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Review of

EASD 2019

Barcelona, Spain

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EMJ HEPATOLOGY 2019

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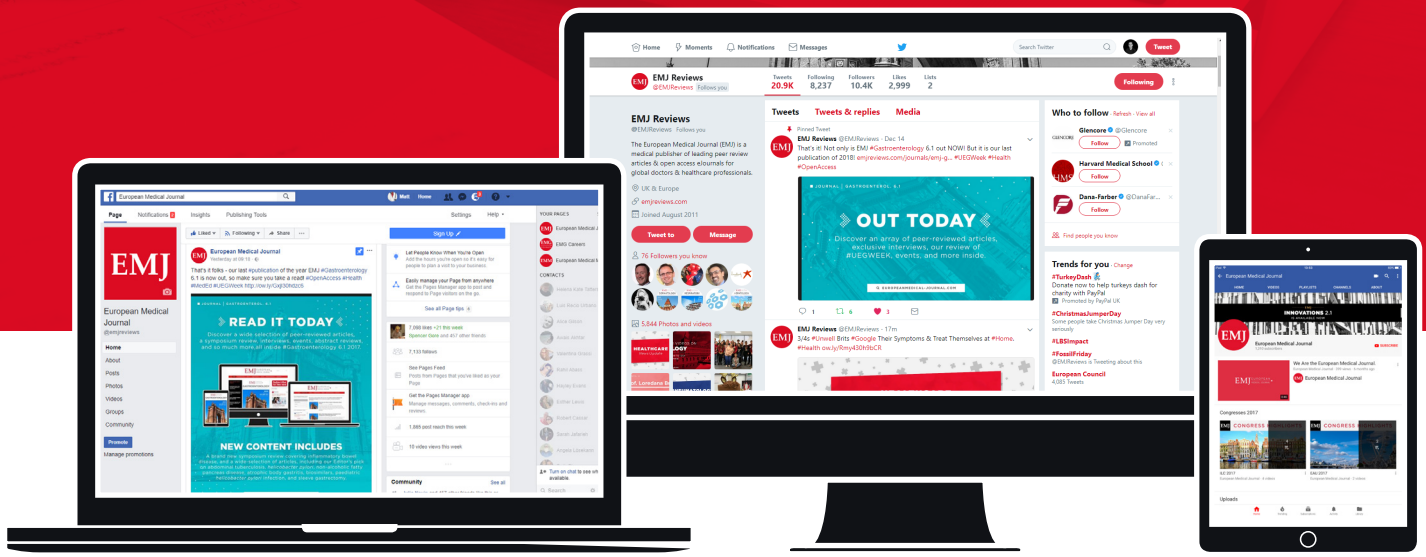

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Welcome

It is with great pleasure that I welcome all our readers to this year's edition of *EMJ Diabetes*, an exciting highlight of our publishing year that we are confident provides an assortment of highly relevant breakthroughs from the diabetes field. Once again, we were on hand at the European Association for the Study of Diabetes (EASD) meeting in the bustling metropolitan hub of Barcelona, Spain, to absorb all the latest advances in the field to which we have incorporated into this edition alongside a selection of brilliant peer-reviewed articles.

Celebrating its 55th anniversary, EASD pointed a spotlight on some of the most important topics within the field, including e-learning for diabetic complications, the diabetes–brain axis, and diabetic retinopathy. Throughout our congress review, you will receive a comprehensive look at some of the biggest stories to break at the meeting: a new combination drug approach is set to take the field by storm through optimisation of the treatment given to newly diagnosed Type 2 diabetes mellitus patients, gluten intake has been identified as key indicator of Type 1 diabetes mellitus risk, and gestational diabetes mellitus prevalence has a correlation revealed in women who have undergone assisted reproductive technology treatment. A concise selection of abstract summaries is also provided for your reading pleasure. No stone of inquiry was left unturned at EASD 2019, as the whole diabetic spectrum was given a thorough analysis and update.

An assortment of interviews will provide you with personal reflections on the field, including the Medical Director for Research & Development for Swansea Bay University Health Board, Swansea, Wales, UK, Steve Bain. It is our intention for these insightful discussions from key opinion leaders to compliment the other elements of the journal and inspire further discussion between you and your friends or colleagues. Also included in the journal are written contributions from experts in diabetes research and practice across the world. In an informative feature, McElfish et al. contribute a brilliant review of the family models of diabetes self-management education, identifying five considerable gaps in the literature that are keeping interventions from being translated into clinical practice.

I would like to personally thank all our contributors, partners, and staff for all their hard work put in to make this journal such a success. Considering the importance of the work the diabetic field does towards disseminating life-changing information, it is always a very proud moment of the year for us when *EMJ Diabetes* meets publication. Enjoy!

Spencer Gore

Chief Executive Officer, European Medical Group

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Foreword

Dear colleagues,

It is my pleasure to welcome you to *EMJ Diabetes 7.1,* a journal dedicated to the sharing of ideas, research, updates, and discussion points directly from the European Association for the Study of Diabetes (EASD) Congress to readers across the world. The journal presents research on both Type 1 and Type 2 diabetes mellitus, providing exceptional and inclusive coverage of the field today.

This year's congress presented research on many pertinent topics, and I am proud to present EMJ's review of the event for those who were not able to attend. Of course, even those in attendance may not have been able to see everything on offer in such a busy scientific programme, so for those wishing to supplement their experience of the event, the Congress Review will prove invaluable. Abstract reviews written by their presenters explore topics such as disease perception, prediabetes in immigrants, biomarkers, among others which will all add important updates to the existing literature. The EMJ team has worked hard to ensure coverage of the most pressing news stories from EASD as well as featuring interviews with some pre-eminent diabetologists, from whom we can all take some words of wisdom.

In my Editor's Pick for this year's edition, Eaglehouse et al. discuss diabetes prevention in the context of cancer survivorship and how best to support cancer survivors at risk of developing Type 2 diabetes mellitus. The successful induction of such programmes has the potential to improve the quality of life in cancer survivors by changing health behaviours and chronic risk factors. Alongside this, peer-reviewed papers featured in the journal include John et al.'s study into diabetic foot syndrome and the understanding about this among patients in India. Findings suggested that understanding was poor, but despite this, foot care was adequate.

Accompanying this, Berberoglu assesses the pathophysiology and risk factors associated with gestational diabetes mellitus, an increasingly prevalent worldwide pregnancy complication, in order to enhance the possibility of effective screening, early intervention, and even prevention. These are just some of the fascinating papers I was privileged to consider for an Editor's Pick this year.

I wish to thank the contributors of the journal, especially the authors and editorial board for their input this year, and of course the EMJ team. I look forward to hearing your feedback from undoubtedly one of our most successful journals yet.

A. M. Felton.

Anne-Marie Felton

Foundation of European Nurses in Diabetes, UK

Congress Review

Review of the 55th Annual Meeting of the European Association for the Study of Diabetes (EASD)

Location: Fira Barcelona, Barcelona, Spain

Date: 16th – 20th September 2019

Citation: EMJ Diabet. 2019;7[1]:10-23. Congress Review.

Barcelona, Spain's mosaic masterpiece, created the breath-taking setting for the European Association for the Study of Diabetes (EASD) Congress 2019. Home to the remarkable La Sagrada Familia, the city welcomed >15,000 delegates from >130 countries, who attended the prestigious event. Amongst the colourful architecture in this cosmopolitan city, attendees to EASD were treated to a cornucopia of abstract presentations, stimulating symposia, and prize lectures. With such a wide range of content to consume, the EMJ team were spoilt for choice on what to cover for our review of this incomparable event in the field of diabetes.

EASD celebrated its 55th anniversary this year, and with the number of people affected by diabetes predicted to rise to 629 million by 2045, it is more critical than ever for diabetologists from all over the world to share knowledge and methods of best practice to improve the possibilities for diabetes diagnosis, treatment, and care. Some stand-out sessions at the congress focussed on a range of hot topics, including diabetic retinopathy, e-learning for diabetic complications, and the relationship between diabetes and the brain.

There were a huge 1,195 abstracts presented at EASD this year on a host of topics within the field of diabetes. We have hand-picked a selection of abstracts and present summaries of each within our congress review. These summaries are written by the researchers themselves, to offer a first-hand account of the work for our readers. Topics include trends in the incidence of prediabetes among immigrants in Canada and perception of living with diabetes gathered via a solutions-focussed therapy exercise through the medium of Twitter.

The air at EASD was buzzing with the influx of late-breaking research. Our review contains a write up of a selection of the most exciting press releases. One stand-out piece of research considered the link between babies being underweight and subsequently developing Type 2 diabetes mellitus as adults. Another press release covered the topic of

assisted reproductive technology increasing the risk of gestational diabetes. In the realm of diabetes treatment, another piece of late-breaking research considered the possibility of treating Type 2 diabetes mellitus with a combination drug approach: vildagliptin with metformin.

We interviewed four key opinion leaders, gaining insight into the field of diabetes from the experts. Dr Dorte Møller Jensen discussed the challenges of treating gestational diabetes and the key areas of focus in this area. Presenter of the session "My gut feeling about glucagon," Dr Filip Krag Knop, outlined the key takeaways for this session and discussed creating successful multi-disciplinary research partnerships. Prof Rayaz Malik took us through the main themes of his lecture "Diabetic neuropathy: A time to challenge the dogma," along with the purpose and importance of international study groups. In our final interview, Prof Steve Bain spoke to us about the elements of his job he finds most fulfilling and exciting updates in diabetic nephropathy research. As the field comes together and collaborates on better prevention and treatment for diabetes, it is inspiring to hear from these thought leaders on their specialist areas.

This year's 5-day meeting in Barcelona was another fantastic event from EASD, with a plethora of thought-provoking content on offer to attendees. Looking ahead to next year, we will be visiting Austria's capital city, Vienna, next September for the 56th EASD Annual Meeting, which is sure to be another unmissable event. But for now, we present our congress review of the brilliant EASD Annual Meeting from September 2019.

"The air at EASD was buzzing with the influx of late-breaking research."

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Newly Diagnosed Type 2 Diabetes Mellitus May Be Optimally Treated Using a Combination Drug Approach

FOR PATIENTS newly diagnosed with Type 2 diabetes mellitus (T2DM), a combination therapy approach using vildagliptin and the first-line treatment metformin could result in better long-term blood sugar control and a reduced rate of treatment failure compared to treatment with the latter drug alone. This is according to findings presented at this year's EASD Congress in Barcelona, Spain, and reported in a press release dated 16th September 2019.

Vildagliptin belongs to a class of drug known as a DPP-4 inhibitor, and helps promote secretion of insulin by the pancreas, inhibition of glucagon production, and control of blood sugar levels.

To date, the recommended first-line treatment for T2DM has been metformin monotherapy, and combination therapy is only introduced in instances of treatment failure.

In the VERIFY study carried out by researchers from the University of Oxford, Oxford, UK, 2,001 patients from 254 centres in 34 countries were split into 2 groups: 1 in which 998 patients were randomised to receive early combination therapy of the 2 drugs, and the other in which 1,003 received metformin alone, both across a 5-year treatment period. The patients' level of HbA1c, a direct measure of blood sugar control, was assessed at multiple time-points across the treatment period.

In the initial period of the study, treatment failure (defined as HbA1c of at least 53 mmol/mol [7.0%]) occurred in 43.6% of patients in the combination treatment group, compared to 62.1% in the monotherapy group. Additionally, the chances of losing blood sugar control (i.e., HbA1c going above 53 mmol/mol [7.0%], twice) were approximately halved in the combination treatment group over the 5-year duration of the study. This sustained 'durability' was deemed to be the result of complementary mechanisms of action shared between both drugs.

Marcia Kayath, Global Head Medical Affairs and Chief Medical Officer, Novartis Pharmaceuticals summarised: "These promising results from the VERIFY study have the potential to improve patient outcomes and the way in which we treat T2DM in the future".

"These promising results from the VERIFY study have the potential to improve patient outcomes and the way in which we treat T2DM in the future"

An Approximately 6-fold Increase in Type 2 Diabetes Mellitus Linked to Obesity

CONSIDERING that the International Diabetes Federation (IDF) expects the number of people living with diabetes to rise above 600 million by the year 2045, there remains a strong need for improving the understanding of the genetic and environmental underpinnings of the disease. Reported in a EASD press release dated 16th September 2019, a group of researchers from the Novo Nordisk Foundation Center for Basic Metabolic Research in Copenhagen, Denmark, have revealed findings that associated obesity with a near 6-fold increase in risk for developing Type 2 diabetes mellitus (T2DM), and that an unfavourable lifestyle and high genetic risk were also implicated to a lesser, but still significant, degree.

"There remains a strong need for improving the understanding of the genetic and environmental underpinnings of the disease."

In the analysis, 9,556 men and women from the Danish prospective Diet, Cancer and Health cohort were applied to a statistical model. T2DM developed, over an average of 14.7 years follow-up, in approximately half of the individuals (49.5%). An 'unfavourable' lifestyle was defined as zero or one of four traits (moderate alcohol consumption, healthy diet, regular physical activity, non-smoker). Genetic risk was stratified into low, intermediate, and high based on a genetic risk score considering 193 genetic variants strongly associated with the disease.

Obesity (defined as BMI ≥30 kg/m^2) and an unfavourable lifestyle were found to be associated with an enhanced risk of T2DM across the cohort, where obesity in particular equated to a 5.8-fold risk increase. The independent effects of genetic risk and lifestyle favourability were not as impactful; high genetic risk conferred a 2-fold increase, whereas a 20% increase in likelihood of diabetes development was associated an unfavourable lifestyle. "The effect of obesity T2DM risk is dominant over other risk factors, highlighting the importance of weight management in T2DM prevention," the authors concluded.

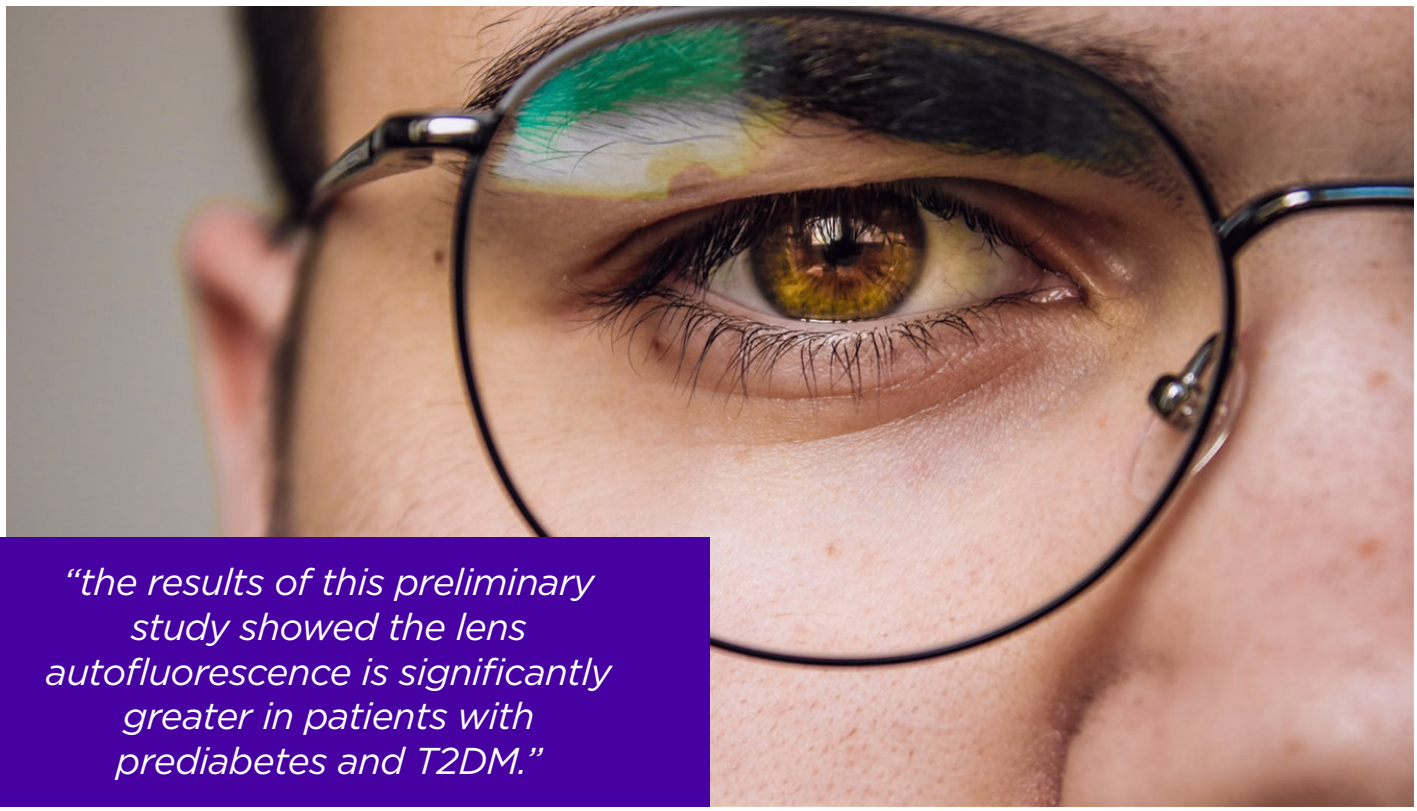
Noninvasive Analysis of the Eye Could Pre-empt Diabetes Risk

EARLY detection of Type 2 diabetes mellitus (T2DM) could help to prevent complications associated with the disease, including retinopathy and neuropathy. A press release dated 16th September 2019 from this year's EASD Congress in Barcelona, Spain, presented a study by Dr Mitra Tavakoli, University of Exeter Medical School, Exeter, UK, which showed that measuring the level of autofluorescence in the lens of the eye can be a useful tool in diagnosing patients with T2DM and impaired glucose tolerance, or prediabetes.

Prediabetes is a condition that can progress to T2DM. There can be a significant delay of up to 10 years between the onset of diabetes and diagnosis of the disease, during which time symptoms become increasingly worse. By predicting not only T2DM, but also prediabetes, complications arising from T2DM can be pre-emptively minimised. Increased levels of advanced glycation end-products (AGE) in those with T2DM are associated with worsening complications of the disease; therefore, by measuring the presence of AGE in the lens of the eye, the researchers were able to predict those at risk of developing T2DM.

The study recruited 20 participants with prediabetes, 20 with T2DM, and 20 control subjects, each of whom completed medical and neurological assessments. A beam of blue light was initially focussed onto the lens by a newly developed biomicroscope. The reflected green light allowed for the level of autofluorescence to be measured, giving a value for the AGE level in the eye. Dr Tavakoli said, "the results of this preliminary study showed the lens autofluorescence is significantly greater in patients with prediabetes and T2DM. The levels of AGE were correlated with the levels of blood sugar."

The substantial increase in AGE shown in participants with either T2DM or prediabetes compared to the control indicates that noninvasive specialist analysis of the lens of the eye could prevent complications occurring in those with undiagnosed diabetes by early detection. Dr Tavakoli concludes: "lens autofluorescence could be a robust marker of long-term diabetes control predicting future complication risks..."



"the results of this preliminary study showed the lens autofluorescence is significantly greater in patients with prediabetes and T2DM."

Reduced Risk of Type 2 Diabetes Mellitus by Delayed Onset of Menopause

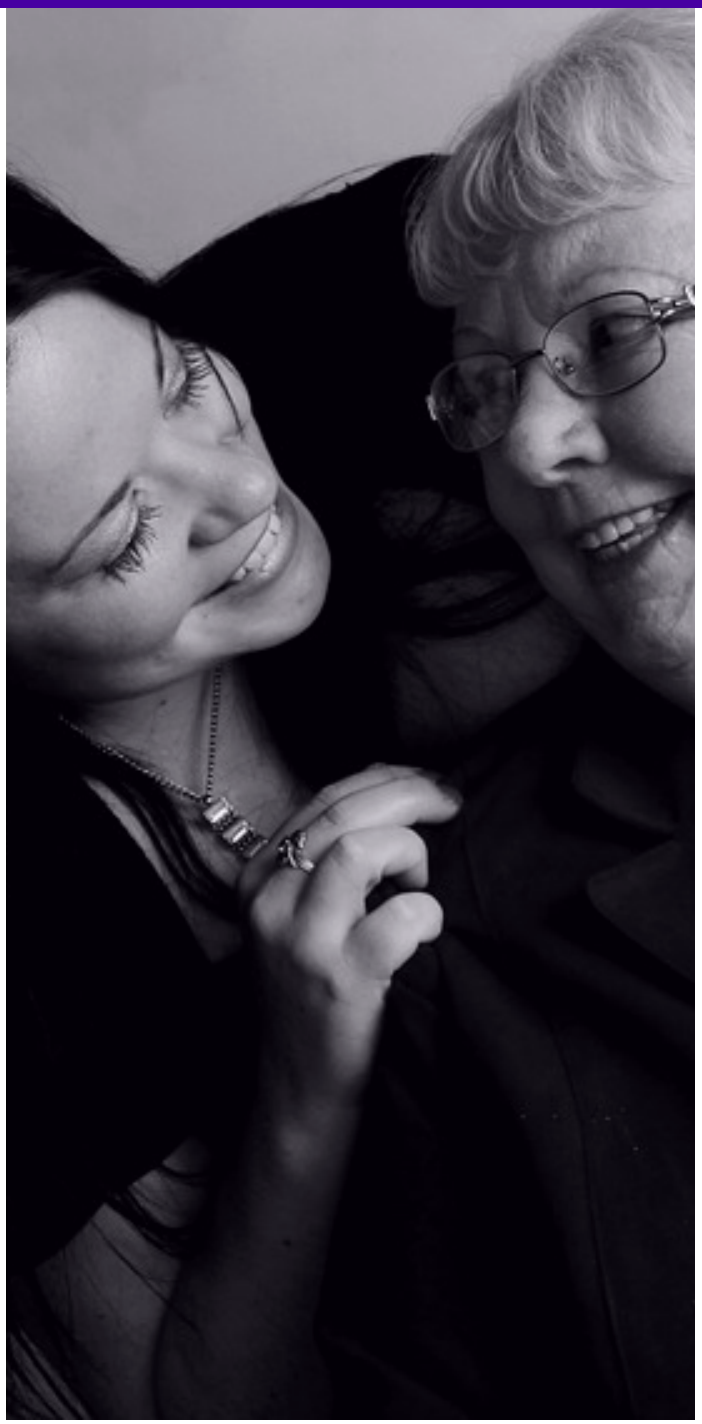
EXPERIENCING puberty and menopause later in life is associated with reduced risk of Type 2 diabetes mellitus (T2DM); contrastingly, taking the contraceptive pill and increased menstrual cycle length is associated with a higher risk of developing the disease. This research was presented at this year's EASD congress in Barcelona, Spain, on 17th September 2019. The aim of the study was to explore the relationship between hormonal factors and T2DM risk in females.

The study, conducted by Dr Sopio Tatulashvili, Avicenne Hospital, Bobigny, France, and colleagues, incorporated 83,799 women from the French E3N prospective cohort study between the years 1992 and 2014. Estimation of risk and statistical significance between hormonal factors and T2DM risk was determined using computer models adjusted for risk factors including BMI, smoking, age, and family history of T2DM, amongst others.

The researchers established that participants who reached puberty aged over 14 years old versus under 12 years had a reduced T2DM risk of 12%. Those who were 52 years or over when they reached menopause had a 30% reduced T2DM risk compared to those who were aged 47 years or under. A 10% reduced risk of developing T2DM was observed in women who had breastfed compared to those who had never breastfed. The study also reported a reduced risk of developing T2DM in those who experienced a greater number of menstrual cycles throughout their lifetime. Experiencing over 470 cycles generated a reduced risk of 25% versus under 390 cycles. Longer time between puberty and menopause, over 38 years versus under 31 years, was also associated with a decreased risk of developing T2DM by 34%.

Risk of T2DM was increased by 33% in women who had taken contraceptive pills at least once in their lifetime, compared to those who had never used them; additionally, participants who had greater menstrual cycle length, lasting over 32 days versus 24 days and under, was associated with a 23% increased risk. The authors said: "It seems that longer exposure to sex hormones but later in life could reduce the risk of later developing T2DM, independent of well-established risk factors..."

"It seems that longer exposure to sex hormones but later in life could reduce the risk of later developing T2DM"



Positive Effects from Alcohol Consumption in People with Type 2 Diabetes Mellitus

ALCOHOL consumption in people with Type 2 diabetes mellitus (T2DM) may exert positive results according to a press release on 17th September at the EASD congress in Barcelona, Spain. A meta-analysis investigating the effects of alcohol consumption on glucose and lipid metabolism has shown that recommendations to moderate alcohol consumption for people with T2DM may need to be reviewed.

The study by Yuling Chen, Southeast University, and Dr Li Ling, Director of the Department of Endocrinology, Zhongda Hospital and School of Medicine, Southeast University, Nanjing, China, analysed randomised controlled trials (RCT) that assessed the association between alcohol consumption and glucose and fat metabolism in adults with T2DM. Clinical trials were extracted from PubMed, Embase, and Cochane up until March 2019. The sourced RCT data was then analysed using computer modelling.

"Larger studies are needed to further evaluate the effects of alcohol consumption on blood sugar management, especially in patients with T2DM."

In total, 10 relevant RCT were found, which included 575 participants, and were included in the review. Meta-analysis revealed decreased triglyceride and insulin levels associated to alcohol consumption; however, no statistically significant effects on glucose levels, glycated haemoglobin, or total cholesterol were found. Further subgroup analysis delineated decreased levels of triglycerides and insulin in accordance with light to moderate amounts of alcohol (≤20 g alcohol per day), which translates to approximately 330 mL of beer (5% alcohol), 200 mL glass of wine (12% alcohol), or a 50 mL serving of 40% alcohol spirit (e.g., gin or vodka [40% alcohol]).

Regardless of the effects on metabolism that the analysis has revealed, various diabetes organisations, including Diabetes UK, advise that people with T1DM and T2DM are cautious with their alcohol consumption, because drinking increases the risk of a hypoglycaemic episode and can additionally cause weight gain and other health issues.

The authors noted that "findings of this meta-analysis show a positive effect of alcohol on glucose and fat metabolism in people with T2DM. Larger studies are needed to further evaluate the effects of alcohol consumption on blood sugar management, especially in patients with T2DM."

Certain Jobs Linked to Higher Risk of Type 2 Diabetes Mellitus

PROFESSION and risk of developing Type 2 diabetes mellitus (T2DM) have been linked according to a new study which was revealed in a press release at this year's EASD on 18th September 2019. The study has shown that professional drivers, manufacturing workers, and cleaners have a three-fold increased risk of T2DM compared to other occupations such as teachers and physiotherapists.

Dr Sofia Carlsson, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, considered the possible association between the 30 most common occupations and T2DM. Dr Carlsson and her team speculated that the differences are linked to the prevalence of lifestyle risk factors; therefore, workplace interventions to reduce weight and increase physical activity would be beneficial to improve the health of the workforce.

All Swedish citizens born between 1937 and 1979 were identified using the Swedish Total Population Register and of these 4,550,892 people were gainfully employed between 2001 and 2013. The Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) was used to acquire information on occupation and education; employment was categorised under the Swedish Standard Classification of Occupations. In addition, a person had to have worked in that occupation for 2 consecutive years to be categorised into a specific occupation. From 2006 until 31st December 2015, follow ups for incidence of diabetes at age 35 or over was performed using the National Patient Drug Register.

The results highlighted major differences amongst the occupational groups. In 2013 the prevalence of diabetes was 4.2% (5.2% men; 3.2% women) in the Swedish working population. In men the prevalence ranged from 2.5% in computer scientists to 7.8% in manufacturing labourers and 8.8% in motor vehicle drivers. In comparison, the prevalence in women ranged from 1.2% in specialist managers to 5.5% in kitchen assistants and 6.4% in manufacturing workers. A separate analysis for those over 55 years of age showed that the prevalence in men was 13.1%, 14.2%, and 14.9% for office clerks, motor vehicle drivers, and manufacturing workers, respectively. In women over 55 years the prevalence was 8.3%, 8.7%, and 10.7% for cleaners, kitchen assistants, and manufacturing workers, respectively.

Further analysis uncovered a 49% higher risk of developing diabetes in male manufacturing, and a 80% higher risk in female manufacturing workers compared with the total Swedish working population. Male college and university teachers showed a 46% reduced incidence and female physiotherapists and dental hygienists a 45% reduced incidence. The study also highlighted a strong positive correlation between incidence of T2DM and BMI in both genders.

According to the authors "the association between occupation and T2DM coincided with vast differences in prevalence of lifestyle factors – individuals in high risk occupations were more likely to be overweight, smoke, and have lower physical fitness than those in low risk occupations, and this most likely contributes to a high prevalence and incidence of T2DM." In conclusion the authors noted that intervention studies have proven that it is possible to reduce diabetes incidence in high-risk groups through lifestyle modification; therefore, if a job title can be used as a risk indicator for T2DM they can be targeted to implement diabetes prevention interventions.

"workplace interventions to reduce weight and increase physical activity would be beneficial to improve the health of the workforce."

"Remarkable" Findings on Diabetes Prediction Possibilities

"It's remarkable that we can see signs of adult diabetes in the blood from such a young age"

PREDICTION of a person's likelihood of developing Type 2 diabetes mellitus (T2DM) later in life could help clinicians to prevent development of the disease at a much earlier stage, a EASD press release dated 18th September 2019 reports. The findings of a study co-led by Dr Joshua Bell, MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK, suggest that predictions could be made in children as young as 8 years of age using genetic testing and metabolomics to identify trends that could indicate a predisposition to T2DM.

