and the uncertainty over the criteria for GDM before 20 weeks gestation.

IS THERE A ROLE FOR EARLY GESTATIONAL DIABETES MELLITUS SCREENING?

The IADPSG GDM diagnostic criteria are based on HAPO 24–32-week gestational data. However, screening for DIP early in pregnancy prior to 24 weeks gestation is also recommended among individuals with risk factors (see Table 1) to identify those with undiagnosed Type 2 diabetes mellitus. The diagnostic thresholds for DIP are the same as the criteria for Type 2 diabetes mellitus (fasting glucose ≥7.0 mmol/L, 2 hour glucose or random glucose ≥11.1 mmol/L, and/or HbA1c ≥6.5% [47 mmol/mol]).[9]

While seeking individuals with DIP at the earliest opportunity, a group with milder forms of hyperglycaemia in pregnancy, early GDM, are inevitably identified and it remains unclear how best to diagnose (especially as 'normal' glucose levels vary with gestational week) and manage these individuals.[26] Patients fulfilling the IADPSG criteria in early pregnancy show characteristics of metabolic syndrome,[27] and a systematic review using different criteria in mostly observational studies has shown that individuals with early diagnosed GDM, despite treatment, had higher perinatal mortality, neonatal hypoglycaemia, and insulin use compared to those diagnosed in later pregnancy.[28] Showing greater adverse outcomes does not mean that improved treatment will effectively reduce risk. A definitive multicentre RCT, the Treatment of BOoking Gestational diabetes Mellitus (ToBOGM) Study,[29,30] is currently underway, evaluating the outcomes of treatment of individuals diagnosed with early GDM (<20 weeks gestation) versus delayed treatment until after a confirmatory OGTT at 24 weeks gestation. The results of the small pilot study[29] demonstrated an increased risk of neonatal intensive care unit admission in the early treatment arm (mainly due to SGA), but an increase in LGA in the nontreatment arm. This highlights the complexity of this issue and the need for high quality interventional studies to evaluate the safety and efficacy of the guideline recommendations. In the interim, and until the release of the ToBOGM results, the systematic review of current evidence[28] recommended a fasting glucose of 6.1–6.9 mmol/L be used to diagnose early GDM.

ARE THE APPROPRIATE GESTATIONAL DIABETES MELLITUS TREATMENT TARGETS AVAILABLE?

Glycaemic Management Targets

There is no worldwide consensus on the GDM treatment targets. Generally, patients are recommended to self-monitor finger prick BG four times a day: fasting and postprandial levels using targets are shown in Table 2.

The Australian Carbohydrate Intolerance Study in Pregnant Females (ACHOIS)[31] RCT showed a reduction in the primary perinatal composite outcome consisting of neonatal death, shoulder dystocia, bone fracture, and nerve palsy, when individuals with GDM (defined by 75 g OGTT criteria of fasting BG <7.8 mmmol/L and a 2-hour BG 7.8–11.0 mmol/L) were treated to the target of fasting BG ≤5.5 mmol/L, and 2 hours postprandial BG ≤7.0mmol/L.

The second major RCT, conducted by the Maternal-Fetal Medicine Units Network (MFMUN)[32] demonstrated that an even tighter glycaemic target of fasting BG <5.3 mmol/L and 2 hours postprandial BG <6.7 mmol/L was associated with a significantly decreased risk of LGA, shoulder dystocia, caesarean section, gestational hypertension, and pre-eclampsia in individuals with GDM diagnosed using the following criteria: fasting BG <5.3 mmol/L, and two or three timed glucose results exceeding the levels of 1 hour 10.0 mmol/L, 2 hours 8.6 mmol/L, 3 hours 7.8 mmol/L on a 100 g 3 hour OGTT. Retrospective cohort studies, by Bogdanet D et al.[33] for example, have found that in GDM, patients treated to a target of fasting BG ≤5.0 mmol/L and 1-hour postprandial BG ≤7.0 mmol/L, there was a similar rate of LGA and SGA as those without GDM. RCT of different glycaemic thresholds, among individuals diagnosed using the IADPSG criteria, are now needed to identify treatment strategies that result in a reduction in fetal adiposity and hyperinsulinaemia and their associated sequelae, without increasing the risk of SGA babies and intrauterine undernutrition.

GESTATIONAL WEIGHT GAIN TARGETS

Gestational weight management is important in individuals with GDM, with targets based on the Institute of Medicine (IOM) guidelines[34] (Table 3). These are based on the effect of gestational weight gain/loss on a series of maternal and fetal outcomes. Individuals who are overweight or obese in the first trimester are not expected to gain weight. Individuals with GDM and gestational weight gain above the recommendations have increased risk of LGA, preterm delivery, and primary caesarean section.[35]

Table 2: Treatment target recommendations for gestational diabetes mellitus.

	ADIPS[9]	ACHOIS[31]	MFMUN[32]
Fasting	≤5.0 mmol/L	≤5.5mmol/L	<5.3 mmol/L
1 hour postprandial	≤7.4 mmol/L	N/A	N/A
2 hours postprandial	≤6.7 mmol/L	≤7.0 mmol/L	<6.7 mmol/L
Number of abnormal results for insulin therapy	≥two elevated levels at a given testing time within 1 week	≥two elevated levels at any testing time or one elevated level ≥9 mmol/L within a 2-week period	Majority of fasting values or postprandial values between study visits were elevated
Basis	2 standard deviations above the mean of glucose levels of pregnant females without GDM from the HAPO study	Australian Carbohydrate Intolerance Study in Pregnant Females	Maternal and Fetal Medicine Units Network randomised trial of Treatment for Mild Gestational Diabetes

ACHOIS: Australian Carbohydrate Intolerance Study in Pregnant Women; ADIPS: Australasian Diabetes in Pregnancy Society; GDM: gestational diabetes mellitus; HAPO: Hyperglycemia and Adverse Pregnancy Outcome; MFMUN: Maternal and Fetal Medicine Units Network.

Table 3: Recommended Gestational Weight Gain in Pregnancy.

Prepregnancy BMI (kg/m²)	Total weight gain (kg)	Rate of weight gain in second and third trimester (mean [range] kg/week)
Underweight (<18.5)	12.5–18.0	0.51 (0.44–0.58)
Normal weight (18.5–24.9)	11.5–16.0	0.42 (0.35–0.50)
Overweight (25.0–29.9)	7.0–11.5	0.28 (0.23–0.33)
Obese (≥30.0)	5.0-9.0	0.22 (0.17–0.27)

Recent debate has largely centred upon whether gestational weight gain among individuals who are obese should remain between 0–5 kg (i.e., loss of maternal body weight after accounting for pregnancy-related weight gain attributable to baby, placenta, breasts). Such negative weight balance might decrease fetal fat mass, but also reduce fetal lean mass with potential long term sequelae (e.g., hypertension, heart disease).[36]

HOW SHOULD GESTATIONAL DIABETES MELLITUS BE TREATED?

Diet

Lifestyle interventions, including medical nutrition therapy and physical activity promotion, are the cornerstone of GDM treatment and for limiting excessive gestational weight gain.[37]

Medical nutrition therapy involves a dietary assessment and tailored recommendations to balance sufficient micro- and macronutrients for maternal wellbeing and fetal growth, without excessive carbohydrate or fat intake, and avoiding excessive gestational weight gain. The Dietary Reference Intakes for pregnancy recommend a minimum of 175 g of carbohydrate, 71 g of protein, and 28 g of fibre per day with refinements based on the individual's biometric measurements.[38] A diet consisting of 1,384–1,863 kcal/day did not impact on pregnancy outcomes in individuals with GDM, while an intake of 1,560–1,630 kcal/day may assist in limiting gestational weight gain in those with GDM with pregestational obesity, without adverse effect.[39] Low-carbohydrate diets may be associated with an increase in insulin resistance and, paradoxically, a higher fasting glucose.[40]

Apart from the Dietary Approaches to Stop Hypertension (DASH) diet rich in fruits, vegetables, whole grains, and low-fat dairy products, which has been shown in GDM to decrease fasting and postprandial glucose levels with concomitant outcomes of decreased medication use, decreased macrosomia, and decreased rate of caesarean sections, there are no specific types of dietary composition that have been identified via RCT to be superior for individuals with GDM.[41] A low glycaemic index diet decreases fasting and postprandial glucose levels as well as the need for insulin use, but without consistent improvements in pregnancy outcomes.[41,42] The Mediterranean Diet has some evidence for decreasing LGA babies without a rise in SGA delivery.[43] In terms of meal frequency, the American Academy of Nutrition and Dietetics currently recommends, via consensus, a distribution of nutritional intake via three main meals and two or more snacks to assist with reducing postprandial glucose rise.[39]

Exercise

An exercise regimen consisting of at least 20–30 minutes per day of moderate-intensity exercise on most days of the week is recommended for individuals with GDM.[38] Both moderate-intensity aerobic and resistance exercise have been shown to lower fasting and postprandial glucose levels in GDM (with no reduction in insulin

requirement).[44] Patients with GDM provided with exercise intervention have been found to have decreased gestational weight gain, macrosomia, caesarean section, preterm birth, and SGA.[45,46] There is emerging evidence that sedentary behaviour (any waking behaviour characterised by an energy expenditure ≤1.5 metabolic equivalents while in a sitting or reclining posture) confers up to 3.8 odds ratio for adverse neonatal outcomes in GDM pregnancy.[47] Therefore, advice should include recommendations for both active exercise and a decrease in sedentary behaviour.

Medication

Insulin

Insulin therapy in combination with lifestyle interventions to reach glycaemic targets reduces adverse pregnancy outcomes related to GDM in major RCT.[31,32] The flexibility of insulin use allows for dose titration to reach glycaemic targets and tailoring to the timing of hyperglycaemia, such as exclusive postprandial hyperglycaemia or fasting hyperglycaemia. Use of the long-acting insulin detemir in pregnancy is noninferior to isophane insulin with regard to efficacy and perinatal outcome. No RCT of glargine have been conducted. Quick-acting insulin analogues such as aspart or lispro, injected approximately 15–20 minutes prior to a meal, can effectively reduce the postprandial peak in glucose level, whilst having similar safety profiles to human insulin, including minimal formation of insulin–antibody complexes.[48]

Metformin

Oral medications address some of the practical issues relating to insulin administration, leading to higher acceptability amongst pregnant patients.[49] Metformin is the most common oral medication used for GDM. Compared to insulin use, metformin has been shown to result in less maternal gestational weight gain, lower postprandial glucose level, less pregnancy-induced hypertension, and less severe neonatal hypoglycaemia.[50] Metformin use is associated with its typical adverse effects (abdominal pain and diarrhoea), as well as more spontaneous preterm delivery without an increase in other prematurity-associated complications.[49] Metformin therapy may require supplemental insulin therapy in 26.8–33.8% of individuals.[50] No short-term adverse fetal outcomes, including fetal malformations, have been described in GDM.[49] However, the long-term effects of metformin on offspring remain uncertain.[51] The MiG-TOFU 2-year follow-up[52] and the MiG-TOFU 7–9-year follow-up[53] showed differences in offspring adiposity, and studies outside of GDM have been associated with raised offspring blood pressure and fasting glucose. Further follow-up studies are needed.

Glibenclamide

Glibenclamide is no longer recommended and is associated with higher fetal birth weight and macrosomia rate compared to both insulin or metformin use, more neonatal hypoglycaemia compared to insulin use, and more maternal gestational weight gain compared to metformin use.[50] A plausible explanation for this adverse outcome profile may be related to the placental transfer of the medication leading to fetal hyperinsulinaemia.[50]

CHALLENGES IN OBSTETRIC MONITORING

Ultrasound monitoring allows detection of fetal malformations, fetal movements, placental insufficiency, and SGA, which may be a reflection of overtreatment of GDM, while LGA or polyhydramnios may suggest suboptimal glycaemic control. Individuals with GDM often have a growth scan performed at approximately the 32nd week of pregnancy, as an increase in the fetal abdominal circumference to >90th centile on ultrasound at this time is associated with an increased rate of macrosomia, caesarean section, and shoulder dystocia.[54] However, there is a suggestion that an earlier growth scan at the 28th week of gestation may be required to detect increased abdominal circumference sufficiently early for glycaemic management to result in a reduction in adverse neonatal outcomes.[55] Antenatal steroid treatment at 37–39 weeks gestation for lung maturation prior to elective caesarean section has recently been shown in a case control study to be associated with increased neonatal hypoglycaemia with no evidence of reduced neonatal respiratory problems, and is another aspect of care warranting an RCT.[56]

As a pregnancy at high risk of pre-eclampsia, aspirin may be indicated; however, trials to date have only included limited numbers of individuals with GDM.

CHALLENGES IN POSTPARTUM MANAGEMENT

Individuals with GDM are at increased risk of developing GDM in future pregnancies as well as an increased lifetime risk of cardiovascular disease[57] and Type 2 diabetes mellitus, including by the time of the next pregnancy (and with it, the risk of fetal malformations). In the HAPO follow-up study, 52.2% of females with GDM according to IADPSG criteria developed either a prediabetes state or Type 2 diabetes in the median 11.4 years of follow-up.[58] For individuals with DIP, 59% are diagnosed with either a prediabetes state or Type 2 diabetes mellitus at the 6–8 week postpartum OGTT.[59] Progression to Type 2 diabetes mellitus can be reduced by up to 50% among patients with prior GDM.[60] In spite of this evidence, wide-scale systematic follow-up programmes remain underdeveloped. There are currently no evidence-based guidelines for the frequency of postpartum follow up of patients who have had GDM, though organisations such as ADIPS have released recommendations:[9]

- Postpartum 75 g OGTT at 6–8 weeks postpartum
- Annual 75 g OGTT if the individual is planning future pregnancy
- In those not planning pregnancy, screening via 75 g OGTT every 3 years, with increase in frequency based on clinical circumstances
- Where OGTT is not feasible, HbA1c can be used but has low sensitivity for impaired glucose tolerance

CONCLUSION

The management of GDM has evolved over the years to focus on evidence-based strategies proven to be safe and efficacious in diagnosis, monitoring, and treatment, aiming to improve maternal and fetal outcomes. Though the finer details may not be uniform across the world, the basic structure of management is consistent as a global practice. However, underneath this relative consistency, a range of GDM-related practices continue to vary globally including screening approaches and diagnostic criteria, dealing with the increasing numbers of individuals diagnosed, weight and glycaemic targets, the use of oral antihyperglycaemic agents, and schedule for postpartum follow-up.

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Metformin: From Immediate Release to Extended Release Formula, Effectiveness, And Safety in Patients With Chronic Kidney Disease

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Disclosure: The authors have declared no conflicts of interest.

Received: 06.10.19

Accepted: 17.08.20

Keywords: Glycaemic control, insulin resistance, metformin extended release (XR), metformin immediate release.

Citation: EMJ Diabet. 2020;8[1]:70-78.

Abstract

Type 2 diabetes mellitus is currently the main cause of chronic kidney disease, leading to end-stage renal disease in most countries around the world. Metformin is the most commonly prescribed oral antihyperglycaemic in the world and after approval by the U.S. Food and Drug Administration (FDA) in 1994, it is currently recommended as the first-line pharmacological agent for newly diagnosed Type 2 diabetes mellitus by many professional diabetes associations. In this review, the authors analysed efficacy and safety of metformin in patients with chronic kidney disease.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is currently the main cause of chronic kidney disease (CKD) leading to end-stage renal disease (ESRD) in most countries around the world. Over the past decade, the United States Renal Data System (USRDS) figures have demonstrated a progressive increase in the number of T2DM cases entering ESRD programmes.[1] Now, more than 40% of all incident patients are diabetic, while other classic nephrology disorders, such as glomerulonephritis, cystic kidney disease, and hypertension, have remained relatively steady as causes of ESRD over the past decade.[2]

Metformin is the most commonly prescribed oral antihyperglycaemic in the world and, after approval by the U.S. Food and Drug Administration (FDA) in 1994, is currently recommended as the first-line pharmacological agent for newly diagnosed T2DM by the American Diabetes Association (ADA)[3] and by the European Association for the Study of Diabetes (EASD).[4] It acts as an antidiabetic

drug via increasing peripheral glucose utilisation and peripheral insulin sensitivity as well as by reducing intestinal glucose absorption and hepatic glucose generation.[5] Lowering blood glucose with metformin in T2DM does not cause hypoglycaemia.[6] Moreover, metformin was found to reduce weight in obese patients,[7] improve lipid plasma levels,[8] and prevent and delay progression of microvascular and macrovascular complications,[2,5] which is of immense importance to reduce the risk of diabetes development and progression of overt T2DM in patients.

METHOD

A search strategy was developed to identify randomised controlled trials in both MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL). The terms "metformin", "biguanides", "fenformin", "efficacy", and "safety" were incorporated into an electronic search strategy that included the Dickersin filter for randomised controlled trials. The bibliographies of all identified randomised trials and review articles were reviewed to look for additional studies of interest. The author's reviewed the citations retrieved from the electronic search to identify relevant articles for this review. The authors subsequently reviewed the potential trials to determine their eligibility. To qualify for inclusion, clinical trials were required to meet a series of predetermined criteria for study design, study population, interventions evaluated, and outcome measured. The following data were abstracted onto standardised case report forms: authors, year of publication, country of study, source of funding, study goal, means of randomisation and blinding, duration of treatment, treatment characteristics, sex, quantity of and reasons for study withdrawal, renal function and age characteristics of the treatment and control groups, outcomes, and adverse event data. A validated, three-item scale was used to evaluate the overall reporting quality of the trials selected for inclusion in the present review. This scale provided scoring for randomisation (0–2 points), double-blinding (0–2 points), and account for withdrawals (1 point). Scores ranged between 0 and 5, and scores of 3 or more indicated a study of high quality, and study selection was restricted to randomised controlled trials to ensure the inclusion of high-quality evidence only. In this review, the authors analysed the efficacy and safety of metformin in patients with CKD.

METFORMIN FORMULATIONS

Metformin reduces plasma glucose levels by acting at several different levels: it reduces hepatic glucose production in the liver by inhibiting gluconeogenesis and glycogenolysis, increases muscular insulin sensitivity and improves the uptake and utilisation of peripheral glucose, and it slows down the intestinal absorption of glucose.[9] Until now, metformin was available as an immediate release (IR) formulation to be taken three times daily at a dosage of 500, 850, and 1000 mg, in tablet or in powdered form. The powder formulation was designed to overcome the challenge of considerable tablet size, which made them difficult to swallow, especially for elderly patients or people with dysphagia. The authors of this review have previously studied powder formulation and showed that the degree of patient satisfaction towards the antidiabetic treatment was increased and led to improved glycaemic control.[10]

Recently, extended release (XR) metformin has become available. Compared to conventional IR formulation, the XR offers some advantages. Firstly, the possibility to take the drug once a day, but with better gastrointestinal tolerability and equal effectiveness.[11] The XR formulation has been designed to allow a more gradual release of the drug in the main absorption site, i.e., the upper gastrointestinal tract, thus improving its tolerability and patient compliance because of reduced administration frequency and a decrease in adverse events. However, apart from a review published on the comparison between metformin IR and metformin XR,[11] few randomised clinical trials have been conducted to directly compare the two formulations. For example, Schwartz et al.[12] conducted a study about a comparison between metformin XR treatment regimens versus metformin IR in a double-blind 24-week trial. Data showed that once- or twice-daily metformin XR was as safe and effective as twice-daily metformin IR and provided continued glycaemic control for up to 24 weeks of treatment. Similar results were reported by Fujioka et al.,[13] who showed that patients with T2DM who had been receiving

twice-daily metformin IR achieved comparable glycaemic control when therapy was switched to once-daily metformin XR, at the same or a greater total daily dose. Derosa et al.[14] conducted a trial to compare metformin XR and metformin IR, recording a better effect of metformin XR compared to metformin IR in improving glycaemic control.