The studied enrolled 4,000 participants from the Children of the 90s study in Bristol, which began in the early 1990s. The participants were all healthy and generally free of chronic diseases such as T2DM. They were assessed using a genetic risk score for adult T2DM and each was assessed four times: aged 8, aged 16, aged 18, and aged 25 years, each time looking at >200 metabolic traits.

The participants who were most susceptible to T2DM were found to have a reduced levels of high-density lipoprotein (HDL) cholesterol at age 8 before other types of cholesterol including low-density lipoprotein (LDL) were raised. Their inflammatory glycoprotein acetyls and amino acids were raised by 16 and 18 years old. These differences became more pronounced over time. Dr Bell explained the significance of these results, saying "It's remarkable that we can see signs of adult diabetes in the blood from such a young age; this is about 50 years before it's commonly diagnosed."

Despite this being a big step forward in understanding about who may be more likely to develop this chronic disease later in life, this is just a small step in the overall goal for diabetes researchers. Dr Bell added: "If we want to prevent diabetes, we need to know how it starts. Genetics can help with that, but our aim here is to learn how diabetes develops, not to predict who will and will not develop it. Other methods may help with prediction but won't necessarily tell us where to intervene."

New Findings on Gluten Intake and Type 1 Diabetes Mellitus Risk

GLUTEN intake in a child at 18 months of age is a greater indicator of later development of Type 1 diabetes mellitus (T1DM) than maternal gluten intake during pregnancy, according to the findings of a study reported in a EASD press release dated 19th September 2019. The Norwegian Mother and Child Cohort Study found no association between maternal gluten intake during pregnancy and development of T1DM in her child.

In the first study to examine both maternal gluten intake during pregnancy and child's gluten intake at age 18 months, 86,306 children born between 1999 and 2009 were enrolled and followed up until April 2018. The primary endpoint was clinical T1DM, confirmed using a nationwide childhood diabetes registry. The data was collected using a semi-quantitative questionnaire about food frequency at Week 22 of pregnancy and at child's age 18 months, completed by the guardian. Statistical modelling was used to calculate increased risk for each subgroup.

A total of 346 children (0.4%) developed T1DM (incidence rate: 32.6 per 100,000 person-years) during a mean follow-up period of 12.3 years. The average gluten intake was 13.6 g/day for mothers during pregnancy, and 8.8 g/day for the child at 18 months of age. Gluten intake in children at 18 months of age was associated with an increased risk of later developing T1DM; the risk increased by 46% for each 10 g per day increase in gluten intake. Maternal gluten intake in mid-pregnancy, however, was not associated with T1DM development in the child.

Commenting on the findings, the authors explained: "There is some evidence that gluten intake may influence the gut microbiota and induce inflammation in so-called 'leaky gut' (increased absorption of dietary antigens and/or gut infections). These are plausible mechanisms, but the exact mechanism explaining our findings is not known. If anything, we believe that gluten works in combination with another environmental factors such as virus infections in predisposed children." They caution that the results of the study are not conclusive enough to warrant the avoidance or reduction of gluten in children's diets; confirmation of the results from future studies is necessary before recommendations can be made: "Our observations may motivate future interventional studies with reduced gluten intake to establish whether there is a true causal association between amount of gluten intake in the child's early diet and T1DM in susceptible individuals."

"Our observations may motivate future interventional studies with reduced gluten intake to establish whether there is a true causal association between amount of gluten intake in the child's early diet and T1DM in susceptible individuals."

Assisted Reproductive Technology Linked to Gestational Diabetes

GESTATIONAL diabetes is more common in women who undergo assisted reproductive technology (ART) treatment, than in women who conceive naturally, as found in a study presented in a press release at EASD on 19th September 2019. The meta-analysis, which studied an estimated 2 million women, found that fertility treatments, such as *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI), increased the risk of diabetes.

The research team completed a meta-analysis and systematic review of 38 studies (with 17 matched controls and 21 unmatched controls) which compared the risk of gestational diabetes in women who underwent spontaneous conception, with those who had singleton pregnancies from IVF and ICSI. Data from 2 million women, and 163,302 gestational diabetes cases, was analysed. Women in the ART group were found to be 53% more likely to have gestational diabetes than the spontaneous conception group.

Researcher Dr Panagiotis Anagnostis, Aristotle University of Thessaloniki, Thessaloniki, Greece, discussed the study: "This rigorous assessment of the best available evidence to date shows that singleton pregnancies achieved by IVF are linked with an increased risk of developing gestational diabetes compared with pregnancies conceived naturally."

In a further analysis of 17 studies, including 21,606 women, which matched participants for age, weight, height, smoking status, and ethnicity, it was found that ART singleton pregnancies resulted in a 42% higher chance of developing gestational diabetes, than in women who conceived naturally.

While this link was observed in the analyses, further study would be needed to confirm the findings as no solid conclusions can be drawn due to the observational method of the research. The researchers recognised the lack of adjustment for important confounders in the study. "The exact mechanism is unclear, and whether this risk is due to the medical intervention or the underlying infertility status of the couples undergoing assisted reproduction, is not yet fully understood and requires further research," concluded Dr Anagnostis.

"whether this risk is due to the medical intervention or the underlying infertility status of the couples undergoing assisted reproduction, is not yet fully understood"

Babies Born Underweight are more Likely to Develop Type 2 Diabetes Mellitus Earlier

UNDERWEIGHT babies are known to be at an increased risk of developing Type 2 diabetes mellitus (T2DM) as adults. Furthering this concerning association, new research from a study that investigated the onset age of T2DM and the physical characteristics of the disease, presented in an EASD press release dated the 19th September, found that underweight babies are younger by >1 year at T2DM diagnosis.

Involving >48,000 individuals who were enrolled in the Walker Birth Cohort (born in Dundee, UK, between 1952 and 1966) and were on the Scotland's national diabetes registry, the observational study investigated the impact of low birthweight on the phenotype of T2DM. Factors included were age at diagnosis, BMI, kidney function (creatinine levels), liver function (serum alanine aminotransferase), high-density lipoproteins (HDL)-cholesterol, triglycerides, and systolic blood pressure. Those born with a weight <2.9 kg were considered to be underweight.

In addition to a younger age of onset of T2DM at 50.0 years versus 51.3 years in babies born >3.6 kg, babies born <2.9 kg had a lower BMI at diagnosis (34 [obese] versus 36 [severely obese]) and had higher HDL-cholesterol at diagnosis (1.13 mmol/L versus 1.09 mmol/L). Furthermore, it was found that this age of onset of T2D in those with a low birthweight occurred irrespective of their adulthood BMI and HDL-cholesterol.

Providing a possible explanation for these results, the researchers concluded that reduced insulin secretion, both in the womb and later in life, could be the link between a low birthweight and age of T2DM onset. "This link between low birthweight and age of onset of diabetes may reflect common genetic factors that both mediate birthweight and diabetes risk, or intrauterine factors such as nutrition or maternal smoking, or the combination of the two," commented the study conductor Mr Christian Paulina, a medical student from the University of Dundee, Dundee, UK.

"This link between low birthweight and age of onset of diabetes may reflect common genetic factors that both mediate birthweight and diabetes risk"

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Interviews

Gestational diabetes, interdisciplinary study, glucagon, and diabetic neuropathy are all topics covered in the following interviews conducted by EMJ with renowned endocrinology specialists.

Featuring: Prof Dorte Møller Jensen, Dr Filip Knop, Prof Rayaz Malik, Prof Steve Bain

Prof Dorte Møller Jensen

Steno Diabetes Center Odense, Odense University Hospital, Odense, Denmark.

Q1 What inspires you to have a strong research focus in the area of gestational diabetes?

Pregnancy is a window to future health. When gestational diabetes is diagnosed, we know that this particular woman has a high risk of later developing Type 2 diabetes mellitus and cardiovascular disease; her child is also at risk of obesity and diabetes in later life. Thus, there is an enormous potential to identify individuals at risk and explore what interventions could be effective in preventing development of disease.

Q2 What do you believe are the biggest challenges in combatting diabetes in pregnancy? How can these be overcome?

The biggest challenge is the increase in obesity and Type 2 diabetes mellitus in young women both in high-income countries but to an even bigger extent in low-income countries. Additionally, the widespread use of endocrine-disrupting chemicals may increase the risk of diabetes in future generations. Identification and treatment of diabetes in pregnancy are costly but also necessary to prevent both short-term and long-term complications. We need more awareness of the diagnosis, focus on nutrition and environmental factors, and education of both health professionals and the society in general.

Q3 What have been the most exciting findings with regard to the discovery of novel biomarkers for gestational diabetes in recent years? To what extent have these translated to the clinic?

Recently, both haemoglobinA1c (HbA1c) and glycated CD59 (GCD59) measured in early pregnancy have been reported to predict gestational diabetes. Furthermore, novel biomarkers developed using proteomic discovery approaches may prove useful in combination with clinical risk factor models. Implementation and validation in a clinical setting is awaited.

Q4 Have you observed any trends in the prevalence and severity of gestational diabetes in recent years? If so, what are the main factors contributing to this?

It is my impression that there is an increase in both numbers and the rate of insulin treatment in gestational diabetes. Increased rates of obesity are a contributing factor, but I also believe in a higher susceptibility to diabetes that could be explained by epigenetic factors like intrauterine exposure to obesity and/or endocrine-disrupting chemicals.

Q5 What is our current understanding of the impact that bariatric surgery has on a mother and her child? How can these insights be most effectively communicated to patients?

The knowledge gaps in this field are many and the literature is sparse. On the one hand, bariatric surgery improves maternal glucose metabolism and reduces obesity, resulting in a lower risk of gestational diabetes and large-for-gestational-age infants. On the other hand, there is a risk of insufficient gestational weight gain, maternal hypoglycaemia, vitamin deficiency, and fetal growth restriction. Studies addressing how we can identify and treat the pregnant women with these conditions are urgently needed, because we need to improve the information communicated to these women before they undergo bariatric surgery.

"...the widespread use of endocrine-disrupting chemicals may increase the risk of diabetes in future generations"

Q6 In your position as a consultant, what do you find are the best approaches and advice in helping pregnant women with gestational diabetes?

Diet and exercise are of course the cornerstones in treatment of gestational diabetes; therefore, the advice should be given by a multidisciplinary team. There is no quick fix, but I think that an unprejudiced approach is very important.

Q7 What do you believe the key areas of focus in research should now be to better understand how to prevent diabetes in children following pregnancies complicated by gestational diabetes?

Again, I think we should do more research in endocrine-disrupting chemicals and start acting on the knowledge that is already out there. Women with previous gestational diabetes and their children should be kept in touch with, and we should explore methods for preventing diabetes at a family level. Furthermore, new technologies including apps should be studied.

Q8 More generally, to what extent have you observed a greater emphasis being placed on preventative treatment strategies in diabetes in recent years?

It is my impression that there is a high focus on this research area. Recently, a number of systematic reviews have come out and core outcome sets for follow-up in gestational diabetes have been published.

Q9 Are there any topics upon which you would like to see a greater emphasis placed at major diabetes events such as the annual EASD Congress in future years?

I think that glucose variability in pregnant women with previous bariatric surgery deserves more attention. Some of these women have

severe symptoms of hypoglycaemia and there is no treatment apart from dietary advice. Some women have the opposite problem, with numerous high glucose peaks >15 mmol/L during the day. No one knows whether these conditions are harmful for the woman herself or for the fetus. Furthermore, the association between depression/anxiety and diabetes/prediabetes is another topic that I think could be addressed at an EASD congress.

Q10 You chaired the session "Hyperglycaemia in pregnancy: Treatment and risk for mother and child" during this year's EASD congress. What is the key to fulfilling the role of chair effectively in your experience?

It is important to stick to the time, to keep a good tone, and make sure the speaker understands and answers the questions from the audience appropriately.

Dr Filip Knop

Center for Clinical Metabolic Research, Herlev-Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark

Q1 What originally attracted you to pursue a career in the field of endocrinology?

My research career started in 1999 at the University of Texas, Austin, Texas, USA, as a medical student where I trained with Prof Christopher B. Newgard and was introduced to the fascinating world of diabetes research. Chris' infectious fascination with new data and his eagerness to delineate new aspects of biology got me hooked on research in general and, in particular, diabetes research. Upon my return to Denmark, I was recruited to perform clinical diabetes studies with Thure Krarup and Tina Vilsbøll at Gentofte Hospital, University of Copenhagen where the combination of clinical work, human physiology, and research became logical to me. I completed medical school and, alongside clinical training, I immersed myself in clinical research projects focussing on the role of the gut in human glucose metabolism. It was a natural incentive to pursue clinical endocrinology and ever since, I have mingled my interest in the gut's integrative role in human metabolism and appetite regulation with clinical endocrinology and diabetology, and developed research projects centred on human metabolism and related pathophysiology.

Q2 To what extent has our understanding of the role of the gut in human glucose metabolism increased during your career? And how far have these advances in knowledge translated into the clinic?

Back in the days when I attended medical school the gut was 'owned' by the gastroenterologists. The gut was considered important for the digestion and absorption of nutrients, but in terms of glucose metabolism the gut's role was not well-acknowledged. Nevertheless, at that point, in the late 1990s, investigation of gut hormones (e.g., by Jens J. Holst and colleagues) had started to disclose important gluco-metabolic effects of the gut-derived incretin hormones: glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). Additionally, new gluco-metabolic effects of other gut hormones were appearing. When I entered the field, I was whirled into clinical studies showing that the insulinotropic effect of GIP was lost as a consequence of the diabetic state whereas GLP-1's glucose-lowering effect, mediated by its insulinotropic and glucagonostatic properties, remained in patients with Type 2 diabetes mellitus. It is amazing to think about how much

has happened regarding the development of GLP-1-based treatment modalities over the last two decades. Today, I often prescribe GLP-1-based treatments for my patients knowing full well that they improve glycaemic control, without increasing the risk of hypoglycaemia, cause weight loss, and reduce the risk of cardiovascular hard endpoints. Furthermore, research into gut endocrinology has significantly changed the conception of the gut, which today is considered an organ orchestrating appetite control and nutrient deposition via complex paracrine, endocrine, and neural mechanisms.

"It is amazing to think about how much has happened regarding the development of GLP-1-based treatment modalities over the last two decades."

Q3 During EASD 2019, you presented the 54th Minkowski Lecture 'My gut feeling about glucagon'. Could you give us an overview of your talk and what you think the main takeaways were?

Glucagon similarly to insulin is considered a pancreas-specific hormone that regulates blood glucose levels. In contrast to the glucose-depositing nature of insulin, glucagon is a glucose-mobilising hormone ensuring adequate blood glucose levels to support vital functions during shortage of nutrient supply (e.g., during prolonged fasting). Glucagon primarily mobilises glucose from hepatic glycogen stores, but also stimulates the liver to produce glucose from amino acids, which in turn also prevents accumulation of toxic ammonia from amino acid breakdown. Despite glucagon's essential role in human physiology, glucagon research has been shadowed by the 'insulinocentric' understanding of diabetic pathophysiology and the fundamental role of insulin in the treatment of diabetes. Nevertheless, nowadays hyperglucagonaemia, in the fasting state as well as after meal ingestion, constitutes an acknowledged part of diabetes pathophysiology contributing substantially to hyperglycaemia characterising diabetes. However, the cause and the mechanisms underlying elevated glucagon levels in diabetes patients are incompletely understood. The general understanding is that the glucagon-secreting alpha cells in individuals with diabetes are less sensitive to the glucagon-suppressive effects of glucose and insulin and therefore secretes too much glucagon. Yet, as outlined in my lecture we have challenged this notion with a number of studies suggesting that the gut and the liver may play hitherto underestimated roles in diabetic hyperglucagonaemia. Our studies suggest that elevated blood glucagon levels in the fasted state arise as a consequence of obesity-associated fat accumulation in the liver and ensuing hepatic glucagon resistance at the amino acid metabolism level. This results in increased circulating amino acids, which signal to the pancreas to secrete glucagon, and thus constitute a new explanation of diabetic/obesity-related hyperglucagonaemia. Based on these findings we have proposed that circulating glucagon levels are regulated by amino acids in a feedback loop involving glucagon-induced turnover of amino acids in the liver and amino acid-induced secretion of glucagon from the pancreatic alpha cells; the liver-alpha cell axis.

Correspondingly, we have performed a number of studies showing that high circulating levels of glucagon after meal ingestion are caused by gut-derived glucagonotropic factors, e.g., the gut-derived hormone GIP, and/or as recently proven from studies in patients who have undergone surgical removal of the pancreas, that glucagon, hitherto considered a pancreas-specific hormone, may also be secreted from the small intestine.

Thus, the main takeaway from my talk included a new conception of how circulating glucagon levels are regulated and novel insights into the mechanisms underlying fasting as well as postprandial hyperglucagonaemia known to play important roles in the development of diabetic hyperglycaemia. Hopefully, this new understanding of glucagon and its involvement in diabetic pathophysiology will provide new targets for the future treatment of diabetes.

Q4 Are there any topics you would like to see the EASD Congress place a greater emphasis on in future years?

I always enjoy human findings. I think so-called translational research, in the traditional sense where findings from e.g., rodent studies are applied to human settings, often disappoints due to the vast differences between mice and men. Therefore, I would like to see EASD focus on so-called retro-translational science in which investigations are centred on relevant findings in humans that can be tested mechanistically in in vitro and in animal studies and then be reapplied to a human setting. Furthermore, I have a weakness for human physiology and pathophysiological investigations driven by curiosity and knowledge gaps and not necessarily an overarching strategic focus.

Regarding more specific research fields, I am very happy to see that the gut-derived incretin hormone GIP is re-entering the scientific stage as a potential candidate for the treatment of metabolic disease. In respect to pathophysiologic advances, I am looking forward to new results delineating the mechanisms underlying the development of nonalcoholic fatty liver disease and its interaction with other metabolic conditions.

Q5 Many areas of your research require high levels of collaboration with researchers from other fields. What is the key to creating successful multi-disciplinary research partnerships in your experience?

The collaborative aspect of research is very important to me. One of the hallmarks of successful translational and retro-translational metabolic research is open-minded and cross-disciplinary collaborations between different research groups, disciplines, and committed clinical specialities. Such collaborations enable synergy and provide the optimal foundation for the investigation of human metabolism. The main key to creating successful multi-disciplinary research partnerships is to adopt a holistic view of the research question you want to address. In physiology, there is a long-standing tradition for this, and the integration of multiple physiological systems has provided new and useful knowledge over the years. In clinical science there has been a tradition of working and researching in silos without too much interaction between different scientific societies and research groups. However, over the last 10–15 years in clinical research, I have experienced improved intention and increased desire to work and collaborate across medical and surgical specialities, especially among younger clinical scientists. In my personal early clinical career, I was lucky to work in a department with both endocrinologists and gastroenterologists, providing great opportunities for me to integrate clinical science from both specialities. It turned out that several low-hanging fruits in the cross-field between gastroenterology and endocrinology were right under my nose, and I have exploited the knowledge and enteroscopic expertise of gastroenterology colleagues, and together we have conducted several successful investigations of gut endocrinology. Likewise, I have developed collaborations with dermatologists, cardiologists, surgical gastroenterologists, neurosurgeons, paediatricians, clinical and nuclear physiologists, radiologists, and several other specialities. I truly enjoy these collaborations and feel that important scientific questions can be addressed from new angles when collaborating.

Q6 What have been the most exciting research findings you have been involved in that are related to the human physiology and pathophysiology in recent years? What do you think the implication of these findings will be for patient care?

Some of the most exciting research I have been involved in so far have contributed to the understanding of how the gastrointestinal tract and the liver play integrative and important roles in human glucose metabolism and appetite regulation. Especially, the new understanding of how the gut and the liver contribute to prevailing glucagon levels as discussed in my Minkowski lecture. I very much recognise that we stand on the shoulders of giants when we research into these matters and that our findings represent small steps in the delineation of human physiology and pathophysiology. Nevertheless, adding these new bricks to the house of knowledge that scientists have been building for thousands of years makes perfect sense to me. I reckon that I was awarded the Minkowski Prize 2019 because my group has been lucky to add a few cohesive bricks and thus, contributed to the understanding of the pathophysiological

elevations of fasting and postprandial glucagon levels observed in diabetes. To me, the prize represents a big honour and it gives me confidence that our findings are of importance to people outside my lab. As I mentioned before, hopefully this new knowledge will provide new targets for the future treatment of diabetes and other metabolic diseases.

Q7 This year, you started in a new position as Head of Center for Clinical Metabolic Research, Herlev-Gentofte Hospital, University of Copenhagen. What are the main research areas you and your team are prioritising currently in this department?

Presently, there is a need for new and better management of metabolic disorders including obesity, diabetes, heart diseases, liver diseases such as nonalcoholic fatty liver disease, gallbladder diseases, bile acid malabsorption, thyroid diseases, renal diseases, exocrine pancreatic diseases, and more. As alluded to earlier, the way forward in the development of successful preventive and therapeutic strategies in the field of metabolic disorders involves the adoption of a scientifically holistic perspective encompassing strong interactions between basic scientists and a range of clinical specialities which is something we will continue to prioritise. Herlev-Gentofte Hospital embodies a range of different clinical departments, which manage a vast number of patients suffering from a wide range of metabolic diseases and conditions. From a clinical metabolic research perspective, the patient categories managed at Herlev-Gentofte Hospital constitute the optimal foundation for a better understanding of pathophysiology and delineation of new treatment targets. Thus, the heterogeneity of patients treated at Herlev-Gentofte Hospital and the wide range of clinical and scientific expertise across the clinical departments of the hospital make Herlev-Gentofte Hospital the ideal base for a clinical research hub focussing on clinical metabolic research. Furthermore, the many different patient categories represent an invaluable source regarding 'translationalability' of findings from basic metabolic research performed at University of Copenhagen. I truly hope that we will be able to fill in the currently unmet need for a strong and wide-spanning clinical collaborator to significantly increase the translational impact of metabolic research generated at University of Copenhagen. Lastly, Herlev-Gentofte Hospital's future close-connection to the Steno Diabetes Center Copenhagen will also enable clinical research spanning diabetes in its many varied forms.

Q8 What have been the main challenges you have faced during your clinical career?

The biggest challenge I have faced during my clinical career is the decreasing amount of time for clinicians to see individual patients. Our limited time with the patients has made way for a massive documentation demand, which has created a work environment restricting the 'free space' necessary for a successful apprentice-master relationship. The lack of time also prevents many clinicians from addressing scientific questions. This, combined with the increasingly time-consuming administrative and regulatory workloads associated with clinical research projects, has made it difficult to combine clinical and research work. Instead of spending time on administrative tasks, I would much rather spend time on seeing patients, discussing patient cases with colleagues, reading new literature, attending scientific meetings, thinking, writing papers, and developing ideas and new projects.

Q9 Are there any anomalies or specific challenges in regard to diabetes in Denmark and the Nordic region compared with other parts of the world?

I think we have great opportunities for clinical metabolic research in Denmark. We have a long-standing tradition within the field of diabetes research, which over the years has expanded to encompass prediabetic conditions including obesity and its related comorbidities. We also have a strong track-record within clinical gastroenterology research, which makes research within the cross-field of endocrinology and gastroenterology, for instance research in nonalcoholic fatty liver disease, particularly attractive in Denmark. Furthermore, we have good universities focussing on the education of scientists and we have relatively good funding opportunities as well.

Q10

Are there any new areas you would like to focus research efforts on in the future?

One of the new avenues I would like to pursue is the early-life environment and its impact on metabolic health. I think it is of importance to understand how environmental factors, from the earliest possible point, push the body towards metabolic diseases e.g., how intrauterine conditions may affect later development of metabolic disease. Another field in which we are currently investing time is how commonly used drugs affect metabolic health. For example, presently we are trying to discover how topical steroids used in the treatment of atopic dermatitis affect insulin sensitivity, bone homeostasis, and adrenal function. Thirdly, I am trying to follow the explosive development in molecular biology techniques which continuously provide us with new and better modalities for the investigation of our biological samples. Nevertheless, good old human physiology and pathophysiogical studies in the field of metabolic health and disease will continue to form the launch pad of the main part of my research.

Prof Rayaz Malik

Weill Cornell Medicine, Ar-Rayyan, Qatar

Q1

During this year's EASD Congress, you delivered the 34th Camillo Golgi Lecture: "Diabetic neuropathy: a time to challenge the dogma". Could you take us through the main themes of this talk and why you selected this particular topic?

Despite over 40 years of clinical trials in the field of diabetic neuropathy, we still do not have a US Food and Drug Administration (FDA)-approved, disease-modifying treatment for this condition. Multiple pathogenetic pathways have been established in animal models but none have been translated into therapies. One must therefore ask whether the science is bad, or whether we have failed to adequately test whether the therapies are working. This is where we have to 'challenge the dogma' which has dictated to both clinical investigators, pharma, and the FDA the use of symptoms and signs or electrophysiology as primary endpoints to define therapeutic efficacy. Trials using these endpoints have a 100% failure rate and yet the dogma continues. My talk shared my story of the development of a technique called corneal confocal microscopy, a rapid, objective means of quantifying neuronal degeneration and regeneration. I showed how we have established the diagnostic and prognostic capability of this technique and translated it into a surrogate endpoint for clinical trials of new therapies for diabetic and other peripheral neuropathies. Our most recent data published in Diabetologia shows that corneal confocal microscopy (CCM) identifies nerve regeneration within 6 months of simultaneous pancreas and kidney transplantation which is then followed by an improvement in the current FDA-approved endpoints (symptoms/nerve conduction) after 36 months. Most clinical

"There has to be an emphasis on earlier diagnosis and the use of smarter tools to assess therapeutic efficacy in clinical trials."

trials have only been undertaken for 18–24 months! Thus, many potential therapies may have failed not due to a lack of true therapeutic effect, but because the endpoints in the clinical trials were wrong.

Q2 What are the main ways you have observed the EASD Congress evolve or change over the years you've attended the event?

It has become bigger and better: more clinically relevant with presentations on the latest therapies that benefit our patients. It also includes cutting-edge science to provide new insights into the cause and treatment of diabetes and its complications. It is now arguably the leading annual diabetes meeting in the world.

Q3 You undertake a lot of research in the area of diabetic neuropathy. What do you consider to be the main advances in our understanding of the pathophysiology of this condition over recent years?

An awareness that there is no single pathway or target for diabetic neuropathy, even though inflammation may be a common final pathway that should be targeted for new therapies. The pathophysiology of autonomic neuropathy is very poorly explored and there are limited treatments. The treatment of painful diabetic neuropathy has not evolved over the last 20 years and the current drugs have limited efficacy. Better phenotyping and genotyping may help to identify patients who are more responsive to certain drugs based on the presence of mutations in sodium channels or those with a predominant defect in the descending inhibitory pathway, identified by alterations in rate dependent depression. Vitamin D may be a simple and effective treatment for painful diabetic neuropathy.

Q4 You have previously been Chairman of Neurodiab, the international EASD study group for diabetic neuropathy from 2009 to 2012. What are the main purposes of international study groups such as this and how effective are they in achieving their aims in your experience?

These study groups are key to bringing together small numbers of like-minded scientists and clinicians who are focussed on a particular disease area, e.g., diabetic neuropathy, to enable more rapid translation of basic ideas into the clinic. I got the idea of using rate dependent depression in patients after a conversation with Prof Nigel Calcutt, who is a basic scientist working in experimental diabetic neuropathy. Similarly, Prof Mark Yorek has utilised CCM in animal models after he saw our work in patients. I would never have met them unless we had the Neurodiab meeting.

Q5 Would you like to see a greater emphasis in research placed on any aspects of the relationship between diabetes and neurology?

Diabetic neuropathy is the commonest long-term complication of diabetes with a very high morbidity and mortality and yet it is the 'Cinderella complication'. The diagnosis of diabetic neuropathy is made far too late for any therapy to be effective. We ignore the fact that the 5-year mortality of a patient with a diabetic foot ulcer due to diabetic neuropathy is higher than most common cancers including breast, prostate, and lung. Research funding is often directed to retinopathy and nephropathy at the expense of neuropathy, something that has to change. There has to be an emphasis on earlier diagnosis and the use of smarter tools to assess therapeutic efficacy in clinical trials. I would argue that CCM can address both these issues.

Q6 What do you consider to be the most significant research advances to have occurred in diabetes during your career and in what ways have they influenced patient care?

HbA1c has enabled us to easily and accurately assess glycaemic control and alter therapies. Additionally, the introduction of GLP-1 therapies and SGLT2-I has and will continue to make a major difference in relation to outcomes for our diabetic patients.

Q7 Your current position is Professor of Medicine at Weill Cornell Medicine in Qatar. Are there any unique challenges in

regard to diabetes in Qatar compared to other parts of the world?

The prevalence of diabetes and obesity is one of the highest in the world in Qatar. This is due to the rapid modernisation of this population and has grim consequences in relation to the development of complications in the future. However, there is a genuine commitment from her highness to education, and the Ministry of Health and Qatar Foundation are aiming to address both obesity and diabetes.

Q8

You are also responsible for supervising numerous students to completion of their qualification. What do you believe are the most important attributes a supervisor needs to have to carry out these duties effectively?

The supervisor must have infectious enthusiasm and commitment with a clear vision to make a difference to patient outcomes.

Q9

What advice do you have for young medical professionals, about to embark on a career in the field of diabetes?

There is a great deal of work to be done to improve the outcomes of our patients. This is a massive task as the burden of the disease is only going to grow. Focus and commit to achieving something good, forget about an easy life, and work towards a better future for people with diabetes.

Q10

Finally, do you believe you will move into any new areas of diabetes research in the future?

No, I intend to deliver on a commitment which started in 2001, when I undertook my first study using CCM. CCM will be used to diagnose early diabetic neuropathy, alongside retinal screening, and will be used to enable FDA approval of a disease modifying therapy for diabetic neuropathy.

Prof Steve Bain

Clinical Director of the Diabetes Research Unit Cymru
Medical Director for Research & Development for Swansea Bay University Health Board, Port Talbot, UK

Q1

What originally inspired you to pursue a career in the field of diabetes?

My wife was one of the first research nurses in the UK to work in the field of diabetes. She persuaded me to get involved in the field and then persuaded her boss, Prof Tony Barnett, to employ me as a research fellow in Birmingham, UK. At the time, I was a middle-grade (registrar) hospital doctor working in general medicine in Birmingham.

Q2

What have been the research findings in the area of diabetic nephropathy in recent years that you believe will lead to particularly major benefits to patients?

The recent discovery that sodium glucose co-transporter 2 (SGLT2) inhibitors slow the decline in glomerular filtration rate in people with Type 2 diabetes mellitus and significantly reduce hard renal endpoints is very exciting.

Q3 What does the evidence found so far indicate about the role of genetics in the development of diabetic nephropathy?

The fact that most individuals with Type 1 diabetes mellitus never develop nephropathy, irrespective of their level of glycaemic control, almost certainly indicates an inherited predisposition to this diabetes complication. Unfortunately, despite huge amounts of investigation since the 1990s, no clinically useful genetic markers have been identified.

Q4 You have been Principal Investigator for several multicentre trials investigating novel therapies for diabetes. Could you tell us about the most exciting outcomes of these investigations?

The finding in the LEADER trial that liraglutide gave a significant reduction in major adverse cardiovascular events (MACE) was both exciting and surprising in equal measure. Subsequently, other glucagon-like peptide-1 (GLP-1) receptor agonists have also been found to reduce MACE in Type 2 diabetes mellitus.

Q5 What, in your view, have been the most exciting new therapy options for diabetes that have been made available in recent years?

The SGLT2 inhibitors and GLP-1 receptor agonists are fantastic drug classes with good glucose-lowering, weight reduction, and cardiovascular benefits.

Q6 In your position as Diabetes Lead Clinician for the Swansea Bay (recently renamed) University Health Board, have you observed any trends regarding the prevalence and severity of diabetes patients in recent years? If so, what factors might explain this?

There are undoubtedly more people developing Type 2 diabetes mellitus than previously and this increase is being driven by the obesity epidemic, promoted by excessive consumption of carbohydrates, and a more sedentary lifestyle.

Q7 You are a frequent participant at the annual EASD Congress. What are the main ways in which this event can assist your day-to-day work?

Excellent symposia give updates on all aspects of diabetes. There is also the opportunity to see new data presented and network with international colleagues. I will be attending the PIONEER symposium at this year's EASD, as well as sessions on the CONCLUDE study, DAPA-HF and updates on cardiovascular outcomes studies. Meeting colleagues who are collaborators on international studies is always a bonus from these gatherings.

Q8 What are the key features of community diabetes services? What have been their main impact in your experience?

Community diabetes services should bring care closer to the individual with diabetes and involve different groups of healthcare professionals. However, it is not necessarily any cheaper than more traditional models of care.

Q9 Which aspect of your work do you find most fulfilling?

Seeing people with diabetes in clinics when they feel better having used the modern interventions, both therapy and monitoring devices, that we can now offer. Diabetes is a set of chronic conditions that can leave individuals feeling helpless and concerned; it is a pleasure to be able to help resolve symptoms and reduce the long-term complications.

"It is a pleasure to be able to help resolve symptoms and reduce the long-term complications."

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Rewriting Medical Textbooks: The Kidney as a Window to the Heart – The Role of Sodium–Glucose Transport Protein 2 Inhibitors in Cardiovascular and Renal Disease in Type 2 Diabetes Mellitus

This symposium took place on 18th September 2019, as part of the 55th Annual Meeting of the European Association for the Study of Diabetes (EASD) in Barcelona, Spain

Chairpeople: Luca De Nicola[1]

Speakers: Ralph DeFronzo,[2] Per-Henrik Groop,[3] Vlado Perkovic[4]

1. University of Campania Luigi Vanvitelli, Naples, Italy
2. Diabetes Division, University of Texas Health Science Center, San Antonio, Texas, USA
3. University of Helsinki and Helsinki University Hospital, Helsinki, Finland
4. The George Institute for Global Health, Sydney, Australia

Disclosure: Prof De Nicola has received fees as scientific consultant and lecturer from Astellas, AstraZeneca, Janssen, Mundipharma, Vifor, and Fresenius. Prof DeFronzo received grants from AstraZeneca, Janssen, and Merck; is a member of the speaker bureau for AstraZeneca, Novo Nordisk, and Mundipharma; is on advisory boards of AstraZeneca, Novo Nordisk, Janssen, Intarcia Therapeutics, and Boehringer Ingelheim. Prof Groop received honoraria from Astellas, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Elo Water, Genzyme, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk, PeerVoice, and Sanofi; received grants from Eli Lilly, and Roche; is on advisory boards for Abbott, AbbVie, Astellas, AstraZeneca, Boehringer Ingelheim, Cebix, Eli Lilly, Janssen, Medscape, MSD, Mundipharma, Novartis, and Sanofi; is a board member of Oy Medix Ab and EASD. Prof Perkovic led or served on the Steering Committees of trials for the National Health and Medical Research Council of Australia, Janssen, AbbVie, GSK, Boehringer Ingelheim, Eli Lilly, Gilead, Novartis, Novo Nordisk, Retrophin, Tricida, and Pfizer; received honoraria for scientific presentations and/or advisory board attendance from AbbVie, Amgen, Astra Zeneca, Bayer, Baxter, Boehringer Ingelheim, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Pharmaling, Pfizer, Reata, Relypsa, Roche, Sanofi, and Servier.

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Meeting Summary

This symposium took place during the 2019 meeting of the European Association for the Study of Diabetes (EASD). Focussing on the kidney as a window to the heart, the speakers discussed connections between the kidney and the heart, potential mechanisms, and the role of sodium–glucose co-transporter 2 (SGLT2) inhibitors in patient management. Prof De Nicola set the scene

with projected numbers of patients with diabetes and diabetic nephropathy. Prof DeFronzo gave a description of the natural history of diabetic nephropathy, microalbuminuria as a predictor of chronic kidney disease (CKD), and the Steno hypothesis linking impaired vascular endothelial dysfunction with vascular leakage of albumin. He concluded his talk by describing why patients with CKD are predisposed to cardiovascular disease (CVD). Prof Groop provided insights into the mechanisms of renal protection by SLGT2 inhibitors. He explained the 'tubular hypothesis', whereby SLGT2 inhibitors correct glomerular hypertension by inhibiting tubuloglomerular feedback (TGF). Prof Perkovic highlighted data from randomised controlled trials which enhanced understanding of the potential effects that might be achieved with SLGT2 inhibitors. The meeting concluded with a lively discussion between panel members and the audience.

Welcome and Objectives

Professor Luca De Nicola

The objectives of the meeting were to actively exchange scientific knowledge with the faculty and the audience on Type 2 diabetes mellitus and the potential role of SGLT2 inhibitors in reducing CV and renal events. The number of patients on dialysis is expected to double in the next few years, exceeding 5 million by 2030.[1] Data from the Global Burden of Disease study suggests that >275 million people had renal disease in 2016.[2] Diabetes is the primary reason why patients need renal replacement therapy,[3] and approximately half of all patients with Type 2 diabetes mellitus worldwide also have diabetic kidney disease.[4] Existing therapeutic tools for diabetic nephropathy are insufficient. Renin–angiotensin–aldosterone system (RAAS) inhibition alone only reduces the risk of end-stage renal disease by up to 25%.[5,6]

The Kidney as a Window to the Heart

Professor Ralph DeFronzo

Early in the natural history of diabetic nephropathy, there were few clinical or laboratory abnormalities that identified patients at risk of developing clinically overt diabetic kidney disease.[7,8] Patients with diabetes may appear to have good kidney function and even a normal kidney biopsy. Despite this, the kidney is not perfectly normal. A study of individuals with a strong family history of diabetes who had a kidney biopsy showed evidence of hyperfiltration 3 years before diabetes was diagnosed.[9]

In the first 15 years after diabetes onset, there is a clinically silent period until proteinuria develops. Kidney biopsies reveal continuing hyperfiltration and glomerular sclerosis. Once macroproteinuria develops, progression to end-stage renal disease is relatively inevitable. Within 4 years azotaemia develops, and 3–4 years later patients require dialysis or transplantation; however, there is another clue that indicates the need for earlier intervention: the development of microalbuminuria. This typically occurs about 5 years before the onset of macroproteinuria and effective intervention may slow, and possibly prevent, overt disease.[7]

Multiple studies have documented that Type 1 diabetes mellitus patients with microalbuminuria have a 10–20-fold increased likelihood of developing advanced renal disease within 10 years.[10-13] Although not as strong a predictor as in Type 1 diabetes mellitus, microalbuminuria is also linked with a 4–5-fold increased risk of diabetic nephropathy in patients with Type 2 diabetes mellitus.[14] Microalbuminuria predicts overall survival in patients with Type 2 diabetes mellitus. Over a 9.5-year period, survival relative to the general population reduces as the severity of microalbuminuria in Type 2 diabetes mellitus patients rises.[14] The dramatic fall in survival is primarily due to an increase in CVD.

People with microalbuminuria have marked widespread endothelial dysfunction, primarily due to lack of nitric oxide which is a powerful vasodilator and antiangiogenic molecule. Microalbuminuria also tracks with dyslipidaemia, hypertension, left ventricular (LV) diastolic dysfunction (the characteristic cardiac dysfunction in patients with diabetes), and plasminogen activator inhibitor-1 levels which predisposes to hypercoagulability increasing CV risk.

Microalbuminuria is part of the insulin resistance or metabolic syndrome, which encompasses all of the risk factors associated with accelerated CVD.[15,16] These include obesity, prediabetes, diabetes, hypertension, dyslipidaemia, increased plasminogen activator inhibitor-1, endothelial dysfunction, lipotoxicity, liver disease, inflammation, atherosclerotic CVD, and hyperinsulinaemia. As it can be considered that uraemia (glomerular filtration rate [GFR] <25 mL/min/1.73 m^2) is a state of insulin resistance, patients with advanced renal disease can be said to have metabolic syndrome.[16-18] Numerous prospective epidemiologic studies have established that insulin resistance and the insulin resistance syndrome predict CVD and future diabetes. People with insulin resistance have a 2.5–3-fold higher likelihood of a CV event over the next 10 years.

The Steno hypothesis proposed that albuminuria results from widespread vascular damage.[19,20] Microalbuminuria reflects impaired vascular function and is associated with susceptibility to both CV and renal events. This hypothesis links impaired vascular endothelial function with vascular leakage of albumin detected in the urine; thus, it can be said that the kidney becomes a window to the vasculature with 'leaky' renal vessels reflecting the widespread permeability of the vasculature. Albuminuria predicts the risk of myocardial infarction, stroke, heart failure, and death in people with and without diabetes.[21,22] Studies also show that CKD is related to an elevated likelihood of CV events and death.[23] CV event rates progressively increase with declining GFR.[24]

Patients with CKD are predisposed to CVD because the two conditions share the traditional risk factors for atherosclerosis.[25] Patients at high-risk tend to be older, males, smokers, and physically inactive. Comorbidities such as hypertension, dyslipidaemia, diabetes/insulin resistance, LV hypertrophy, and a prothrombotic state also increase risk. Additional risk factors related to CKD include endothelial dysfunction, vascular calcification, uraemic toxins that trigger inflammation, increased reactive oxygen species and oxidative stress, excess extracellular fluid, and glomerular hyperfiltration. Renal hyperfiltration is also a strong predictor of CV events.[26] Potential mechanisms for the relationship between renal hyperfiltration and CVD include endothelial dysfunction, increased renin–angiotensin system activity, increased Na^+/H_3 pump, hyperglycaemia and insulin resistance, oxidative stress, inflammation, fibrosis, and hypertension.

In summary, patients with CKD are at markedly increased risk for CVD. Risk factors for CVD in patients with CKD include both classic and additional risk factors. Microalbuminuria is a major risk factor for future kidney disease and atherosclerotic CVD. If renal vessels are damaged, this is a marker of damaged vessels throughout the body; thus, the kidney serves as a window to the health of the heart and arterial system.

The Interlinking of Cardiovascular and Renal Disease in Type 2 Diabetes

Professor Per-Henrik Groop

Mortality is higher in patients with CKD and Type 2 diabetes mellitus than in people without diabetes.[27] With the development of albuminuria or reduced estimated GFR (eGFR), or both, the risk of premature mortality is many times higher. Diabetic kidney disease comes with real consequences, and this is mainly due to CVD.[28] As kidney function declines and more albumin leaks into the urine the risk of CV death increases. Impaired renal function has far-reaching systemic effects, which include insulin resistance,[29] arterial calcification, anaemia, hypertension, inflammation, LV hypertrophy,[30] sympathetic nervous system activation, RAAS activation,[31] and endothelial dysfunction.[32]

A recent meta-analysis of the exploratory secondary renal endpoints of worsening, end-stage renal disease or renal death in the SGLT2 inhibitor CV outcomes trials suggested clinically important effects on these endpoints both in patients with established CVD and in those with multiple risk factors.[33] The question

arises as to why do SGLT2 inhibitors work so well in the kidneys? Looking at renal physiology, the kidney autoregulates the flow of blood through the glomerulus by altering arteriole tone.[34] The tone of the afferent arteriole decreases by a number of mechanisms: nitrogen oxide bioavailability, COX-2 prostaglandins, kallikrein-kinins, atrial natriuretic peptide, angiotensins I-VII, hyperinsulinaemia, and inhibition of TGF (Figure 1).[35] The macula densa works as the control tower of the glomerulus and plays a major role in the autoregulation of glomerular blood flow. Factors that cause a net increase of efferent arteriolar pressure are angiotensin II (one of the most potent vasoconstrictors), thromboxane A2, endothelin 1, and reactive oxygen species. This balance between the afferent and efferent arterioles by autoregulation is very important for the function of the kidney.

In situations where there is an imbalance, the intraglomerular pressure can increase with the development of glomerular hypertension. This causes glomerular damage and subsequent progressive nephron loss.[36] The remaining nephrons adapt, but by further increasing filtration via glomerular hypertension.[36] SGLT2 inhibitors appear to improve renal outcomes by reducing pathological intraglomerular pressure and may consequently slow nephron loss.[35,36]

A leading theory to explain how SLGT2 inhibitors act to prevent kidney decline is the so-called 'tubular hypothesis'.[35] With large amounts of glucose being filtered, the kidney upregulates the SLGT2 receptors to preserve glucose; consequently, more glucose is reabsorbed from the tubules along with co-transported sodium. This has the effect of less sodium reaching the macula densa. This is interpreted physiologically as a drop in glomerular filtration pressure. Inappropriate autoregulation by the macula densa causes an increase in both the filtration and blood pressure within the glomerulus. SLGT2 inhibitors correct this abnormal situation by blocking glucose and sodium absorption in the proximal tubule.

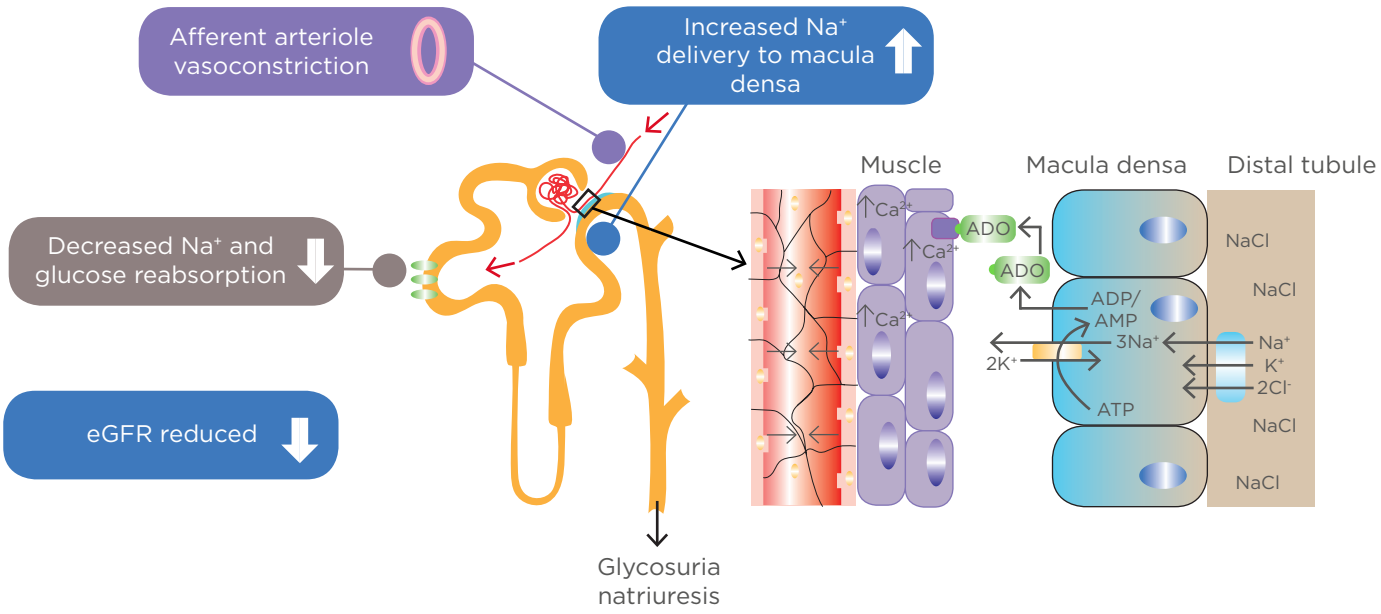

Figure 1: Sodium–glucose transport protein 2 inhibition and tubuloglomerular feedback.

ADO: adenosine; ADP: adenosine diphosphate; AMP: adenosine monophosphate; ATP: adenosine triphosphate; eGFR: estimated glomerular filtrate rate; SGLT2: sodium–glucose co-transporter.

Adapted from Heerspink HJ et al.[35]

More sodium ultimately reaches the macula densa, and via autoregulation, the afferent arteriole contracts thereby reducing overall glomerular pressure.

There are numerous studies supporting this hypothesis. SGLT2 blockade reduces afferent artery diameter and single nephron GFR (SNGFR) in diabetic mice.[37] In diabetic rats, acute SGLT2 blockade reduced SNGFR by 33% compared to control ($p<0.0005$), while chronic SGLT2 blockade reduced SNGFR by 16% versus control ($p<0.03$).[38] There was a significant difference between acute and chronic blockade.[38]

In patients with Type 1 diabetes mellitus, angiotensin-converting enzyme (ACE) inhibitors reduce glomerular hyperfiltration by opening up the 'back door' of the glomerulus (the efferent arteriole)[39] and SGLT2 inhibition reduces glomerular hyperfiltration to a similar extent, but act by closing the 'front door' (the afferent arteriole).[40] The effects of SGLT2 inhibition on renal blood flow and vascular resistance mediate the reduction in hyperfiltration.[40] There is also evidence that SGLT2 inhibition and RAAS blockade may have synergistic effects since their effects are mediated on afferent and efferent arterioles, respectively.[41] In both the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program[42] and (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME),[43] the effect of SGLT2 inhibition on renal markers occurred irrespective of the use of an ACE inhibitor or angiotensin receptor blocker. In patients with Type 2 diabetes mellitus and impaired renal function, SGLT2 inhibition also reduces blood pressure and glycated haemoglobin (HbA1c).[44] Other studies show that SLGT2 inhibitors increase albuminuria regression compared with placebo.[45,46] SGLT2 inhibition also increases urinary ketone bodies.[47]

An additional reason for the effectiveness of SLGT2 inhibitors is that they may spare the kidneys from hypoxia. When diabetes is induced in mice, within 3 days the kidneys become relatively hypoxic.[48] In rats, hypoxia (induced by uncoupling the mitochondria) causes kidney disease independently of hyperglycaemia and oxidative stress.[49] The phenotype of that induced hypoxia is proteinuria or albuminuria, inflammation, and cell damage, as seen in diabetic kidney disease. In patients, reduced cortical oxygenation predicts progression of renal decline.[50] Data also show that SGLT2 inhibition improves mitochondrial function.[47]

Hyperfiltration in diabetes increases sodium handling in the proximal tubule[51] and 90% of oxygen consumption in the kidneys is due to sodium handling by the proximal tubule.[52] Increased sodium handling increases oxygen consumption and so raises the risk of renal hypoxia and CKD.[51] SGLT2 inhibitors prevent this hypoxia[53] without inducing acute kidney injury.[45,54,55]

In summary, SGLT2 inhibitors protect the kidney through loss of calories due to glucosuria leading to modest weight loss,[35] osmotic diuresis and modest natriuresis,[35] reduction in the development or worsening of albuminuria,[35,56] reduced glomerular hyperfiltration via TGF feedback,[35] and possible synergistic effects with hypertensive agents.[57]

The Role of the Sodium–Glucose Transport Protein 2 is Changing in Cardiovascular and Renal Outcomes

Professor Vlado Perkovic

Approximately half of all patients with Type 2 diabetes mellitus have concomitant diabetic kidney disease;[4] thus, renal outcomes and their effects on CVD are highly relevant. Over the last half century, although there has been a two-thirds reduction in deaths due to CVD in the USA, the number of people with kidney failure has dramatically increased.[58,59] Diabetes is the leading driver of kidney failure and better therapies are needed.

The only proven treatment for renal disease to date is RAAS blockade. Angiotensin receptor blockers and ACE inhibitors produce a 23–28% reduction in end-stage renal disease (Figure 2),[5,6] with a suggestion that these drugs delay kidney failure by 6–12 months, a relatively modest impact on these clinically important outcomes.

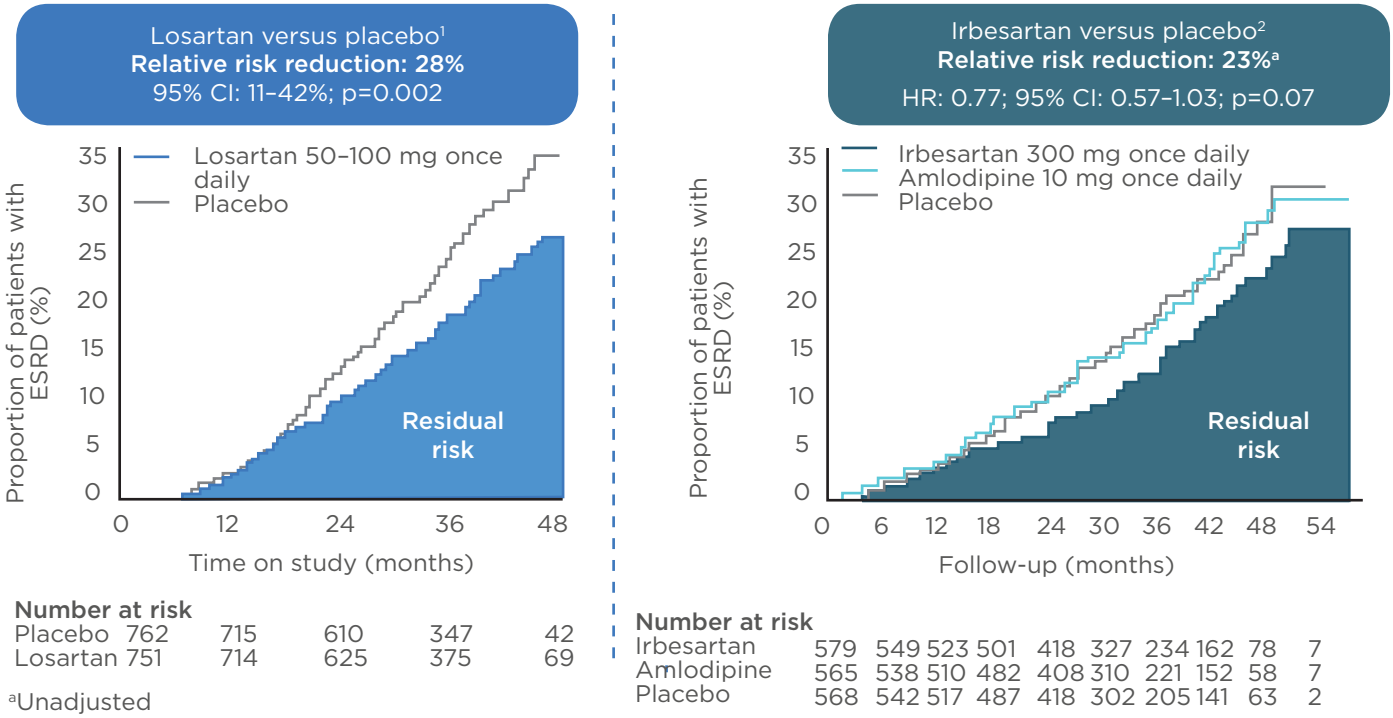

Figure 2: Renin–angiotensin system inhibition alone does not reduce the risk of end-stage renal disease adequately.

N.B., trials shown had different designs and patients populations and cannot be directly compared.

CI: confidence interval; ESRD: end-stage renal disease; HR: hazard ratio; RAAS: renin–angiotensin–aldosterone system.

Adapted from Brenner BM et al.[5]

In patients who received irbesartan in The Irbesartan Diabetic Nephropathy Trial (IDNT) or losartan in the Reduction of Endpoints in NIDDM [non-insulin-dependent diabetes mellitus] with the Angiotensin II Antagonist Losartan (RENAAL) Study, the proportion who developed kidney failure was still large: one-quarter over 4 years in RENAAL and a similar proportion in IDNT. It is clear that new treatments are required to curb the rising numbers of patients with kidney failure around the world.

Since 2008, regulatory agencies have required CV outcome trials for new diabetes drugs. These studies have also shed light on their effects on the kidney through exploratory renal endpoints. In the four CV safety trials of dipeptidyl peptidase-4 (DPP4) inhibitors (SAVOR-TIMI 53,[60,61] TECOS,[62] EXAMINE,[63] and CARMELINA),[64] no strong signal of renal benefit was observed. In the CARMELINA trial, for example, the secondary renal composite outcome was not reduced with linagliptin, even though it lowered HbA1c by about 0.35%.[64]

For the glucagon-like peptide 1 receptor agonists, a meta-analysis of CV outcome trials shows an overall 17% reduction in risk of the composite kidney outcome (hazard ratio [HR]: 0.83; 95% confidence interval [CI]: 0.78–0.89).[65] Most trials, however, included new-onset macroalbuminuria as a component of that outcome. If macroalbuminuria is removed and the focus is only on major kidney outcomes i.e., doubling of serum creatinine, or substantial losses of kidney function, the collective HR is 0.87 (95% CI: 0.73–1.03). This suggests a modest overall benefit for the glucagon-like peptide 1 receptor agonists, despite quite profound effects on HbA1c.

The SGLT2 inhibitor CV safety trials had secondary renal composite outcomes of worsening renal function, end-stage renal disease, and renal death. The findings

suggested a benefit, even though those trials that did not include patients at high renal risk.[33] When the results are broken down by baseline eGFR (≥90, 60–90, and <60 mL/min/1.73 m^2) there is evidence of benefit in all groups (HR: 0.44; 95% CI: 0.32–0.59, HR: 0.56; 95% CI: 0.46–0.70, HR: 0.67; 95% CI: 0.51–0.89, respectively). There is an indication, however, of declining kidney function attenuation (p=0.0258). There were relatively few patients with an eGFR <60 mL/min/1.73 m^2; so, it remains unclear whether the benefit of SGLT2 inhibitors persists down to lower levels of kidney function.

Additional limitations of these CV safety trials are that the renal outcomes, when prespecified, were secondary exploratory endpoints; definitions of renal endpoints differed; baseline characteristics of the study population varied, and the follow-up period was short (2.4–4.2 years).[43,45,55,66] This is reflected in the small number of hard renal endpoints in these trials. Despite recruiting >34,000 patients and completing almost 100,000 years of patient follow-up in total, 54 patients, across all 3 trials, developed end-stage kidney disease and 69 progressed to renal replacement therapy or experienced renal death. While these trials support a benefit, they are not sufficient to definitively demonstrate the renal benefits of SGLT2 inhibitors.

With regards to CV events in these patients, a meta-analysis of the three CV safety trials suggested that protection against heart failure is greatest in patients with reduced kidney function, a 40% reduction in risk (p=0.0073).[38] Consistent findings for heart failure were reported in the renal outcomes trial;[30,69] similarly, there is a clear overall benefit of SGLT2 inhibitors on major CV events, particularly in patients with an eGFR <60 ml/min/1.73 m^2.[33,67,68]

What is the price to be paid for this 'triple whammy' of benefit on kidney failure, heart failure, and major CV events? A renal outcomes trial with canagliflozin showed an increase in the risk of genital mycotic infections in men and women, which were generally easily treatable and did not require discontinuation of treatment, and a raised likelihood of diabetic ketoacidosis.[56] There was no increased risk of urinary tract infection, volume depletion adverse events, acute kidney injury, fracture, or lower extremity amputation.[56]

The latter result differed from CANVAS Program, where an elevated risk of lower extremity amputation was observed.[69] Following the signal in CANVAS, a protocol amendment was introduced into the renal outcomes trial recommending closer foot care. This amendment did not impact recruitment to the trial and there was no change in the relationship between study drug and lower extremity amputation before and after the protocol was amended. In CANVAS this was not a prespecified outcome whereas in the renal outcomes trial it was prospectively tested, raising the possibility that the finding in CANVAS was a chance observation.