The same can be said about the lipid profile, with an improvement of total cholesterol and low-density lipoprotein cholesterol with metformin XR compared to IR. The positive effects of metformin on the lipid profile have been shown in rats.[15] The authors also observed a visfatin improvement with metformin XR, not recorded with metformin IR. Visfatin is a protein expressed by adipocytes, and also by the liver, muscle, bone marrow, and lymphocytes.[16] Visfatin exerts insulin-mimetic effects in cultured adipocytes, hepatocytes, and myotubes, and lowers plasma glucose in mice.[17] Visfatin binds to the insulin receptor with similar affinity, but at a site distinct from insulin with insulin-sensitising effects. An improvement of visfatin improves insulin sensitivity.[18]

The better effects of metformin XR compared to metformin IR could be explained by better patient compliance and the minor incidence of adverse events.[19] These data should not be surprising as one of the factors that affect glycaemic control is patient compliance to therapy. Patient compliance is related to the complexity of the treatment, total number of tablets taken daily, size of the tablets, difficulty in swallowing, side effects, and the cost of therapy.[20]

Timmins et al.[21] obtained results for adverse events which were slightly different to those reported by Derosa et al.[22] Timmins et al. found that adverse events with metformin XR were similar to those reported with metformin IR. However, they did not directly compare the two different formulations; moreover, they conducted the study in healthy subjects and not in patients with diabetes. Derosa et al. recorded that TNFα and high-sensitivity C-reactive protein were lower with metformin XR compared to baseline and to metformin IR, this could be attributed to the better improvement of glycaemic control obtained with metformin XR. It has already been shown that hyperglycaemia induces endothelial damage;[22] postprandial glycaemia induces an acute, but repeated, systemic inflammation that could influence the development of cardiovascular disease in patients affected by disorders of glucose metabolism.[23] Metformin XR better reduces glycaemic control with consequential minor endothelial damage and a reduction of inflammatory markers.

METFORMIN SAFETY

Metformin is a well-tolerated antidiabetic compound with additional metabolic protective effects, but there are some concerns for use of the drug in patients with T2DM with reduced renal function. There are no differences regarding renal safety among the different metformin formulations, even if many studies have been conducted on metformin IR and few on metformin XR, which were later available.

To understand the challenges for the use of metformin in patients with impaired renal function, it is beneficial to understand the pharmacokinetics of the compound. At a usual dosage of 500–1500 mg, metformin has an absolute oral bioavailability of 50–60%.[24] The drug is not protein-bound and therefore has a wide volume distribution with maximum accumulation in the small-intestine wall. This biguanide is exclusively eliminated unchanged in the urine. Approximately 90% of absorbed metformin is eliminated via the renal route within the first 24 hours. In normal renal function, healthy people have an estimated glomerular filtration rate (eGFR) >90 mL/min/1.73 m^2 with a plasma elimination half-life of metformin of approximately 5 hours, and there is minimal accumulation of the drug with multiple dosing.[25] Compared with healthy individuals, patients with CKD show reduced metformin clearance which leads to an increase in metformin systemic exposure, increasing the risk of lactic acidosis (LA).[26]

Metformin decreases clearance of lactic acid by inhibiting the mitochondrial oxidation, thereby resulting in higher serum lactate concentrations.[27-30] LA is defined as blood lactate concentrations >5 mmol/L and arterial pH <7.35.[5] There are two forms of LA. Anaerobic LA (Type A LA), caused by lactate overproduction to regenerate ATP in the absence of oxygen, is usually seen in the presence of circulatory

collapse, such as heart failure, sepsis, and shock. Aerobic LA (Type B LA), caused by underutilisation of lactate as a result of impaired removal by oxidation or gluconeogenesis, is associated with high anion gap, and is the type seen in liver disease, diabetes, cancer, and alcohol and metformin intoxication, or metformin-associated lactic acidosis (MALA). Combinations of Type A and B are possible. Lalau and Race[31] have suggested that, since many cases of MALA are generally unrelated to metformin, the term MALA should be divided into metformin-unrelated LA and metformin-induced LA. The latter (Type B) is defined by raised metformin concentration and the risk of mortality is approximately 10%. Metformin-unrelated LA is primarily caused by Type A LA and bears a very high mortality of 50%.[32-35]

Even though toxic doses of metformin are a cause of LA, there are few data regarding the level predisposing to hyperlactataemia. Multiple studies suggest that elevated circulating lactate levels, often attributed to metformin, may actually not be caused by the drug. The therapeutic trough level for metformin is 0.7 (0.3–1.0) mg/L,[36] while the pragmatic upper therapeutic limit is 5 mg/L.[37] Intentional metformin overdose usually leads to hyperlactataemia, and often to LA. This can be fatal in cases with plasma metformin >50 mg/L.[38] This has led to the sparsely science-based opinion that metformin is contraindicated for the treatment of patients with severe renal pathologies. There is no epidemiological evidence that metformin use increases the risk of LA. MALA is well described in case reports and case series throughout the literature. However, by most accounts, the risk of LA with therapeutic metformin use is considered minimal.

A Cochrane meta-analysis including 347 comparative controlled studies covering 70,490 patient-years, for those with T2DM, of metformin use revealed no cases of LA and no significant change in plasma lactate. Importantly, at the time this study was conducted, the use of metformin in patients with CKD was not permitted and only used in exceptional cases.[39] No correlations were found between metformin and lactate levels. In this analysis, 53% of prospective studies allowed for inclusion of renal insufficiency, but patient-level serum creatinine concentrations were not always available for review. Based on statistical inference, the estimated upper limit of true incidence of LA was 4.3 cases per 100,000 patient-years. This investigation confirmed that LA is extremely rare.

A second meta-analysis was performed on all published studies in MEDLINE and Cochrane databases between 1950 and 2014 on 65 articles including pharmacokinetic/metabolic studies, large case series, retrospective studies, meta-analyses, and a clinical trial.[40] The authors found that metformin plasma levels generally remained within the therapeutic range and lactate concentrations are not substantially increased when used in patients with moderate CKD (Stage 3). The overall incidence of MALA varied across studies from approximately 3 per 100,000 to 10 per 100,000 person-years and was generally indistinguishable from the background rate in the overall population with T2DM. The authors proposed a maximum metformin daily dose of 1,000 mg in patients with Stage 3b CKD. They also suggested that the risk of MALA is unlikely when the renal function remains stable and the patient is closely observed, even in patients with moderate CKD (eGFR: 30–59 mL/min). In this study, the authors showed that there is no risk.

Frid et al.[41] observed the serum metformin levels of 137 patients with T2DM, of whom 20 had CKD (14 with Stage 3 and six with Stage 4), in a follow-up study for 2 months. There were few patients with metformin serum levels >20 µmol/L and median level was 10 µmol/L. The authors concluded that metformin may be safely used at an eGFR >30 mL/min and very high metformin levels are needed to cause LA. Lalau et al.[42] conducted a study to define a safe, effective dose regimen for metformin in moderate and severe CKD (Stages 3a/3b and 4, respectively). After 4 months on these regimens, patients displayed stable metformin concentrations that never exceeded the generally accepted safe upper limit of 5.0 mg/L. Hyperlactataemia (>5 mmol/L) was absent (except in one patient with myocardial infarction), and glycated haemoglobin (HbA_{1c}) levels did not change. There were no significant differences in pharmacokinetic parameters among the CKD stage groups. Further studies to assess the long-term safety of metformin in patients with T2DM with moderate renal impairment have not revealed increased risks in varying degrees of renal impairment.[43-45]

Table 1: Use of metformin during different stages of chronic kidney disease.

CKD stage	eGFR (mL/min/1.73 m²)	Recommended dosage (mg daily)	All-cause mortality HR (95% CI; p value)
1 and 2	>60	1.70–3.00	0.87 (0.81–0.94; p<0.001)
3a	45 to <60	1.70–2.00	0.87 (0.77–0.99; p<0.05)
3b	30 to <45	1.00	1.02 (0.84–1.24; p<0.05)
4	15 to <30	Cease use	No data available
5	<15	No use	1.35 (1.20–1.51; p<0.001)

CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HR: hazard ratio.

Taking into account the results of previous studies, Schernthaner and Schernthaner-Reiter[46] calculated the hazard ratio (HR) of all-cause mortality for the use of metformin at different stages of CKD (Table 1).[46] The authors recommended avoiding premature cessation of metformin therapy in patients with T2DM and CKD to counter poor glucose control and further increase in the already high risk of cardiovascular disease. Based on their meta-analysis and available data on efficacy and safety, they recommended the use of metformin in patients with CKD including Stage 3b, up to 1,000 mg/day, but not in Stage 4.

METFORMIN, TYPE 2 DIABETES MELLITUS, AND ADVANCED CHRONIC KIDNEY DISEASE

Globally, drug regulatory agencies have issued specific cautions and restrictions related to the use of metformin in patients with T2DM and advanced CKD. The concrete metabolic and cardiovascular benefits associated with metformin therapy derived from clinical and scientific evidence have encouraged some authors to extend the therapy options to patients with CKD Stage V, both in dialysis and conservative treatment.

Hung et al.[47] conducted a retrospective observational cohort study on patients with T2DM and CKD Stage 5 using Taiwan's National Health Insurance Research Database (NHIRD) between 2000 and 2009. Approximately 8% of patients (12,350) were using metformin despite contraindication and were matched at a ratio of 1:3 with nonusers by propensity score and followed-up for 2.1 years. After multivariate adjustment, metformin use was associated with a higher, but nonsignificant, risk of metabolic acidosis of 1.6 versus 1.3 events per 100 patient-years (adjusted HR: 1.3, p=0.19), and no dose correlation was observed (HR: 1.8 in ≤500 mg/day; 1.4 in 500–1,000 mg/day; and 1.5 in ≥1,000 mg/day).[47] In patients using metformin, ESRD was significantly lower (HR: 0.76, p<0.0001) in comparison to the control group and metformin was associated with an increased mortality (HR: 1.35, p<0.001) in a dose-dependent manner (HR: 1.14 in ≤500 mg/day; 1.30 in 500–1,000 mg/day; 1.57 in ≥1,000 mg/day). After this study, the Taiwan National Health Insurance (NHI) announced that metformin use was contraindicated in females and males with serum creatinine concentrations of >1.5 and >1.4 mg/dL, respectively.

In a pilot experience, 35 patients on automated peritoneal dialysis with T2DM were treated with metformin, despite their very low eGFR.[48] After 11 months of treatment with metformin at doses 0.5–1.0 g/day, a reduction of 7.4% to 6.4% HbA_{1c}, 1.5 kg/m² in BMI, and -30% insulin requirements was observed. Metformin concentrations were elevated in 81% of samples and markedly

elevated (>5 mg/L) in 4% of samples, no change in anion gap or pH was seen, and only 0.76 % of blood samples had a plasma lactate >2 mmol/L. There was no correlation between metformin concentration and lactate and no cases of LA. The authors suggested that peritoneal dialysis, by causing rapid removal of lactate and restitution of acid base balance, may protect against LA itself.

COMPLICATIONS OF METFORMIN IN DIABETIC NEPHROPATHY

Another important issue regarding metformin use concerns kidney transplant patients. Nondiabetic kidney transplant recipients are at risk for developing new onset diabetes after transplant, a common complication associated with kidney transplant that can affect allograft and patient survival.[49] To prevent complications associated with diabetes, proper glycaemic control is imperative; however, the extent of metformin use among kidney transplant recipients is currently uncertain. In 2008, Kurian et al.[50] demonstrated that metformin was safe in 24 kidney transplant recipients for a mean duration of 16.4 months up to a maximum of 55 months.[50] Although the study found no cases of LA, eGFR decreased in all patients. Patients with pre-existing diabetes experienced significant changes in eGFR. More recently, an observational study showed that 9.8% of kidney transplant recipients who filed at least one prescription for an antiglycaemic agent also had at least one claim for metformin or a metformin-containing agent.[51] Metformin was associated with lower adjusted HR for both living donors and deceased donor allograft survival at 3 years post-transplant, and with lower mortality.

The many risks for LA in patients with renal impairment could be partially circumscribed to specific predisposing risk factors. Renal function is dynamic, and renal dysfunction in T2DM is typically progressive. Thus, the renal thresholds for the acceptability of metformin therapy should ideally account for the stage in the CKD progression. The renal thresholds for prescription of metformin therapy should consider the stage and progression of CKD. The assessment of renal function in clinical practice occurs periodically, and the degree of renal dysfunction may change appreciably between these assessments. Therefore, it is essential to know how quickly eGFR declines in the typical spectrum of nephropathy among patients with T2DM, particularly when considering metformin therapy.

The most common side-effects observed in association with metformin use in patients with T2DM with mild to moderate renal impairment are gastrointestinal events including diarrhoea, nausea, vomiting, abdominal pain, and decreased appetite, among others. Few studies have, however, systematically evaluated the effect of rate of progression of renal dysfunction and the risk of LA in the diabetic population.

In a matched case control study conducted by Grenoble Hospital University Center, La Tronche, France, to evaluate the strength between the association between LA and well-recognised risk factors,[52] metformin was not associated with a higher risk of LA in patients with T2DM. Metformin was significantly associated with a higher LA probability in cases of acute kidney injury (odds ratio [OR]: 1.79, $p<0.02$) but not in patients without acute kidney injury. Intercurrent diseases such as acute decompensated heart failure, acute respiratory failure, and sepsis, were significantly associated with LA (OR: 3.55, $p<0.001$; 9.58, $p<0.001$; and 8.28, $p<0.001$, respectively), while other chronic medical conditions had a minor impact on LA incidence, except hepatocellular dysfunction.

Special attention should be given to contrast-induced nephropathy, a common complication after administration of iodinated contrast media. Metformin, by itself, is not a risk factor for contrast-induced nephropathy,[53] but the risk of acute renal function deterioration increases the risk of acute kidney injury, which is the main risk factor for metformin accumulation.[54] In a cohort study,[55] which included patients with T2DM with moderate CKD (eGFR <60 mL/min) under metformin treatment, no significant changes in renal function were observed after endovenous administration of iodinated contrast. However, the authors' optimistic conclusions were limited by the low sample size and the retrospective study design. Lepelley et al.[52] found a higher risk for LA with the use of contrast media (OR: 8.58, $p<0.001$) compared to metformin (OR: 1.79, $p=0.02$).

Based on the European Society of Urogenital Radiology (ESUR),[56] patients receiving endovenous iodinated contrast should stop taking metformin 48 hours before contrast administration if their eGFR falls <45 mL/min. Renal function should be revalued 48 hours after contrast administration and metformin should only be restarted if it has not deteriorated further. The Canadian Association of Radiologists (CAR) uses a threshold of <60 mL/min.[53]

CURRENT GUIDELINES AND FUTURE IMPLICATIONS

These studies highlight the lack of randomised clinical trials to test the specific hypothesis that metformin is safe in patients with mild to moderate CKD. Randomised trials would help to better inform evidence-based guidelines. Nevertheless, given the rarity of LA in the setting of metformin therapy, a study would need to examine hundreds of thousands of patients for many years to demonstrate noninferiority compared with other hypoglycaemic agents, which might not be feasible. National patient registries might be a reasonable alternative; however, for regulatory bodies at this time, the best available evidence is limited to meta-analyses, retrospective studies, and smaller mechanistic investigations reported herein.

Contraindications to the use of metformin are based on the cut-off points of serum creatinine values, discouraging its use at or above the 1.4 and 1.5 mg/dL levels in females and males, respectively. In any case, the current recommendations for metformin are not clear and univocal for advanced CKD. The latest Kidney Disease Outcomes Quality Initiative guidelines recently updated by the National Kidney Foundation (NKF KDOQI) are perfectly in line with this criterion.[2] Despite this, some practice guidelines present substantial differences for the use of metformin in renal patients. In the ADA guidelines, for example, renal thresholds are actually not discussed.[4] In the statement position of the ADA and EASD,[57] the members reports are that metformin appears to be safe unless the noninferior eGFR fall to 30 mL/min for 1.73 m^2.

Other non-American guidelines considered the use of eGFR to determine the safety of metformin. The National Institute for Health and Care Excellence (NICE) recommends using metformin with caution in patients[58] for whom serum creatinine >130 µmol/L (1.47 mg/dL) or eGFR <45 mL/min. Doses should be lower and prescribed with increased frequency of monitoring. In patients already taking metformin, the drug should be discontinued if the serum creatinine >150 µmol/L (1.70 mg/dL) or GFR <30mL/min.

Other associations such as the Canadian Diabetes Association (CDA)[58] and Australian Diabetes Society (ADS) practice guidelines are now based solely on eGFR, recommending caution with eGFR of 60 mL/min per 1.73 m^2 and contraindicating its use with eGFR of 30 mL/min per 1.73 m^2.[59] The European Renal Association/European Dialysis and Transplant Association (ERA-EDTA) have recently published the clinical practice guideline in the management of patients with diabetes and CKD Stage 3b or higher (eGFR <45 mL/min).[60] Metformin is recommended as a first-line agent in a dose adapted to the renal function, when lifestyle measures alone are insufficient to lower HbA_{1c} to the desired range. The committee has based their recommendation on the most positive benefit amongst all treatment classes. A maximum daily dose of 850–1,500 mg/day for CKD Stage 3b is suggested. In CKD Stage 4, 500 mg/day should not be exceeded.

The Kidney Disease Improving Global Outcomes (KDIGO) guideline proposed that the dose of metformin should be reduced to a maximum of 1,000 mg/day when eGFR reaches 45 mL/min, and should generally be discontinued when eGFR reaches 30 mL/min.[61] The use of metformin may be appropriate in patients with even more advanced CKD (eGFR 15–29 mL/min) if the kidney disease is stable and if alternative treatments to manage glycaemia are unavailable or produce significant side effects.

CONCLUSION

Although different formulations of metformin have been evaluated in recent years, generally, metformin is a bulwark in the treatment of diabetes, and it is also currently recommended for patients with nephropathy by monitoring renal function. There is clear recognition that renal failure may be a risk factor for adverse

events with metformin use, even if there is a significant divergence in opinion around the world regarding the optimal definition of safety. Provided that the dose is adjusted for renal function, metformin treatment appears to be safe and pharmacologically efficacious in moderate-to-severe CKD.