A recent meta-analysis of the CV safety trials and renal outcomes trial indicates a benefit of SGLT2 inhibition on substantial loss of kidney function, end-stage kidney disease, or renal death, even in patients with a baseline eGFR <45 ml/min/1.73 m^2.[66] The analysis suggested some attenuation of relative risk reduction in patients with the lowest baseline eGFR (p value for heterogeneity=0.073), although the absolute benefits were at least as large in this subgroup.[66] When the results were examined according to baseline albuminuria, there were broadly consistent benefits across all trials, even in patients with microalbuminuria or normal values.[66] Across the 4 trials, there was also an overall 25% reduction in acute kidney injury with SGLT2 inhibitors (relative risk: 0.75; 95% CI: 0.66–0.85).[66]

Other SGLT2 inhibitor renal outcomes trials with dapagliflozin and empagliflozin are ongoing, these will define whether the kidney benefits are a class effect or not, and provide further insights into patients with and without diabetes, and varying levels of baseline eGFR and albuminuria.[70,71]

Standards of care are already changing. The American Diabetes Association (ADA) guidelines have a Grade A recommendation for the use of SGLT2 inhibitors in patients with Type 2 diabetes mellitus and kidney disease to prevent both CKD progression and CV events.[72]

The 2019 European Society of Cardiology (ESC) guidelines have also recommended SGLT2 inhibitors in patients with CKD and Type 2 diabetes mellitus.[73] One issue for clinicians following the guidelines in treating CKD with the SGLT2 inhibitor class is that current labelling does not allow their use in patients with eGFR <45 ml/min/1.73 m^2. This may change as the regulators review the emerging data from this class.

Interactive Panel Discussion

Professor Luca De Nicola, Professor Ralph DeFronzo, Professor Per-Henrik Groop, Professor Vlado Perkovic

The session concluded with a lively and lengthy discussion among panel members and the audience. Topics included the causes of diabetic nephropathy, how best to monitor patients on SGLT2 inhibitors, the need for concomitant treatments, and how to improve implementation of this new class of drugs.

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Abstract Reviews

Our Abstract Review section showcases some of the most exciting presentations from the Congress and is brought to you by the presenters themselves in their own words. Find out about how the incidence of Type 2 diabetes mellitus in immigrants in Canada differs between age groups, the latest results from the SUSTAIN 10 trial, and how a solutions-focussed therapy group could improve outcomes for diabetes patients.

Perceptions of Life with Diabetes Revealed through a Solution-Focussed Brief Therapy Exercise via Twitter

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Keywords: Diabetes, empowerment, 'miracle question' (MQ), qualitative research, solution-focussed approach.

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The 'Miracle Question' (MQ) is a questioning tool used in a solution-focussed approach to care. The goal is to help individuals envision a desired future state and focus on what 'will happen' as opposed to what they 'will not be doing'.[1] Incorporating this approach ultimately reframes the conversation towards one of solutions instead of 'problem talk'.

In the oral podium presentation at the European Association for the Study of Diabetes (EASD) Congress, the authors presented data from a Twitter chat that took place on World Diabetes Day: November 14, 2018. During the Twitter chat, constituting 1 hour of a longer diabetes social

media advocacy (#DSMA) chat, the attendees were walked through a virtual implementation of the MQ approach in order to understand their perceptions of life with diabetes and what their desired future state would look like. Through this process, the authors hoped to understand the common and overarching themes regarding life with diabetes when the 'problems are gone'.

The original MQ is: 'Suppose tonight while you sleep, a miracle happens. When you wake tomorrow morning, what will you see yourself doing, thinking, or believing, about yourself that will tell you a miracle has happened in your life?'[2] For this study the MQ was modified for a diabetes-specific population: 'If you could fast-forward to a time where you feel satisfied with your diabetes management, what will be different in your life that will let you know things are better?' Ten questions were asked during the 1-hour chat to progress through the MQ process.

To analyse the Twitter chat data, the authors implemented a qualitative content analysis. The five themes that resulted from the analysis indicate that the desired future state of participants included more of a 'living' life, laughter and humour, self-compassion, resilience, and support. Most importantly, this style of engagement was successful; participants expressed gratitude and positive sentiment towards the approach. A previous survey conducted by the authors showed that people with diabetes are not satisfied with existing diabetes education services. Survey respondents asked for more psychosocial and behavioural aspects of diabetes to be addressed. They desire mutual respect between clinicians and people with diabetes and improved communication. These research and survey data set the foundation for more research in diabetes care and education adopting a solution-focussed approach.

The MQ and a solution-focussed approach also addresses the language we use when speaking to or about people with diabetes. The approach requires a person-centered, person-first, empowering approach to elicit outcomes. We know that healthy communication is required to improve health outcomes.[3]

Traditional diabetes management is problem-focussed. That focus may also result in feelings of blame and shame. The use of a solution-focussed approach in medicine can improve behavioural and psychosocial outcomes.[4] The authors encourage the diabetes healthcare community to consider adopting a solution-focussed approach to conversations with clients with diabetes to help them envision their future, generate solutions, and set small, achievable goals to get there.

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Trends in the Incidence of Prediabetes Among Younger and Older Immigrants in Canada, 2011–2017

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Keywords: Epidemiology, ethnicity, immigrant health, public health, Type 2 diabetes mellitus.

Citation: EMJ Diabet. 2019;7[1]:48-50. Abstract Review No: AR02.

BACKGROUND AND AIMS

The burden of prediabetes appears to be increasing worldwide. According to the International Diabetes Federation (IDF), low and middle-income countries have the highest prevalence of prediabetes.[1] If left untreated, individuals with prediabetes have an elevated risk of progressing to Type 2 diabetes mellitus. Thus, identifying prediabetes early may help to implement effective intervention strategies targeting diabetes prevention. While non-European populations have an increased risk of developing diabetes, it is unclear if trends in prediabetes incidence and prevalence over time differ according to ethnicity and age group.

MATERIALS AND METHODS

Linked health, laboratory, and immigration data were used to identify adults aged 20–84 who immigrated to Ontario, Canada, who were free of diabetes. Data from hospital and commercial laboratories were used to identify individuals who underwent diabetes screening between 2011 and 2017. Prediabetes cases were defined using World Health Organization (WHO) criteria (fasting plasma glucose: 6.1–6.9 mmol/L, 2-hour plasma glucose: 7.8–11.0 mmol/L on a 75 g oral glucose tolerance test, or HbA1c: 6.0–6.4%). Immigrants were classified into distinct world region of origin based on validated algorithms using country of birth, mother tongue, and surnames. The authors used direct age and sex standardisation methods with 2011 Canadian census data to calculate prediabetes incidence over time among adults aged 20–34, 35–49, 50–64, and ≥ 65 years, across different ethnic origins.

RESULTS

Overall, the prevalence and incidence of prediabetes in Canadian immigrants rose between 2011 and 2014, followed by a subsequent decline in 2017. The largest increases in the prevalence and incidence of prediabetes between 2011 and 2014 were observed among South Asian, Southeast Asian, and Sub-Saharan African/Caribbean populations. Over the 7-year period, the age-adjusted and sex-adjusted prevalence of prediabetes decreased only slightly from 20.0%, 17.0%, and 14.1% in 2011 (N=510,144) to 16.7%, 17.8%, and 13.8% in 2017 (N=600,437) among South Asians, Southeast Asians, and Sub-Saharan African/Caribbeans, respectively. Similar trends were observed for age-adjusted and sex-adjusted incidence of prediabetes across most non-European ethnic groups and ages ($p<0.001$). However, among European populations, prevalence and incidence of prediabetes only declined to a lesser degree over time. The incidence and prevalence of prediabetes rose sharply by age for immigrant populations across all ethnic groups. However, South Asians had the largest increases in prediabetes incidence by age. For instance, the incidence of prediabetes was highest among South Asians, ranging from 3.8 per 100 person-years at ages 20–34, 7.6 per 100 person-years at

ages 35–49, 14.2 at ages 50–64, and 18.1 per 100 person-years at ages ≥ 65 years in 2011 (Figure 1). Similar observations were made for prevalence of prediabetes by ethnicity and age group over the study period (data not shown).

DISCUSSION

The incidence and prevalence of prediabetes appears to be generally declining in Ontario among adults of different ethnicities and age

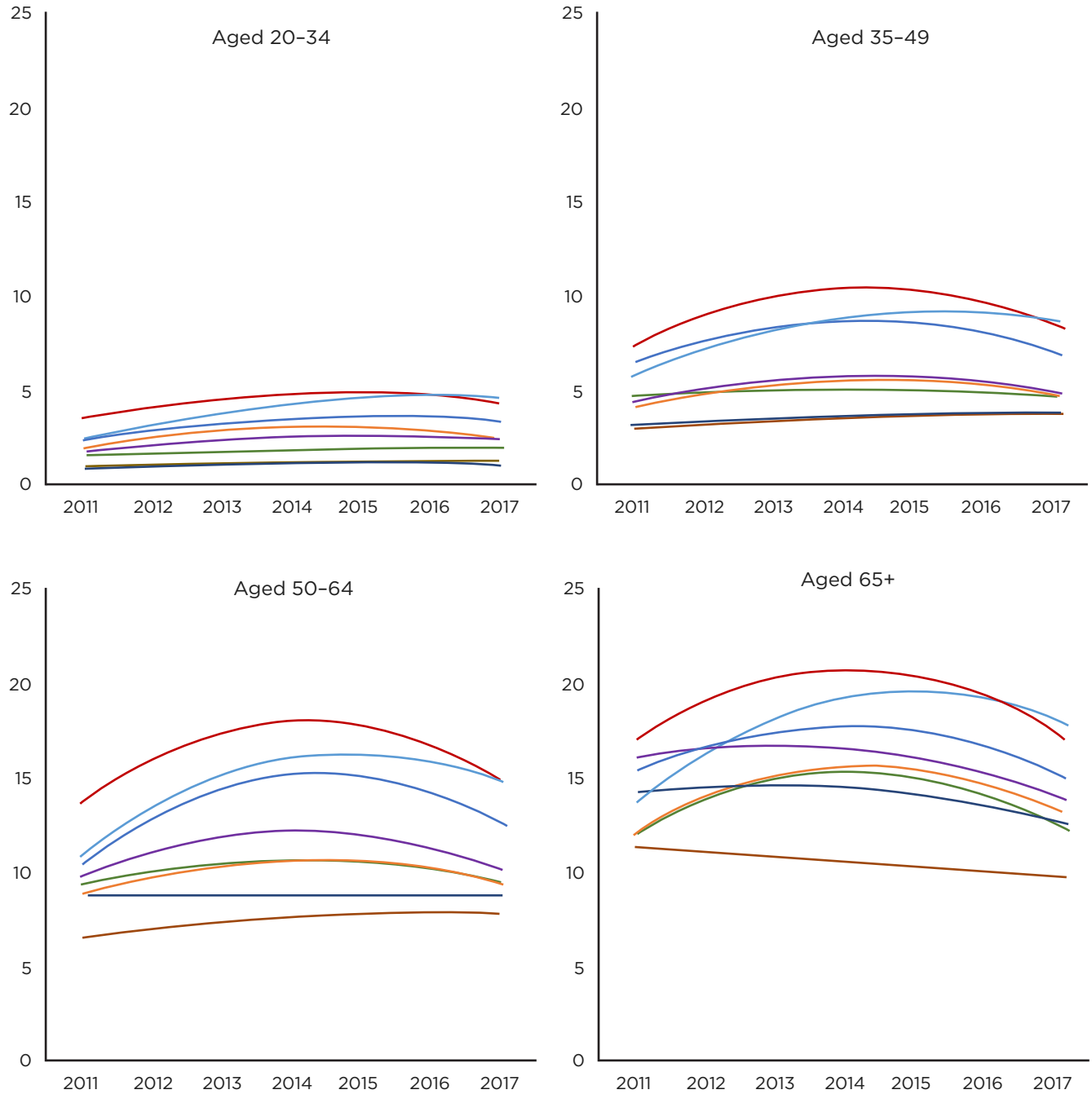

Figure 1: Age/sex standardised incidence of prediabetes (with 95% confidence intervals) between 2011 and 2017 among immigrants by ethnicity and age group.

*All lines based on line of best fit using a polynomial equation, R^2>0.99 for each.

*Age-adjusted and sex-adjusted rates are directly standardised with the 2011 Canadian Census data.

*Ethnic groups were derived based on country of birth, mother tongue, and a validated algorithm that identifies ethnic groups based on surnames for South Asian and Chinese populations only.

groups, which may be attributed to screening and prevention practices, adoption of health promotion strategies, and other health care system interventions. We may also be observing an overall decline in diabetes risk factors or a combination of these factors in our population. Nonetheless, close surveillance and access to lifestyle interventions is important for reducing the burden of Type 2 diabetes mellitus in these high-risk populations. As well, further research is necessary to understand the trends of prediabetes prevalence and incidence among immigrants by ethnicity and age groups.

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Once-Weekly Semaglutide versus Daily Canagliflozin in Type 2 Diabetes Mellitus (SUSTAIN 8): How Do They Compare?

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Keywords: Body weight, canagliflozin, semaglutide, glucagon-like peptide-1 receptor agonist (GLP-1RA), glycaemic control, sodium–glucose cotransporter-2 inhibitor (SGLT-2i), SUSTAIN, Type 2 diabetes mellitus (T2DM).

Citation: EMJ Diabet. 2019;7[1]:50-52. Abstract Review No: AR03.

ABSTRACT

Both glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium–glucose cotransporter-2 inhibitors (SGLT-2i) are effective and well-tolerated treatment options approved for the treatment of Type 2 diabetes mellitus (T2DM).[1,2] The T2DM guidelines recommended

them as second-line therapy after metformin use.[3] Head-to-head trials between GLP-1RA and SGLT-2i are scarce, so little information is available to prescribers and patients to guide an informed choice between these two options. Subcutaneous once-weekly (OW) semaglutide, a GLP-1RA, has demonstrated superior glycaemic control and body weight reductions versus placebo and active comparators across the SUSTAIN clinical trial programme[1,4,5] Canagliflozin, an SGLT-2i, also has proven efficacy for glycaemic control and weight loss compared with placebo and active comparators.[6–8] Additionally, both OW semaglutide and canagliflozin have shown cardiovascular (CV) benefits in T2DM patients with high CV risk.[9,10] The SUSTAIN 8 trial was undertaken as a head-to-head comparison of subcutaneous OW semaglutide with oral once-daily (OD) canagliflozin in patients with T2DM uncontrolled with metformin.

SUSTAIN 8 was a Phase IIIb, randomised, double-blind, double-dummy, active-comparator, parallel-group trial, conducted worldwide across 11 countries. The trial included 788 adults with T2DM and HbA1c 7–10.5%, randomised 1:1 to receive either semaglutide 1.0 mg OW and canagliflozin placebo OD, or canagliflozin 300 mg OD and semaglutide placebo OW for 52 weeks. Primary and confirmatory secondary endpoints included changes from baseline in HbA1c and body weight, respectively. Other efficacy endpoints, along with safety, were also assessed.

The key results from the trial are reported in Table 1. OW semaglutide was superior to canagliflozin for the primary endpoint of reduction in HbA1c (-1.5%-point versus -1.0%-point). Estimated treatment difference was-0.49%-point (95% confidence interval [CI]: -0.65; -0.33), p<0.0001. Semaglutide also led to superior reductions in body weight versus canagliflozin (-5.3 kg versus -4.2 kg). Estimated treatment difference was -1.06 kg (95% CI: -1.76;-0.36), p=0.0029. Greater proportions of subjects achieved HbA1c targets (<7.0% and ≤6.5%) and weight-loss responses (≥5% and ≥10%) with semaglutide versus canagliflozin (p<0.0001 for all [except the difference for weight-loss responses ≥5%; p=not significant]).

Table 1: Key primary and secondary endpoints in SUSTAIN 8.

	Overall baseline (mean)	**Change from baseline at Week 52 (mean)**		**ETD (95% CI)**	**p-value**
		Semaglutide 1.0 mg n=394	**Canagliflozin 300 mg n=394**		
HbA1c (%)	8.3	-1.5	-1.0	-0.49 (-0.65; -0.33)	<0.0001
Body weight (kg)	90.2	-5.3	-4.2	-1.06 (-1.76; -0.36)	0.0029
FPG (mmol/L)	9.4	-2.3	-2.0	-0.36 (-0.62; -0.09)	0.0094
7-point SMBG: mean, (mmol/L)	10.4	-2.8	-2.0	-0.86 (-1.14; -0.58)	<0.0001
Postprandial increment of 7-point SMBG, (mmol/L)	2.2	-0.7	-0.4	-0.26 (-0.49; -0.02)	0.036
		Proportion of responders at Week 52 (%)		**OR (95% CI)**	
		Semaglutide 1.0 mg n=394	**Canagliflozin 300 mg n=394**		
HbA1c <7.0%		66.1	45.1	2.77 (1.98; 3.85)	<0.0001
HbA1c ≤6.5%		52.8	23.6	4.19 (2.97; 5.92)	<0.0001
Weight loss ≥5%		51.1	46.6	1.22 (0.90; 1.66)	0.2099
Weight loss ≥10%		22.3	8.9	2.99 (1.89; 4.75)	<0.0001

CI: confidence interval; ETD: estimated treatment difference; FPG: fasting plasma glucose; HbA1c: haemoglobin A1c; OR: odds ratio; SMBG: self-measured blood glucose.

Overall, 76.0% of subjects treated with semaglutide and 71.8% of subjects treated with canagliflozin experienced adverse events. Consistent with previous SUSTAIN trials, the most frequent adverse events with semaglutide were gastrointestinal (46.9% versus 27.9% with canagliflozin), whereas the most frequent adverse events with canagliflozin were infections and infestations (34.5% versus 29.1% with semaglutide). The rates of premature treatment discontinuation due to adverse events were 9.7% (semaglutide) and 5.1% (canagliflozin), and severe or blood glucose-confirmed symptomatic hypoglycaemia occurred in 1.5% and 1.3% of subjects, respectively.

In summary, the SUSTAIN 8 trial provides clinically relevant information regarding the head-to-head comparison of a GLP-1RA and SGLT-2i in patients with T2DM. Semaglutide 1.0 mg OW demonstrated superior efficacy compared with canagliflozin 300 mg OD in patients treated with metformin who had uncontrolled T2DM. Both treatments were generally well tolerated, with low rates of hypoglycaemia. Gastrointestinal side effects were more common with semaglutide, while infections were more common with canagliflozin. These study outcomes may be used to guide clinical decision-making when treatment intensification is needed following metformin therapy in T2DM.

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SUSTAIN 10: Efficacy and Safety of Semaglutide 1.0 mg Once Weekly versus Liraglutide 1.2 mg Once Daily

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Keywords: Body weight, clinical practice, glucagon-like peptide-1 receptor agonist (GLP-1RA), glycaemic control, liraglutide, semaglutide, SUSTAIN, Type 2 diabetes mellitus (T2DM),

Citation: EMJ Diabet. 2019;7[1]:53-55. Abstract Review No: AR04.

Subcutaneous semaglutide once weekly (OW) and subcutaneous liraglutide once daily (OD) are two glucagon-like peptide-1 receptor agonists (GLP-1RA) approved for the treatment of Type 2 diabetes mellitus (T2DM).[1,2] Both drugs decreased HbA1c, reduced body weight, and provided cardiovascular benefits in pivotal Phase III trials.[3] Given the positive efficacy profiles and recent recommendations from international associations,[4,5] both semaglutide and liraglutide are GLP-1RA that clinicians may consider prescribing to patients with T2DM; the clinical decision making involves choosing between an established OD formulation and a recently approved OW formulation that may be perceived as more convenient. Comparative head-to-head data would help resolve this clinical prescribing dilemma and provide evidence relevant to clinical practice. However, prior to the SUSTAIN 10 clinical trial, a Europe-based head-to-head comparison of the two drugs had not been conducted. SUSTAIN 10 compared the efficacy and safety of semaglutide 1.0 mg OW with that of liraglutide 1.2 mg OD. The doses were chosen to represent the most common (liraglutide 1.2 mg)[6] and the anticipated most common (semaglutide 1.0 mg) prescription patterns in Europe and, thereby, increase the clinical relevance of the results.

This Phase IIIb, 30-week, open-label trial was conducted in 11 European countries and included 577 subjects with T2DM inadequately controlled with 1–3 antidiabetic drugs, i.e., metformin, sulphonylurea, and sodium–glucose cotransporter-2 inhibitors. Subjects were randomised 1:1 to subcutaneous semaglutide 1.0 mg OW or subcutaneous liraglutide 1.2 mg OD.

Table 1: Key primary and secondary endpoints in SUSTAIN 10.

	Overall baseline (mean)	Change from baseline at Week 30 (mean)		ETD (95% CI)
		Semaglutide 1.0 mg n=290	Liraglutide 1.2 mg n=287	
HbA1c, %	8.2	-1.7	-1.0	-0.69* (-0.82; -0.56)
Body weight (kg)	96.9	-5.8	-1.9	-3.83* (-4.57; -3.09)
FPG (mmol/L)	9.9	-2.7	-1.4	-1.24* (-1.54; -0.93)
7-point SMBG: mean (mmol/L)	10.3	-3.0	-2.1	-0.89* (-1.15; -0.64)
Postprandial increment of 7-point SMBG (mmol/L)	2.3	-0.9	-0.4	-0.53* (-0.77; -0.28)
		Proportion of responders at Week 30 (%)		OR (95% CI)
		Semaglutide 1.0 mg n=290	Liraglutide 1.2 mg n=287	
HbA1c <7.0%		80	46	5.98* (3.83; 9.32)
HbA1c ≤6.5%		58	25	4.84* (3.21; 7.30)
Weight loss ≥5%		56	18	5.89* (3.93; 8.81)
Weight loss ≥10%		19	4	4.99* (2.57; 9.68)
HbA1c <7.0% without severe or BG-confirmed symptomatic hypoglycaemia and no weight gain		76	37	6.07* [4.02; 9.15]

*p<0.0001.

BG: blood glucose; CI: confidence interval; ETD: estimated treatment difference; FPG: fasting plasma glucose; HbA1C: haemoglobin A1C; OR: odds ratio; SMBG: self-measured blood glucose.

The primary and confirmatory secondary endpoints were, respectively, change from baseline to Week 30 in HbA1c and body weight. Other efficacy endpoints, together with safety and patient-reported outcomes, were also assessed.

The main results are shown in Table 1. Semaglutide was superior to liraglutide for the primary and confirmatory secondary endpoints: from baseline to Week 30, HbA1c decreased by 1.7%-point versus 1.0%-point (baseline 8.2%), and weight decreased by 5.8 kg versus 1.9 kg (baseline 96.9 kg), with semaglutide versus liraglutide, respectively (both p<0.0001). The proportions of subjects achieving HbA_{1c} targets (<7.0% and ≤6.5%), weight-loss responses (≥5% and ≥10%), and clinically important composite endpoints were higher with semaglutide versus liraglutide (p<0.0001 for all). Similar results were seen with other glycaemic and weight parameters. Treatment satisfaction (as measured by the Diabetes Treatment Satisfaction Questionnaire [status version] summary score) improved with both treatments (estimated treatment difference 0.63; p=0.0814), and although statistical significance was not reached with all parameters, the data favoured semaglutide versus liraglutide.

Safety profiles were generally similar with both treatments, except that higher proportions of subjects with semaglutide versus liraglutide experienced gastrointestinal adverse events (AE): nausea: 21.8% versus 15.7%; diarrhoea: 15.6%

versus 12.2%; vomiting: 10.4% versus 8.0% and AE leading to treatment discontinuation (11.6% versus 6.6%; driven by gastrointestinal AE). These findings are consistent with the known safety profile of GLP-1RA: the most common AE observed with this class are gastrointestinal.[7]

In summary, SUSTAIN 10 confirmed that both treatments were effective in reducing HbA1c and body weight in subjects with T2D, and demonstrated superior efficacy with semaglutide 1.0 mg OW compared with liraglutide 1.2 mg OD. Both treatments were generally well-tolerated. These findings are consistent with those from the SUSTAIN 3 and 7 trials, which compared semaglutide with other GLP-1RA (exenatide extended release and dulaglutide, respectively).[8,9] In conclusion, the SUSTAIN 10 results support semaglutide as a favourable treatment option in clinical practice.

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Deep Serum Proteomics Reveal Biomarkers and Causal Candidates for Type 2 Diabetes Mellitus

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BACKGROUND AND AIMS

The prevalence of Type 2 diabetes mellitus (T2DM) is expected to increase rapidly in the next decades, posing a major challenge to societies

worldwide. The emerging era of precision medicine calls for the discovery of biomarkers of clinical value for prediction of T2DM, so that causal biomarkers can suggest novel therapeutic targets. However, only fragmentary data are currently available for protein biomarkers for prediction of incident T2DM.[1] The aim of the current study was to utilise deep serum proteomics data to identify biomarkers for prevalent and incident T2DM and evaluate their predictive value over clinical traits. Furthermore, genetic information was integrated to evaluate the causal relationships between serum proteins and T2DM.

MATERIALS AND METHODS

Serum levels of 4,137 human proteins were measured with multiplex SOMAmer technology (SomaLogic, Inc., Boulder, Colorado, USA) in the population-based AGES cohort of 5,438 Icelanders as previously described,[2] of which 654 had prevalent T2DM. Of the 2,940 individuals free of diabetes at baseline who participated in a 5-year follow-up visit, 112 developed T2DM within the study period. Protein associations with prevalent or incident T2DM were evaluated with logistic regression adjusting for age and sex, and considered significant when the Bonferroni-corrected p-value <0.05. LASSO penalised logistic regression analysis combined with bootstrap resampling was applied to prioritise a panel of proteins to predict incident T2DM and compared with a clinical model using variables from the Framingham Offspring Risk Score.[3] The prediction model was evaluated in a validation sample consisting of 1,844 AGES participants who did not participate in the 5-year follow-up visit but among which 46 incident T2DM cases were defined from linked prescription and medical records. A two-sample Mendelian randomisation (MR) analysis was performed to identify causal candidates for T2DM. Here, genetic instruments for protein levels identified in AGES were integrated with genome wide association study summary statistics for T2DM from the DIAMANTE consortium[4] and a Benjamini-Hochberg FDR <0.05 in the MR analysis was considered significant.

RESULTS

The study identified 520 and 99 proteins associated with prevalent or incident T2DM, respectively, where 83 proteins were overlapping (Fisher's p: 7.2×10^{-63}). Proteins associated with prevalent T2DM were enriched for extracellular matrix-receptor interaction, complement and coagulation cascades, metabolic processes, and liver-specific gene expression. By contrast, proteins associated with incident T2DM were mainly enriched for metabolism, lipid transport, and response to insulin, as well as gene expression in liver and adipose tissue, supporting the involvement of these pathways in the preclinical phase of the disease.

Using LASSO analysis, a panel of 20 protein biomarkers was identified that together with clinical risk factors predicted incident T2DM in the validation sample with an AUC of 0.84 (95% confidence interval [CI]: 0.78–0.91), which was a significant ($p=6.6\times10^{-3}$) improvement over the clinical model alone (AUC=0.80, 95% CI: 0.72–0.88). Of 536 proteins associated with either prevalent or incident T2DM, genetic instruments were identified for 246 proteins in AGES, of which 16 were supported (FDR<0.05) as having a causal effect on T2DM. Here, the strongest support for causality was observed for the proteins MMP12, HIBCH, and WFIKKN2.

CONCLUSION

These results demonstrate a major shift in the serum proteome before and during the diabetic stage. The proteomic changes observed in the preclinical stage of the disease were mainly related to insulin sensitivity. A multivariate model with serum proteins adds significantly to the prediction of T2DM over traditional clinical risk factors, although our findings require replication in an independent cohort and further evaluation of any clinical utility. Finally, the MR analysis highlighted a number of proteins that may have a causal role in the development of the disease. These proteins could be of particular interest for follow-up studies as novel therapeutic targets.

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Effect of the Time of Day of Food Intake and Eating Occasions on Clock Gene mRNA Expression, Weight Loss, HbA1c, and Overall Glycaemia in Type 2 Diabetes Mellitus

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BACKGROUND AND AIM

Most of the metabolic processes involved in obesity, glycaemic control (i.e., β-cell function), muscular glucose uptake, and hepatic glucose production exhibit diurnal variations and are controlled by endogenous circadian clock genes (CCG).[1] Consequently, human glucose metabolism is optimised for eating in the early hours of the day and fasting and sleeping in the evening and during the night. Meal timings that are not aligned with CCG, i.e., skipping breakfast, snacking all day, or high-carbohydrate (CHO) consumption in the evening, may lead to disrupted CCG, obesity, and hyperglycaemia.[2,3] Traditional diet intervention (DI) aimed at weight loss and glucose control in Type 2 diabetes mellitus (T2DM) entails several small meals and snacks with calories and CHO uniformly distributed throughout the day, including a snack at night to avoid nocturnal hypoglycaemia.[4] Although this DI is usually accompanied by antidiabetic drugs, many patients still require insulin treatment, which is gradually increased. This progressive increase in the total daily insulin dose (TDID), in turn, leads to weight gain and increased insulin resistance, and may result in a cycle of increased insulin, continued weight gain, decreased likelihood of achieving glycaemic targets, and insulin dose-depended cardiovascular risk and mortality.[5] The authors recently showed that circadian misalignment by skipping breakfast versus eating breakfast led to downregulation of pivotal CCG, resulting in higher glucose, deficient insulin, and glucagon-like peptide-1 (GLP-1) secretion after subsequent meals.[6]

The aim of this study was to explore whether, in insulin treated T2DM patients, a 3-month DI aligned with their CCG, consisting of three meals a day with most CHO consumed in the early hours of the day (Bdiet) and a smaller dinner would upregulate CCG, leading to more efficient weight loss and glycaemic control. Furthermore, if this was accompanied by less TDID compared

to isocaloric traditional DI with CHO evenly distributed in three small meals and three snacks throughout the day (All-dayDiet).