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Reproductive Dysfunctions in Males with Type 2 Diabetes Mellitus: An Updated Review

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Disclosure: The authors have declared no conflicts of interest.

Received: 15.07.20

Accepted: 24.09.20

Keywords: Erectile dysfunction (ED), hypogonadism, infertility, obesity, phosphodiesterase inhibitors, testosterone therapy, Type 2 diabetes mellitus (T2DM).

Citation: EMJ Diabet. 2020;8[1]:79-89.

Abstract

Deterioration in reproductive functions is one of the most serious complications of Type 2 diabetes mellitus (T2DM). Neuropathy, angiopathy, oxidative stress, and psychological deviation are the important causative factors in developing reproductive dysfunctions in diabetes. In males, the principal complications are erectile dysfunction (ED), ejaculatory disorders, and functional hypogonadism. Low serum testosterone is frequently observed in males with T2DM but the neuroendocrine pathophysiology is yet to be defined; this reduction in testosterone levels decreases libido. Evaluation of testosterone levels of male diabetic patients with hypogonadism symptoms is recommended. Hypogonadal males with diabetes might benefit from testosterone replacement therapy. However, there is a need for adequately powered long-term studies in this context. Impairment in sexual function is a common complication in males with diabetes. The pathophysiology of sexual dysfunction in diabetes is multifactorial. Males with diabetes have a >3-fold increase in the risk of ED compared to their nondiabetic counterparts. Phosphodiesterase type 5 inhibitors should be considered as first-line therapy in males with T2DM and ED. Nearly 50% of male diabetic patients presented some degree of subfertility or infertility. Alterations in sperm parameters and hormone levels can contribute to diabetes-related male infertility. Endocrinologists, diabetologists, and physicians should address sexual complaints of their patients since these problems can significantly impair their quality of life.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major health concern worldwide. The Southeast Asian region has the second largest number of people with diabetes in the world. The prevalence of T2DM is six times greater in males of Southeast Asian origin.[1] T2DM can affect multiple physiological systems, including the reproductive system. T2DM causes sexual dysfunctions in males through autonomic neuropathy and endothelial dysfunction.[2] The most frequently reported sexual dysfunction is erectile dysfunction (ED), the prevalence of which among males with diabetes varies from 35 to 75%.[3] In males,

strong evidence linking low testosterone levels to T2DM and metabolic syndrome (MetS) is there. Up to 40% of males with T2DM and MetS have hypogonadism.[4] Hypogonadal males with diabetes have a higher risk for cardiovascular (CV) mortality than eugonadal males.[5] Altogether, these abnormalities may lead to a decrease in male fertility. However, a comprehensive overview regarding pathophysiology, consequences, evaluation, and treatment of reproductive complications of T2DM in males is lacking. Therefore, this paper aims to provide an updated review of the various aspects of this complication.

IMPACT OF DIABETES ON MALE SEXUAL AND REPRODUCTIVE FUNCTIONS

The pathophysiology of reproductive dysfunction in diabetes is multifactorial. The longer the duration of diabetes and the older the patient, the more likely that they are to have sexual dysfunction.[6] Comorbidities including hypertension, dyslipidaemia, CV disease (CVD), or other endocrine dysfunctions, and their treatments, can further expedite sexual and reproductive impairment.[2] In males with diabetes, low testosterone levels are more common and can cause reduced libido and ED. Finally, the complex role of psychological issues in diabetes contributes to impaired sexual function. The following sections will detail the issues related to hypogonadism and sexual dysfunction in males with diabetes.

Hypogonadism in Males with Diabetes

In males with T2DM, subnormal free testosterone concentrations in association with inappropriately low luteinizing hormone (LH) and follicle-stimulating hormone concentrations were first described by Dhindsa et al.[7] These abnormalities were not dependent on the severity of hyperglycaemia. The reported prevalence of hypogonadotropic hypogonadism (HH) in males with T2DM is 30–40%.[8-10] Chandel et al.[11] found that younger males with T2DM also have a similarly high prevalence of HH. In all the studies, testosterone levels were inversely correlated to BMI and insulin resistance (IR).[12] A high prevalence of symptoms suggestive of hypogonadism has been found in males with T2DM with low testosterone concentrations.[8] Given the inverse relationship between BMI and testosterone levels in T2DM, HH is most likely related to IR.[7, 9]

Pathophysiological mechanisms underlying HH

The causative mechanism of diabetes-induced HH remains to be elucidated but is probably multifactorial. Several factors may be associated with the pathophysiology, including age, IR, obstructive sleep apnoea (OSA), and visceral obesity.[10,13]

It has been theorised that increased oestrogen production due to aromatase activity in the obese may potentially suppress the hypothalamic gonadotropin-releasing hormone (GnRH) secretion. However, Dhindsa et al.[14] have shown that total and free oestradiol levels in males with HH are considerably lower than in those without HH. So, it appears that the low testosterone levels in diabetes-related HH are not the consequence of oestradiol-induced suppression of the hypothalamic–pituitary–gonadal (HPG) axis.

Obesity and T2DM are associated with decreased insulin signalling in the central nervous system. While the site responsible for hypogonadotropism in neuronal IR is unknown, it is apparent that insulin action and responsiveness in the brain are essential for the functional integrity of the HPG axis.[5]

Leptin appears to serve as a signal of energy reserves to regulate the HPG axis with nutritional status. Leptin resistance in the hypothalamus or some other neurons may be related to the hypogonadotropism found in diabesity.[5,15] Kisspeptin and the presence of kisspeptin receptors on the GnRH neurons are required for the GnRH release. Kisspeptin infusion raises LH and testosterone levels in males with T2DM and HH.[16,17] Both leptin and insulin receptors are expressed in kisspeptin neurons. Hence, the hypothalamic defect in male T2DM patients with HH is either at kisspeptin level or proximal to it.

TNFα and IL-1β have been demonstrated to suppress hypothalamic GnRH release in experimental animals.[18] Thus, it is relevant that C-reactive protein concentrations are significantly increased in males with HH and T2DM.[19] It is, therefore, possible that inflammatory mediators may be responsible for the suppression of

the HPG axis and consequently HH in T2DM. The presence of inflammation may also lead to IR.[20]

In summary, various interconnected mechanisms are underlying HH in males with T2DM (Figure 1). The absence of an increase in gonadotropin levels suggests that the primary defect is at the HP level.[5]

Consequences of hypogonadism in Type 2 diabetes mellitus

Sexual dysfunction

A high prevalence of low libido (64%), ED (74%), and fatigue (63%) has been found in hypogonadal males with T2DM.[8] It is often difficult to establish whether the aetiology of symptoms is hypogonadism or any other comorbidity. Nevertheless, the prevalence of sexual symptoms is higher in males with HH than eugonadal males.[21] In hypogonadal males with T2DM, trials of testosterone replacement therapy (TRT) have also shown an improvement in libido.[21,22]

Insulin resistance

Dhindsa et al.[21] have shown that males with T2DM and HH are less insulin sensitive than those without HH and that TRT increases insulin sensitivity.

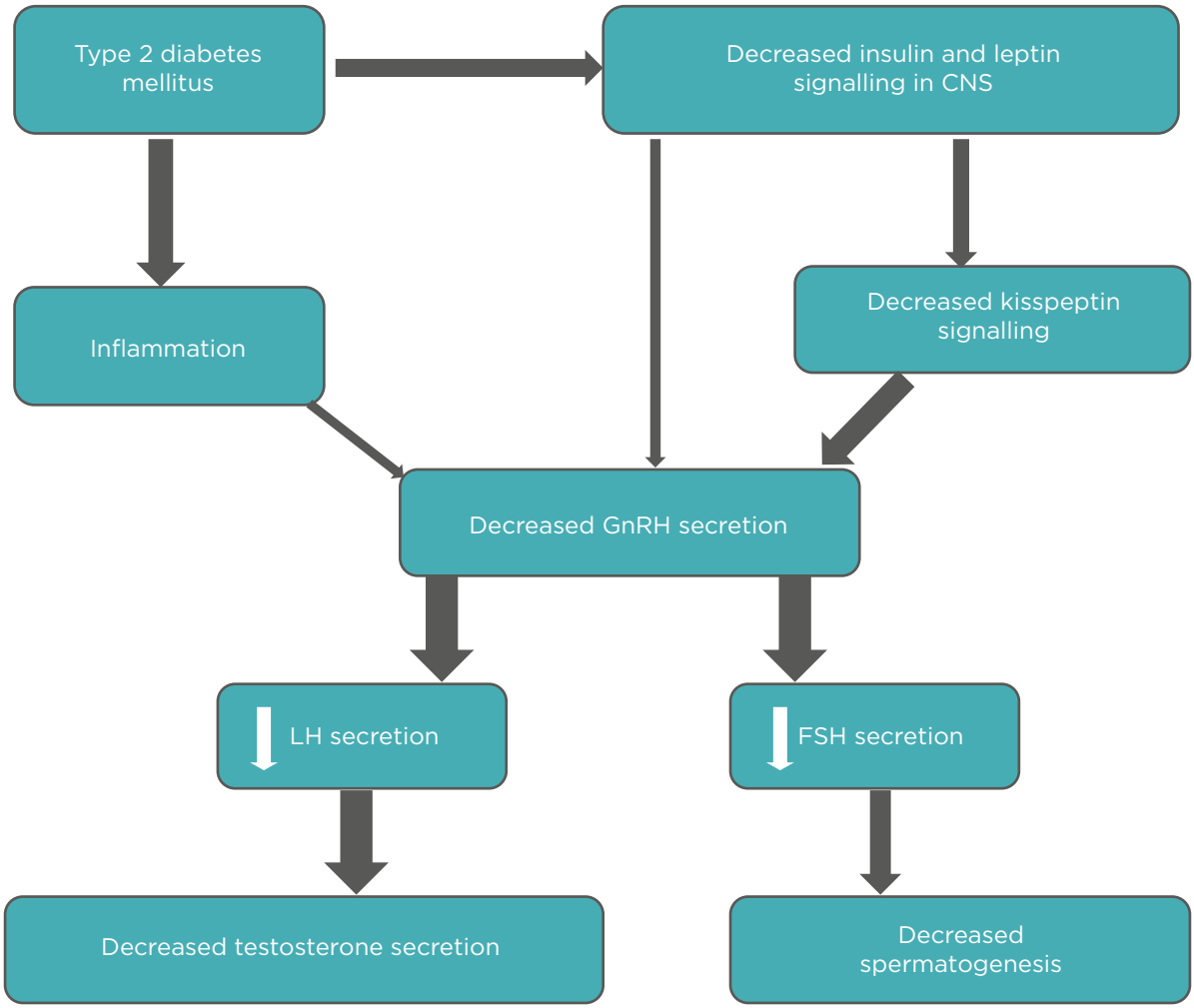

Figure 1: Interplay of different factors in diabetes-associated hypogonadotropic hypogonadism.

The thickness of arrows is proportional to the strength of available evidence.

CNS: central nervous system; FSH: follicle-stimulating hormone; GnRH: gonadotropin-releasing hormone; LH: luteinizing hormone.

Adapted from Dhindsa et al.[5]

However, two trials did not show a change in HOMA-IR after testosterone replacement in hypogonadal males with T2DM.[23,24] Since TRT increases muscle mass, TRT may have a more notable effect on muscle glucose uptake rather than HOMA-IR. Thus, testosterone mediated insulin sensitisation is not an immediate effect and may be related to changes in body composition. The improvement in insulin sensitivity following TRT was also associated with suppression of inflammatory mediators.[5] Whether they are the direct actions of testosterone remain to be determined.

Cardiovascular disease

Low circulating testosterone levels lead to greater visceral adiposity and increased cardiometabolic risk.[4] The inverse relationship of mortality with endogenous testosterone levels has been observed in males with diabetes.[25] Hypogonadism has been associated both with CVD risk factors in males with T2DM,[26] and an increased risk of myocardial infarction and increased CV mortality.[27,28] However, no randomised control trials (RCT) have been conducted to address whether TRT changes CV outcomes in males.

Anaemia

Males with T2DM and HH have a lower haematocrit than those with normal testosterone concentrations. The prevalence of normocytic normochromic anaemia in such patients is higher in comparison to eugonadal males.[19] However, it remains undetermined whether the association of anaemia with hypogonadism in males with T2DM is causative.

Bone density

Hypogonadism is associated with a decline in bone mineral density and an increase in fracture rate.[29] In epidemiological studies, oestradiol concentrations correlate more strongly with bone mineral density than testosterone concentrations in males. However, testosterone appears to be an independent predictor of cortical bone density.[30] Free testosterone levels have shown a positive association with bone density in arms, ribs, and lumbar spine in males with T2DM.[31] No data are available on the fracture rates in males with T2DM and HH.[12]

Evaluation and treatment of hypogonadism

Evaluation of hypogonadal symptoms

Low testosterone concentrations are associated with symptoms such as fatigue, lack of libido, and ED. Importantly, patients may also slide slowly into this clinical state without any obvious symptoms.[12] The high prevalence of low testosterone levels in T2DM justifies screening for HH in every patient with T2DM; however, biochemical testing is recommended in males with diabetes who are symptomatic. In 2016, the American Academy of Clinical Endocrinologists (AACE) recommended screening for hypogonadism in all males with T2DM.[32] In contrast, the 2018 Endocrine Society (ES) guidelines continue to advocate against testosterone screening but do acknowledge the high prevalence of hypogonadism in T2DM.[33] The recent reclassification of hypogonadism by the ES refers to T2DM-related hypogonadism as "functional". The American Diabetes Association (ADA) in 2018 acknowledged the high prevalence of HH in T2DM and recommended testosterone measurement in males with symptomatic hypogonadism.[34] The ES focusses on correct diagnosis and proper assay techniques, though there is little that the clinician can do about the assay method. Ideally, free testosterone should be measured in the morning (fasting) by accurate methodology, preferably equilibrium dialysis/mass spectrometry. Subnormal free testosterone should be confirmed at least once. A male with confirmed hypogonadism should have LH concentrations checked. T2DM and obesity are associated with reduced sex hormone-binding globulin (SHBG) concentrations. Thus, a physiological lowering of total testosterone concentrations is expected in obese males with T2DM. Therefore, free or bioavailable testosterone measurement is necessary to assess the gonadal status in these patients.

OSA is very common in people with T2DM and obesity. However, OSA per se is not the main contributor to the decline of testosterone concentrations.[5] Prostate-specific antigen concentrations are found to be lower in hypogonadal than in eugonadal males with diabetes.[35]

Treatment of hypogonadism

Studies with TRT suggest remarkable benefits in sexual function, quality of life, lean muscle mass, and bone density.[4] ADA recommends considering TRT in cases for which evidence indicates likely improvements, but it does not consider any further metabolic role for TRT.[34] The ES guideline recommends against TRT for glycaemic control but does endorse TRT in males with ED and low sexual desire.[33] A complete discussion of risks and benefits between the patient and physician should precede a trial of TRT. Monitoring the effects of testosterone should be done as per available guidelines, such as those recommended by the ES. Of note, the hypogonadism in diabetes is associated with reduced responsiveness to testosterone.[5]

Weight loss associated increase in testosterone concentrations is likely mediated by the restoration of neuronal leptin and insulin sensitivity. Many studies have also shown that weight loss increases total testosterone and SHBG concentrations.[36] Nevertheless, the results of lifestyle intervention as the sole therapy for hypogonadism in T2DM are discouraging.

Metabolic effects of testosterone therapy in males with Type 2 diabetes mellitus

The current evidence on the metabolic effects of TRT in men with T2DM and MetS is reviewed.[4] RCT of TRT suggest considerable benefits in terms of improved IR, decreased fat mass, increased lean muscle mass, and reductions of inflammatory markers. Altogether, these might be expected to translate into reduced long-term CV risk. However, critical evaluation of clinical trials has been complicated by various factors. Since all males with T2DM are routinely prescribed a statin irrespective of lipid level, it would be very difficult to conduct RCT of TRT in dyslipidaemia. Several longitudinal and observational studies also suggest long-term persistent improvements in metabolic parameters. However, presently TRT is not considered a mainstream intervention in standard diabetes practice. Although no studies have demonstrated an association between TRT and increased risk of major adverse CV events (MACE), some effects of testosterone might enhance CV risk.[37] The ongoing TRAVERSE study[38] is likely to clarify the testosterone effects on CVD.

Sexual Dysfunction in Males with Diabetes

Sexual dysfunction is a distressing complication in males with diabetes. It negatively impacts the quality of life and it is often an early clinical indication of endothelial dysfunction, thus predicting future CVD.

Erectile dysfunction

The prevalence of ED depends on the age of the patient, duration of diabetes, and presence of other comorbid conditions.[39] According to a recent meta-analysis, the prevalence of ED in diabetes was 52.5%, and it increased with the duration of diabetes.[40]

Pathophysiology

Erection is a vascular process that is initiated by the autonomic nervous system and maintained by endothelial cell-derived nitric oxide (NO) and endothelium-derived hyperpolarising factor (EDHF), which are responsible for smooth-muscle relaxation in the corpus cavernosum. Hyperglycaemia disrupts this physiology in multiple ways.

- Endothelial dysfunction: failure of endothelium-derived NO and EDHF occurs much before significant autonomic neuropathy.[41] Thus, there is difficulty in maintaining an erection.
- Low testosterone: this leads to a reduction in smooth muscle sensitivity to vasodilators and structural abnormalities in the erectile tissue.[42]
- Large vessel disease: narrowing of large vessels supplying corpora cavernosa can lead to vascular impotence.
- Autonomic neuropathy: erection is initiated by cholinergic and non-cholinergic non-adrenergic neurotransmitters from the parasympathetic nervous system. They initiate the relaxation of the cavernosal smooth muscle. Autonomic neuropathy impairs this response.
- Drugs: β-blockers, thiazide diuretics, tricyclic antidepressants, and spironolactone are the major culprits.[43]
- Others: penile structural diseases, such phimosis and Peyronie's disease, or recurrent mycotic balanitis may have a contributory effect on ED in males with diabetes.[44]

ED is a harbinger of future cardiovascular dysfunction

Numerous investigators reported ED as a marker of potential future CV events.[45] Yamada et al.[46] found a significant association of ED with all-cause mortality and CV events in a meta-analysis. However, ED often precedes overt CVD, which clinicians often pay less attention to.

Clinical assessment

Most patients hesitate to initiate discussion about their sexual dysfunction. However, once initiated, ice can be broken easily. Clinicians need to first ascertain the degree of ED, presence or loss of libido, association with premature ejaculation (PME) or retrograde ejaculation, and presence/absence of nocturnal penile tumescence. Several validated questionnaires can be used for the diagnosis of ED. The International Index of Erectile Function (IIEF)[47] is currently the most widely used questionnaire. Situational or psychogenic ED can be easily diagnosed by a simple stamp paper test or RigiScan® (Gesiva Medical, Eden Prairie, Minnesota, USA), a device that monitors for the spontaneous nocturnal penile tumescence during rapid eye movement (REM) sleep. An overnight recording is done in a single room with quiet surroundings. The normal response is defined as >70% rigidity and 3–4 erections lasting >10 min.[48]

Investigations

Every patient should be evaluated for glycaemic control, CV, renal, retinal, and neurological status. Hypogonadism should be excluded by measuring serum testosterone levels. The pharmacological test with intracavernosal injections of papaverine and Doppler evaluation of the pre- and postapplication blood flow are often needed to exclude vascular cause of ED.

Treatment

- General advice

  Optimal glycaemic control should be achieved in all patients. The use of statin and ramipril has also been reported to reduce ED.[49,50] Most patients with situational ED improve with simple tips and advice, whereas few couples need psychosexual counsellors.
- Oral agents

  Phosphodiesterase type 5 (PDE5) inhibitors are first-line therapies (Table 1). They inhibit the breakdown of cyclic guanosine monophosphate (cGMP), which acts as a second messenger for NO-induced smooth-muscle relaxation. In males with T2DM, the efficacy rates have been reported to be between 50% and 55% and the average dose required is higher than the general population.[48] Recent evidence suggests therapy with PDE5 inhibitors improves insulin sensitivity.[51] Clinicians have generally shown a preference for tadalafil over sildenafil due to the long half-life, ease of administration, and favourable safety profile. Nonresponders are diagnosed when satisfactory sexual function is not achieved despite using an agent at least eight times in the highest recommended or tolerated dose.
- Injectables

  Alprostadil is supplied in a self-injection pen device. In a 6-month self-injection study involving 683 males, the participants reported achieving satisfactory sexual activity after 94% of the injections.[52] Prolonged erections, priapism, penile fibrotic complications, and haematoma or ecchymosis were the most common side effects. Despite its high efficacy, the discontinuation rate was very high.[53]
- Surgical options

  Surgical options for ED are either correction of penile structural and vascular disease or insertion of a penile prosthesis. A penile prosthesis is best reserved for those in whom conventional treatments have failed and who are keen to resume full sexual activity. [54]

Ejaculatory dysfunction

Ejaculatory disorders are a heterogeneous group of disorders that are very common in people with diabetes and include premature and retrograde ejaculation.

Premature ejaculation

PME is defined as ejaculation that always or nearly always occurs before or within approximately 1 minute of vaginal penetration or inability to delay ejaculation on all or nearly all vaginal penetrations that lead to negative personal consequences.

In diabetes, psychological factors, such as depression, impaired self-body image, and performance anxiety, may play a role in the development of PME. Although a smaller number of couples seek medical attention for PME, it may be highly distressing in some instances.[55]

Table 1: Comparison of available PDE5 inhibitors.

	Sildenafil	Tadalafil	Vardenafil	Avanafil
T_{max}	1 hour	2 hours	1.5 hours	0.75 hour
V_d	105 L	63 L	208 L	--
Protein binding	96%	94%	95%	99%
Major Metabolism	CYP3A4	CYP3A4	CYP3A4	CYP3A4
Half-life	4 hours	17.5 hours	4–6 hours	5 hours
Ingestion with high-fat meals	↓C_{max} 29% ↑T_{max} by 1 hour	Not affected	↓C_{max} 35%	↓C_{max} 24-39 ↑T_{max} by 1.12–1.25 hours
Usual dosage	25–100 mg/day	5–20 mg/day (as needed); 2.5–5 mg/day once daily	5–20 mg/day	50–200 mg/day
Administration time	1 hour before sexual activity	At least 0.5 hours before sexual activity	1 hour before sexual activity	0.5 hours before sexual activity
Time frame of efficacy	0.5–4 hours post dose	Up to 36 hours post dose	--	As early as 0.25 hours post dose
Common adverse reactions	Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis, visual abnormalities	Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis, back pain, myalgia	Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis, visual abnormalities	Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis
Time required from last dose to administration of a nitrate	24 hours	48 hours	24 hours	12 hours

C_{max}: maximum concentration; CYP3A4: cytochrome P450 3A4; PDE5: phosphodiesterase 5; T_{max}: time to reach maximum concentration; V_d: volume of distribution.

Retrograde ejaculation

Retrograde ejaculation as a complication of diabetes is unappreciated and under-recognised. The exact prevalence of retrograde ejaculation in diabetic patients is unknown. It is the propulsion of seminal fluid from the posterior urethra retrograde to the bladder through a relaxed internal vesical sphincter. It is considered to be a feature of diabetic autonomic neuropathic manifestation,[56] and presents with infertility. Spermatozoa can be retrieved from centrifuged urine after a sexual act. Medical treatment with

imipramine and pseudoephedrine have been tried, but with limited efficacy. Alternatively, spermatozoa retrieval from post-ejaculatory urine can be a good alternative to couples presenting with infertility.

DIABETES MELLITUS AND MALE INFERTILITY

There will be a growing number of males of reproductive age with diabetes, as there is an increase in the number of adolescent males with T2DM.[57] The view that diabetes has insignificant effects on male reproductive function has been questioned by current data.[58]

Diabetes can have deleterious effects on male reproductive health, which can lead to increased infertility. Various studies have reported diverse pathologies and consequent reproductive defects. Selected mechanisms are summarised in Figure 2.

Modified Semen Parameters

Modified semen parameters can contribute to male infertility in diabetes. Diabetes induces subtle molecular alterations affecting sperm quality and function. Semen analysis revealed a significant decline in sperm motility, including the number of rapid progressive cells in males with diabetes.[59] Another study revealed decreased sperm motility and increased abnormal sperm morphology of male diabetic partners.[60] Diabetic patients may have a decrease in semen volume, sperm count, and motility along with increases in seminal glucose levels and decreases in zinc concentration.[61,62] Mitochondrial dysfunctions may also account for the deteriorated sperm parameters.[2] Advanced glycation end products in seminal plasma could be a major contributor to oxidative stress and therefore sperm nuclear DNA damage.[63] Larger studies are necessary to confirm many of these findings.

Hyperglycaemia-Related Male Infertility

To date, several studies have addressed the issue of diabetes-induced male infertility but comprehensive evidence as to how hyperglycaemia impairs male fertility is absent. The hyperglycaemia may cause testicular dysfunction by disrupting both steroidogenesis and spermatogenesis. Additionally, hyperglycaemia impairs male reproductive function through increased oxidative stress.[64] Diabetes-related testicular dysfunction includes decreased spermatogenesis due to an increased rate of germ cell apoptosis, poor sperm reproductive parameters, and reduced testosterone synthesis, resulting in infertility.[58] Hyperglycaemia should be investigated in more detail to fully understand the impact on male reproductive health.

Treatment of Diabetes-Induced Male Infertility

Currently, a specific treatment to improve reproductive dysfunctions in T2DM patients is not available. Hormonal approaches with growth hormone and human chorionic gonadotropin were tried in diabetes-induced infertility.[65] While the effects of hyperglycaemia reduction by the use of insulin and few oral drugs have been reported, more clinical trials providing high-quality evidence on the positive effects on male reproduction are necessary.[64] Antioxidant therapy remains highly debated despite the reported improvement of sperm quality.[66]

CONCLUDING REMARKS

Currently, T2DM is growing rapidly among adolescent males, resulting in a significant increase in the prevalence of reproductive dysfunction among young males. Males with T2DM may demonstrate hypogonadism, ED, and ejaculatory dysfunction, leading to infertility. The low testosterone level seen in males with T2DM is associated with increased comorbidity and mortality. The available evidence suggests that males with T2DM, MetS, and properly diagnosed HH are likely to benefit from TRT. Results of ongoing trials can provide a more unified perspective on testosterone. All adult males with T2DM should be screened for ED with a sexual function history and PDE5 inhibitors should be offered to males who would like to undergo treatment for ED. Psychosexual therapy can be helpful when sex cannot return to normal for the patient. Clinicians should not only educate their patients about the possible impact of diabetes on male reproductive health, but also address their sexual complaints.

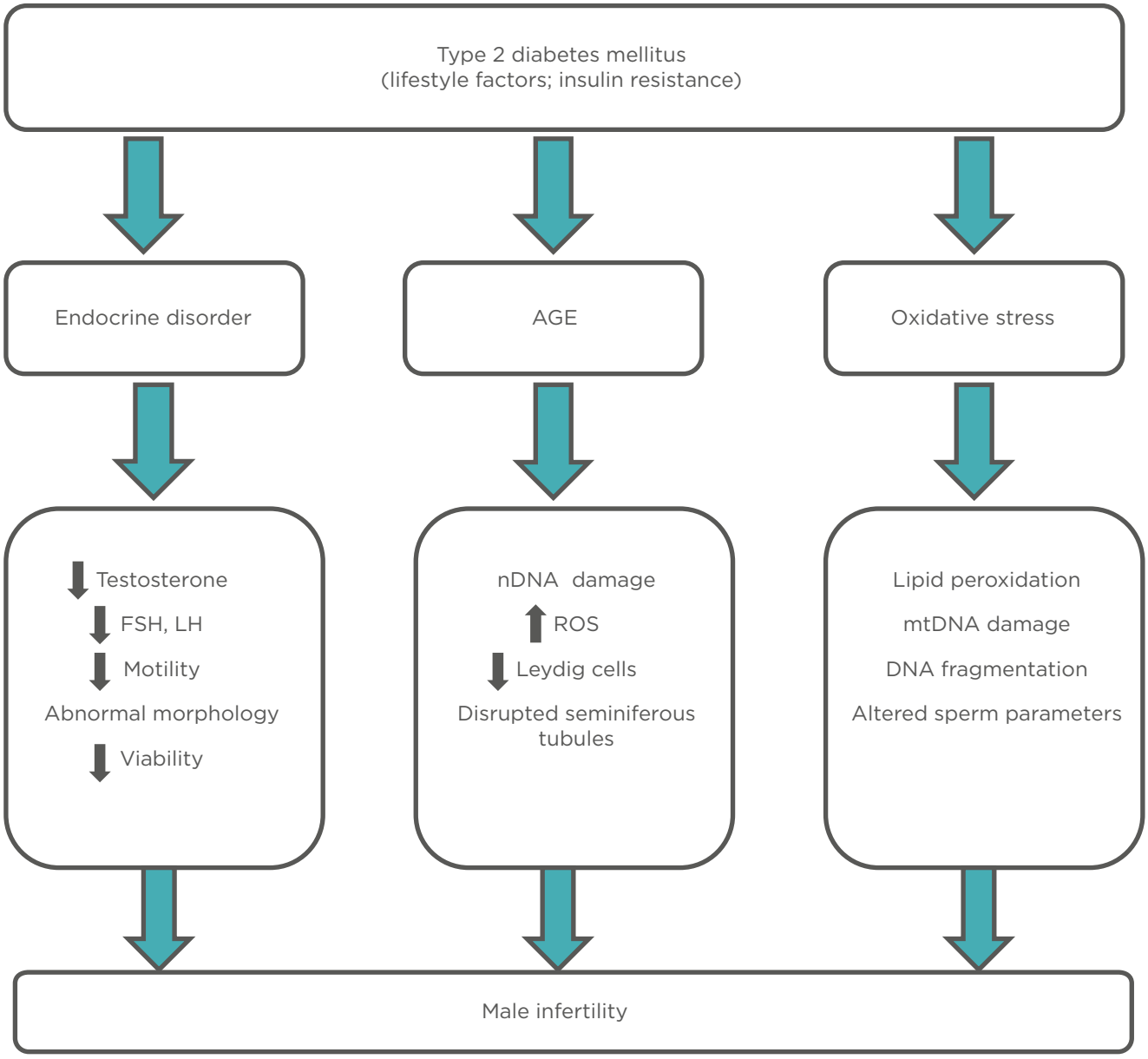

Figure 2: Mechanisms through which diabetes affects reproductive functions in males.

AGE: advanced glycation end products; FSH: follicle-stimulating hormone; LH: luteinizing hormone; mtDNA: mitochondria DNA; nDNA: nuclear DNA; ROS: reactive oxygen species.

Adapted from Temidayo et al.[58]

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Psychological Aspects of Diabetes

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Disclosure: The authors have declared no conflicts of interest.

Received: 10.07.20

Accepted: 04.09.20

Keywords: Cognitive dysfunction, diabetes, personality, psychological aspects, psychological interventions.

Citation: EMJ Diabet. 2020;8[1]:90-98.

Abstract

Diabetes is fundamentally a chronic metabolic disorder, yet it has established psychological connections and consequences. The present article offers an overview of some of the established findings with respect to the psychological aspects of diabetes among adults and adolescents. This narrative review describes the psychological impact of diabetes and the manner in which psychological functioning of the individual affects the development, management, and outcome of diabetes. Diabetes can lead to a great deal of distress, common mental health problems such as anxiety, depression, and sleep disorders, and can increase the risk of suicide. It also affects cognitive functioning across multiple domains such as attention, concentration, memory, executive function, and information processing speed. Diabetes is a burdensome life condition that significantly reduces quality of life. Personality characteristics can have both positive and negative impacts on self-management of diabetes, and some personality profiles, especially the distressed/Type D personality, are indicative of poor prognosis and greater chances of developing medical complications. Psychological interventions such as cognitive behaviour therapy, acceptance and commitment therapy, behavioural activation, and counselling strategies such as educational programmes, problem solving training, and motivational interviewing have proven very effective in coping with diabetes distress, managing comorbid mental health problems, and increasing adherence to self-care and antidiabetic behaviours. Additionally, yogic practices have also shown promising results for self-management of diabetes. Paediatric diabetes especially presents unique psychosocial challenges to patient management and affects academic performance of children and career choices of affected individuals.

INTRODUCTION

Diabetes, like other chronic, noncommunicable diseases, has a definite psychological impact on the affected individuals and their families. Conversely, the psychological makeup and functioning of the affected individual also affects several aspects of diabetes morbidity outcomes. The aim of this review article was to provide an update of the major psychological aspects that are affected in patients with diabetes, as well as those that affect the development, management, prognosis, and outcomes of diabetes. This review has used a narrative synthesis approach

and examined relevant articles from databases such as PsychINFO, PubMed, and Google Scholar. The key search terms used in this review consisted of a standard prefix and a variable suffix term. The prefix across the search terms was 'diabetes mellitus and', and the suffix terms included the following: mental health, depression, anxiety, distress, coping styles, coping, suicide, suicidal ideation, personality characteristics, Type D personality, quality of life (QoL), health-related QoL, psychological interventions, Cognitive Behaviour Therapy (CBT), Acceptance and Commitment Therapy (ACT), behavioural activation, counselling strategies, yoga, and COVID-19 pandemic. The other separate search terms included diabetes in children and adolescents, paediatric diabetes, and issues or challenges in paediatric diabetes. Only relevant articles with a focus on diabetes in relation to the suffix search terms and those published after January 2010 were included in this review.

DIABETES AND COMMON MENTAL HEALTH DISORDERS

Diabetes not only has physical comorbidities, but also mental health comorbidities such as depression and anxiety, which are common among patients with diabetes.[1] People with Type 1 and Type 2 diabetes mellitus are three times and two times more likely to develop depression compared to people without diabetes, respectively.[2] Approximately 30% of the children and adolescents with Type 1 diabetes mellitus have depressive symptoms.[3] A cross-national study reported a 10.6% prevalence of clinical depression and 17.0% prevalence of moderate-to-severe depressive symptoms among patients with diabetes.[4] Additionally, sex, education, diabetes distress, and a history of major depression were found to be risk factors for developing depression.[4] Patients with diabetes may develop depression because of increased burden of disease management or because of associated biochemical changes accompanying diabetes. Alternatively, patients with depression may have poorer clinical parameters and outcomes of diabetes because of the difficulty in maintaining health behaviours such as increased physical activity, a healthy diet, and medication compliance. Depression may thus be both a consequence as well as a risk factor for diabetes.[5] Patients with diabetes have been reported to exhibit a 36% higher risk of developing microvascular complications and 25% higher risk of macrovascular complications.[6]

Patients with diabetes lead a life that is demanding, constantly challenging, and full of uncertainties. They share a constant concern about maintaining normal levels of blood glucose, medical complications, episodes of hypoglycaemia, hyperglycaemia, and other characteristics of diabetes morbidity. As a result, it is obvious that patients with diabetes may develop symptoms of anxiety or anxiety disorders. A cross-national study revealed that 18.0% of diabetic patients had at least one type of anxiety disorder and 2.8% had multiple anxiety disorders;[7] generalised anxiety disorder was the most common (8.1%), followed by panic disorder (5.1%).[7] Female sex, diabetic complications, longer duration of illness, and glycaemic control were significant risk factors for developing anxiety among patients with diabetes..[7]

Apart from common mental health issues, patients with diabetes also experience greater sleep-related problems.[8] For example, 69% of patients with diabetes had diagnosed breathing-related sleep disorders and 27% had restless leg syndrome, which are far below the general population prevalence of 2–4% and 6%, respectively.[8] Conversely, the risk of developing Type 2 diabetes mellitus was 28% higher among adults with a sleep duration of <5–6 hours per night and 48% higher among adults with a sleep duration of >8–9 hours per night.[9] The incidence of Type 2 diabetes mellitus was 57% higher among those who had difficulty in initiating sleep, and this reached 84% among those who had difficulty in maintaining sleep.[9] Shorter durations of sleep have been specifically associated with greater incidences of Type 2 diabetes mellitus, poorer glycaemic control, and reduced insulin sensitivity.[10] However, these findings are not conclusive as the results vary with the use of objective parameters versus self-report.

DIABETES DISTRESS AND COPING

Diabetes distress refers to a range of negative emotional states that arise from diabetes morbidity and self-care behaviours that patients

engage in for better management of their diabetes.[11] Diabetes distress is not the same as depression (Table 1), and the two conditions do exist simultaneously and independently.[12] Diabetes distress is largely an emotional response to the challenges posed by diabetes and may include emotional reactions such as fear, worry, anger, guilt, sadness, frustration, and burn out.[12] On the other hand, depression involves significant cognitive, affective, social, motivational, and vegetative disturbances in an individual. Both have been reported to have distinct outcomes and associations with clinical parameters related to diabetes self-care. Diabetic patients with comorbid depression are more likely to develop clinical complications compared to non-depressed patients.[6] Similarly, diabetic distress has been associated with cross-sectional and time-concordant levels of haemoglobin A1C (HbA1c) among adults, whereas no such association has been found between depressive symptoms or clinical depression and HbA1c.[13,14] Diabetes distress, rather than depressive symptoms, predict self-reported HbA1c levels among adolescents.[15]

The sources of diabetic distress can be multiple, and one study has factor analytically derived seven major sources of distress in diabetic patients (Table 2): powerlessness, negative social perceptions, physician distress, friend/family distress, hypoglycaemia distress, management distress, and eating distress.[16] Severity of diabetic distress is directly associated with longer duration of illness, elevated levels of HbA1c, higher BMI, decreased social support, younger age, excessive sleepiness during day time, and lower self-efficacy.[17-19] Management of diabetes distress is important as unmanaged distress is associated with poor glycaemic control, medication adherence issues, decreased QoL, lower self-efficacy, negative health beliefs, and poor self-care behaviours.[13,15,20-21]

Psychoeducational approaches that address both diabetes and emotion have been reported to be effective for diabetes distress;[22] this is preferably delivered by a generalist. A group format may also be effective,[22] whereas motivational interviewing, though useful for several long-term conditions, has been reported to be equivocal in the management of diabetes distress.[22]

Table 1: Differentiating between diabetes distress and depression.