METHODS

Twenty-eight T2DM patients (aged 69±7 years; BMI: 32.2±5 kg/m^2; 19.9±8 years with T2DM; HbA1c 8.1±1.1 mmol/mol) were treated with insulin and randomly assigned to 12 weeks of either the BDiet with high-energy, CHO breakfast, and low CHO dinner (1,600±200 kcal; breakfast[B]:lunch[L]:dinner[D]; 50:33:17%), or the All-dayDiet with calories and CHO evenly distributed throughout the day (1,600±200 kcal, B:L:D 20:25:25% plus 3 snacks, 10% each). The study assessed body weight; daily 24-hour and nocturnal (00:00 to 06:00) glycaemia, using continuous glucose monitoring (CGM); appetite; craving scores; and CCG mRNA expression in white blood cells at 08:00, 12:00, 15:30, and 23:00, at baseline and after 2-week and 12-week DI, along with TDID.

RESULTS

Results showed that the BDiet led to greater weight loss (-5.4±0.9 versus +0.26±0.30% kg; p<0.05); reduced HbA1c (1.2±0.3% versus 0.2±0.4%; p<0.05); reduced fasting glucose (p=0.005), and reduced daily 24-hour mean glucose by 40±10 mg/dL versus 18±16 mg/dL (p<0.05). Mean nocturnal glucose decreased in the BDiet to 108.8±5.0 mg/dL versus 141.3±13.0 mg/dL in the All-dayDiet (p=0.03). CGM in the BDiet group showed a significant decrease in daily time spent in hyperglycaemia (>180 mg/dL) from 8 hours 59 minutes (37%) at baseline, to 3 hours 3 minutes (13%; p<0.01). Additionally, in the BDietthere was a reduction in the nocturnal time spent in hyperglycaemia from 1 hour 18 minutes (22%) at baseline, to 20 min (6%; p<0.05), compared to no change in the All-day diet (p=0.06). The craving scores (particularly for CHO or starches) assessed by the Food Craving Inventory questionnaire, were augmented by 4±5.1% with the All-dayDiet, while in participants in the BDiet group were significantly reduced by 36.0±7.7% (p<0.05).

The BDiet led to significant upregulation of the oscillation and amplitude of *Brain and Muscle ARNT-Like 1*, *Period 2*, *Cryptochrome 1*, and *RAR-Related Orphan Receptor Alpha* gene expression, as well as higher *RAR-Related Orphan Receptor Alpha* and *Sirtuin 1* relative levels versus the All-dayDiet (p<0.01).

At the end of the intervention, TDID increased by 4.9±14 units/day (from 70.6±17 to 75.5±11 units/day) in the All-dayDiet; whereas, the TDID was significantly reduced by 27±16 units/day (from 73.5 ±16 to 33.8±15.2 units/day) in the BDdiet (p<0.05).

CONCLUSION

The BDiet with high-energy and high CHO breakfast appears to be more effective than the All-dayDiet, in which calories and CHO are spread throughout the day. This leads to reduction in weight, HbA1c, appetite, and daily and nocturnal glycaemia, with significantly reduced TDID. The upregulation of CCG expression in the BDiet may be the underlying mechanism, enhancing β-cell secretion and muscle and hepatic insulin sensitivity, leading to improvement in daily and nocturnal glucose metabolism.

Shifting calorie and CHO consumption to the early hours of the day and eating for fewer occasions, is an effective strategy for the achievement of better diabetes control and outcomes with less total daily insulin dose.

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Family Models of Diabetes Self-Management Education: The Current Evidence and Critical Gaps in Knowledge

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Abstract

This commentary outlines the effectiveness of family-centred models of diabetes self-management education (Family-DSME) interventions and identifies five considerable gaps in the available literature that are keeping Family-DSME interventions from being translated into clinical practice. These include: (a) confounding effects of including cultural tailoring in many Family-DSME studies; (b) variations in duration and dosage of Family-DSME interventions; (c) most studies failing to assess the effects of Family-DSME on the included family members; (d) lack of cost-effectiveness data; and (e) lack of implementation research on Family-DSME interventions. It is crucial that clinical researchers focus efforts on filling the gaps in knowledge that constrain Family-DSME from being translated into clinical practice.

INTRODUCTION

The U.S. Centers for Disease Control and Prevention (CDC) estimates that 29 million people (9%) in the USA have Type 2 diabetes mellitus (T2DM), and rates are expected to continue to increase over the next decade.[1] It is well-established that people with T2DM who adopt recommended self-management practices are more likely to maintain metabolic control and experience fewer diabetes-related complications.[2,3] The Chrvala et al.[4] meta-analysis of 118 standard diabetes self-management education (DSME) interventions reported a median reduction of HbA1c of only 0.57%.[4]

Self-management of T2DM is complex and requires changes that are often difficult for patients to adopt in their everyday life in the contexts of work and family.[5] Poor self-management, while frequently attributed to patients, is often the product of their social environment. A large and growing body of evidence documents that the primary context of diabetes self-management resides within the family.[6-11] Through their communications, habits, and attitudes, family members influence patients' decisions to follow recommended treatment and self-care regimens.[8,10,11]

A growing body of literature suggests that family-centred models of DSME (Family-DSME) may be effective. Family-DSME explicitly addresses diabetes self-management within a family context by using family motivational interviewing and family goal setting, providing education on supportive and nonsupportive behaviours in the family environment, and focussing on

family behavioural changes.[6,7] Recent systematic reviews by Baig et al.[6] and Pamungkas et al.[7] have documented the effectiveness of 38 implementations of Family-DSME on a range of diabetes-related outcomes.

The studies demonstrate the potential of Family-DSME to achieve a statistically and clinically significant reduction in A1c, with some studies achieving a mean reduction of 1.40% (15.3 mmol/mol).[6,7] These Family-DSME have used a broad definition of family that has not been constrained by family configuration, sex, or sexual preference. Furthermore, the reviewed studies have also shown improvement in patient-reported outcomes such as family support, self-efficacy and empowerment, quality of life, positive emotional control, self-management behaviours, diabetes-related distress, and depression.[6,7] While evidence has demonstrated Family-DSME is effective at improving a range of diabetes-related outcomes, several critical gaps in knowledge remain, and it is unlikely that Family-DSME will be translated into mainstream clinical practice until those gaps are filled.

CULTURAL TAILORING

The majority of Family-DSME interventions have been culturally-tailored for specific populations, such as Pacific Islanders, Hispanics, and South Koreans, and were not evaluated in real-world clinical settings.[6,7] While these studies have been informative and important, the confounding effects of including both cultural tailoring and family involvement in the same study make it difficult to understand to what degree either contributed to improved outcomes. Therefore, it remains unclear if Family-DSME without cultural tailoring is effective among patient populations in real-world clinical settings.

VARIATIONS IN DOSAGE AND DURATION OF TREATMENT

Prior Family-DSME studies have varied in duration and dosage, with interventions ranging from <10 hours of education over 8 weeks, to >60 hours of education over 12 months.[6,7] Most studies that included a control group did not directly compare Standard-DSME with Family-DSME implementations that were equivalent in duration and dosage. The lack of a direct comparison and inconsistency in duration and dosage has limited the clinical value of these studies.[6,7]

EFFECTS ON FAMILY MEMBERS

Only a few Family-DSME studies have assessed health and psychosocial effects on both patients and family members.[6,7] T2DM affects the health and quality of life of patients and family members.[12] Failure to assess effects on family members provides an incomplete picture regarding the effectiveness of Family-DSME.

COST-EFFECTIVENESS

Prior studies lack a cost-effectiveness analysis that measures the relevant costs for both patients and family members, as well as the benefits to patients and the spillover benefits to family members. A systematic review showed Standard-DSME produced net cost savings and met generally accepted cost-effectiveness thresholds.[13] However, evaluations of Family-DSME cost-effectiveness based on accepted guidelines for clinic-based interventions have not yet been conducted. Understanding the cost-effectiveness for patients and the spillover benefits for family members is important for broad translation of Family-DSME into clinical practice.[14]

IMPLEMENTATION RESEARCH

Lastly, no implementation research has been conducted on Family-DSME. Implementation research is critical to document the barriers and facilitators to implementation in real-world clinical practice.[15] Implementation studies of Family-DSME should be conducted to inform and promote the uptake of the scientific knowledge of Family-DSME into routine practice.

CONCLUSION AND RECOMMENDATIONS

Multiple studies of Family-DSME have shown promising results.[6,7,16,17] The available research shows that Family-DSME could be twice as effective as Standard-DSME.[4,6,7,17] However, there is not wide clinical adoption because there

has been no research directly comparing the effectiveness of Family-DSME to Standard-DSME without cultural tailoring. It is imperative that future studies compare Family-DSME that is not culturally tailored to Standard-DSME with consistent duration and dosage across both interventions. Ten hours of DSME is reimbursable by many insurance companies and is therefore an appropriate dosage to consider. Future Family-DSME studies should measure the effects of the interventions on both patients with T2DM and their family members. Finally, the translation of science into clinical practice requires that future studies of Family-DSME conduct both cost-effectiveness analyses and implementation research. It is crucial that clinical researchers focus their efforts on filling these gaps in knowledge that constrain Family-DSME from being translated into clinical practice. As these critical gaps in knowledge are filled, it is possible to see a shift in clinical care to Family-DSME with better outcomes for both patients and family members.

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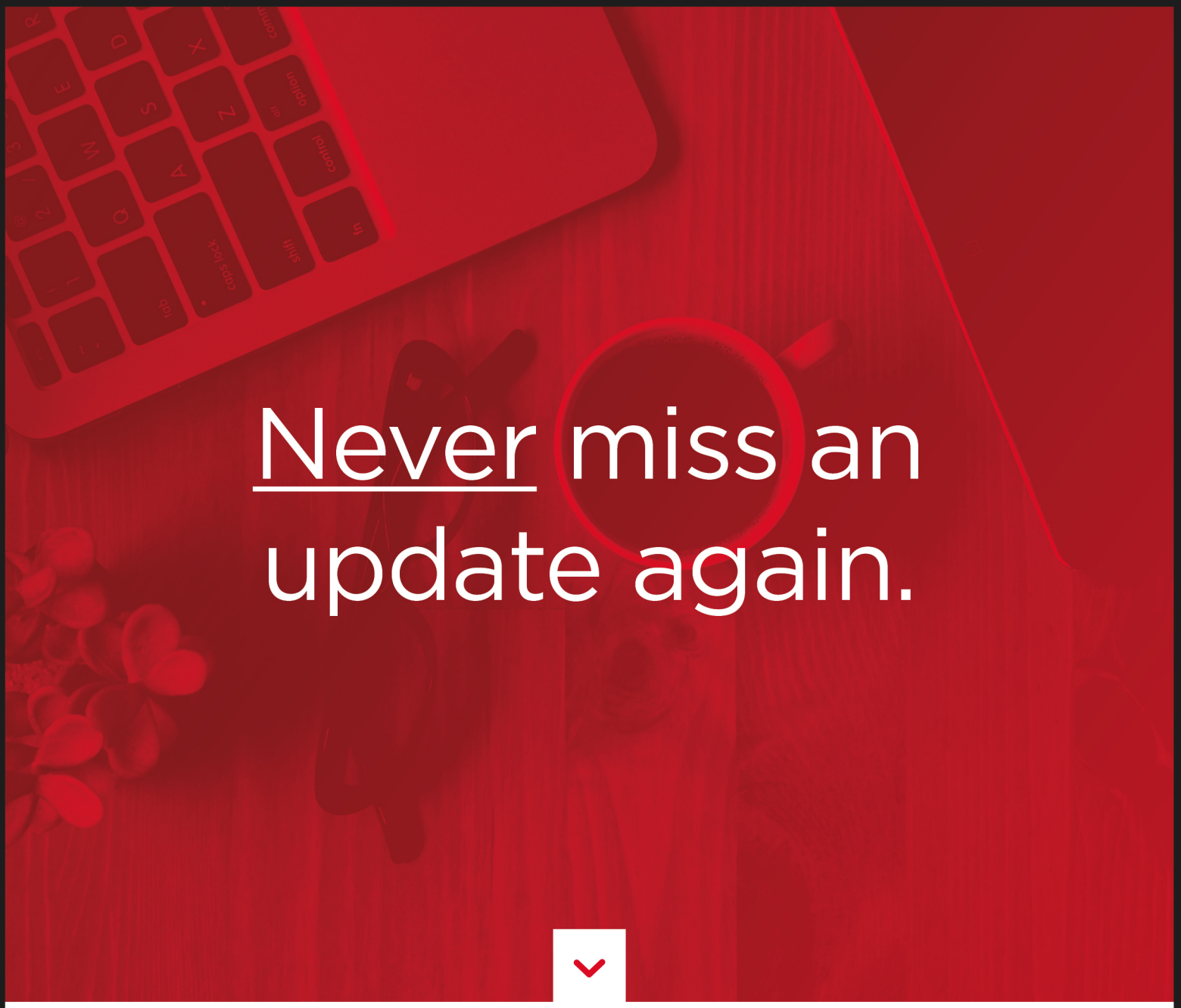

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Feasibility of a Diabetes Prevention Programme as Part of Cancer Survivorship Care

EDITOR'S PICK

With cancer survivorship on the rise, this timely paper explores the risk factors of cardiovascular disease and Type 2 diabetes mellitus for cancer survivors. The trial of an adapted Diabetes Prevention Programme delivered optimistic results, and as such Eaglehouse et al. demonstrate the huge potential of these programmes to improve health behaviours and risk factors for this growing population.

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Abstract

Introduction: Excess body weight and low physical activity levels may be detrimental to cancer survivorship and to the development of diabetes and cardiovascular disease (CVD). This study aimed to test the feasibility and acceptability of an adapted Diabetes Prevention Programme (DPP) for cancer survivors who have risk factors for Type 2 diabetes mellitus and CVD.

Methods: Overweight (BMI >25 kg/m^2) adults aged 50–79 who were diagnosed with nonmetastatic breast or colon cancer within the prior 5 years were recruited through a research registry and oncology clinics. Eligible individuals enrolled in a 13-week group lifestyle programme with goals of 5–7% weight loss and 150 minutes of moderate-intensity physical activity. Programme attendance, adherence to recommended behaviours, weight, and physical activity information were collected.

Results: A total of 44 individuals were screened for eligibility; 23 were eligible and 17 enrolled in the programme. Participants attended a median of 10 out of 13 lifestyle sessions and were able to meet dietary and activity goals 72.7% and 56.3% of the time, respectively. At the end of the programme, median weight loss was 4.5% and median activity was 297 minutes/week (median change +164 minutes/week).

Conclusion: The modified DPP intervention was feasible to deliver to this group of cancer survivors who had risk factors for diabetes or CVD. Incorporating successful prevention programmes such as the DPP into cancer survivorship care has the potential to improve health behaviours and chronic disease risk factors in the cancer survivor population.

INTRODUCTION

There are currently 14 million cancer survivors in the USA, a number that is expected to increase as the population ages.[1] Competing health risks associated with ageing, such as Type 2 diabetes mellitus and cardiovascular disease (CVD), require special consideration because survival time after a given cancer diagnosis is increasing. Lifestyle factors, including excess body weight and low physical activity levels, are detrimental both to the development of cancer and clinical outcomes upon diagnosis,[2-4] and to the development of diabetes and CVD.[5] These risk factors may persist after cancer treatment. Maintaining a healthy body weight and getting adequate physical activity can reduce the risk of all-cause mortality among cancer survivors;[6-8] however, population-based surveys indicate that cancer survivors generally fare worse in meeting weight and physical activity recommendations than the rest of the population.[9] In consideration of this, there is a need for lifestyle programmes that support healthy behaviours and the unique health needs of cancer survivors. The purpose of this study was to test the feasibility and appropriateness of a curriculum developed from the USA Diabetes Prevention Program (DPP)[10,11] for individuals previously treated for breast or colon cancer.

METHODS

Study Population

Individuals aged 50–79 years who had a diagnosis of breast (ductal carcinoma *in situ*, Stages I–III) or colon (Stages I–III) cancer in the prior 60 months were invited to participate in the study. Individuals who completed primary treatments (surgery, radiation, or chemotherapy), did not report a personal history of Type 1 or Type 2 diabetes mellitus (T1/T2DM), had a BMI >25 kg/m^2, and who self-reported one additional risk factor for T2DM or CVD were eligible to enrol. These additional self-reported risk factors included elevated blood glucose or prediabetes, hypertension, high blood pressure, or taking medications to control blood pressure; dyslipidaemia (high total cholesterol, low high-density lipoprotein cholesterol) or taking medications to control cholesterol; or a family history of T1/T2DM in parents or siblings. The study protocol was approved by the University of Pittsburgh Human Research Protection Office (Institutional Review Board), Pittsburgh, Pennsylvania, USA.

Recruitment

Individuals were recruited between April and June 2016 through a university-sponsored research registry and through the clinics of five medical oncologists who practice within the university hospital system. Information about the study was disseminated to 322 members of the research registry via newsletter and advertised on the research registry online portal. Potential participants contacted by newsletter were those who had indicated a history of cancer (any type) and an interest in weight loss, physical activity, lifestyle, or health and wellness-related research upon enrolling in the registry. Oncologists were approached by study staff and agreed to assist with patient recruitment. Potentially eligible patients were identified by a third-party honest broker who used cancer registry data to identify patients who fit the inclusion criteria and were treated by one of the collaborating oncologists. The identified patients were then mailed a letter with information about the study and signed by the oncologist. In total, 301 letters were mailed to individuals who met the criteria. The oncologists also had clinic staff pre-screen patients who were attending clinic for potentially eligible participants. However, this method was discontinued because

undergoing active treatment and thus ineligible for the study.

Eligibility Screening and Enrolment

The target enrolment was 20 participants over a 3-month period. The enrolment target was selected to allow for at least two groups of 8–12 individuals and to minimise the wait time between eligibility screening and the start of lifestyle sessions. Individuals interested in the study were asked to contact the principal investigator by phone to complete a screening interview, following verbal consent. Eligibility screening included questions about cancer diagnosis (month and year, tumour site, and tumour stage) and current diabetes status. If participants met the inclusion criteria for cancer history and diabetes status, they were asked questions about additional T2DM and CVD risk factors, as described above. Participants were provided further information on enrolment if eligible.

Assessment Visits

Eligible participants were invited to attend two assessments, one before and one after the lifestyle programme, scheduled in the cancer centre's outpatient clinic. At the pre-intervention assessment, written informed consent was obtained. At both assessment visits, participants were asked to complete physical, behavioural, and psychosocial measurements and to provide a fasting blood and urine sample. Blood collection was completed by a registered nurse into 3–10 mL tubes, for a total collection of 30 mL at each visit. Participants were provided with a 90–120 mL urine collection cup and asked to provide a specimen in a private bathroom during a single void. Blood and urine samples were processed immediately by qualified staff and stored in the cancer centre biobank for future analysis.

A trained study staff member performed physical measurements which included weight, height, and waist circumference. Participants' weight was measured in light clothing and without shoes to the nearest 0.1 lb on a digital scale. Participants' waist circumference was measured at the midpoint between the iliac crest and the bottom of the 12th rib to the nearest 0.250 inch using a disposable tape measure. Participants' height was measured without shoes to the nearest 0.125 inch using a stadiometer. Each measurement was repeated once to improve accuracy and averaged for analyses. BMI was calculated from measured weight and height.

Physical activity was assessed by an interviewer-administered questionnaire modified from the 2010 National Health and Nutrition Examination Survey (NHANES).[12] The NHANES questionnaire is derived from the Global Physical Activity Questionnaire (GPAQ), which is considered a valid and reliable instrument for capturing moderate and vigorous physical activity.[13] The NHANES questionnaire captures time spent in vigorous and moderate intensity activity as part of work and recreation in a typical week. The sedentary behaviour section was modified for this study to individually query time spent in sitting activities in a typical day for occupation, transportation, leisure screen-time (television and computer), and other leisure (e.g., reading, playing cards, and socialising). The questionnaire was scored using the available codebook and algorithms from NHANES.[12]

Psychosocial measurements included fatigue and quality of life elements. Fatigue was captured by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale.[14] The FACIT-F includes 13 Likert scale items that assess fatigue symptoms over the past 7 days. Item responses range from 'not at all' to 'very much' (0–4). For scoring, positive responses are given a higher value and a higher score indicates less fatigue. Quality of life was captured by the SF-12® version 1.[15] The SF-12 includes 10 Likert scale questions and 2 'yes or no' response questions. Available scoring algorithms were used to calculate an overall score and to calculate the physical and mental composite subscales. A higher score signifies a better quality of life.

Intervention

The DPP-Group Lifestyle Balance (DPP-GLB) is a modified DPP curriculum developed at the University of Pittsburgh for use in community settings[16] and is available online.[17] The main modifications from the original DPP include: 1) group-based sessions rather than individual; 2) condensation of core material from 16 to 12 sessions; and 3) the addition of post-core maintenance sessions to support participants in sustaining weight and physical activity changes. The DPP-GLB topics include healthy eating,

physical activity, planning, and problem solving. For this pilot, the first 12-weekly DPP-GLB sessions plus 1 session on resistance exercises were offered, beginning in August 2016 and concluding in October 2016. The introduction in Session one was modified to present information on the link between diabetes risk factors and cancer development and outcomes. Consistent with the DPP,[10,11] participants were given calorie, fat, and physical activity goals to facilitate a 5–7% weight loss. Calorie (1,200–2,000 kcal per day) and fat (33–50 g per day) goals were determined from initial body weight and could be adjusted based on safe, progressive weight loss of 1–2 lb per week. The physical activity goal was a minimum of 150 minutes per week of moderate activity, similar in intensity to a brisk walk, consistent with recommendations for those with a history of cancer.[7] Physical activity goals began at 60 minutes per week in Session 4 and progressed to the minimum goal of 150 minutes per week over the remaining 8 weeks of the programme. For participants with higher starting activity levels, their goals were adjusted to meet desired weight loss and lifestyle change. Participants were asked to track their daily weight, calorie and fat intake, and physical activity during the programme in either a paper diary that was supplied by the programme or in online or mobile applications of their choice. The programme was offered in two groups; each session was held both in the morning and evening to accommodate a variety of schedules. Each group had 8–12 participants, with some flexibility to allow participants who could not attend their regular group meeting to attend the other group. Sessions were held in classroom-style conference rooms at the university's cancer centre and each session was 1 hour. Additionally, parking vouchers were offered to reduce burden on participants and improve attendance. The lifestyle coach was an exercise physiologist and public health professional who received training to deliver the DPP-GLB programme from the University of Pittsburgh Diabetes Prevention Support Center.

Outcomes

The primary outcomes were feasibility metrics as suggested by the National Center for Complementary and Integrative Health (NCCIH).[18] The study investigators collected information on the number of individuals reached, screened, eligible, and enrolled; and the costs associated with recruitment and programme delivery. The costs associated with research activities were not included in the feasibility metrics since these costs would not be applicable to community-based delivery of diabetes prevention programmes. Once enrolled, investigators collected participant attendance and adherence to recommended healthy lifestyle behaviours. Attendance was recorded in a weekly log by the lifestyle coach. In-person, phone, or email contact to deliver and discuss the session materials was documented as attending a session. Dietary and physical activity records in self-monitoring books were evaluated for adherence to the weekly dietary and physical activity goals. Participant feedback about the programme features they liked best and least and suggestions for improvement were collected at the end of the study. Completion of the study assessment visits was also considered as a feasibility measure. The study investigators appraised the time required for the assessment visits and the willingness of participants to complete the research measures, including providing a blood and urine sample to be banked for future biomarker analysis (not performed as part of this study). Secondary outcomes included weight, waist circumference, physical activity and sedentary behaviour, and psychosocial measures.

Statistical Analyses

Descriptive statistics were used to summarise feasibility metrics, participant characteristics, and baseline measurements. Paired-samples t-tests and Wilcoxon rank sum tests were used to evaluate changes in secondary outcomes. Statistical significance was not evaluated as this was not the aim of this pilot work and is not appropriate.[18]

RESULTS

Recruitment and Enrolment

Study information was directly sent to 623 potential participants through the research registry and mailed letters (Figure 1). A total of 44 individuals responded to study advertisements or recruitment letters and were screened for eligibility in the study. Of those screened, 23 (52.3%) were eligible, and 17 (73.9%) of those who were eligible were subsequently enrolled in the study.

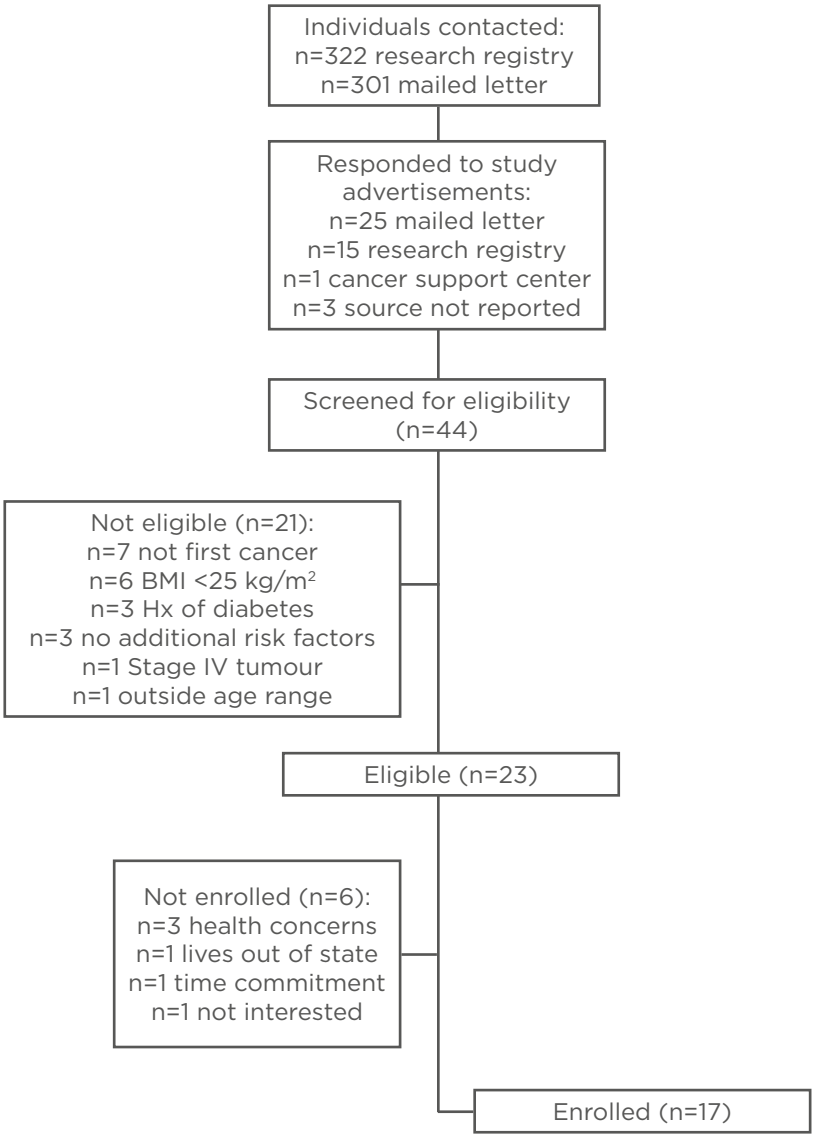

Figure 1: Recruitment, enrolment, and follow-up of participants in a diabetes prevention programme for cancer survivors.

The flow of participants and reasons for ineligibility and not enrolling, respectively, are depicted in Figure 1. At the end of the recruitment period, 85.0% of the target enrolment was reached. According to the interviewer-administered questionnaire at the baseline assessment visit, the mean age of enrolled participants was 60.1 (standard deviation [SD]: ±7.8) years. The mean time since diagnosis was 554.4 (SD: ±516.2) days (approximately 18.5 months). Participants were predominantly women (94.1%) and ethnicity was identified as white (70.6%) or black (29.4%). Participants' educational attainment was 5.9% high school diploma, 41.2% associate degree, 23.5% bachelor degree, and 29.4% graduate degrees. Most participants were either working full-time (52.9%) or were retired (23.5%). Participants had mostly been treated for breast cancer (94.1%) and had Stage I (41.2%) or Stage II (29.4%) cancer.

Costs for Recruitment and Programme Delivery

The total cost for printing and direct mailing to potential participants was $175 ($30 for printing, $145 for postage at $0.48 per piece). The contact with participants through the online research registry had no direct measurable costs. Recruitment costs were approximately $10 per enrolled participant.