Diabetes distress	Depression
Mainly an affective response to diabetes morbidity and burden of the disease	A complex response and involves a range of other reactions dissimilar from the affective response
Specific affective reactions may include worry, fear, guilt, sadness, anger, frustration, and burnout	Response usually includes cognitive, affective, social, motivational, vegetative, and interpersonal disturbances
Prevalence is greater	Prevalence is relatively lesser
Diabetes and diabetic distress seem to be linearly related	Diabetes and depression seem to have reciprocal connections in many cases
Not a significant risk factor for developing medical complications	Is a significant risk factor for developing medical complications
Has been a relatively consistently associated with HbA1c levels	Has not been shown to have consistent associations with HbA1c levels
Interventions may involve psychoeducation, supportive therapy, counselling, and other simple behaviour management methods	Interventions may involve use of complex psychological interventions such as CBT and ACT

ACT: acceptance and commitment therapy; CBT: cognitive behavioural therapy.

Table 2: Seven factor analytically derived sources of diabetic distress.

Source of distress	Description
Powerlessness	A state of helplessness when individuals unsuccessfully try to control several challenging, and often uncontrollable, aspects of diabetes
Negative social perceptions	Feelings of social mistreatment and discrimination by people and employers
Physician distress	Feelings of mistrust and incompetence about the physician treating diabetes
Friend/family distress	Feeling of being treated as sick and different by family members and friends. Feeling that family and friends exaggerate the threat posed by diabetes
Hypoglycaemia distress	Fearful feelings of experiencing sudden episodes of hypoglycaemia such as during driving or sleeping, and fear of failing to notice signs of hypoglycaemia
Management distress	Feeling distressed over not constantly monitoring one's blood glucose levels and feelings of not being sufficiently considerate to diabetes care
Eating distress	Feeling distressed over unhealthy eating and not exercising disciplined eating behaviour to support better management of diabetes

Fisher et al.[16] used qualitative interviews and factor analytic procedures to derive seven major sources of diabetes distress among adults with Type 1 diabetes mellitus.

COGNITIVE DYSFUNCTION AND DIABETES

Diabetes is accompanied by dysfunction in both basic- and higher-order domains of a patient's cognitive functioning.[23] A systematic review of cognitive functioning in Type 2 diabetes mellitus revealed significantly poorer performance in six domains: motor function, executive function, processing speed, verbal and visual memory, and concentration.[24] The effect size difference between diabetic and nondiabetic individuals was small-to-moderate for most of these cognitive domains, and smallest for the attention concentration domain.[24]

The cognitive dysfunction in diabetes may manifest in a very subtle form known as diabetes-associated cognitive decrements (DACD). DACD does not cause significant disruption in the daily activities of patients with diabetes and hence is not considered abnormal enough to warrant formal neuropsychological assessment.[23] The relatively noticeable cognitive impairment in diabetes is subsumed under mild cognitive impairment (MCI), which is regarded as a transitional state between DACD and severe forms of cognitive impairment such as dementia.[23] A subtype of MCI, amnesic MCI, is concerned with memory-related issues and forgetting, and leads to noticeable disruption in a patient's life, which necessitates formal neuropsychological testing and management. Severe cognitive impairment in diabetes is diagnosed when cognitive dysfunction progresses to the level of formal cognitive disorders such as dementia. It is associated with significant impairment in multiple domains of cognitive functioning and causes a significant disruption to instrumental daily activities.

Cognitive dysfunction has shown associations with clinical characteristics and management of diabetes. Patients using metformin have been shown to have greater risk of cognitive impairment and exhibit decreased cognitive performance compared to those not using

metformin.[25] Uncontrolled glycaemic levels also present a significant risk factor for cognitive impairment. Longer duration of illness and early age of onset have been associated with development of dementia or a greater risk of progression from mild to severe cognitive impairment among patients with diabetes.[26-27] Apart from clinical characteristics, risk and severity of cognitive dysfunction also varies with sociodemographic characteristics such that dysfunction is severe among older patients with diabetes and less severe among patients with higher levels of education.[28]

Cognitive dysfunction in diabetes has multiple potential underlying bases which include uncontrolled glycaemia, decreased functional connectivity of working memory networks, vascular disturbances at micro and macro levels, and disturbances in insulin signalling.[29,30] Specifically, insulin signalling is believed to influence long-term potentiation in the hippocampus, which has a high density of insulin receptors and is involved in learning and memory.[29,30] Insulin also affects the levels of neurotransmitters, such as acetylcholine, epinephrine, and norepinephrine, that are implicated in memory functioning.[29]

DIABETES AND QUALITY OF LIFE

QoL is a broad and multidimensional construct that refers to an individual sense of general wellbeing. Diabetes is a burdensome life condition and patients face significant issues and challenges at the physical, emotional, psychological, social, occupational, and interpersonal levels. Constant monitoring and maintaining of normal blood glucose levels, consistent use of antidiabetic drugs, fear of hyper or hypoglycaemic episodes, fear of developing medical complications, psychiatric comorbidities, restricted food choices, travel constraints, obligation to routine physical exercises, financial costs, mobility issues, and reduced social interactions can be overwhelming.[31] As a result, individuals living and dealing with diabetes experience a range of negative emotions such as worry, fear, anger, guilt, sadness, helplessness, hopelessness, frustration, and burnout, which all considerably decrease their QoL.[11]

In view of the decreased QoL, the focus of diabetes treatment is not just to control glycaemic levels and prevent medical complications, but also to improve QoL by lessening the overall burden of disease. Besides improvement in therapeutics, additional and more affordable options for medical care, effective psychological and educational interventions for diabetes management, and the presence of support groups have considerably improved the quality of patient's life.[32] There is a greater need for assessment of QoL in diabetes care and research has led to the development of tools such as the Audit of Diabetes-Dependent QoL (ADDQOL) and Diabetes QoL (DQoL).[33]

DIABETES AND PERSONALITY CHARACTERISTICS

Management of diabetes, like many other chronic illnesses, is affected by personality characteristics. Certain personality characteristics are known to interfere with self-care behaviours, coping with diabetes distress, and affect the diabetes outcome. The personality profile of individuals with diabetes has been examined using the framework of the five-factor model.[34] The five factors include openness, conscientiousness, extraversion, agreeableness, and neuroticism. Conscientiousness is strongly associated with better diabetes self-care, especially glycaemic control.[34] This is because conscientious individuals are more organised and less impulsive and hence exhibit consistency in self-caring behaviours such as glucose monitoring, physical activity, regular visits to a physician, and effective control over impulsive eating. Patients who exhibit higher levels of neuroticism, an index of emotional instability, tend to worry persistently; are anxious, fearful, and overthink; and have persistently negative moods. It is likely to interfere with self-management, adherence, and may also contribute to increased likelihood of developing psychiatric comorbidities among patients with diabetes.[34,35]

Another thread of research has focussed on distressed/Type D personality, characterised by higher levels of negative affectivity, social inhibition, and constricted expression of negative emotions in social interactions.[36] 52% of patients with diabetes were found to have Type

D traits that have significant implications for diabetes self-care and clinical outcomes of the disease.[37-38] Type D patients have been shown to struggle with treatment compliance, especially medication adherence and routine visits to the physician.[37-38] They exhibit a relatively lacklustre attitude towards maintaining antidiabetic behaviours such as adherence to physical activity recommendations, avoiding consumption of high calorie foods, emotional eating, control over BMI, and cholesterol levels.[37] These individuals have greater chances of experiencing mental health issues such as depression and anxiety.[37] Type D personality is also an indicator of poor prognosis and adverse clinical consequences of diabetes.[39]

SUICIDE AND DIABETES

Patients with diabetes have a significantly higher risk of suicidal ideation, attempted suicide, and completed suicide.[40] The prevalence for suicidal ideation is 16.2%, much higher than the 9.2% found in the general population.[40] Annually, approximately 94,000 completed cases of suicide occur worldwide among patients with diabetes.[41] The reasons for higher rates of suicidal ideation or suicide can be multiple and may include comorbid depression, which is a significant risk factor for suicide.[4,6] Additionally, patients with diabetes may be overwhelmed by the extreme burden of the disease: taxing diabetes care, financial costs, poor QoL, deterioration in interpersonal relationships, negative cognitions such as constant worry or hopelessness, and poor prognosis. Further, the risk of suicide is modified by clinical characteristics of diabetes, sociodemographic characteristic of the patients, presence of comorbid mental health issues, and specific personality traits and coping styles.[42]

PSYCHOLOGICAL INTERVENTIONS AND COUNSELLING STRATEGIES IN DIABETES

Psychosocial issues surrounding diabetes care have brought a greater focus on psychological interventions in the overall diabetes management. Several psychological interventions such as CBT, ACT, and behavioural activation strategies have been used to target different dimensions of diabetes morbidity. They include symptoms of depression, anxiety, interpersonal functioning, glycaemic control, diabetes specific distress, QoL, adherence to medication regimens, and maintenance of important self-care activities including physical activity, dietary recommendations, and regular self-monitoring of blood glucose levels. A modified form of CBT known as CBT for adherence and depression (CBT-AD) integrates conventional CBT for depression with CBT designed to improve overall treatment adherence.[43] CBT-AD consists of a single stand-alone session in the beginning to foster adherence to medical regimens and self-care behaviours. The latter part of CBT-AD consists of four modules of 9–11 sessions that focus on adherence and depression.[43] These sessions include motivational interviewing and typical CBT methods and techniques such as behavioural activation and activity scheduling, monitoring of mood, glucose levels, dietary and physical activities, monitoring of thoughts, maladaptive cognitions and their restructuring, problem solving, and relaxation exercises.[43] CBT-AD has been effective for control of glycaemic levels, adherence to medication and self-monitoring of blood glucose, reduction in depression severity, and significant improvement in diabetes self-care behaviours.[43-44]

ACT has shown promising results in improving self-care behaviours and glycaemic control.[45] Contrary to CBT, the ACT does not attempt to confront or change the content of thoughts and feeling of patients with diabetes. Rather, ACT creates an attitude of acceptance towards distressing thoughts, feelings, emotions, and sensations that result from diabetes morbidity. Less complex psychological interventions such as behavioural activation embedded in exercise programmes for patients with diabetes and depression have shown positive results in terms of greater enjoyment of physical activity and cessation of avoidance behaviours.[46] Other strategies such as teaching problem solving skills, including the use of technology for diabetes problem solving, have been used in the management of diabetes.[47]

Motivational interviewing, as an independent counselling approach, has been employed to elicit and build motivation for undertaking antidiabetic behavioural changes.[48] It is an effective method for helping patients with diabetes to overcome the resistance,

ambivalence, and self-efficacy issues that generally hinder their engagement in self-care behaviours to manage diabetes or prevent the development of poorer diabetic outcomes.[49] Motivational interviewing is a collaborative venture between care provider and patient that is patient-focussed and patient-directed.[48-49] It is different from the traditional didactic approach of educating patients about the importance of behaviour change. The counsellor adopts and guides the patients through a process of change that involves four major sequential steps: engaging, focussing, evoking, and planning.[49] Motivational interviewing has demonstrated effectiveness in bringing about successful dietary changes, weight loss, glycaemic control, and improvements in BMI among patients with diabetes.[50]

Complementary therapeutic practices such as yoga are also effective for Type 2 diabetes mellitus care and management. Yogic practices improve not only the primary diabetic symptoms but also have beneficial effects on multiple other functions that are adversely affected by diabetes. Yoga has been shown to have a significant improvement on glycaemia control, HbA1c and fasting blood glucose levels, postprandial blood glucose, lipid levels, and body composition.[51-52] Yoga has also been found to be associated with reductions in BMI, anxiety, depression, and oxidative stress, and enhanced cognitive functioning, improved blood pressure, QoL, and general wellbeing.[53-55]

PSYCHOSOCIAL ISSUES IN PAEDIATRIC DIABETES

The management of diabetes in children and adolescents presents unique challenges; specifically, its management is complicated by developmental changes taking place, their need for autonomy and psychosocial immaturity, peer pressure, and family dynamics.[56] Nonadherence to medical regimens such as insulin therapy, as well as other self-care behaviours such as not attending physical activity classes, refusing dietary changes, and maladaptive behaviours, may be observed.[56] Risk-taking behaviours such as substance abuse and eating disorders can complicate the management process, or may worsen diabetes outcomes. Children in families with dysfunctional social interaction patterns have been shown to exhibit poorer control of certain diabetes parameters. Type 1 diabetes mellitus not only affects children and adolescents directly, but it also has a significantly negative impact on the family. Paediatric diabetes leads to increased stress among parents, conflicts over mismanagement of children's diabetes, fear of adverse diabetes-related complications such as hypoglycaemia, hyperglycaemia, ketoacidosis, and hospitalisations.[56, 57]

Paediatric diabetes is also associated with experiencing diabetic distress, anxiety, depression, eating disorders, externalising problems, cognitive dysfunction, and overall reduced QoL. It also affects the performance of children and adolescents in academic as well as nonacademic domains such as sports and exercise, and has adverse implications for their employment and career prospects.[58] Children with early-onset diabetes and longer duration of illness are particularly at a higher risk for these negative outcomes.[58]

DIABETES, COVID-19, AND MENTAL HEALTH

Patients with diabetes have been uniquely affected by the current coronavirus disease (COVID-19) pandemic. Complete lockdowns, restrictions on travel and movement, and general anxiety about the pandemic directly and indirectly have all affected clinical aspects of diabetes and self-care. Access to medical services such as physician consultations, antidiabetic drugs, testing and monitoring services, and self-care behaviours such as outdoor physical activities, were all differentially hampered.[59] As a result, the COVID-19 pandemic affected glycaemic control of diabetic patients, which was associated with poorer clinical outcomes such as the need for intensive care and even death.[60] The anxiety caused by lack or irregularity of medical services, fear of being vulnerable to poorer COVID-19 outcomes, and greater mortality rates may have added to pre-existing diabetes distress and further exacerbated the mental health issues of patients with diabetes.

SUMMARY AND CONCLUSION

Patients with diabetes have manifold risk of developing common mental health conditions such as anxiety and depression. A significantly greater proportion of patients experience diabetes distress in response to disease burden and their perceived threats of the disease. Patients with diabetes also experience cognitive dysfunction ranging from very subtle to very severe levels. Additionally, diabetes significantly reduces the QoL of patients. Both patients with diabetes and with mental health disorders have been affected by the current COVID-19 pandemic, which may lead to poor outcomes. In addition to medical management, psychological interventions and counselling strategies have been developed or adapted to deal with diabetes distress, mental health issues, poor QoL, difficulties in self-management of diabetes, and adherence to medical regimens and antidiabetic behaviours. Core psychological therapies such as CBT, ACT, counselling strategies, motivational interviewing, and yogic practices have proven effective for glycaemic control, improved adherence to medication, self-care behaviours, reducing depression severity.

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Advanced Approaches in Immunotherapy for the Treatment of Type 1 Diabetes Mellitus

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Disclosure: Dr Lakey serves as scientific advisor to XoStem. The other authors have declared no conflicts of interest.

Received: 10.03.20

Accepted: 21.05.20

Keywords: Diabetes, immunosuppression, immunotherapy, stem cells, transplantation.

Citation: EMJ Diabet. 2020;DOI/10.33590/emjdiabet/20-00062.

Abstract

The cure for Type 1 diabetes mellitus (T1DM) is likely to require an effective strategy for suppressing or evading the immune system. When considering curative treatments, it is almost inevitable to consider novel ways of inducing tolerogenicity to insulin-producing β cells. While the main mechanism of achieving tolerogenicity is restoring regulatory T cell (CD4+CD25+Fox3+) to effector T-cell (CD4+Fox3-) homeostasis, the means of achieving this are multifarious. The advent of a glucocorticoid-free immunosuppressive regimen was an early indication of how immunotherapeutics affect β-cell function. As newer biologics are developed, suppressing the immune system continues to become more specific and dynamic. An ever-evolving field of immunology has shifted the paradigm of how T1DM is understood, and the repurposing of T-cell-based biotechnology has the potential to change the way that it is treated. Regulatory T cells can be bioengineered to express T-cell receptors with affinity for peptide–human leukocyte antigen complexes that are frequently encountered in T1DM. Exosomes with embedded T-cell receptors can be isolated from regulatory T cells for use as an off-the-shelf therapy.

INTRODUCTION

While the precise aetiology and pathological mechanisms remain to be completely understood,[1] Type 1 diabetes mellitus (T1DM) is a chronic metabolic disorder caused by the autoimmune destruction of insulin-producing β cells. The suboptimal release of insulin, at levels below the range required for metabolic homeostasis, is a consequence of the ample loss of β cells. T1DM is diagnosed by measurements of unusually high HbA1c and low levels of C-peptide, a byproduct of insulin production.[2] The subcutaneous administration of exogenous insulin is currently the standard form of treatment. Along with the difficulties of precisely measuring and frequently administering insulin for appropriate conditions, the limitations of exogenous insulin administration include lifelong dependency, inadequate metabolic control, a moderate risk of inadvertently inducing severe hypoglycaemia, an undiminished risk of comorbidity, and reduced quality of life.[3]

The possibility for diagnostics to predict the risk of T1DM with high sensitivity and specificity, up to decades before its onset, seems to challenge the acceptance of autoimmune destruction of insulin-producing β cells as an inevitable fate of T1DM.[4] The presence of genetic polymorphisms of human leukocyte antigen (HLA)-DQ and multiple autoantibodies that target islet self-antigens, which appear early in life, are highly predictive of T1DM.[5] Autoantibodies target the islet cytoplasm (islet cell antibody [ICA]), native insulin (insulin autoantibody [IAA]), islet antigen-2 (IA-2), the 65-kDa isoform of glutamic acid decarboxylase (GAD65), and variants of zinc transporter 8 (ZnT8). Given that a small percentage of patients with T1DM demonstrate an absence of the aforementioned autoantibodies, non-HLA single nucleotide polymorphisms should be considered when determining combined risk.[6,7] Before prevention becomes a standard form of treatment, diagnostics must be optimised for this purpose. To not be misled into treating false positives, it is critical to minimise the value of Type I errors and establish an acceptable threshold. Minimising Type II errors enables the opportunity to reduce the cumulative burden of morbidity in a population. Conceptually, prevention straightforwardly aims to preserve the interrelated mass and insulin-secretory function of β cells. There is early evidence that immunotherapy can delay the onset of the autoimmune destruction of β cells.[8] Specific combinations of HLA haplotypes and autoantibodies are associated with increased risk for T1DM (Figure 1). Genetic screening for inherited HLA haplotypes identifies patients at risk for T1DM. In patients with at-risk HLA haplotypes, autoantibodies diagnostics inform its progression.