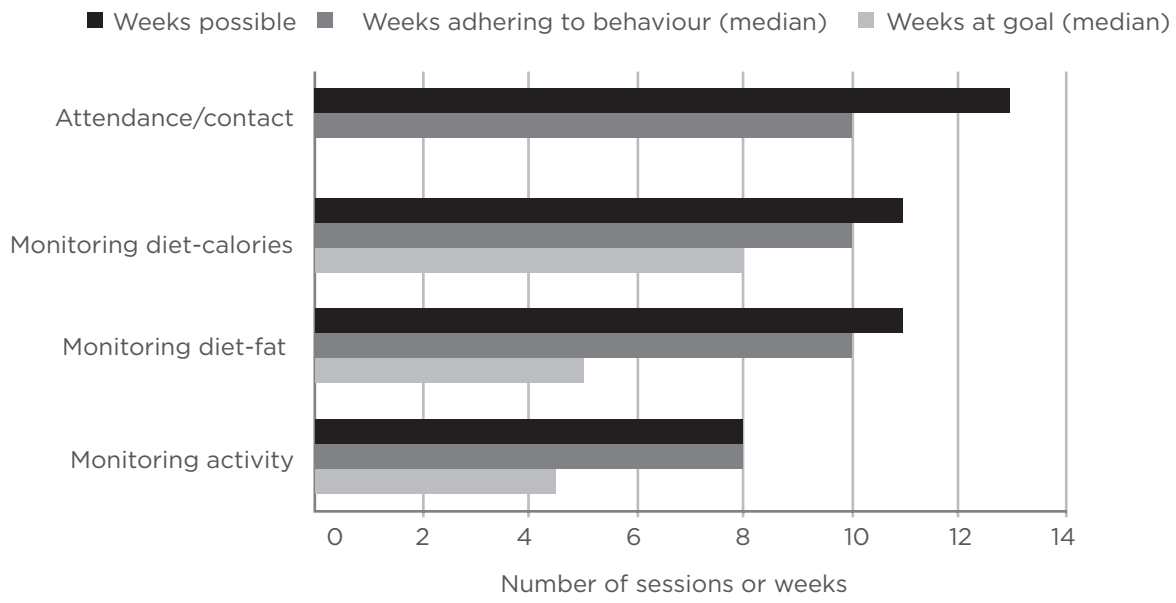

Figure 2: Attendance and adherence to recommended programme behaviours and self-monitoring during participation in a diabetes prevention programme for cancer survivors.

The materials (approximate costs) for the DPP-GLB delivery included a digital scale ($100), food models ($240), participant handouts ($110), participant binders ($60), keeping track booklets ($165), Calorie King® books ($144), pedometers ($124), resistance bands with door stop anchor ($412), and resistance exercise DVD ($85). The total cost for intervention materials and supplies was $1,440 and the cost per enrolled participant was approximately $85. The wages for the lifestyle coach were not included in the programme delivery costs in this study.

Attendance and Adherence

The median attendance was 10/13 sessions (76.9%) (Figure 2), with 82.4% of the participants completing at least 10 sessions. Of the 17 participants who enrolled, 14 actively engaged in the lifestyle programme via contact with the lifestyle coach either face-to-face at sessions or by phone and email. Three participants discontinued the programme due to work schedule conflicts. Overall, participants demonstrated moderate adherence to self-monitoring and meeting diet and physical activity goals (Figure 2). Median submission of diet records was 10/11 (90.9%) and submission of activity records was 8/8 (100.0%). Participants were able to meet goals for calories a median of 8/11 weeks (72.7%), fat grams a median of 5/11 weeks (45.5%), and goals for physical activity a median of 4.5/8 weeks (56.3%).

Study Assessment Visits: Physical, Behavioural, and Psychosocial Outcomes

Each study assessment visit required about 1 hour for study questionnaire administration, physical measurement, and specimen collection. The pre-intervention assessment required an additional 15 minutes for informed consent. Overall, participants were willing and able to complete the study assessments. For the main behaviours of weight and physical activity, participants started the programme with an average BMI of 33.1 kg/m^2 and moderate levels of physical activity (Table 1). The median weight loss was 4.5% of initial body weight, with a range of 0.4–11.6%. The median physical activity at the end of the programme was 297 min/week. Participants reported increased physical activity, decreased sedentary time, and favourable changes in psychosocial measurements (Table 1).

Participant Satisfaction and Feedback

Overall, participants had a favourable view of the programme, indicating that they liked "the encouragement," "weekly group sessions with progression of the topics," and "group interaction."

Table 1: Weight, physical activity, fatigue, and quality of life outcomes following a 13-week diabetes prevention programme adapted for cancer survivors.

	Baseline (n=14)	Post-intervention (n=14)	Change
	Mean (SD); Median (IQR)	Mean (SD); Median (IQR)	Mean (SD); Median (IQR)
Physical measurements			
Weight (lbs)	193.7 (44.4); 187.4 (177.8, 226.0)	184.4 (45.2); 173.6 (163.6, 209.2)	-9.3 (5.8); -6.8 (-13.6, -5.0)
BMI (kg/m^2)	33.1 (6.6); 30.9 (29.1, 38.5)	31.5 (6.8); 29.1 (26.9, 35.6)	-1.6 (1.0); -1.2 (-2.2, -0.9)
Waist circumference (inches)	40.3 (6.0); 39.9 (35.0, 44.2)	39.3 (5.6); 40.0 (33.3, 43.5)	-1.0 (1.9); -1.2 (-2.4, -0.3)
Physical activity			
Total min/week	256.0 (232.9); 157.5 (120, 360)	700.5 (827.4); 296.5 (181.5, 930)	+444.5 (705.4); +163.8 (-10, 577.5)
Moderate intensity min/week	225.3 (174.7); 157.5 (120, 360)	518.4 (721.2); 250 (175, 498)	+293.1 (648.2); +129 (-60, 340)
Vigorous intensity min/week	30.7 (79.6); 0 (0, 0)	182.1 (317.3); 30 (0, 270)	+151.4 (260.8); +30 (0, 120)
Sedentary min/day	586.8 (224.1); 645 (390, 720)	482.1 (185.5); 495 (330, 640)	-104.6 (156.4); -65 (-150, -15)
Participant-reported outcomes			
FACIT-F	40.4 (10.7); 44.5 (31.0, 49.0)	46.5 (6.6); 48.5 (44.0, 52.0)	+6.1 (8.5); +3.5 (-1.0, 8.0)
MCS	48.9 (8.8); 52.1 (46.6, 54.3)	49.9 (8.2); 51.3 (46.6, 57.9)	+0.0 (10.0); -0.9 (-4.9, 6.9)
PCS	47.9 (8.3); 51.3 (42.9, 53.9)	52.5 (5.5); 53.8 (51.0, 55.0)	+4.5 (5.7); +3.9 (0.7, 8.2)

FACIT: functional assessment of chronic illness therapy; IQR: interquartile range (25th percentile, 75th percentile); MCS: mental component summary; PCS: physical component summary; SD: standard deviation.

Some participants expressed the desire to continue lifestyle sessions and wanted a longer programme.

Feedback for improving the programme included employing a lifestyle interventionist with specialty oncology training to better tailor the programme and answer participant questions. Some participants reported a negative emotional reaction to being at the cancer treatment centre as part of the lifestyle programme.

DISCUSSION

In this feasibility study, individuals with a history of breast or colon cancer were invited to participate in a 13-week lifestyle modification programme. The overall reach was low (44/623 [7.06%] potential participants responded), indicating the need to explore additional strategies for recruitment of cancer survivors to lifestyle programmes. However, once participants enrolled, the DPP-GLB curriculum was feasible to implement as measured by participant attendance and adherence to recommended dietary and physical activity behaviours.

Given the availability of programme training and resources to nurses, dieticians, and health professionals, DPP such as GLB[17] and other recognised curricula[19] may be suitable for incorporation into cancer survivorship care to address health behaviours as well as diabetes and CVD risk factors. Health professionals, such as nurse oncologists, may play a key role in future efforts that leverage the success of the DPP by identifying patients who may benefit, engaging

these patients in the lifestyle programme, and monitoring patient progress in lifestyle change.

The DPP–GLB programme content was well-received and participants were able to make healthy diet and physical activity changes. The weekly programme goals for calories, fat, and physical activity were met 50–75% of the time. Variations in goal achievement between the three outcomes may be related to the notion that lifestyle change is not an 'all-or-nothing' approach and barriers to achieving each on a weekly basis may differ (e.g., time required for physical activity and competing commitments). Another possible barrier to increasing physical activity includes long-term side effects of cancer treatment (e.g., fatigue), which should be considered when adapting lifestyle programmes for cancer survivors. Participant adherence to self-monitoring and dietary goal achievement in this study likely contributed to overall weight loss. The amount of weight loss observed is in line with what has been shown in larger scale DPP translations for other high-risk populations.[20,21] Furthermore, the observed median weight loss of 4.5% is approximate to that which is recommended for chronic disease risk reduction.[22] One prior attempt to translate the DPP to a population of breast cancer survivors[23] was feasible and demonstrated similar changes in body weight as those seen in this study. For weight loss, these studies support further testing and evaluation of DPP-based programmes for weight management among cancer survivors. In the present study, participants met the physical activity goal with slightly less frequency than dietary goals. Nevertheless, the results of increased physical activity, decreased sedentary time, and improvements in quality of life metrics here are consistent with other community interventions using the DPP–GLB programme[20] and may demonstrate potential for additional cancer survivorship benefit.[8,24]

The cost of delivering primary and secondary prevention programmes is a concern, especially in the USA where healthcare costs continue to escalate.[25] In this study, the estimated costs per participant were about $85. When delivered in the community setting, additional costs may include facility rentals, lifestyle coach wages, and administrative fees which were not accounted for in this study. While this may increase overall costs, partnerships within the community and use of existing space and resources can help minimise these costs. Also, for DPP–GLB programme delivery, some items that were purchased such as a digital scale and food models may be used in subsequent programme delivery and thus reduce future costs. In the current delivery model, providers or participants are responsible for the costs of prevention programmes. The Centers for Medicare & Medicaid Services (CMS) has led the way in reimbursement for participation in US Centers for Disease Control and Prevention (CDC) recognised DPP programmes.[19,26] Other public and private insurers are following in these footsteps. This is anticipated to ease the burden of cost from the provider and participant perspective, while supporting the belief that dollars spent on prevention will pay dividends in future averted medical costs related to diabetes and obesity.

Although the lifestyle programme was delivered with high retention and participant satisfaction, there were limitations to the research. First, enrolment fell short of the modest target of 20 participants. This may be because of the short time frame (3 months) that the study team attempted to recruit or the effectiveness of the approaches (i.e., research registry and mailed letters). Second, there were few potential participants who contacted the study team who had a history of colon cancer, resulting in 94.1% of participants having a history of breast cancer. Alternate strategies, such as peer-led recruitment, may be needed to engage those with a history of colon cancer in lifestyle programmes.[27] Thus, the findings from this study may not extend to individuals with a history of other cancers. Third, self-reported participant risk factors for diabetes or CVD may lead to misclassification of actual diabetes or CVD risk at time of study enrolment. The results for secondary outcomes should be interpreted cautiously, because hypothesis testing and determination of statistically significant changes in the outcomes was not the focus of this pilot research. Lastly, healthy volunteer bias may result in a participant sample with fewer complications related to cancer treatment and thus limit the generalisability of the findings.

CONCLUSION

Overall, this article supports larger efforts to evaluate use of DPP curricula for breast cancer survivors with risk factors for T2DM and CVD.

The results of this study suggest additional approaches may be needed to recruit cancer survivors into diabetes prevention programmes. However, once enrolled, this pilot demonstrated feasibility in achieving participant engagement and adherence to the lifestyle goals. Leveraging successful prevention programmes like the DPP into new fields, i.e., cancer survivorship, has the potential to improve health behaviours and chronic disease risk factors in an increasing portion of the ageing population.

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Multidisciplinary Approach to Management and Care of Patients with Type 2 Diabetes Mellitus

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Abstract

The management of adults with Type 2 diabetes mellitus (T2DM) was traditionally delivered in a single specialist setting with a focus on glycaemic control. As the treatment landscape evolved to consider the need to prevent cardiovascular disease and/or microvascular complications, so did the requirement to manage this complex multisystem condition by multiple healthcare providers in both primary care and specialist settings. This article discusses the key studies that changed the way T2DM is managed to incorporate an interdisciplinary approach to care, the principles of the multidisciplinary teams, examples of multidisciplinary teams in real-world clinical practice, and associated patient outcomes.

INTRODUCTION

Diabetes is a global epidemic affecting an estimated 425 million adults aged 20–79 years. In 2017, there were 58 million individuals in Europe with diabetes and this figure is set to rise to 67 million by 2045.[1] Adults with Type 2 diabetes mellitus (T2DM) make up 90% of all patients with diabetes.[2,3] T2DM prevalence is increasing due to population ageing, changes in dietary behaviours, obesity, and sedentary lifestyles, all of which have severe implications for healthcare systems in terms of the morbidity and cost burden.[3,4] There is a large unmet need to streamline services using multidisciplinary teams (MDT) for optimal management of the large number of patients with T2DM.

T2DM pathogenesis is multifactorial and characterised by a combination of increased glucose production, impaired insulin secretion by pancreatic beta cells, and the development of peripheral insulin resistance. For T2DM to occur, both insulin resistance and inadequate insulin secretion must exist.[5,6] T2DM morbidity and the correlation between hyperglycaemia and vascular complications results from multiple biochemical pathways. Individuals with T2DM may experience cardiovascular disease (CVD) and/or microvascular complications that affect the kidney, retina, and nervous system.[3,5,7-9] Complications in patients with T2DM are common, with approximately 27% and 50% of patients experiencing macrovascular and microvascular complications, respectively.[3]

DIABETES TREATMENT LANDSCAPE PROGRESSION AND EVOLUTION TOWARDS A MULTIDISCIPLINARY APPROACH

The T2DM treatment landscape has evolved considerably over the past 40 years. The clinical endpoints that physicians use to determine the optimal care of patients has changed from glycaemic control (HbA1c) to a focus on prevention of macrovascular disease, in particular the prevention of cerebrovascular, renal, and cardiac disease.[10] During this time, new agents and drug classes have become available that are effective in the prevention of these morbidities.[11,12]

Diabetes landscape evolution can be classified into several time periods:

1. Before 1998 where control of glycaemia was assumed to be beneficial.

2. 1998–2015 where glucose-lowering studies largely demonstrated reduction in microvascular events but raised concerns about CVD risk.

3. 2015 onwards where studies of new glucose lowering therapies demonstrated cardiovascular (CV) and renal benefits in addition to improving hyperglycaemia.

The pre-1998 control of glycaemia-only approach was challenged by the UK Prospective Diabetes Study (UKPDS).[13-15] The study commenced in 1977 and evaluated if long-term intensive blood glucose control by either sulphonylureas, insulin, or conventional treatment could reduce the risk of microvascular and macrovascular complications in 5,102 patients with newly diagnosed T2DM. Over a 10-year period, the UKPDS found that reducing glucose exposure from HbA1c 7.9% to 7.0% with sulphonylurea or insulin therapy, reduced the risk of 'any diabetes-related endpoint' by 12% and microvascular disease by 25%. A nonsignificant relative risk reduction for myocardial infarction (MI) of 16% (p=0.052) was also found.[13,15] The legacy of UKPDS was that the achievement of tight glycaemic control could result in lower rates of microvascular complications but perhaps not CVD.[13-15]

As the UKPDS associated an HbA1c of 7% with better outcomes, further studies were conducted to determine if tighter glycaemic control to HbA1c 6.0–6.5% in patients with established T2DM was associated with additional morbidity benefits.[14] Studies such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD), the Veterans Affairs Diabetes Trial (VADT), and Action in Diabetes and Vascular Disease Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study found that it was possible to achieve tighter levels of glycaemic control using conventional agents such as metformin, sulphonylureas, thiazolidinediones, and insulin, yet none demonstrated significant improvements in combined vascular end points.[14,16-19] Furthermore, the ACCORD and VADT studies found that intensive management of glycaemia compared with standard approaches was associated with 20% increased mortality and a higher number of deaths (hazard ratio [HR]: 1.07; p=NS), respectively.[16,18] Further concerns regarding the CV safety of agents used to manage patients with diabetes then emerged. In 2007, a meta-analysis evaluating rosiglitazone studies reported a significant increase in the risk of MI (odds ratio [OR]: 1.43; 95% confidence interval [CI]: 1.03–1.98; p=0.03), and an increased risk of death from CV causes (OR: 1.64; 95% CI: 0.98–2.74; p=0.06).[20] These findings were of concern to physicians and they also changed the way new diabetes therapies were assessed as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) issued a requirement that all new therapies for diabetes undergo assessment of CV safety through large-scale cardiovascular outcome trials (CVOT).[21,22]

This treatment landscape evolution was a new opportunity for the diabetologist and cardiologist, in the setting of a multidisciplinary approach, to concomitantly improve glycaemic control and reduce the risk of CV events in patients with T2DM. The benefits of multifactorial care involving intensive therapy with tight glucose regulation and administration of renin-angiotensin system blocker, aspirin, and lipid-lowering agents in patients with T2DM were beginning to be recognised. These included a lower risk of death from CV causes (HR: 0.43; 95% CI: 0.19–0.94; p=0.04) and of CV events (HR: 0.41; 95% CI: 0.25–0.67; p<0.001).[23] The management of patients with T2DM progressed to a combined approach and in 2007, as part of ten practical steps for healthcare providers (HCP) to enable them to achieve their glycaemic goals, the Global Partnership for Effective Diabetes Management recommended the implementation of MDT.[24]

MULTIDISCIPLINARY TEAM APPROACH IN THE ERA OF CARDIOVASCULAR OUTCOMES TRIALS

Multiple trials have been performed that incorporate CV safety when evaluating the newer antihyperglycaemic drugs, such as sodium glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists.[25] The first of the modern CVOT trials to show superiority over placebo was the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG) study; this reported not only CV safety, but also a 38% reduction in CV death, a 35% reduction in hospitalisation for heart failure, and a 32% reduction in the risk of death from any cause.[26] Other trials such as the CANagliflozin cardiovascular Assessment Study (CANVAS), in patients with T2DM and high CV risk treated with canagliflozin, demonstrated significantly lower risk of the composite outcome of major adverse CV events (MACE; CV death, nonfatal MI, or nonfatal stroke; HR: 0.86; 95% CI: 0.75–0.97; p<0.001), hospitalisation for heart failure, and improved renal outcomes. Further trials assessing these and other SGLT2 inhibitors have also shown CV and renal benefits, including a reduction in the risk of end-stage renal disease or renal death.[27-33] Studies assessing GLP-1 receptor agonists, liraglutide, albiglutide, dulaglutide, and semaglutide have found significant reductions in composite major cardiovascular events (CV death, non-fatal MI, or stroke), and/or albuminuria.[34-37]

A positive outcome from CVOT in terms of the MDT approach was that they included assessments of CV safety with strict glucose control and the incorporation of the CVD standard of care. This was an important step in the management of patients with T2DM and an improvement from earlier trials that were undertaken before blood pressure-reducing drugs, statins, anti-platelet medications, and an active approach to coronary revascularisation were part of routine care for patients with T2DM.[38] The high rates of chronic kidney disease (CKD) in patients with T2DM and the renal benefits associated with newer glucose-lowering therapies mean that nephrologists, in addition to cardiologists and endocrinologists, were increasingly included as part of the MDT.

MULTIDISCIPLINARY TEAM STRUCTURE, PRINCIPLES, AND CONCEPTS

The MDT approach should be focussed on integrated management with multiple treatment goals including glucose, blood pressure and lipid control, life style management, regular appointments, and screening for the prevention of T2DM morbidities.[39,40] For those patients who are considered to have less complex clinical needs, integrated care with MDT should be anchored in the primary care setting.[41,42] This structure has led to cost savings and a reduction of disease burden for healthcare systems related to fewer hospitalisations and vascular events.[43] Whilst primary care physicians (PCP) are the first point of contact and a source of continuous comprehensive care, they do not work in isolation but involve other specialities, such as podiatrists, nurses, and dietitians.[39]

Patients with complex needs and high rates of morbidities are referred to endocrinologists and are typically seen in hospital outpatient settings.[41] Optimal diabetes interdisciplinary care of these patients is complex and the number of HCP involved rises due to the need to prevent and

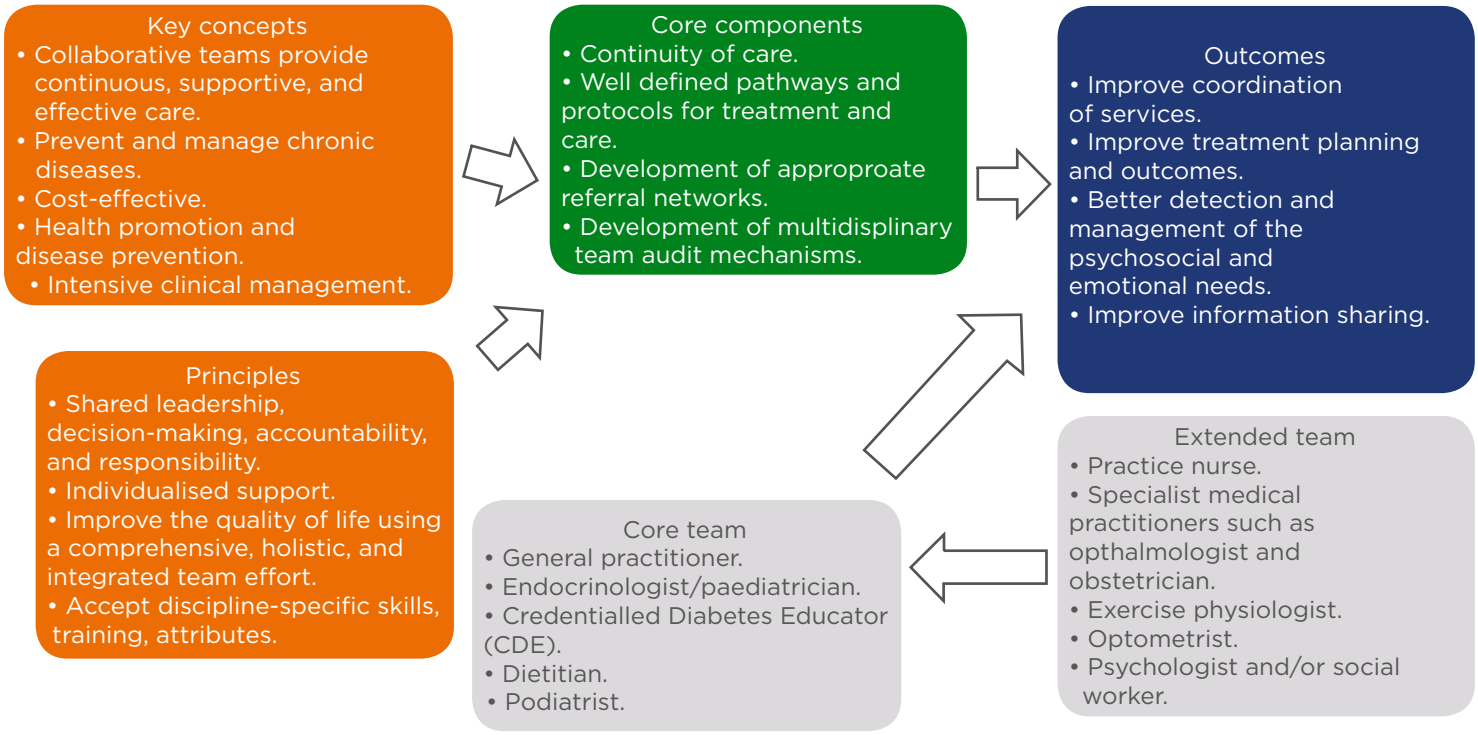

Figure 1: Key concepts, principles, members and pathways of typical multidisciplinary teams involved in the care of patients with Type 2 diabetes mellitus.

Adapted from The National Institute of Diabetes and Digestive and Kidney Diseases Health Information Center (NIDDK)[42] and Australian Diabetes Educators Association (ADEA).[46]

manage multi-morbidities such as CKD and heart failure. The hospital-based team may include ophthalmologists, cardiologists, nephrologists, a diabetic foot team, and the PCP.[39,40,44,45]

The principles, key concepts, and core components for multidisciplinary care are displayed in Figure 1. All the MDT team members need to be actively involved to ensure an effective approach to the provision of care. Key concepts and principles include the importance of a team approach with shared responsibility and decision making, in addition to a respect for all team members and the MDT should also be mindful to the needs of the patient.[42,46] The MDT approach must feature a continuity of care with well-defined processes and protocols that include appropriate referral pathways.

Further to the MDT, optimal diabetes management programmes also include different components such as registration systems,[39] audit and feedback, clinician reminders, patient and HCP education, and IT systems.

THE ROLE OF THE PATIENT IN MULTIDISCIPLINARY TEAMS

The role of the patient in the MDT must not be overlooked. Studies have shown that patients who do not participate in the MDT care approach are less likely to reach their treatment targets. A considerable proportion of diabetes management is undertaken by the patient, such as lifestyle modifications and treatment adherence. HCP have limited ability to control how patients manage their disease outside of visits. It is important that the MDT must consider the numerous variables that are outside their control but impact disease management and educate the patient accordingly to empower them to take an active role in their care. An investigation assessing patient (N=53) perspectives of MDT care reported barriers such as lack of co-ordination among many HCP and the large number of appointments they needed to attend with many different HCP.[47] Yet, patients were strongly in favour of the team-based approach

Figure 2: Examples of local initiatives to deliver models of integrated diabetes care in several UK locations.

GP: general practitioner.

Adapted from Diabetes UK.[48]

and stated that highly interdisciplinary teams (IDT) were desirable. Patients did not believe that diverse teams would be associated with fragmentation but appreciated having a single point of contact for their care. In conclusion, patients felt that appropriate management of T2DM was too complex for a single HCP, but co-located teams were more convenient.[47]

EXAMPLE OF NHS ENGLAND REAL-WORLD EXPERIENCE OF MULTIDISCIPLINARY TEAMS IN PRACTICE

In 2009, Portsmouth Hospitals NHS Trust identified that a lack of co-ordinated and communicated plans across HCP was one of the main barriers to improving the care of patients with T2DM. They developed a new model of care that transitioned most patients who were considered less complex out of specialist care. However, some patients still required care under the auspices of a specialist setting.[43,48] Patients within one of the following six categories in the 'Super Six Model' remained within specialist care:[41,43,48]

- Patients on insulin pumps.
- Women with antenatal diabetes.
- Those requiring diabetic foot care.
- Patients with low estimated glomerular filtration rate (eGFR) or who require dialysis.
- Inpatients with T2DM.
- Patients with Type 1 diabetes mellitus (individuals with poor control or young people).

Yet, collaboration between PCP and specialists still occurred and these HCP maintain regular communication in addition to 6 or 12-monthly specialist consultations.[43,48]

This model was further expanded in Leicester, UK, whereby clinics were segregated according to different tiers and included patient education activities.[48] The new system provided integrated care with supplementary services. Different tiers enabled PCP to manage increasingly complex patients and was proven to be cost-effective by reducing the healthcare resource burden associated with hospitalisation.[48] Further similar initiatives have been implemented in Derby, Wolverhampton, and north-west London. Outlines of these models, pathways, and enablers are shown in Figure 2. All of the models rely on enablers that include:[48]

- A single central IT system used by both primary care providers and the specialist teams to enable rapid communication, accurate recording keeping, information dissemination, and appropriate referrals.
- Aligned finances and responsibilities which may include single budgets or trusts to remove boundaries, incentivised payments for primary care staff training.
- Engagement, networks, and leadership with MDT groups for particular workstreams or regular meetings to provide opportunities to discuss and identify efficiencies in the collaboration.
- Clinical governance, including integrated management boards, operational groups, monthly review boards with accountability and responsibilities to drive success, review outcomes, refine pathways, and ensure high quality service delivery.

OUTCOMES AND MULTIDISCIPLINARY TEAMS

MDT must be associated with improved outcomes for patients. Assessment of feasibility and effectiveness of IDT specifically has been assessed in a Belgian study that determined if the implementation of an IDT was feasible in a healthcare setting with historically low rates of shared care, and if patients who made use of an IDT would have improved outcomes over an 18-month period.[49] A two-arm cluster randomised trial found that the use of the IDT was significantly associated with improvements in HbA1c (p=0.00001) and LDL-cholesterol (p=0.00039), an increase in the use of statins (OR: 1.902; p=0.04308), and anti-platelet therapy (p=0.00544).[49] IDT also significantly increased the number of clinical targets reached (p=0.005). The results of this trial demonstrated that the use of IDT teams in primary care that are actively guided and supported by a specialist team are associated with important improvements in clinical outcomes.

A European-wide systematic literature review and meta-analysis of randomised controlled trials evaluated the effectiveness chronic care

programmes for T2DM from January 2000 to July 2015.[50] These programmes were characterised by integrative care and a multicomponent frame work for enhancing healthcare delivery compared with usual diabetes care. Of the seven trials, four evaluated the impact of MDT in addition to other factors such as the impact of guideline-based care, patient education, shared decision making, and annual screening in patients with either prevalent diabetes or screen-detected diabetes.[50] Two of the trials reported no significant differences in HbA1c levels between intervention groups and control groups after 1 year. One study that assessed combined interventions from Denmark, the Netherlands, Cambridge, and Leicester over a 5-year period found significant improvements in HbA1c in the intervention group versus the control group (-0.08%; 95% CI: -0.14 to -0.02 versus -0.9 mmol/mol; 95% CI: -1.5 to -0.2). Of all the trials that assessed MDT, only the pooled 5-year data from the Addition trials and a Dutch study reported significant improvements in total cholesterol concentrations in intervention patients compared with control patients (Addition pooled data: -0.27 mmol/L; 95% CI: -0.34 to -0.2 and Dutch trial mean difference -0.2 mmol/L; 95% CI: -0.3 to -0.1). Of the four studies that included MDT as part of their intervention groups, three reported higher reductions in patients BMI compared with control patients.[50]

The processes of care were evaluated by three studies and all of which reported that those receiving MDT-based care reached their treatment targets defined as HbA1c ≤7% (53 mmol/mol), systolic blood pressure ≤140 mm Hg, total cholesterol ≤4.5 mmol/L, and LDL-cholesterol ≤2.5 mmol/L.[50] Process quality measures at 1 year, defined as the proportion of patients receiving guideline-adherent foot examinations, eye examinations, and HbA1c examinations were also higher in the MDT groups compared with the control group. The meta-analysis reported improved patient outcomes in Europe for management approaches that included MDT in addition to other interventions.[50]

Other systematic global or USA-specific systematic reviews[51-55] that assessed an integrated approach to the care of patients with T2DM compared with the usual diabetes care have found improvements in HbA1c, blood pressure, and blood lipid outcomes. Improvements were also reported for increased screening rates for retinopathy, peripheral polyneuropathy, and foot lesions, measuring proteinuria and rate of lipid HbA1c monitoring.[53,56,57] Furthermore, one study also reported an economic benefit for integrated care.[58] However, two other systematic literature reviews reported only small improvements on patient outcomes or process of care.[59,60]

Despite the evidence that suggests MDT improves patient outcomes and is cost effective, there is some doubt if the processes used in studies can be effectively replicated in 'real-world' situations due to economic pressures on primary care and the large number of patients with T2DM.[39,50,56] Furthermore, most studies assessing MDT approaches have limited study periods compared with the time that MDT need to be in place in real-world clinical practice. This hypothesis was tested in a study that assessed the quality of care provided by the Health and Safety Executive Midlands Diabetes, Structured Care Programme that was established in 1997 in Ireland.[39] The study found significant improvements in data recording, in the proportion of patients achieving blood pressure and lipid targets over a 16-year period. However, foot assessment and annual review attendance declined in 2016 and only 29% of the patients had all eight of the National Institute for Health and Care Excellence care processes recorded.[39]

FUTURE OF TYPE 2 DIABETES MELLITUS AND MULTIDISCIPLINARY TEAMS

Physicians and HCP involved in the care of patients with T2DM face several challenges in the future including the management of other comorbidities such as non-alcoholic fatty liver disease (NAFLD), the implementation of new treatment options, and individualised care.

In addition to CVD and renal risk, patients with T2DM have increased susceptibility of NAFLD and higher progression rates to cirrhosis, hepatocellular carcinoma, and death compared with patients with NAFLD without T2DM.[61-63] Given the synergistic relationship between NAFLD or non-alcoholic steatohepatitis and T2DM, it is possible to conceive that hepatologists may

need to be involved in the MDT care of patients, especially when pharmacological therapies for non-alcoholic steatohepatitis become available.

The evolving treatment landscape, which may, in the future, incorporate precision medicine, using targeted individualised therapy, should be part of the risk and outcome-centred care approach meaning that the place of MDT teams will continue to be pivotal to the success of any future management approaches.

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Knowledge, Practices, and Risk of Diabetic Foot Syndrome Among Diabetic Patients in a Tertiary Care Hospital in Bengaluru, India

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Abstract

Diabetic foot syndrome is common in uncontrolled diabetes and is a constellation of symptoms and signs that include neuropathy, infection, and ischaemia. It has become a global concern and a frequent cause of hospitalisation among diabetics. In this study, the authors' objective was to assess the knowledge, practices, and risk of diabetic foot syndrome among diabetic patients seeking outpatient care at a tertiary hospital in Bengaluru, India. A cross-sectional study involving 198 patients with diabetes aged ≥18 years was conducted using a structured questionnaire, followed by examination using Inlow's 60-second diabetic foot screen tool. The results were based on the International Working Group on the Diabetic Foot (IWGDF) risk classification system. The knowledge regarding diabetic foot syndrome was inadequate for fungal infections (23.5%), shoe bites (26.5%), and changes in foot colour and temperature. Footcare practices were satisfactory, with the exception of wearing footwear indoors (25.0%) and applying moisturiser to feet (19.0%). Lack of education, diabetic neuropathy, peripheral vascular disease, history of foot ulcer, and a lack of knowledge regarding dry skin, special footwear, and inappropriate footwear were important risk factors. The researchers concluded that the knowledge level of the subjects was relatively poor. Foot practices, such as inspecting and washing feet every day, were followed by the majority of subjects. Lack of education, complications such as neuropathy, peripheral vascular disease, dry skin, and lack of information obtained on foot care practices were significantly associated with diabetic foot syndrome.

INTRODUCTION

India has been called the 'diabetic capital of the world' because of the predominant Westernisation of its inhabitants, which includes people of different age groups, from adolescents to the elderly, in all sections of society. According to the World Health Organization (WHO), the global prevalence of diabetes in the 2014 among individuals aged >18 was 422 million.[1] In a study done in 2001 in India to assess the prevalence of diabetes and impaired glucose tolerance in six major cities, covering all the regions of the country, it was found that the age-standardised prevalence of diabetes and impaired glucose tolerance were 12.1% and 14.0%, respectively, with no gender difference.[2] The study also showed that diabetes and impaired glucose tolerance had an increasing trend with age.[2] The International

Diabetes Federation (IDF), India, states that approximately 37.2% of the Indian urban population has diabetes.[3]

Some of the long-term complications of diabetes include retinopathy, nephropathy, and peripheral neuropathy, which are linked to the development of foot ulcers and amputations, Charcot joints, and autonomic neuropathy. Diabetes also contributes to lipid metabolism dysfunction, as well as hypertension.[4]

A common, but most often undetected, complication of diabetes is diabetic foot syndrome (ICD 20 code: E11.621). Diabetic foot syndrome can be defined as a constellation of signs and symptoms in which neuropathy, ischaemia, and infection are the main pathological mechanisms.[5] It is often associated with minor trauma, foot deformity, and peripheral vascular disease.[6]

Diabetic foot syndrome is the most common cause of hospitalisation in diabetic patients[7] and is a common cause of lower limb amputation.[8] According to a study carried out involving diabetic foot ulcer patients in north India, the overall amputation rate was 28.4%.[9]

The symptoms suggestive of neuropathy are pain, paraesthesia, and sensory loss.[10] The major risk factors for diabetic foot include previous foot ulcers, improper footwear, old age, tobacco use, chronic kidney disease, and low socioeconomic status. Increased risk for diabetes and its various complications are primarily associated with age, ethnicity, family history of diabetes, smoking, obesity, and physical inactivity.[11]

The global prevalence of diabetic foot ulcer is approximately 6.3% and is higher in males compared to females.[12] In America, 5.0% of diabetics develop foot ulcers and 1.0% of them require amputation, thereby indicating that diabetic foot syndrome is the major cause of nontraumatic lower limb amputation.[13] In a study completed in north India, 14.3% of diabetic patients had foot ulcers.[14] In a similar study from south India, recurrence of foot infections was as prevalent as 52.0% in diabetic patients.[15]

The knowledge and practices among the diabetics regarding foot care is poor. This was substantiated in a study completed in a tertiary medical centre in Malaysia.[16] Some of the factors associated with poor knowledge were male sex, low education, and shorter duration of diabetes.[17] Illiteracy also invoked significant challenges to diabetic attentiveness and imposed increased foot complications.[18] A perfect correlation exists between knowledge and practice regarding foot care among diabetic patients.[19] Risk factor recognition is vital in helping clinicians predict, and hopefully prevent, the occurrence of diabetic foot ulcers.

OBJECTIVES

- To assess the knowledge and practices regarding diabetic foot syndrome among diabetic patients attending the outpatient department of a tertiary care hospital in Bengaluru.
- To assess the risk of diabetic foot syndrome among the study population.
- To study the factors associated with the risk of diabetic foot syndrome in the study population.

METHODOLOGY

The authors conducted a cross-sectional study in a tertiary care hospital in Bengaluru from January 2017 to June 2017. The study population included all outpatients with diabetes seeking care at the departments of medicine and endocrinology of the selected hospital who were aged ≥18 years. Patients with gestational diabetes mellitus and Type 1 diabetes mellitus were excluded. Ethics approval was obtained from the Institutional Ethics Committee, St. John's Medical College, Bengaluru, India, [IEC Ref No 181/2016]. The departments of medicine and endocrinology at St John's Medical College Hospital cater to a daily outpatient load of approximately 250 patients, of whom approximately half have Type 2 diabetes mellitus. The study population was selected purposively from the patients with Type 2 diabetes mellitus attending the outpatient departments in medicine and endocrinology.

The authors estimated the sample size, basing it on a study published in the Journal of Diabetic Foot Complication in north India, which reported the prevalence of diabetic foot syndrome to be 14.3%.[14] Using this as the expected prevalence, and at an absolute precision of 5% and at 95%

confidence level, the authors calculated the sample size for the study to be 188 diabetics. There were not any nonresponders and therefore the authors added an additional 10 participants to the study participant number, making the final sample size 198 participants. After obtaining informed consent, the patients enrolled into the study were administered a structured interview schedule. The interview schedule included the following sections:

- **Section 1**: Sociodemographic details of the study population.
- **Section 2**: Details about diabetes.
- **Section 3**: Knowledge about diabetic foot syndrome.
- **Section 4**: Practices related to diabetic foot syndrome.

The survey was conducted by a face-to-face interview which was administered by three interviewees. The interviewees for this study were medical students who were also the investigators involved in the designing of the study and the data collection form. All the participants who were approached for the study consented to participate. The forms were checked for completeness by the interviewers themselves.

Following this, all the recruited patients were screened for risk of diabetic foot syndrome using Inlow's 60-second diabetic foot screen tool.[20] This tool was developed by the Canadian Association of Wound Care (CAWC). The tool consists of 12 elements to assess the risk of developing diabetic foot syndrome. Four elements (skin, nails, deformity, and footwear) are to be scored by inspection, three elements (temperature-hot, temperature-cold, and range of motion of the big toe) by touching, and five elements (sensation [monofilament testing, sensation] four questions, pedal pulses, dependent rubor, and erythema) to be assessed through questioning and testing. Each of these elements are scored separately for the right and left foot based on the guidelines given in the tool and the total score for each foot is calculated. Based on the value for each category, care recommendations are provided, specific to the patient's needs. The sum of the scores for each foot will dictate the recommended follow-up. The tool has been validated and requires only a 10-g monofilament, as well as good clinical knowledge and assessment skills. Participants who scored <6 were categorised as low risk, those with scores of 7–12 were categorised as moderate risk, and those with a score of ≥13 were categorised as high risk.

This tool classifies risk of diabetic foot into six categories based on the International Working Group on the Diabetic Foot (IWGDF) risk classification system (Modified1). The six categories are as follows:

- 0: normal - no neuropathy.
- 1: loss of protective sensation.
- 2a: loss of protective sensation and deformity.
- 2b: peripheral arterial disease
- 3a: previous history of ulceration.
- 3b: previous history of amputation.

The researchers were trained on the use of this tool prior to the start of the study.

Data were entered into Microsoft-Excel and analysed using SPSS. The sociodemographic profile of the study population and details of diabetes have been outlined using descriptive statistics such as proportions and means. The risk of diabetic foot among the diabetics, knowledge pattern, and practices were computed using proportions.

The factors associated with diabetic foot syndrome were identified using the Chi squared test for association or Fischer's exact probability test as applicable. All the factors that showed a significant association with the risk of developing diabetic foot on bivariate analysis were put into a multiple logistical regression model. Risk of developing diabetic foot (moderate or high) was considered to be the outcome variable and the variables showing significant association as co-variants. The odds ratios and the 95% confidence intervals (CI) were calculated. A p value <0.05 was considered as significant for all analysis.

RESULTS

Among the 198 diabetic subjects interviewed, the mean age of the people was 56.08 years with a standard deviation of 10.15 years, 52.0% were males, 60.5% originated from an urban background, and the majority of the patients (71.5%) were Hindus. The majority of the males were graduates (32%), followed by secondary school graduates (27%), and among the females, the majority were uneducated (32%), followed

by secondary school graduates (26%). The most common occupation among males was within business (32%) while most of the females were housewives (81%). Out of the 198 participants, 102 were employed and their mean monthly family income was ₹21,332 (£245.45). Around one third of the total population belonged to upper socioeconomic status according to BG Prasad scale.[21]

The mean duration of diabetes was 8.6 years, with a standard deviation of 8.12 years. The majority of the study subjects (91%) had altered their diet habits and were on oral hypoglycaemic agents. Only 24.4% of the patients were on insulin, and 83.4% of the patients used to take their medications regularly. Based on the normal cut-offs of glucometer random blood sugar, fasting blood sugar, post-prandial blood sugar, and glycated haemoglobin, only 11.0% of the patients had their sugar values under control.

The most common complication was neuropathy, which occurred in 43.0% of the subjects, followed by retinopathy, observed in 39.8%. Roughly 2.5% of the subjects had a history of amputations.

Approximately 53.2% of the patients were hypertensive, of whom 57.0% were females; hypercholesterolaemia was observed in 29.0% of the patients. Tobacco had been consumed by 26.0% of the subjects. Among them, cigarette smoking was the predominant type, found in 12.5% of the patients. Alcohol had been consumed by 22.5%.

Among the 198 patients, 13% had previous history of trauma to their feet, and approximately 63% of the subjects had heaviness, tightness, pains, or cramps in their feet or legs.

Table 1 shows the knowledge and practices around foot practices among diabetic patients. The authors found that knowledge was poor regarding risk factors such as fungal infections (23.5%) and shoe bites (26.5%). Interestingly, only 12% of the patients knew about the importance of changes in colour and as few as 9% knew about that of change in temperature. Only one third of the patients knew that uncontrolled diabetes could lead to reduced blood flow to feet, reduced sensations in feet, and foot ulcers; furthermore, only half of the patients knew that calluses were a risk factor for diabetic foot ulcer formation. Similarly, knowledge regarding special diabetic footwear was present in only half of the patients. Two-thirds of the patients knew that cracked feet and trauma were risk factors. The second section of Table 1 shows practices among diabetic patients regarding foot care. This study showed that the majority of the subjects had good practices, especially for washing their feet every day (97.0%) and wearing footwear outdoors (98.5%). For practices such as applying moisturiser (19.0%) and wearing footwear indoors (25.5%), they fared poorly. Roughly 45% of the patients dried their feet in between their toes, which is a significant finding because the presence of moisture is an important predisposing factor for developing fungal infections.

Table 1: Knowledge and practices about diabetic foot syndrome in the study sample.

Knowledge	Total (198)
Risk of developing foot complications among diabetics	107 (53.5%)
Uncontrolled diabetes causes reduced blood flow to leg	63 (31.5%)
Uncontrolled diabetes can lead to lack of sensation in foot	78 (39.0%)
Uncontrolled diabetes can lead to foot ulcers	70 (35.0%)
Smoking increases the risk of foot ulcers	41 (20.5%)
Diabetics should wear footwear indoors	88 (44.0%)
Special footwear is available for diabetics	103 (51.5%)
Inspect for cracked feet	135 (67.5%)
Inspect for calluses	107 (53.5%)
Inspect for fungal infections	47 (23.5%)

Table 1 continued.

Inspect for shoe bites	53 (26.5%)
Inspect for change in colour	24 (12.0%)
Inspect for change in temperature	19 (9.5%)
Inspect for ingrown toenail	43 (21.5%)
Inspect for foreign objects	73 (36.5%)
Cutting nails straight through is appropriate	97 (48.5%)
Inspect for injuries	132 (66.0%)

Practices	
Wash feet every day	194 (97.0%)
Reach bottom of feet	184 (92.0%)
Dry well between toes	89 (44.5%)
Moisturising cream	38 (19.0%)
Wear footwear indoors	51 (25.5%)
Wear footwear outdoors	197 (98.5%)
Foreign object inspection	124 (62.0%)
Heating pad application.	59 (29.5%)

Additionally, 61% of patients checked their feet for the presence of foreign bodies.

Table 2 categorises the 198 patients into three groups based on a foot examination. The table depicts factors that show a significant association with the risk of developing diabetic foot, on bivariate analysis, with respect to the various categories. The factors related to diabetic foot were a lack of formal education, diabetic neuropathy, nephropathy, peripheral vascular disease, hyperlipidaemia, smoking, history of trauma, and foot ulcers. Among the subjects with moderate risk of developing diabetic foot, 68.9% were not educated. Of the patients who had a moderate-to-high risk of developing foot ulcers, diabetic neuropathy (77.9%), nephropathy (77.4%), peripheral vascular disease (PVD) (89.0%), and smoking (73.6%) were related risk factors.

History of foot ulcers was associated with increased risk (92%) of developing diabetic foot, while history of foot trauma increased the risk by 72%. Lack of knowledge regarding diabetic complications was also a contributing factor.

Table 3 shows the independent factors associated with development of diabetic foot ulcers. All the factors that showed a significant association with the risk of developing diabetic foot on bivariate analysis (Table 2) were put into a multiple logistical regression model and the authors calculated the odds ratios (OR) and the 95% CI.

Factors independently associated with a risk of diabetic foot were: lack of education (OR: 3.8; 95% CI: 1.2–11.6), diabetic neuropathy (OR: 5.6; 95% CI: 2.3–13.6), PVD (OR: 5.0; 95% CI: 1.6–14.8), history of foot ulcers (OR: 8.7; 95% CI: 1.3–59.4), lack of knowledge about application of moisturiser (OR: 2.72; 95% CI: 1.2–6.3), lack of knowledge about special footwear (OR: 2.8; 95% CI: 1.2–6.4), and practices of wearing uncovered shoes (OR: 3.6; 95% CI: 1.4–8.9).

DISCUSSION

The study shows that knowledge about diabetic foot complications was poor among patients with Type 2 diabetes mellitus seeking outpatient care in a tertiary care hospital.

Table 2: Factors associated with risk of developing diabetic foot.

Risk factor		Risk of diabetic foot Low (<6) N=78 n (%)	Risk of diabetic foot Moderate (7–12) N=103 n (%)	Risk of diabetic foot High (13–19) N=17 n (%)	p-value
Information that uncontrolled sugars caused foot problems	Yes	32 (52.5)	23 (37.7)	6 (9.9)	0.02
	No	45 (33.1)	80 (58.8)	11 (8.1)	
Education	No education	7 (15.6)	31 (68.9)	7 (15.6)	0.001
	Primary schooling and above	71 (46.4)	72 (47.1)	10 (6.5)	
Diabetic neuropathy	Yes	19 (22.1)	56 (65.1)	11 (12.8)	0.001
	No	59 (52.7)	47 (42.0)	6 (5.4)	
Diabetic nephropathy	Yes	7 (22.6)	17 (54.8)	7 (22.6)	0.004
	No	71 (42.5)	86 (51.5)	10 (6.0)	
Peripheral vascular disease	Yes	7 (10.9)	48 (75.0)	9 (14.1)	0.001
	No	71 (53.0)	55 (41.0)	8 (6.0)	
Hyperlipidaemia	Yes	25 (42.4)	34 (57.6)	0 (0.0)	0.019
	No	53 (38.1)	69 (49.6)	17 (12.2)	
Smoking	Yes	14 (26.4)	29 (54.7)	10 (18.9)	0.002
	No	64 (44.1)	74 (51.0)	7 (4.8)	
History of trauma	Yes	10 (27.0)	19 (51.4)	8 (21.6)	0.004
	No	68 (42.2)	84 (52.2)	9 (5.6)	
History of foot ulcer	Yes	2 (7.7)	16 (61.5)	8 (30.8)	0.001
	No	76 (44.2)	87 (50.6)	9 (5.2)	
Knowledge about wearing footwear indoors	Yes	46 (54.8)	30 (35.7)	8 (9.5)	0.001
	No	32 (28.1)	73 (64.0)	9 (7.9)	
Knowledge about dry skin	Yes	48 (56.5)	30 (35.3)	7 (8.2)	0.001
	No	30 (26.5)	73 (64.6)	10 (8.8)	
Knowledge about special footwear	Yes	49 (47.6)	47 (45.6)	7 (6.8)	0.045
	No	29 (30.5)	56 (58.9)	10 (10.5)	
Wear covered shoes	Yes	50 (59.5)	26 (31.0)	8 (9.5)	0.001
	No	28 (24.6)	77 (67.5)	9 (7.9)	

Table 3: Independent risk factors associated with diabetic foot.

Risk factor		Risk of diabetic foot Low (<6) N=78 n (%)	Risk of diabetic foot Moderate/high (7–19) N=120 n (%)	Adjusted OR [95% CI]	p-value
Education	No education	7 (15.6)	38 (84.4)	3.8 1.2–11.6	0.02
	Primary schooling and above	71 (46.4)	82 (53.6)		
Diabetic neuropathy	Yes	19 (22.1)	67 (77.9)	5.6 2.3–13.6	0.01
	No	59 (52.7)	53 (47.3)		
Peripheral vascular disease	Yes	7 (10.9)	57 (89.1)	5.0 1.6–14.8	0.04
	No	71 (53.0)	63 (47.0)		
History of foot ulcer	Yes	2 (7.7)	24 (92.3)	8.7 1.3–59.4	0.03
	No	76 (44.2)	96 (55.8)		
Knowledge about dry skin	Yes	48 (56.5)	37 (43.5)	2.7 1.2–6.3	0.02
	No	30 (26.5)	83 (73.5)		
Knowledge about special footwear	Yes	49 (47.6)	54 (52.4)	2.8 1.2–6.4	0.02
	No	29 (30.5)	66 (69.5)		
Wearing of covered shoes	Yes	50 (59.5)	34 (40.5)	3.6 1.4–8.9	0.007

A lack of formal education and lower socioeconomic status were associated with poor knowledge in the participants.

The first step towards controlling this problem is awareness of risk factors for diabetic foot complications and the measures that should be taken to prevent them. Awareness levels were similar for men and women. Viswanathan et al.[15] reported that poor knowledge and practices were slightly more common in women (78.5%) than in men (62.5%).

Approximately 79.5% of the subjects believe that smoking does not carry the risk of developing foot ulcers. In a similar study conducted by Desalu et al.,[22] smoking was not considered to be a risk factor for foot ulcers by 75% of the patients, attributable to a lack of knowledge surrounding possible side effects of tobacco. This finding emphasises the need for health education campaigns towards explaining the ill effects of tobacco. Just 51.5% of the subjects were aware of the availability of special footwear for diabetics. Based on a study completed in south India, 19.1% of the diabetic patients had evidences of neuropathy.[22]

Despite poor awareness levels regarding diabetic foot syndrome, the study found that foot care practices were adequate with majority of the participants washing feet every day and wearing footwear outdoors. Only 25.5% of the study subjects wore footwear indoors. This may be attributable to religious sentiments in Indian settings in which footwear is typically left outside the house. Specific attention towards foot care is not shown in many of the cases, such as drying well in the web spaces, which can be the factor

predisposing the feet to fungal infections, further increasing the risk of developing ulcers. Practices regarding diabetic foot care range from poor to adequate in studies from different parts of India. This could be because of differences in availability of healthcare and local cultural practices.[23-25]

According to a similar study to the present one by Al-Rubeaan,[26] PVD (OR 14.47; 95% CI:8.99–23.31), neuropathy (OR 12.06; 95% CI: 10.54–13.80), and nephropathy (OR 2.88; 95% CI: 2.43–3.40) were independent risk factors. A history of foot ulcers was also an independent risk factor (OR 8.7; 95% CI: 1.3–59.4). In a similar study by Abbott et al.[27] a history of foot ulcers showed a similar pattern (OR 3.05; 95% CI: 2.16–4.31). Furthermore, that a lack of knowledge regarding the use of special footwear was an independent risk factor for development of diabetic foot (OR 2.8; 95% CI: 1.2–6.4). However, in a study by Bus et al.,[28] on the effect of custom-made footwear on foot ulcer recurrence in diabetes, adherence to the use of footwear was a more important factor than the type of footwear.

This study was completed in an outpatient setting and provides a snapshot of the awareness and practices among patients with Type 2 diabetes mellitus. A limited sample of patients from a busy hospital were studied; they were selected purposively from those attending the outpatient department. The findings of this study should be viewed with consideration of the above limitations.

CONCLUSION

In the study, the most common complication among patients was neuropathy. The knowledge level among the subjects was relatively poor. Only around half of the people were aware of the complications associated with uncontrolled diabetes such as decreased sensations in the foot and foot ulcers. Most foot care practices were satisfactory, with the exception of wearing footwear indoors and applying moisturiser to the feet. Risk factors for diabetic foot were studied. A lack of education, diabetic neuropathy, peripheral vascular disease, history of foot ulcers, lack of knowledge regarding dry skin, special footwear, and inappropriate footwear were independent risk factors. This calls for increasing awareness among the patients with Type 2 diabetes mellitus on foot care practices. In tertiary care settings, special foot counters can be established where assessment of risk and advice on foot care is provided. These counters can be manned by interns; alternatively, nurse education students can be trained to man this counter. In primary and secondary care settings, the treating physicians should perform a foot examination at every diabetes consultation and offer advice on foot care to the patient. This should be included as part of standard practice. Further research is needed to study the long-term reduction in diabetic foot complications resultant of different models of care in diverse settings across India.

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Evaluation of The Relationship Between Glycaemic Regulation Parameters and Neutrophil-to-Lymphocyte Ratio in Type 2 Diabetic Patients

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Abstract

Background: The neutrophil-to-lymphocyte ratio (NLR) is a simple and inexpensive examination that is considered to show inflammation. In this study, which included a control group, the authors aimed to investigate if there was a relationship between glycaemic regulation parameters and NLR in patients with Type 2 diabetes mellitus.

Material and Methods: A total of 278 Type 2 diabetic patients were included in the study. An additional total of 148 healthy people were also included as a control group. NLR was calculated by dividing the absolute neutrophil number by the absolute lymphocyte number. The patients were divided into two groups: the good glycaemic control group (HbA1c ≤7.5%) and the poor glycaemic control group (HbA1c >7.5%). NLR was compared between the diabetic groups. In addition, NLR was compared with diabetic patients and control group.

Results: The NLR was statistically and significantly higher in the poor glycaemic control group compared to the good glycaemic control group (2.48 [1.97–2.60] to 2.07 [1.72–2.40], respectively; p=0.020). In addition, NLR was significantly higher in the patients than in the control group (2.30 [2.04–2.49] to 2.01 [1.85–2.18], respectively; p=0.002).

Conclusion: According to the authors' knowledge, increased NLR may be associated with poor glycaemic control in Type 2 diabetic patients. NLR may be useful used as an easily measurable, noninvasive, available, and cost-effective parameter for the follow-up of diabetic patients.

INTRODUCTION

Diabetes mellitus (DM) is an important public health problem with a gradually increasing prevalence in the authors' country and worldwide. In Turkey, the prevalence of DM was 7.2% in the TURDEP 1 study conducted in 1998.[1] This ratio increased to 13.7% by showing an increment

of 90% after 12 years in 2010.[1,2] The National Cholesterol Education Program-Adult Treatment Panel 3 (NCEP-ATP3) recommends that DM should be accepted as a coronary artery disease equivalent because of its complications and close association with cardiovascular diseases.[3] In recent years, studies have supported the thesis that even prediabetes might be a coronary artery equivalent.[4]

The association between DM and atherosclerosis has been demonstrated clearly in many studies. It is also known that many complications of DM occur in the atherosclerotic background. Systemic inflammation is a risk factor for atherosclerosis and can be evaluated with many different biomarkers, including high-sensitive C-reactive protein and IL-6, TNF-α, fibrinogen, p-selectin, and serum amyloid A.[5-8]

The neutrophil-to-lymphocyte ratio (NLR) has become a popular inflammation marker recently, and studies have supported that a high NLR negatively affects the frequency and prognosis of coronary artery disease.[9] In a study performed by Sonmez et al.,[10] a close relation was found between high NLR and presence and complexity of coronary artery disease. The relation between DM and NLR has also become a current issue of investigation recently.

In this study, which had a control group, the authors aimed to investigate the relationship between glycaemic regulation parameters and NLR in patients with Type 2 DM (T2DM) and determine how NLR was affected by the changes in HbA1c.

MATERIALS AND METHODS

Patient Selection

In the study, 278 T2DM patients who were being followed up in the authors' outpatient clinic and consecutively presented for follow-up visits between March 1 and June 30, 2017, were included. A total of 148 people admitted to the health committee for a certificate of health were included as the control group. Patients with T1DM, aged <18 years and >65 years, who were pregnant, had evidence of active infection, history of chronic disease other than DM, respiratory failure, coronary artery disease, or cerebrovascular disease were not included in the study. The patients were divided into two groups: the good glycaemic control group (HbA1c ≤7.5%) and the poor glycaemic control group (HbA1c >7.5%). HbA1c, glucose, and haemogram values of some patients after 3 months could be reached and the effect of glycaemic regulation parameters on NLR was investigated in these patients.

Laboratory Tests

Blood samples of the patients were obtained in the morning between 8:00am and 10:00am after a fasting period of at least 8 hours. The blood samples of all patients obtained for complete blood count, fasting plasma glucose, and HbA1c were studied.

For complete blood count, 2 mL of blood was placed in EDTA K3 tubes and the samples were studied for 1 hour using a flow cytometric method by Sysmex XT-2000i (Roche). NLR of the patients was calculated by dividing the absolute neutrophil number by the absolute lymphocyte number. HbA1c levels were measured using the Boronat affinity method by Trinity Biotech Premier HB9210 device (Trinity Biotech plc). Fasting plasma glucose was measured using hexokinase method (enzymatic ultraviolet method) by Beckman Coulter Olympus AU 2700 device (Beckman Coulter®).

Statistical Method

Chi-square test was used in the comparison of the categorical data of the two groups divided by HbA1c levels. Compliance with the normal distribution of numerical variables were controlled by Kolmogorov–Smirnov test. The Mann–Whitney U test was used to compare NLR, glucose, and HbA1c. Wilcoxon signed-ranks test was used to compare the NLR of the patients whose HbA1c, glucose, and haemogram values 3 months after treatment modification could be reached. Statistical evaluation was performed by SPSS 17.0 program (IBM).

RESULTS

A total of 278 patients (female n=180, 64.7%) were included in the study. The median age of the study group was calculated to be 49 (45–51) years. A total of 45.9% of the diabetic population had hypertension, 42.4% had hyperlipidaemia (low-density lipoprotein target of ≥100 mg/dL),

41.9% of the population had obesity (BMI of ≥30), 26.6% had diabetic nephropathy, 18.8% had coronary artery disease, 12.5% had retinopathy, and 3.7% had cerebrovascular disease.