While closed-loop insulin delivery using a control algorithm prototypes the sophisticated technology that mimics the glucose-responsive insulin secretion of β cells,[9] β-cell replacement therapy in the form of islet transplantation is one of the few treatments demonstrating potential for insulin independence.[10] The β cells present in an admixture of α cells, γ cells, δ cells, and ε cells within islets that have evolved closely together to release counter-regulatory hormones for metabolic homeostasis. The restoration of glycaemic control, a reduced risk of severe hypoglycaemia, the reversal of hypoglycaemia unawareness, and a reduced risk of comorbidity are the proposed clinically meaningful outcomes of islet transplantation. However, the duration of insulin independence is low and severe risks caused by complications or prescribed immunotherapeutics compromise its utility. Secondary immune deficiency is an unavoidable aspect of the intended effect and renal decline is not an uncommon side effect of the administration of nonspecific immunotherapeutics.[11] Therapies that aim to replace, preserve, or replicate β cells are limited by less-than-optimal immunotherapies. β-cell replacement therapy is, however, especially limited by a lack of β cell supply. Therefore, the regeneration of β cells from stem cells or even from the endogenous β-cell mass is an extraordinarily complex yet prominent area of research.[12,13] The promise of treating autoimmunity early in life and/or empowering these other forms of curative treatments later in life is contingent on advancing approaches in immunotherapy.

IMMUNOSUPPRESSION IN THE EDMONTON PROTOCOL

Prior to the Edmonton protocol, anti-lymphocyte globulin and small molecules (cyclosporine, azathioprine, and glucocorticoids) were commonly used in a regimen as a means of nonspecifically attaining immunosuppression for islet transplantation.[14] While glucocorticoids are widely used as an immunosuppressive steroid to treat autoimmunity,[15] it is increasingly clear that glucocorticoids adversely stimulate gluconeogenesis in the liver and antagonise the insulin-mediated uptake of glucose.[16] The induction of peripheral insulin resistance is counterproductive to the desired effect of islet transplantation. Enabled by an increase in newer immunosuppressive agents, the regimen included in the Edmonton protocol ventured with a glucocorticoid-free regimen consisting of sirolimus, tacrolimus, and daclizumab.

Sirolimus, also known as rapamycin, is a macrolide that binds to FKB12 and blocks the activation of the cell-cycle specific kinase TOR.[17] Sirolimus indirectly inhibits the proliferation of T cells and B cells. Tacrolimus, discovered for its structural similarity to sirolimus, inhibits calcineurin with a much stronger potency compared to cyclosporine.

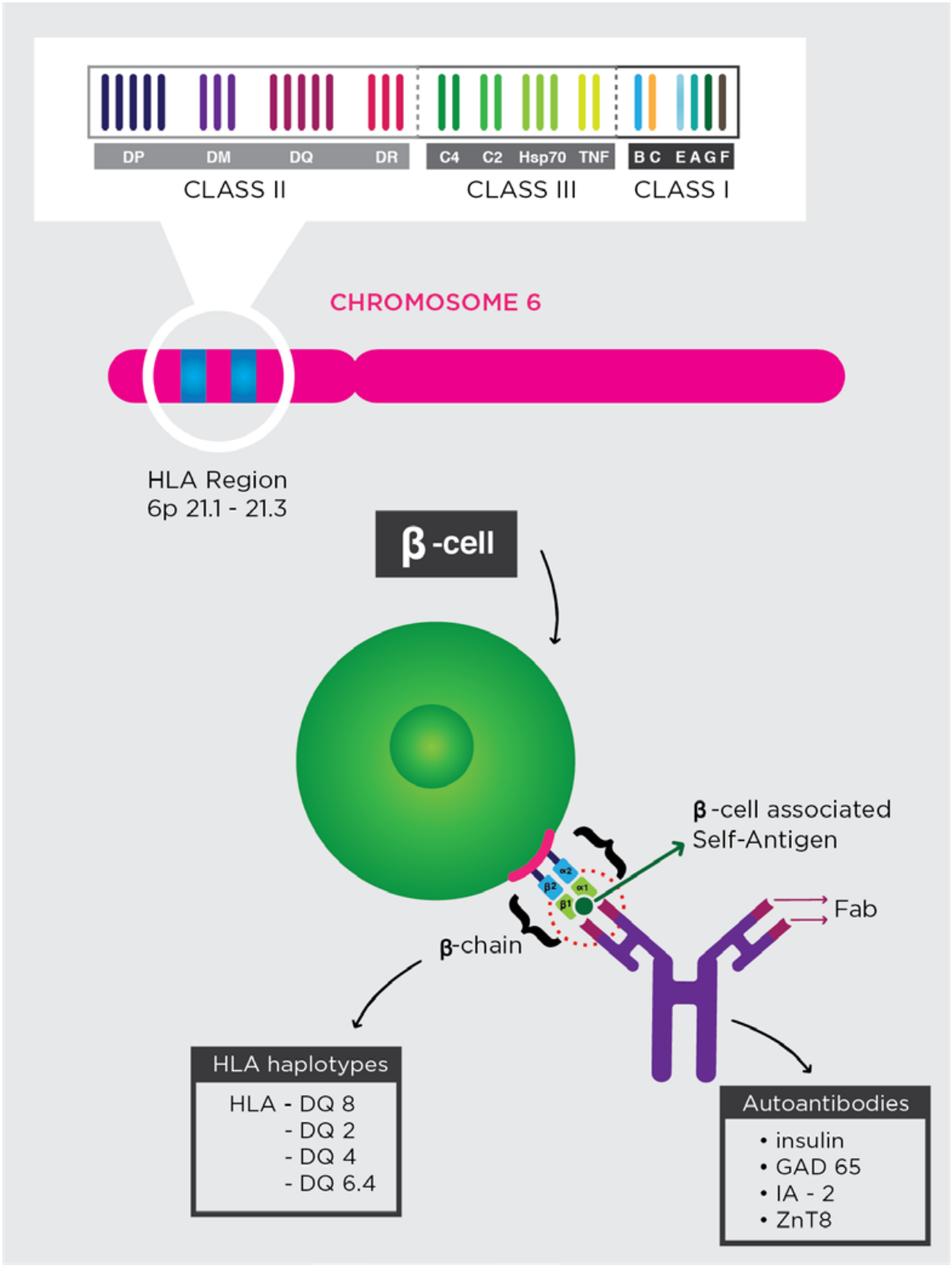

Figure 1: Genetic risk and autoantibody diagnostic.

Specific combinations of HLA haplotypes and autoantibodies are associated with increased risk for T1DM. Genetic screening for inherited HLA haplotypes identifies patients at risk for T1DM. In patients with at-risk HLA haplotypes, autoantibodies diagnostics inform its progression.

Fab: antigen-binding fragment; GAD65: the 65-kDa isoform of glutamic acid decarboxylase; IA-2: islet antigen-2; T1DM: Type 1 diabetes mellitus; ZnT8: zinc transporter 8.

A significantly lower dose of tacrolimus is therefore required to efficaciously induce immunosuppression and is considered the risk-averse alternative to cyclosporine.[18] However, the risks associated with calcineurin inhibitors, including a decline in renal function and dialysis, are not sufficiently eliminated.[19] Given that tacrolimus causes β-cell dysfunction and sirolimus biphasically induces insulin resistance,[20] cotreatment with a GLP-1 agonist suggests that these counterproductive effects are reversible and can be prevented.[21]

Daclizumab, a monoclonal antibody that blocks the CD25 subunit of the IL-2 receptor, decreases IL-2 signalling at this high-affinity receptor. Due to the increased availability of IL-2, it inadvertently increases IL-2 signalling in cells expressing intermediate-affinity receptors.[22] While daclizumab ameliorates autoimmunity with clinically meaningful effects, immune-mediated risks are concerns. Having received more scrutiny as severe, unintended effects are reported, including serious inflammatory disorders and death, its use is restricted and monitored.[23] With the benefit to risk ratio as a priority, the immunotherapeutic regimen included in the Edmonton protocol is far from ideal.

BIOLOGICS AS OPTIONS FOR TARGETED IMMUNOSUPPRESSION

The immune system is regulated by cytokines. Upon binding to receptors on immune cells, cytokines turn on complex signalling pathways that activate key transcriptional factors. The transcriptional factors then promote the differentiation of naïve immune cells into specific lineages. In response to a large number of cytokines, naïve T cells differentiate into at least seven subtypes of helper (CD4+) T cells.[24] While the subset of helper T cells is in an adjustable equilibrium, a disequilibrated regulatory T-cell (Treg) to Th17 cell balance leads to autoimmunity.[25] The TGFβ/IL-6 and IL-2 cytokine axis regulates the differentiation of naïve T cells into either the Treg cell or Th17 cell lineage.[26] Via the TGFβ and IL-6-mediated activation of transcription factors STAT3 and RORγt, Th17 cells are involved in the autoimmune destruction of β cells.[27] Whereas Treg cells inhibit autoreactive CD8+ T cells,[28] Th17 cells activate autoreactive CD8+ T cells. Autoreactive T cells are known to either escape clonal deletion or differentiation into the thymic Treg cell lineage early in life and enter the peripheral lymph nodes of the pancreas.[29] Biologics are the cytokines or antibodies that are manufactured for therapeutic purposes, such as manipulating the cytokine axis to re-enact an equilibrated Treg–Th17 cell balance.

DNA recombinant technology has enabled the engineering of recombinant cytokines and antibodies with specific targets. Subsequent to antigen presentation, IL-2 triggers the expansion of CD25+ Treg cells.[30] Given that CD25+ Treg cells express high-affinity IL-2 receptors, a low dosage of IL-2 is sufficient to trigger the expansion of CD25+ T cells.[31] A low dosage of IL-2 may be a strategy to mimic the Treg–Th17 cell homeostasis. However, other immune cell types also express high-affinity IL-2 receptors. Therefore, it is possible for a long-term low dosage of IL-2 to backfire. Monoclonal antibodies JES6-1 and F5111.2 are strategically attached to IL-2 to stabilise a conformational change that increases its selectivity for the high-affinity receptors on CD25+ Treg cells.[32] This strategy averts off-target effects that are likely to backfire, and can guide the development of antibodies for immunomodulatory cytokines with similar pharmacodynamics. Humanised versions of JES6-1 and F5111.2 are in development.

Whereas an increase in clinical trials indicates a renewed interest in cytokines,[33] antibodies that target cytokines or the corresponding receptors are more commonly used. Monoclonal antibodies, such as adalimumab and etanercept, bind to TNFα with a higher affinity compared to its TNFα receptors.[34] The binding of adalimumab to TNFα induces a conformational change that trimerises TNFα receptors on Tregs and triggers its expansion.[35] More commonly, antibodies are used to suppress Th17 signalling. Brodalumab is a monoclonal antibody that binds to the IL-17 receptor and is approved for certain autoimmune diseases.[36] While preclinical studies suggest that Th17 cells are also involved in T1DM,[37] clinical trials are required to reveal whether antibodies that suppress Th17 signalling have therapeutic effects in T1DM. Teplizumab, an Fc-receptor non-binding, anti-CD3 monoclonal antibody, obstructs the transmembrane assembly of CD3 subunits within the T-cell receptor (TCR).[38] This prevents signalling downstream of the TCR and therefore mimics effector T-cell exhaustion.[39] A randomised,

double-blind Phase II trial demonstrated that a single 14-day course of teplizumab delayed the onset of T1DM by 24.4 months compared to a placebo-treated group.[40] The U.S. Food and Drug Administration (FDA) has granted teplizumab a breakthrough therapy designation to efficiently expedite the process of determining whether there is more evidence to support its approval.[41]

Given a lack of randomised controlled trials comparing the efficacies of different biologics for T1DM, a post hoc study was used for insight into how the outcomes of islet transplantation are related to the type of biologics used.[42] The biologics in this study included an Fc-receptor non-binding, anti-CD3, antithymocyte globulin (ATG) or alemtuzumab alone; ATG or alemtuzumab with TNFα inhibitors; and anti-CD25. The duration of insulin independence provided by transplanted islets was increased when Fc-receptor non-binding, anti-CD3 and ATG, or alemtuzumab with TNFα inhibitors are used. Given that CD4+Fox3- cells express higher levels of CD3 compared to CD4+Fox3+ cells, the anti-CD3 is expected to target the effector CD4+ T cells while mostly sparing Treg cells.[43] ATG, a polyclonal antibody that suppresses lymphocytes and other immune cell types through diverse mechanistic pathways to prevent acute rejection, is shown to induce the expansion of Treg cells *ex vivo*.[44] Alemtuzumab, an anti-CD52 monoclonal antibody, similarly depletes lymphocytes.[45] A single course of low-dose ATG delays the decline of C-peptide levels at 1 year after infusion.[46] Because ATG and antibodies against TNFα antibodies have demonstrated potential to expand Treg cells, there is consistency with inducing tolerogenicity to transplanted β cells via restoring Treg to effector T-cell homeostasis.

Many of the biologics used in cancer immunotherapy are repurposed for autoimmunity. Among these, biologics that target costimulation and co-inhibition are well-known (Figure 2).[47] When an effector T cell recognises an antigen presented on either major histocompatibility complex (MHC) I or II, the B7 family binds to either costimulatory CD28 or co-inhibitory CTLA-4.[48] Binding of the B7 ligands to CD28 is necessary for activation of effector T-cell function. CTLA-4 competes with CD28 for binding to B7 ligands to inhibit this activation. Given that CTLA-4 binds to B7 ligands with a higher affinity, recombinant CTLA-4 fused to Ig, such as abatacept and belatacept, attempt to exploit co-inhibition. CTLA-4 is fused to Ig to increase its half-life. Clinical trials prove that abatacept delays the decline of C-peptide levels in recent-onset T1DM.[49] In principle, anti-CD28 should block costimulation; instead, anti-CD28 facilitates the homodimerisation of CD28 and serves as an agonist.[50] While used as an agonist for cancer immunotherapy, the anti-CD28-mediated cytokine storm serves as a reminder of the risks involved when using biologics to manipulate the immune system.[51]

While preclinical and clinical studies suggest that these biologics have potential to ameliorate autoimmunity, none have been approved for T1DM. However, teplizumab is the first to receive a breakthrough therapy designation by the FDA for T1DM.

THE POTENTIAL OF CELL-BASED IMMUNOTHERAPY

Cells integrate environmental signals to execute complex, regulated behaviour. Infusing cells with immunosuppressive therapeutic behaviours, such CD4+CD25+Fox3+ Treg cells and mesenchymal stem cells (MSC), is potentially a more dynamic strategy for restoring tolerance to β cells.[52] The loss of function of Fox3+, an important transcription factor involved in the differentiation of naïve T cells into Treg cells, causes immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome.[53] In an adolescent patient with late-onset IPEX syndrome with T1DM, allogeneic haematopoietic stem cell therapy (aHSCT) delays the decline of C-peptide levels for 15 months.[54] aHSCT reconstitutes an equilibrated population of functional Treg cells and other immune cells from a donor. Given the significant morbidity caused by graft-versus-host disease (GVHD), the clinically meaningful outcomes derived from aHSCT outweigh the morbidity of GVHD only for T1DM patients with underlying IPEX syndrome. The adoptive cell transfer of autologous Treg cells may be the safer counterpart to aHSCT for the majority of T1DM patients who do not have underlying IPEX syndrome. For the adoptive cell transfer of autologous Treg cells, extirpating the recipient's immune system is unnecessary and morbidity from GVHD is not a concern.

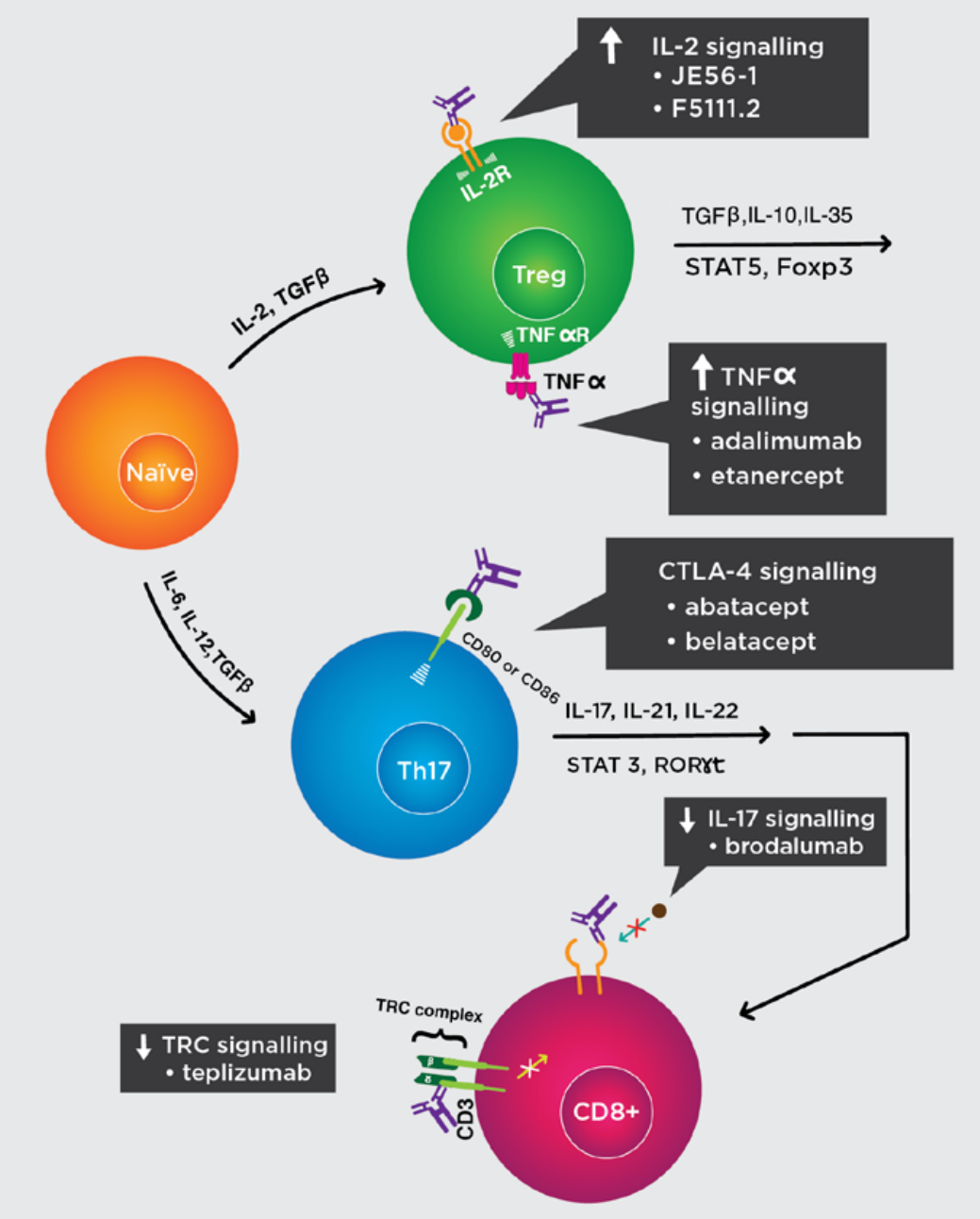

Figure 2: Biologics to restore regulatory T cell to effector T-cell homeostasis.

Mechanisms of biologic activity:

• Increase IL-2 signalling. JES58-1 and F5111.2 preferentially bind to IL-2 receptors on Treg cells and induce its expansion. Humanised versions are in development.

• Increase TNFα signalling. Adalimumab and etanercept trimerise TNFα receptors on Treg cells and induce its expansion.

• Increase CTLA-4 signalling. Recombinant CTLA-4 fused to Ig, such as abatacept and belatacept, exploit co-inhibition and divert away from CD28 co-activation.

• Decrease IL-17 signalling. Brodalumab binds to IL-17 receptors to suppress downstream signalling that activate autoreactive CD8+ T cells.

• Decrease TCR signalling. Teplizumab binds to the CD3 subunits of TCR and prevents downstream signalling that activate T cells.

IL-2R: IL-2 receptor; TCR: T-cell receptor; TNFαR: TNFα receptor; Treg: regulatory T cell.

Adapted from Raffin et al.[47] The concept and content of the figure is the authors' own.

Several good manufacturing practice-compliant protocols for the isolation of autologous Treg cells from peripheral blood have been established.[55] Isolation of a low quantity of Treg cells is sufficient given that small molecules and biologics can be used to induce the *ex vivo* expansion of Treg cells with high purity.[56]

The adoptive cell transfer of autologous Treg cells induces tolerogenicity[57] and clinical trials are underway to determine whether it can efficaciously ameliorate autoimmunity. Treg cells are more potent when genetically engineered to express chimeric antigen receptors (CAR) or TCR that bind preferentially to peptide–HLA complexes.[58] Whereas CAR bind to peptide–HLA complexes at higher affinities, binding to higher quantities of antigen is a requisite for sufficient activation of signalling downstream of CAR.[47] TCR bind at lower affinities yet are activated in the presence of lower quantities of antigen. Therefore, TCR Treg cells are appropriate to autoimmunity considering that the CD4+ T cells with the peptide–HLA complexes of interest are infinitesimal. With CRISPR/Cas 9, the endogenous alleles for the α and β chains of TCR can be precisely cut and replaced with the alleles for the α and β subunits of TCR engineered to target the peptide–HLA complexes of interest.[59] The isolation of autoreactive T cells and overexpression of Foxp3 is another approach but less common because of issues with instability.[60] Since Foxp3 is critical for maintaining the functionality of Treg cells, targeting epigenetic regulators and post-transcriptional modifiers are opportunities to enhance stability.[61]

One of the main safety concerns for Treg cells is the ability to lose Foxp3 expression and acquire an effector T-cell phenotype. Engineering suicide signalling pathways that can be easily triggered by small molecules, in the event that Treg cells become unstable, is a strategy to prevent from paradoxically exacerbating autoimmunity. The final TCR Treg cell product can be expanded using IL-2 and CD28 superagonists.[62] Since manufacturing TCR Treg cells is a labour-intensive and time-restraining process, it is challenging to have this therapy readily available. Determining which peptide–HLA complexes are distributed at higher frequencies among the genetic pool of a representative sample of T1DM patients can inform which TCR Treg cells can be manufactured for off-the-shelf use. Given that the TCR Treg cells are not recognised by the recipient's host system, novel approaches are needed.

Multipotent MSC are therapeutic cells that have been extensively studied for diverse purposes. Via paracrine secretion, MSC release TGFβ, prostaglandin E2, hepatocyte growth factor, indoleamine-pyrrole 2,3-dioxygenase (IDO), nitric oxide, IL-2, IL-4, IL-10, and galectin-1.[63] In the presence of the TGFβ and IL-2, naïve T cells are known to differentiate and expand into CD25+Fox3+ Treg cells. With the exception of hepatocyte growth factor, the released molecules mediate immunosuppression. By catalysing the rate-limiting step of tryptophan metabolism, IDO renders effector T cells and dendritic cells ineffective.[64] While nitric oxide is an immunomodulator, its activity is concentration-dependent yet not uniform.[65] A dose- and frequency-dependent association between the infusion of MSC and the preservation of insulin secretion suggest causality.[66] When infused, MSC reduced exogenous insulin requirement by one-half for 2 years and curbed HbA1c levels for 3 years.[67] While MSC are the most clinically studied cell-based therapy, inconsistent results have clouded therapeutic efficacy and have indefinitely delayed FDA approval.[68] Inconsistencies are partially attributable to differences in cell source and culturing practices.[69] MSC are determined to be moderately safe, albeit with concerns for tumourigenicity and the ability to become trapped in the lung microvasculature.

EXOSOMES AT THE FRONTIER AS AN OFF-THE-SHELF IMMUNOTHERAPY

Exosomes are released via autocrine, paracrine, or endocrine signalling by most cells for intracellular or intercellular communication with neighbouring and distant cells. Minute (30–150 nm) spherical sacs of phospholipid bilayer, exosomes enclose a cargo of proteins, mRNA, and microRNA (miRNA).[70] Exosomes are isolated from the interstitial fluids or specific cell types for diagnostic or therapeutic purposes. Whereas analysing changes in the cargo of plasma-derived exosomes can potentially track the progression of T1DM,[71] exosomes that are isolated from specific cell types are a potentially versatile therapeutic tool.

MSC-derived exosomes enclose IL-2, IL-4, IL-10, TGFβ1, IDO, proteins, and miRNA that are suggested to regulate the expression of IL-6, IL-17AF, IL-12p70, and IL-22.[72,73] MSC-derived exosomes are preferred over MSC because of a lack of tumourigenicity, lower risk of becoming trapped in the lung microvasculature, ability to evade immune recognition, and modifiability of the cargo via transfection with therapeutic nucleic acids.[74] While preclinical studies suggest that the protective effects of MSC-derived exosomes are due to suppressed differentiation of naïve T cells into the Th17 cell lineage, the first clinical trial to investigate the potential of MSC-derived exosomes to ameliorate T1DM has not yet published results.[75] Given that exosomes can be derived from MSC of different origins and manufacturing practices, it is necessary to ensure that protocols comply with good manufacturing practice and establish *in vitro* assays that verify potency.

Whereas CD8+ T cells perform cytotoxic activity in a contact-dependent manner, CD4+ T cells mostly perform via paracrine signalling. Treg cells are a rich source of exosomes that contain immunosuppressive proteins, mRNA, and miRNA. Developed via transfection with the dominant negative form of IKK2, Fox3+CD25- Treg cells secrete exosomes with a unique set of miRNA and isoform nitric oxide synthase mRNA.[76] When engulfed by target T cells, the miRNA and isoform nitric oxide synthase from these exosomes inhibit the transcription of cell-cycle proteins and induce apoptosis. Whereas T cells are targeted by direct exposure to exosomes in *ex vivo* assays, a strategy that facilitates the *in vivo* engulfment of exosomes by autoreactive T cells is needed. Exosomes are formed by inward buddings of endosomal vesicles derived from the plasma membrane.[77] Isolating exosomes from TCR Treg cells is a potential strategy, because engineered TCR are embedded within the membrane of the exosomes. To increase the output of the exosomes with embedded TCR per cell, expression of the engineered TCR needs to be enhanced (Figure 3).[47] While it is unclear whether binding of the TCR to peptide–HLA complexes can be exploited to induce uptake of exosomes, the exosomes are steered toward the autoreactive T cells and accumulate in its vicinity. Clarifying the cellular mechanisms that regulate delivery of exosomes into specific targets can reveal other strategies to improve its uptake. These mechanisms, such as overexpressing key receptors for receptor-mediated endocytosis,[78] can be exploited to induce uptake of exosomes. Exosomes with embedded TCR that recognise the peptide–HLA complexes most frequently encountered in T1DM can be manufactured for off-the-shelf therapeutic use. Exosomes are generally safer than cell-based therapies because of a lack of tumorigenicity and a lower risk of becoming trapped in lung microvasculature. However, there is a chance for exosomes to be cleared by the immune system if integral proteins embedded in the membrane are immunogenic. By knowing the sources of immunogenicity, strategies such as genetic editing can be used to overcome this issue.

CONCLUSION

While insulin delivery systems mimic the glucose-responsive behaviour of β cells, the insulin-release kinetics are inferior to mature β cells. Mature β cells evolved complex mechanistic signalling pathways to regulate glucose-responsive insulin secretion. Preserving, regenerating, and replacing β cells are treatments with the potential for insulin independence. However, these treatments are limited by inadequate and risk-prone immunosuppression. Given that the cure for T1DM is likely to require an effective strategy for suppressing or evading the immune system, advanced immunotherapies are needed. Whereas biocompatible encapsulation is one of the undiscussed approaches that seek to evade immune recognition, other immunotherapies seek to induce tolerogenicity to β cells. Biologics, immunomodulatory cells, and exosomes are exploited to restore Treg cell to effector T-cell homeostasis and thereby induce tolerogenicity to β cells. Exosomes are at the frontier with the potential to become an off-the-shelf therapeutic tool. Having TCR embedded within the exosome membrane that bind preferentially to peptide–HLA complexes, exosomes isolated from TCR Treg cells are a promising immunotherapy. With selectivity for autoreactive T cells, these exosomes are more potent and keep other immune defenses intact. At time of writing, this is a novel concept that has not yet mutated into invention.

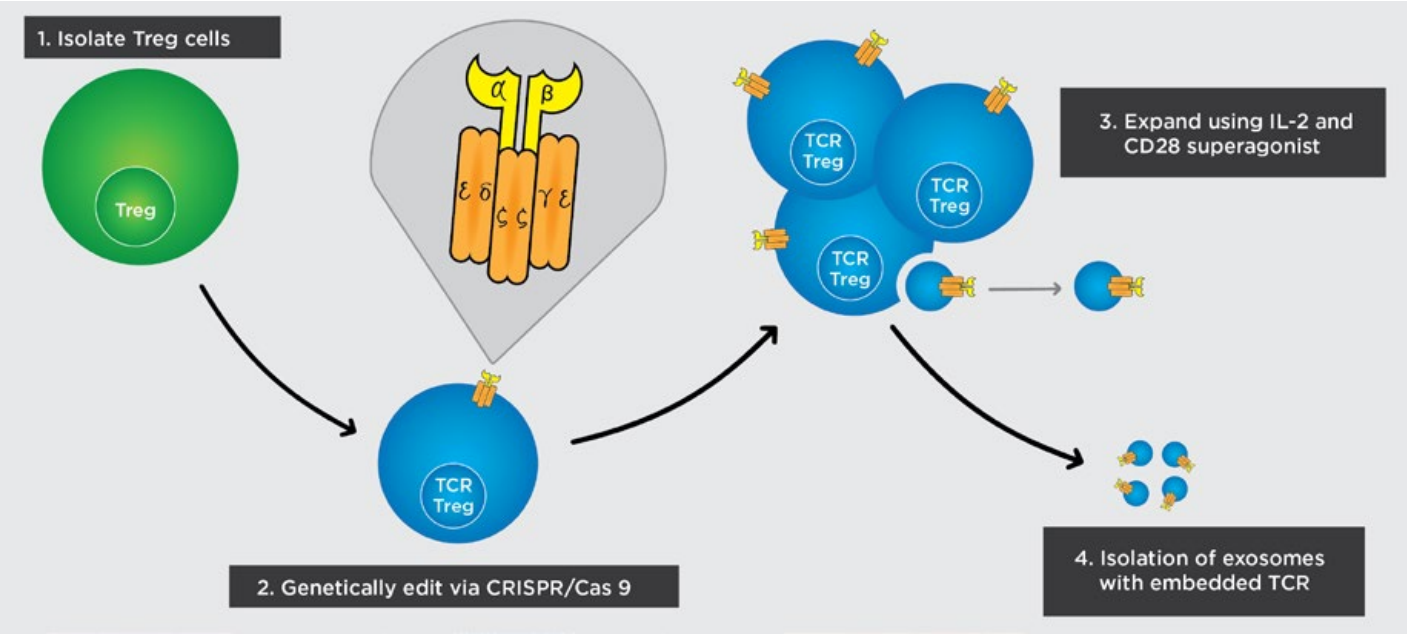

Figure 3: Cell-based approach to inducing tolerogenicity.

The following steps outline how off-the-self exosomes can be manufactured from TCR Treg cells in a simplified diagram.

1) Isolate Treg cells from peripheral blood.

2) Deliver genes for the α and β chains of the engineered TCR into Treg cells and use CRISPR/Cas 9 to replace endogenous genes with delivered genes.

3) Isolate the engineered TCR Treg cells from non-engineered Treg cells and expand using an IL-2 and CD28 superagonist.

4) After culturing TCR Treg and increasing its expression of TCR, isolate exosomes with TCR embedded in the membrane.

TCR: T-cell receptor; Treg: regulatory T cell.

Adapted from Raffin et al.[47] The concept and content of the figure is the authors' own.

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Gestational Diabetes: Comparison of Random and Fasting Plasma Glucose as Modalities of Screening

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Disclosure: The authors have declared no conflicts of interest.

Received: 22.05.20

Accepted: 24.08.20

Keywords: Fasting plasma glucose (FPG), gestational diabetes, oral glucose tolerance test (OGTT), random plasma glucose (RPG), screening.

Citation: EMJ Diabet. 2020;8[1]:110-117.

Abstract

Objective: Gestational diabetes is glucose intolerance of varying severity with onset in the index pregnancy. This study aimed to compare fasting plasma glucose (FPG) with random plasma glucose (RPG) among pregnant females as methods of screening for gestational diabetes.

Methods: A cross-sectional study of 100 pregnant females selected to have screening for gestational diabetes between gestational ages of 24 and 28 weeks using RPG and FPG. All the subjects had 75 g oral glucose tolerance test as the gold standard. Venous plasma glucose assay was performed using glucose oxidase method.

Results: The prevalence of gestational diabetes was 29% using FPG cut-off ≥5.1 mmol/L and 6% using RPG cut-off ≥7.8 mmol/L. The RPG cut-off ≥11.1 mmol/L gave the lowest prevalence rate of 2%, while 75 g oral glucose tolerance test (gold standard test) gave the highest prevalence rate of 30%. RPG cut-off ≥7.8 mmol/L revealed a positive-predictive value of 66.7%, negative-predictive value of 72.3%, and area under the curve of 0.845 compared with FPG level at threshold of 5.1 mmol/L, which gave positive-predictive value of 93.1%, negative-predictive value of 95.8%, and area under the curve 0.920.

Conclusion: This study revealed that FPG threshold of 5.1 mmol/L alone performed excellently as a screening test.

INTRODUCTION

Gestational diabetes is defined as glucose intolerance of variable severity with onset or diagnosis made in the index pregnancy.[1] Before the Canadian physician Fredrick Banting and his medical student Charles Best discovered insulin in 1921, maternal and perinatal morbidities and mortalities associated with diabetes were vast. Despite advances in the diagnosis and treatment

of gestational diabetes, there are still increased adverse perinatal outcomes.[1]

All pregnant females that have identifiable risk factors for gestational diabetes should be screened using fasting plasma glucose (FPG), random plasma glucose (RPG), and/or oral glucose tolerance test (OGTT).[1] Recent studies reveal that FPG will be beneficial for gestational diabetes screening and may reduce the morbidities and mortalities associated with gestational diabetes.[1-5]

Recent studies suggest a trend towards rising cases of gestational diabetes, with a prevalence rate of 6–18% in an African population.[7-12] In Nigeria, studies on gestational diabetes found prevalence rates from 4.9% to 13.9% at different antenatal populations.[8,10,11] A study by Jesmin et al.[10] found prevalence of gestational diabetes to be 9.7% according to World Health Organization (WHO) criteria, but was 12.9% according to American Diabetes Association (ADA) criteria. There is a need for studies on RPG and FPG in the authors' local settings that may give evidence towards formulation of protocols that can translate to better patient management. Available evidence suggests that screening for gestational diabetes within the pregnant population increases the detection of females affected by diabetes in pregnancy and thus improves maternal and perinatal outcomes.[12-16.]

Presently, most laboratory tests for gestational diabetes do not meet the characteristics of screening tests set out by the UK National screening committee (UK NSC), a modified form of WHO criteria for screening tests, and therefore may not be completely adapted to resource-limited settings.[6] This emphasises that a screening test should be simple, safe, precise, and have facilities for diagnosis and treatment.[6] At present, laboratory screening for gestational diabetes is not part of a compulsory universal screening care in antenatal settings in the majority of low-resource settings. Although the current guidelines and recommendations used are adapted from high-incomes settings and may not be very cost effective and generally acceptable in the authors' local settings. Therefore, there is a need for an appropriate screening test that will be universally acceptable and applicable to all pregnant females in low-resource settings. There is possibly a link to cost in diagnosis, which presently limits the universal application of OGTT in low-resource settings and the larger population of females at risk within the population.

A few studies have investigated the significance of the new WHO criteria for diagnosis of gestational diabetes in low-resource settings between 24 and 28 weeks gestational age using FPG ≥5.1 mmol/L (92 mg/dL) and/or 1-hour post OGTT ≥10.0 mmol/L (180 mg/dL), and 2 hour ≥8.5 mmol/L (153 mg/dL) following 75 g OGTT glucose load with one or more abnormal value.

It is crucial to determine the prevalence of gestational diabetes, especially in a low-resource setting such as the authors', as well as to compare the accuracy of low-cost methods such as RPG and FPG in screening for gestational diabetes. Following the change from WHO 1999 to WHO 2013 criteria (the former was based on the maternal impaired glucose tolerance and the risk of the mother developing diabetes in the future, while the latter was based on the odds ratio of 1.75 for adverse neonatal outcomes), no local study in a low-resource setting has evaluated the usefulness of the new FPG cut-off value of 5.1 mmol/L (92 mg/dL) in screening of pregnant females for gestational diabetes, including its sensitivity and specificity as a screening tool. Due to the cost implication associated with OGTT, especially in resource-constrained settings, less invasive and less expensive screening tests such as FPG and RPG could be promising as screening test in this setting. Most females in resource-constrained settings still do not receive routine OGTT in centres that practise universal screening for gestational diabetes.

There is paucity of data on the use of FPG for gestational diabetes screening. Despite the projected increase in prevalence of diabetes and gestational diabetes due to demographic transitions to westernised lifestyle, few investigations comparing FPG with existing methods of gestational diabetes screening have been completed. This study differs from the current literature by comparing FPG and RPG with the standard OGTT as modalities of screening for gestational diabetes and is novel with the aim to develop simpler screening tests for this. The authors adapted a cost-effective and applicable method of gestational diabetes screening in a low-resource setting that will

help in the reduction of adverse maternal and perinatal outcomes associated with gestational diabetes. The objective of this study was to compare RPG and FPG as screening methods for gestational diabetes.

MATERIALS AND METHODS

This was a comparative, cross-sectional study among consecutive pregnant females attending antenatal care with at least one identifiable risk factor for gestational diabetes (as noted in the inclusion criteria).[1,11] The study subjects were recruited using a multistage probability sampling method to assess the screening of gestational diabetes comparing FPG and RPG. The sampling frame was all pregnant females who booked for antenatal care from April 2018 to December 2019 at Federal Medical Centre Abeokuta (FMCA), Abeokuta, Nigeria, between 24- and 28-weeks gestational age. FMCA offers specialised obstetric services to the population of pregnant females residing in Abeokuta community and its surrounding area. Abeokuta is mainly a civil service population comprising federal, state, and local government civil servants, teachers, different cadres of traders, and farmers. The religion composition comprises mainly Christians and Muslims, with a handful of other native traditional African religion practitioners.

The inclusion criteria identifiable risk factors for gestational diabetes were previous fetal macrosomia, birth weight ≥4.0 kg, history of diabetes in first-degree relatives, BMI ≥30 or booking BMI ≥25, history of unexplained perinatal loss or malformed infant, repeated mild glycosuria 1+ or an isolated heavy glycosuria ≥2+, maternal age ≥35 years, history of gestational diabetes or impaired glucose tolerance in previous pregnancies, chronic hypertension, pre-eclampsia and gestational hypertension, polyhydramnios, and larger-than-date uterus in singleton pregnancy.[1,11] Exclusion criteria were pregnant females who did not consent to the study and those with no identifiable risk factor for gestational diabetes. Additionally, those with previous history of diabetes were excluded from the study.

The sample size of 100 participants were calculated using the formula to estimate the mean difference of a continuous outcome based on matched data, according to the formula described by Sullivan.[17] Z_{α}=1.96 for 95% confidence interval, according to studies by Djelmis et al.,[18] 23.1% (1,074) of females were diagnosed with gestational diabetes according to implementation of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. The multistage probability sampling was used to select 100 consenting individuals who met the inclusion criteria from the sampling frame of pregnant women attending antenatal care. The selected subjects had RPG, FPG, and OGTT. The sampling frame included all pregnant females attending antenatal care at FMCA. At the antenatal clinic of FMCA, there are three different units (Firm A, Firm B, Firm C) running their antenatal care at different days of the week: Firm A on Thursdays, Firm B on Mondays, and Firm C on Tuesdays. The sample size of 100 was shared using multistage sampling to recruit 38 participants from Firm A, 31 participants from Firm B, and 31 from Firm C. This was based on the ratio of the last 6 months of antenatal care attendance (July 2017 to December 2017) of 1,156 pregnant subjects in Firm A, 1,428 in Firm B, and 1,162 in Firm C, giving a ratio of 31%, 38%, and 31%, respectively.

The bio-data and brief information, such as gestational age, parity, previous history of gestational diabetes, and diabetes, were obtained from the subjects who consented to the study. They had RPG at contact (having ensured that the patient was not in a fasting state)[19,20] and thereafter FPG and 75 g OGTT were scheduled to be performed during subsequent antenatal care visits between gestational age of 24 and 28 weeks.[19,20] Samples of venous blood were collected into sodium fluoride containers. There was no delay in separating the plasma and, usually, the sample analyses were performed expediently to prevent the breakdown of the glucose. The glucose oxidase method of estimation of plasma glucose was performed, which involved the use of glucose oxidase reacting with glucose, water, and oxygen to form gluconic acid and hydrogen peroxide. The hydrogen peroxide produced oxidises a chromogen or the consumption of oxygen measured to estimate the amount of glucose present.[21]

The diagnosis of gestational diabetes was made using at least one abnormal result using the WHO 2013 criteria.[22] This included fasting ≥5.1 mmol/L,

1 hour ≥10.0 mmol/L, 2 hour ≥8.3 mmol/L, and 3 hour ≥7.8 mmol/L. Positive screening test is considered as RPG ≥7.8 mmol/L and/or FPG ≥5.1 mmol/L. The test of accuracy was calculated using sensitivity and specificity of the screening test compared to the gold standard.

The primary outcome was measured as the accuracy of RPG and FPG in screening of patients for gestational diabetes. Secondary outcome was the prevalence of gestational diabetes according to RPG, FPG, and OGTT. Limitation was that the study participants had at least one risk factor for gestational diabetes.

Data entry and analyses were performed using International Business Machines Statistical Package for Social Sciences (IBM SPSS) version 22. The data were presented as frequency tables and graphs with the continuous variables that are normally distributed presented as mean (± standard deviation). Associations were tested using chi squared test for categorical variables and the differences in mean values using student t test and analysis of variance (ANOVA) for continuous variables. Significance level were set at p value <0.05. The accuracy of RPG and FPG were calculated using sensitivity and specificity as stated below. Receiver operating characteristics (ROC) curve was used to plot the probability of detecting gestational diabetes cases. Data analysis was conducted by the investigator with assistance of the medical statistician. Ethical clearance approval was given by the Health Research Ethics Committee of Federal Medical Centre, Abeokuta, Nigeria.

RESULTS

During this study, a total of 100 eligible pregnant females were screened for gestational diabetes using FPG, RPG, and the 75 g OGTT. The mean age ± standard deviation of the participants was 34.81±4.04 years, mean BMI was 31.46±7.29, and modal parity was 1 (32%). The majority of the pregnant subjects (74%) had tertiary level of education. The mean RPG of the participants was 5.53±1.57 mmol/L, while the mean FPG was 4.70±1.02 mmol/L. The prevalence of gestational diabetes was 29% using FPG cut-off ≥5.1 mmol/L, 16% using FPG cut-off ≥5.3 mmol/L, and 6% using RPG cut-off ≥7.8mmol/L. The RPG cut-off ≥11.1 mmol/L gave the lowest prevalence rate of 2%, while 75 g OGTT gave the highest prevalence rate of 30%. The percentage of females with positive test, sensitivity, specificity, and positive- and negative-predictive values for various FPG and RPG cut-off values are presented below. The FPG cut-off values between 5.1 mmol/L and 5.5 mmol/L classified 29% and 16% of the subjects, respectively, as having a positive test. The sensitivities decreased as cut-off values for FPG were increased, from 90.0% at 5.1 mmol/L, to 43.3% at 5.5 mmol/L, and 6.7% at 7.0 mmol/L. Additionally, increasing the FPG cut-off from 5.1 mmol/L to 5.5 mmol/L decreased the specificity from 97.1% to 95.7%, while the efficiency of the test decreased from 95% to 80%, respectively. The highest efficiency of the screening tests was 95%; this was obtained at FPG cut-off value of 5.1 mmol/L. The area under curve (AUC) was plotted for RPG with the gold standard OGTT test (Figure 1) giving AUC of 0.845, which can be classified as a good test with a statistically significant curve (p=0.000). The ROC constructed in order to compare the ability of FPG with OGTT in differentiating between subjects with diagnosis of gestational diabetes gave AUC of 0.920, which can be classified as excellent (Figure 2).

DISCUSSION

The prevalence rate of gestational diabetes was 29% by using FPG cut-off value 5.1 mmol/L, while 30% prevalence rate was obtained by using the standard 75 g OGTT. The findings from this study was higher than that by Mortensen et al.[23] in a prospective community study in Copenhagen, Denmark, in which they used a risk-based approach and clinical criteria for potential diabetes for screening. This study also found higher prevalence rate of gestational diabetes than that quoted by Djelmis et al.[18] in a cohort study of 4,646 pregnant females who underwent 75 g OGTT in Croatia. Djelmis et al.[18] found the prevalence of gestational diabetes, according to IADPSG and National Institute for Health and Care Excellence (NICE) criteria, to be 23.1% (1,074) of gestational diabetes cases and 17.8% (826) of gestational diabetes cases, respectively.[18] FPG levels of 5.1–5.5 mmol/L comprised 409 (8.8%) of cases, while 50 (1.1%) had overt diabetes.

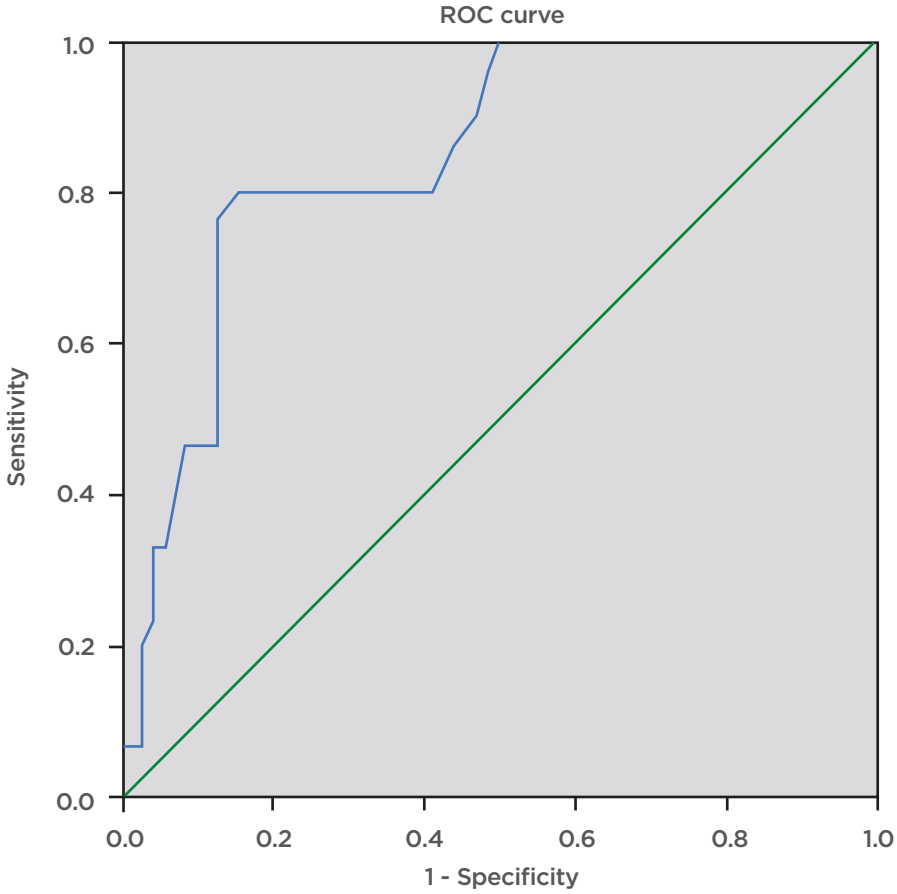

Figure 1: Receiver operating characteristics curve for the accuracy of random plasma glucose (≥7.8 mmol/L) in prediction of gestational diabetes.

The ROC curve was constructed in order to compare the ability of random plasma glucose with the oral glucose tolerance test to differentiate between subjects with diagnosis of gestational diabetes. The area under curve was plotted for random plasma glucose with the gold standard oral glucose tolerance test which gave area under the curve of 0.845, which can be classified as a good test with a statistically significant curve (p=0.000).

ROC: receiver operating characteristics.

This is comparable to the findings in this study in which two (2.0%) of the subjects had overt diabetes. The mean FPG found in this study was 4.70±1.02 mmol/L, higher than 3.81±0.85 mmol/L, quoted by Afolabi et al.[24] in Lagos, Nigeria.

The accuracy of the screening tests for gestational diabetes in this study revealed FPG to have the high sensitivity of 90.0% and specificity of 97.1% at the cut-off value of 5.1 mmol/L and sensitivity of 60.0% and specificity of 97.1% at the threshold value of 5.3 mmol/L. This is similar to the findings by Trujillo et al.,[3] who calculated a sensitivity of 96.9%, although the FPG cut-off value used was 4.4 mmol/L. Additionally, they observed a sensitivity of 92.0% at cut-off 4.7 mmol/L. The higher sensitivity value reported by Trujillo et al.[3] was due to the low cut-off value of FPG used for gestational diabetes screening in that study. However, Trujillo et al.[3] found a sensitivity of 86.8% at FPG cut-off value of 5.1 mmol/L (92 mg/dL), which is lower than the sensitivity found at this study (90.0%) at the same FPG cut-off value of 5.1 mmol/L. Cuscheri et al.[20] found that RPG (sensitivity: 69.2%; specificity: 43.3%; AUC: 0.598; standard error: 0.36; p=0.005; 95% confidence interval: 0.527–0.668) was an inferior predictor test when compared to FPG at an indicative predictor gestational diabetes cut-off point for FPG and RPG of 4.5 mmol/L. Khan et al.,[19]

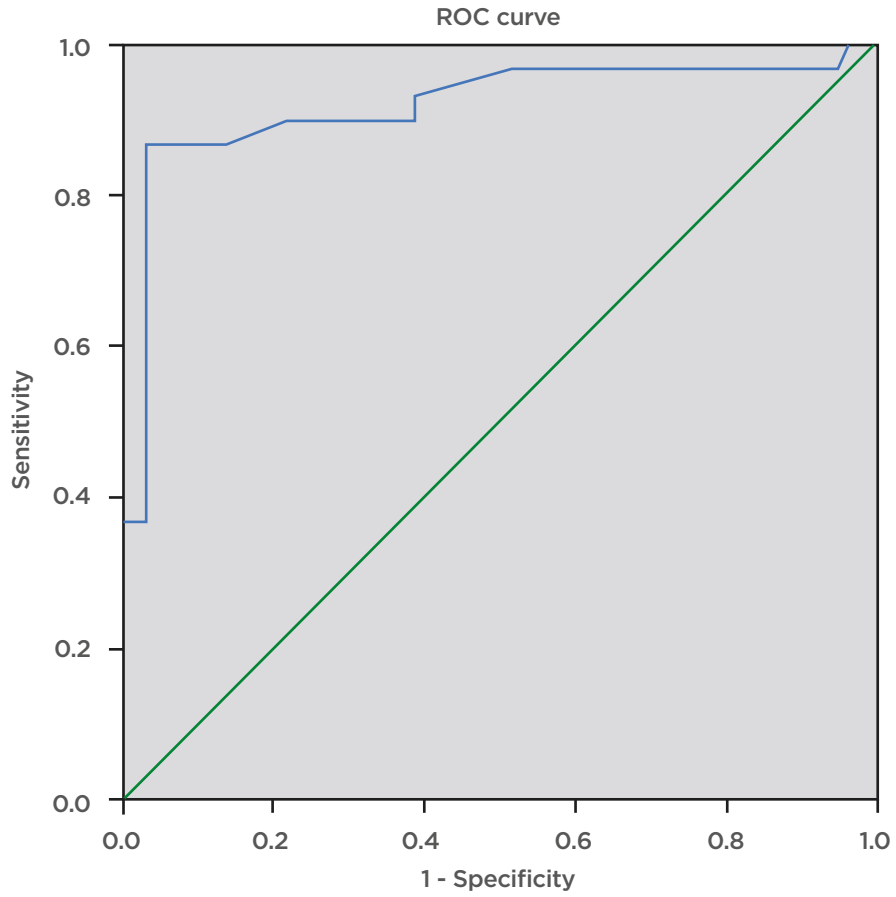

Figure 2: Receiver operating characteristics curve for the accuracy of fasting plasma glucose (cut-off ≥5.1 mmol/L) in prediction of gestational diabetes.

The ROC curve was constructed to compare the ability of fasting plasma glucose with the oral glucose tolerance test to differentiate between subjects with diagnosis of gestational diabetes. The ROC curve revealed area under the curve of 0.920, which can be classified as excellent.

ROC: receiver operating characteristics.

in a study in Karachi, Pakistan, found FPG cut-off of 5.1 mmol/L to be the most efficient investigation and gave sensitivity of 66.66% and specificity of 81.25%. Agbozo et al.[25] found a sensitivity of 68.0% for gestational diabetes screening using FPG threshold ≥5.1 mmol/L, which is lower than the findings in this study. The highest specificity found in this study was at FPG threshold of ≥7.0 mmol/L and RPG ≥11.0 mmol/L, which gave specificity of 100.0%. The FPG threshold ≥5.1 mmol/L gave a specificity of 97.1%, which is lower than the specificity of 100.0% found in a study by Trujillo et al.[3] at same FPG cut-off. Agbozo et al.[25] found a specificity of 81.0% at FPG threshold of ≥5.1 mmol/L, which is substantially lower than the specificity of 97.1% found by this study at the same threshold. Although both studies were performed in pregnant individuals, Agbozo et al.[25] screened subjects using a universal approach when compared to the selective screening based on risk factors that was used in this study. This could have accounted for the higher specificity found in this study; however, the finding was higher than the positive-predictive value found in a study by Saeedi et al.,[26] which gave positive-predictive value of 78% at FPG threshold of 5.2 mmol/L. However, Saeedi et al.[26] screened a population of pregnant females with known risk factors for gestational diabetes and the study was carried out in Swedish population. Geographical variation in risk factors may be possible explanations for these differences observed. In a study by Mohan et al.[27] in an

Indian population, the authors found a positive-predictive value of 54.5% at RPG threshold of 7.8 mmol/L, while Reyes-Muñoz et al.,[28] in a study in a Mexican population using FPG threshold values of 4.5 mmol/L, 4.7 mmol/L, and 5.0 mmol/L, found positive-predictive values of 12% (9–15%), 23% (18–28%), and 64% (54–73%), respectively.

The efficiency of the screening tests was found to be 95% at FPG threshold of 5.1 mmol/L, 86% at FPG threshold of 5.3 mmol/L, and 72% at RPG threshold of 7.0 mmol/L. This is higher than the result quoted by Bhavadharini et al.[5] in Southern India, who found efficiency of 40% at RPG threshold of 7.7 mmol/L.

The ROC curve plotted is comparable to AUC value of 0.960 for FPG found by Trujillo et al.[3] in a Brazilian cohort study. The findings are also similar to the result of Rajab et al.[4] in a Bahrain population, who found an AUC of 0.962 at FPG threshold of 5.6 mmol/L. Agbozo et al.[25] in a study at Volta region of Ghana found an AUC of >0.8 for FPG to be very good and AUC of 0.6 for RPG to be poor and therefore concluded that RPG was unnecessary for selective gestational diabetes screening. Saeedi et al.[26] in a study in Swedish population found an AUC of 0.92 for FPG threshold of 5.0 mmol/L for gestational diabetes screening.

CONCLUSION

The findings from this study revealed that FPG threshold of 5.1 mmol/L has a high sensitivity of 90.0% and specificity of 97.1%, as well as AUC of 0.920, which is excellent for a screening test. The use of RPG threshold of 7.8 mmol/L gave a sensitivity of 13.8% and specificity of 97.1% with an AUC of 0.845. FPG was superior to RPG in screening for gestational diabetes among pregnant females, and gave a prevalence rate of 29%, close to the prevalence rate of 30% that was diagnosed with standard OGTT. The possibility of use of FPG alone for gestational diabetes screening as an alternative to OGTT can be considered in guidelines.

RECOMMENDATION

The findings from this study revealed that FPG alone is an excellent screening test for gestational diabetes and can be considered as an alternative to standard OGTT, especially in resource-constrained settings where cost, facilities, and workforce, especially in the primary healthcare level, may hinder gestational diabetes screening using the standard OGTT.

STATEMENT OF ETHICS

Ethical approval was granted by the health ethics and research committee of the Federal Medical Centre Abeokuta with the protocol identification number FMCA/470/HREC/10/2016/07. NREC assigned number is NHREC/08/10-2015 and federal wide assurance is US/REG NO: FWA/Q0018660/02/28/2017. Written informed consent was signed and obtained from the subjects prior to their participation in the study.

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