The NLR was significantly higher in patients than in the control group (2.30 [2.04–2.49] to 2.01 [1.85–2.18], respectively; p=0.002). A total of 43.9% of the patients (n=122) were in the good glycaemic control group (HbA1c ≤7.5%) and 56.1% (n=156) were in the poor glycaemic control group (HbA1c >7.5%). The good glycaemic control group, poor glycaemic control group, and healthy control group were similar in terms of age and gender distribution (p=0.7 and p=0.9, respectively). The median HbA1c value was 6.7% (6.0–7.1%), the median fasting glucose was 110 mg/dL (95–127 mg/dL), and the median NLR was 2.07 (1.72–2.40) in the good glycaemic control group. In the poor glycaemic control group, the median HbA1c value was 10.1% (8.2–11.0%), the median fasting glucose was 225 mg/dL (182–270 mg/dL), and the median NLR was 2.48 (1.97–2.60). A significant difference was found between the two groups in terms of HbA1c, fasting plasma glucose, and NLR (p<0.001, p<0.001, and p=0.02, respectively). In the healthy control group, the median HbA1c value was 5.6% (5.5–5.9%), the median fasting glucose was 89 mg/dL (78–100 mg/dL), and the median NLR was 2.01 (1.85–2.18). There were no significant differences between the three groups in terms of median leukocyte, neutrophil, and lymphocyte counts (p=0.6, p=0.6, and p=0.3, respectively). Comparison of the demographic properties, glycaemic regulation parameters, and NLR values of the patients is shown in Table 1. The glycaemic regulation parameters and NLR values of 278 patients who were studied in the authors' outpatient clinic at 3-month intervals were also evaluated.

In these 68 patients, the median HbA1c value was 9.3% (8.1–10.1%), the median fasting plasma glucose was 198 mg/dL (149–248 mg/dL), the median number of leukocytes was 7,920/mm^3 (7,200–8,440/mm^3), the median number of neutrophils was 4,350/mm^3 (4,090–4,710/mm^3), the median number of lymphocytes was 1,840/mm3 (1,750–2,050/mm^3), and the median NLR value was 2.36 (1.90–2.70) in the first evaluation. In the second evaluation in the outpatient clinic, the median values after 3 months were

Table 1: Comparison of the demographic data of the patients and the groups.

	Patients	Patients	Significance	Healthy control group
Parameters	Good glycaemic control (HbA1c ≤7.5 %)	Poor glycaemic control (HbA1c >7.5)	p*	
n%	122.0–43.9	156–56.1		148
Gender (n%)	Male: 42.0–34.4 Female: 80.0–65.6	Male: 56.0–35.9 Female: 100.0–64.1	0.9	Male: 60.0–40.5 Female: 88.0–59.5
	Median (95% CI)	Median (95% CI)		Median (95% CI)
Age (years)	50 (46–51)	48 (45–50)	0.7	52 (48–53)
BMI (kg/m^2)	28 (26–30)	28 (27–30)	0.4	27 (26–29)
Duration of DM (years)	12 (11–14)	14 (13–15)	0.6	
HbA1c (%)	6.7 (6.0–7.1)	10.1 (8.2–11.0)	<0.001	5.6 (5.5–5.9)
FPG (mg/dL)	110 (95–127)	225 (182–270)	<0.001	89 (78–100)
Leukocyte/mm^3	8,130 (7,410–8,800)	8,410 (7,510–8,820)	0.6	7,950 (7,520–8,300)
Neutrophil/mm^3	4,460 (4,010–4,720)	4,690 (4,110–4,750)	0.6	4,120 (3,940–4,400)
Lymphocyte/mm^3	2,150 (2,020–2,220)	1,890 (1,960–2,290)	0.3	2,285 (2,000–2,300)
NLR	2.07 (1.72–2.40)	2.48 (1.97–2.60)	0.02	2.01 (1.85–2.18)

CI: confidence interval; DM: diabetes mellitus; FPG: fasting plasma glucose; HbA1c: haemoglobin A1c; NLR: neutrophil-to-lymphocyte ratio; p*: comparison of patient groups.

Table 2: Comparison of the glycaemic regulation parameters and neutrophil-to-lymphocyte ratio values belonging to March and June (quarterly).

Parameters	March Median (95% CI)	June Median (95% CI)	p-value
HbA1c (%)	9.3 (8.1–10.1)	7.6 (7.0–8.2)	<0.001
FBG (mg/dL)	198 (149–248)	157 (128–189)	<0.001
Leukocyte/mm³	7,920 (7,200–8,440)	7,810 (7,150–8,410)	0.9
Neutrophil/mm³	4,350 (4,090–4,710)	4,020 (3,850–4,520)	0.4
Lymphocyte/mm³	1,840 (1,750–2,050)	2,220 (2,010–2,280)	0.1
NLR	2.36 (1.90–2.70)	1.81 (1.63–2.10)	0.001

CI: confidence interval; FBG: fasting blood glucose; HbA1c: haemoglobin A1c; NLR: neutrophil-to-lymphocyte ratio.

7.6% (7.0–8.2%) for HbA1c, 157 mg/dL (128–189 mg/dL) for fasting plasma glucose, 7,810 mm³ (7,150–8,410/mm³) for number of leukocytes, 4,020/mm³ (3,850–4,520/mm³) for number of neutrophils, 2,220/mm³ (2,010–2,280/mm³) for number of lymphocytes, and 1.81 (1.63–2.10) for NLR. A significant difference was found between the HbA1c, fasting plasma glucose, and NLR values between two data points in the patients for whom the values belonging to these 2 months could be found (p<0.001, p<0.001, and p=0.001, respectively). There were no differences in the number of leukocytes, neutrophils, and lymphocytes in both groups (p=0.9, p=0.4, and p=0.1, respectively). Table 2 compares the HbA1c, fasting plasma glucose, leukocyte, neutrophil, lymphocyte, and NLR values of 68 patients whose records belonging to both measurements could be accessed.

DISCUSSION

This study is important in demonstrating the relationship between glycaemic parameters and NLR. Recently, many studies related with NLR have been conducted because it is a practically calculable method. Binnetoglu et al.[11] investigated the relation between NLR and proteinuria in patients with chronic renal failure without a diagnosis of DM and consequently found an increase in the frequency and severity of proteinuria as NLR increased. In a study performed by Tanindi et al.[12] including 151 patients, a higher NLR value was found in the patients in whom angiography was performed because of acute myocardial infarction compared to the patients in whom angiography was performed because of stable angina.

Lee et al.[13] investigated the relation of NLR with long-term complications following myocardial infarction in 2,559 consecutive acute myocardial infarction patients and found that NLR was an independent risk factor for long-term complications in diabetic patients. Yilmaz et al.,[14] who investigated the benefit of NLR in the diagnosis of gestational DM, found a higher NLR value in pregnant women with gestational DM compared to pregnant women without gestational DM, and found that a NLR value >2.93 had a sensitivity of 76% and a specificity of 94% for gestational DM. Shiny et al.[15] examined the relation between glucose intolerance and NLR. Conclusively, they found a higher NLR value in patients with a diagnosis of DM compared to the patients with impaired fasting glucose, and in patients with impaired fasting glucose compared to normal individuals. In another study, increased NLR in diabetic individuals was reported to be a risk factor for sensorineural hearing loss.[16]

The relation between diabetic complications and NLR was examined in the study performed by Ulu et al.[17] A significant relation was found between increased NLR and the severity of retinopathy. In geriatric diabetic patients, the relation between microvascular complications and NLR was investigated and an increase in the prevalence of microvascular complications was found with increased NLR.[18] A close relation was found between NLR and urinary albumin and protein

excretion in newly diagnosed T2DM patients.[19] A higher NLR was found in nondipper hypertension, which shows a close association with DM and insulin resistance compared to dipper hypertension.[20] Xu T et al.[21] showed that NLR is significantly correlated with diabetic polyneuropathy, which suggested that NLR may be an independent risk factor of diabetic neuropathy.

The NLR was significantly higher in the poorly controlled DM group compared to the well-controlled DM group in the study performed by Sefil et al.,[22] which reported results that were similar to those found in this present study. The difference of this study from the study performed by Sefil et al.[22] was the fact that the mean NLR value was also reduced in the patients in whom glycaemic parameters improved 3 months later. Hussain et al.[23] reported similar results between NLR and glycaemic regulation. They found a significant association between NLR and HbA1c among the groups divided into three according to the glycaemic control status. In this study, NLR values after treatment were not investigated.

In a prospective study by Guo X et al.[24] on a nondiabetic 38,074-strong cohort, an average of 6-year follow-up NLR was associated with the incidence and prevalence of T2DM. This result suggests that the NLR is a predictor for the development of diabetes.

In this study, there was a significant relationship between NLR and glycaemic regulation with both diabetic groups when compared to the control group. This result suggests that NLR changes from the early stages of diabetes. The study by Lou M et al.[25] supported this study and showed a relationship between insulin resistance and NLR in newly diagnosed diabetics.

Contrary to the present authors' research, Mendes et al.[26] showed that hyperglycaemic subjects had a NLR similar to that of normoglycaemic subjects, but had a lower platelet-to-lymphocyte ratio. However, most of the studies in the literature support this present study.

As in the current international guidelines, the national guideline is targeted at 7% below HbA1c for T1DM, pregnancy, and uncomplicated T2DM. However, in patients with complications, especially in patients with cardiovascular and neurological comorbidities and in the elderly population, it is recommended to be around 8% for HbA1c targets.[27,28] Because the patient population was not a homogenous group, HBA1c target was taken as 7.5%. It is well known that impaired glycaemic control initiates an inflammatory process and is associated with diabetic complications.

The limitations of the study included failure to reach the complication states of the patients, the lack of knowledge about the therapies used, and the changes made as a result of outpatient evaluation.

CONCLUSION

In diabetic patients, NLR deterioration is associated with glycaemic disorder, which increases the importance of haemogram in diabetic patients. In cases in which HbA1c measurement cannot be performed, and if the glycaemic condition is not evaluated earlier, NLR can be a useful examination. Improvement of NLR after glycaemic regulation has suggested that this parameter may be more useful in demonstrating glycaemic regulation rather than complications.

NLR may be useful as an easily measurable, noninvasive, available, and cost-effective parameter for the follow-up of diabetic patients. Larger-scale, randomised, controlled studies should be performed in this area.

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Pathophysiology of Gestational Diabetes Mellitus

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Abstract

Gestational diabetes mellitus (GDM) is a pregnancy complication defined as a glucose intolerance of varying severity with onset or first recognition during pregnancy. The prevalence of GDM is growing rapidly worldwide. Two major metabolic disorders, chronic insulin resistance and β-cell dysfunction, are currently linked to the pathogenesis of GDM, although the cellular mechanisms involved are not yet completely understood. Maternal genetic predisposition coupled with environmental and fetoplacental factors initiates a chain of events that affects mother and fetus, both in the short and long term. Understanding of pathophysiology and risk factors will enhance the possibility of effective screening, early intervention, and even prevention.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as a glucose intolerance of varying severity with onset or first recognition during pregnancy. According to the 2017 International Diabetes Federation (IDF) estimates, GDM affects 14% of pregnancies worldwide, representing ~18.4 million births annually.[1] GDM develops when insulin secretion fails to overcome the physiologic insulin resistance (IR) during pregnancy.[2] Known risk factors, such as advanced maternal age, overweight, obesity, westernised diet, ethnicity, intrauterine environment, hypertension, family history of GDM or Type 2 diabetes mellitus (T2DM), and personal history of GDM or polycystic ovarian syndrome, are either directly or indirectly associated with impaired β-cell function and/or insulin sensitivity. Therefore, GDM may represent a transient 'unmasking' of pre-existing latent metabolic disturbances. Maternal genetic predisposition coupled with environmental and fetoplacental factors initiates a chain of events affecting mother and fetus in both the short and long term.[2] Understanding of the pathophysiology will enhance the possibility of effective screening, early intervention, and even prevention. This review will discuss molecular processes underlying the pathophysiology of GDM. Potential mechanisms behind GDM are summarised in Table 1.

MATERNAL PREDISPOSITION OR PREGNANCY-MEDIATED EXACERBATION?

IR and β-cell dysfunction are critical pathophysiologic components of both GDM and T2DM. These impairments exist prior to pregnancy and can be progressive, representing an increased risk of T2DM after pregnancy,

Table 1: Potential mechanisms behind gestational diabetes mellitus.

Physiological area	Mechanisms
Brain	↑ Appetite ↓ Energy expenditure
Adipose tissue	Insulin resistance ↑ Leptin ↓ Adiponectin, IL-10 ↑ Lipolisis, ↑ free fatty acids ↑ M1 macrophages, T helper 1, and T cytotoxic lymphocytes ↑ Proinflammatory cytokines (TNF-α, IFN-γ, IL-1, IL-6) ↓ Expandability ↑ Adipocyte hypertrophy and death ↑ Lipotoxicity
Muscle	Insulin resistance Ectopic fat deposition ↓ Mitochondrial function ↑ ROS
Liver	Insulin resistance ↑ Gluconeogenesis Ectopic fat deposition ↑ ROS
Gut	Altered gut microbiome
Placenta	Insulin resistance ↑ Proinflammatory cytokines ↑ Placental leptin ↑ Placental transport ↑ Fetal growth ↑ T helper 17
Pancreas	β-cell dysfunction

IFN-γ: interferon-γ; ROS: reactive oxygen species.

ranging between 17% and 63% within 15 years.[3] The development of both diseases is governed by a complex interaction of environmental factors with multiple genes. Polymorphisms of susceptible genes of T2DM have been shown to relate to development of GDM, suggesting a considerable overlap between the genetic contributors.[4] The majority of susceptibility genes are related to β-cell function, including *KCNJ11*, *KCNQ1*, *MTNR1B*, *IGF2BP2*, and *rs7754840* and *rs7756992* in *CDKAL1*.[4]

During pregnancy, the combination of hormonal changes and disturbed endocrine function of adipose tissue and placenta are added to genetic predisposition and environmental factors (Figure 1). There is a uniform 50–60% decrease in insulin sensitivity with advancing gestation in both normoglycaemic and diabetic women.[5] The decreased insulin sensitivity in GDM, however, occurs with a background of chronic IR preceding pregnancy to which the physiological IR of pregnancy is partially additive.[5] Thus, the metabolic and endocrine changes accompanying the second half of gestation, inducing physiological IR, unmask and worsen the underlying pre-existing metabolic disturbances, leading to the full clinical picture of GDM.[6] The physiological IR abates rapidly following delivery, but women with GDM end up, on average, with considerably greater IR than normal women.

The pathophysiological changes responsible for IR in GDM are not fully clarified. Insulin receptor abundance is usually unaffected.[7] Genetic variants associated with IR and abnormal use of glucose (*PPARG*, *TCF7L2*, *GCK*, *GCKR*) show associations with GDM risk.[4]

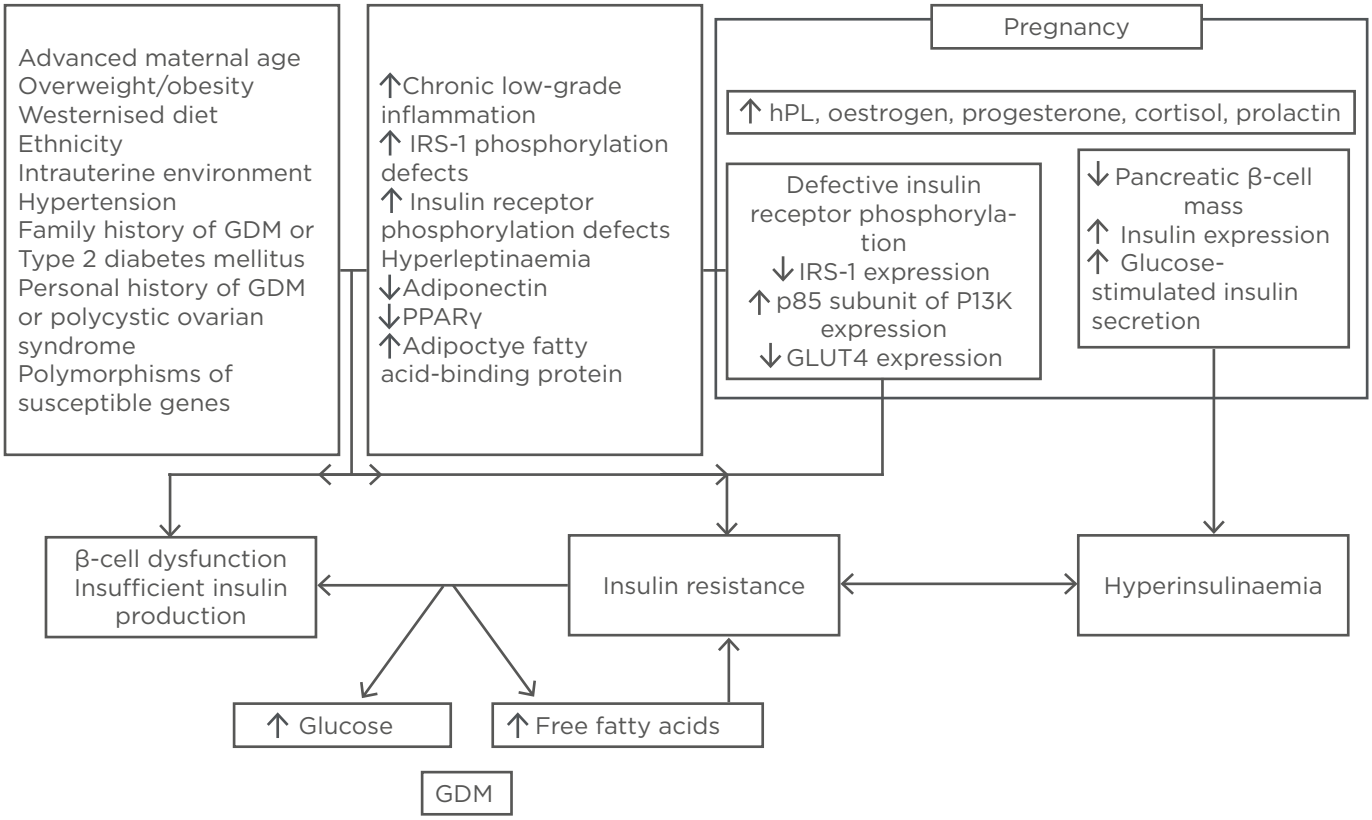

Figure 1: Mechanisms underlying insulin resistance in normal pregnancy and gestational diabetes mellitus.

A pronounced physiological decrease in peripheral insulin sensitivity occurs as pregnancy proceeds. This decrease is mediated by a number of factors such as increase in the levels of hPL, oestrogen, progesterone, cortisol, and prolactin, among other factors. In addition to altering components of peripheral insulin signalling cascades, they also activate various mechanisms enhancing β-cell function. GDM develops when insulin secretion fails to overcome the physiologic insulin resistance during pregnancy. The metabolic/endocrine changes accompanying the second half of gestation and inducing physiological insulin resistance unmask and worsen the underlying pre-existing metabolic disturbances, leading to the full clinical picture of GDM.

GDM: gestational diabetes mellitus; hPL: human placental lactogen; IRS-1: insulin receptor substrate 1; PPAR-γ: peroxisome proliferator-activated receptor gamma.

Altered expression and/or phosphorylation of downstream regulators of insulin signalling, including insulin receptor substrate (IRS)-1, phosphatidylinositol 3-kinase (PI3K), and glucose transporter (GLUT)-4, reduced expression of peroxisome proliferator-activated receptor (PPAR)-γ, and increased expression of the membrane glycoprotein PC-1 have been described during and beyond pregnancy.[6,7] IR exacerbates β-cell dysfunction.[2]

PLACENTAL VERSUS MATERNAL TISSUES ROLE IN GESTATIONAL DIABETES MELLITUS

At the onset of gestation, the interaction of maternal insulin with the syncytiotrophoblast may lead to altered synthesis and secretion of cytokines that, in turn, will act on the mother, thus forming a feedback loop. This functional interplay contributes to the low-grade systemic inflammation during the third trimester of uncomplicated pregnancy by expressing a common repertoire of cytokines.[8] This situation is exacerbated in obese pregnancies and those with GDM.[8] However, the relative contribution of maternal adipose tissue, as well as the placenta, to this inflammation is yet to be determined.

ROLE OF FETOPLACENTAL UNIT IN GESTATIONAL DIABETES MELLITUS

Placental-Derived Exosomes

Placental-derived exosomes play a role in maternal immunomodulation through suppression of natural killer cell and macrophage activation, and induction of lymphocyte apoptosis.[9] They suppress T-signalling components such as CD3-zeta and JAK3, while inducing suppressor of cytokine signalling (SOCS)-2.[10] This counteracts allograft rejection of the fetus and sustains cellular adaptation in the face of physiological changes associated with pregnancy. Placenta-derived exosomes carry syncytin-1, which mediates trophoblastic syncytialisation and regulates endothelial cell migration, thereby sculpting the maternal-fetal circulation.[11]

The total number of exosomes in maternal plasma between 11 and 14 weeks of gestation is up to 2-fold greater in women with GDM.[12] The released exosomes from trophoblasts in GDM subjects induce secretion of proinflammatory cytokines from endothelial cells.[12] Furthermore, upregulation of microRNA-326 in diabetic patients in a comparison analysis negatively correlated with its target, adiponectin.[13] This mechanism potentially mediates the inflammatory phenomena typically associated with GDM. However, with regard to several microRNA candidates as biomarkers for GDM, the results are often discordant. Exposure to bisphenol A has been associated with GDM and with alterations in methylation.[14] This could be because bisphenol A induces exosome signalling from the placenta.

Hormonal Effect in Gestational Diabetes Mellitus

Progesterone is a major contributor to IR whereas oestrogen is protective.[15] Since oestrogen receptor-α appears to play a major role in adipose tissue, its decreased expression in subcutaneous fat of patients with GDM may contribute to the development of IR.[16] Additionally, progesterone may prohibit normal adaptation of β-cell reserves during pregnancy and affect the susceptibility to diabetes.[17] An observational study found significantly higher levels of serum cortisol in women with GDM.[18] In skeletal muscle, glucocorticoids induce IR by decreasing transcription of IRS-1, while increasing transcription of protein tyrosine phosphatase type-1B and p38 mitogen-activated protein kinase (MAPK) which counteract insulin action.[19]

Human placental lactogen (hPL) displays both insulin-like and anti-insulin effects. It acts via the prolactin receptor (PRLR) on maternal β-cells to mediate increases in β-cell mass and function, and to address the increased metabolic demands of pregnancy.[20] In contrast, it causes profound IR by decreasing phosphorylation of IRS-1.[20] Additionally, the hPL-related increase in free fatty acid (FA) levels directly interferes with insulin-directed entry of glucose into cells. Placental hPL messenger RNA levels were found to be higher in GDM patients;[21] therefore, hPL is considered as a major, physiologic antagonist to insulin action during pregnancy.[21]

Human placental growth hormone (hPGH) may contribute to IR by specifically increasing the expression of the p85-regulatory unit of PI3K, resulting in a marked reduction in IRS-1-associated PI3K activity.[22] In contrast, treatment with the 20-kDa hPGH-variant was suggestive of enhanced insulin sensitivity in an animal trial. It demonstrated diminished diabetogenic properties compared to the native pituitary 22-kDa hGH-N.[23]

Prolactin largely regulates its functions on β-cell via the JAK-2/signal transducer and activator of transcription (STAT)-5 pathway.[24] Pathway disruption and single nucleotide polymorphisms of the 5′-untranslated region and promoter region of the *PRLR* gene have been shown to be associated with increased risk for GDM.[25] On the contrary, another study found no difference in prolactin concentrations before and during the oral glucose tolerance tests between normal and diabetic pregnancies, neither in pregnancy nor postpartum.[26] There was no correlation between the deterioration in glucose tolerance and the prolactin concentrations in either group. These discrepancies may be attributable to the complex crosstalk between PRLR and insulin receptors. Further research is required to determine the physiopathological importance of prolactin in the development of GDM.

Placental Inflammation and Adipokines in Gestational Diabetes Mellitus

The placenta may play an active role in mediating inflammation in women with obesity

and GDM. Women with GDM in the third trimester of pregnancy had a higher proportion of T-helper 17 cells (proinflammatory response) which was balanced with a parallel higher proportion of T-helper 2 and regulatory T cells (anti-inflammatory response).[27] The co-operation between different maternal and fetal cell types may propagate a vicious cycle for enhancement of cytokine production. This condition can alter placental metabolic and endocrine functions, which are likely to contribute to the placental changes, and eventually affect insulin action at the fetoplacental unit leading to GDM *in utero*.[28] Among pathways upregulated by GDM insult in placentas, TNF-α signalling is one of the most relevant to placental growth;[29] additionally, it links inflammation to defective insulin action and may reinforce the endocrine mechanism of pregnancy-induced IR by adding a placental component.[28] Elevated TNF-α transcription in the placenta has been associated with markedly decreased insulin signalling in GDM.[28] It is possible that TNF-α downregulates insulin action through serine phosphorylation of placental insulin receptors.[28]

Hyperleptinaemia may also contribute to enhanced IR in the GDM mother.[30] Increased placental leptin expression and synthesis in GDM amplifies low-grade inflammation by stimulating production of both CC-chemokine ligands and proinflammatory cytokines, which further enhances leptin production;[30] therefore, a vicious circle develops, aggravating the inflammation. However, it would be challenging to differentiate the relative contribution of placental versus maternal tissues for regulation through TNF-α and leptin. The effect of adiponectin that may be implicated in IR with advancing gestation in normal and GDM pregnancies through a decrease in maternal concentrations is exclusively of maternal origin due to the absence of ligand, but expression of adiponectin receptors in the placenta.[30]

Proinflammatory cytokines upregulate insulin-stimulated amino acid transporter system-A activity, while IL-1β downregulates it in cultured primary human trophoblasts.[31,32] Additionally, leptin and TNF-α activate phospholipase A2, which generates docosahexaenoic acid, an essential ω-3 polyunsaturated FA. An accumulation of ω-3 FA has been recently demonstrated in the placenta of offspring of GDM mothers with increased adiposity at birth.[33] These may be potential mechanisms by which local placental inflammatory mediators and responses influence placental nutrient transport and increase lipid substrate availability for fetal fat deposition, thereby linking inflammation in maternal obesity to changes in fetal growth. However, maternal inflammation in obese women or women with GDM may influence fetal development by impacting placental function, rather than directly influencing the fetal inflammatory profile.[33] Most maternal cytokines do not cross the trophoblast barrier and, hence, do not reach the fetal circulation.[34] It is therefore possible that the placenta acts as a mediator and an adaptor in pregnancy, sensing and responding to the maternal inflammatory environment to maintain pregnancy and to limit exposure of the fetus to inflammation and oxidative stress despite GDM insult.[34]

ROLE OF MATERNAL ADIPOSE TISSUE IN GESTATIONAL DIABETES MELLITUS

Neurohormonal Network

The neurohormonal network regulates appetite, energy expenditure, and basal metabolic rate. It contributes to GDM by influencing adiposity and glucose usage. This network is highly regulated by the circadian clock, which may explain why pathological sleep disorders or those individuals undertaking shift work are correlated with GDM.[35]

Adipokines Involved in Gestational Diabetes Mellitus

Based on the evidence thus far, the adipokines adiponectin, leptin, TNF-α, and adipocyte fatty acid-binding protein (AFABP), seem to be the most probable candidates involved in the pathophysiology of GDM.

Leptin increases insulin sensitivity by influencing insulin secretion, glucose usage, glycogen synthesis, and FA metabolism. In skeletal muscle, it stimulates basal, but not insulin-stimulated, glucose uptake through the PI3K-dependent pathway and prevents the accumulation of lipids by stimulating FA oxidation through activating AMPK and, in turn, suppression of the activity of acetyl coenzyme-A carboxylase.[36] In isolated hepatocytes, it causes significant reduction of

glucose production from different gluconeogenic precursors through PI3K-dependent activation of phosphodiesterase-3B (PDE3B).[37] Leptin can suppress insulin secretion through several mechanisms, including the decrease of proinsulin messenger RNA levels in β-cells under high glucose concentrations; inhibition of glucose transport into β-cells; PI3K-dependent activation of PDE3B that leads to a reduction of cAMP levels and, in turn, suppression of protein kinase-A involved in the regulation of Ca^{2+} channels and exocytosis; and inhibition of the phospholipase-C/protein kinase-C pathway.[38]

Both obesity and pregnancy are characterised by leptin resistance associated with impaired leptin signalling in the hypothalamus.[39] Although the reasons are not yet known, maternal leptin levels increase from the earliest stages of pregnancy, implying that the increases are not solely due to maternal weight gain. Leptin may contribute to the pathophysiology of GDM by effects related to appetite control, body weight and composition, energy expenditure influences, and direct influence on pancreas function.[39] A cohort study has demonstrated that hyperleptinaemia at <16 weeks gestation was predictive of increased risk of GDM later in pregnancy and that each 10 ng/mL increase in leptin concentration was associated with a 20% increase in GDM risk, independent of maternal pre-pregnancy adiposity and other confounders; however, further prospective studies are required to determine predictive ability in GDM.[40] The dysregulation of leptin metabolism and/or function in the placenta may be implicated in the pathogenesis of GDM. Nonetheless, there are conflicting reports regarding placental leptin expression in GDM.[41,42]

Adiponectin may improve insulin signal transduction via an increase of tyrosine phosphorylation of insulin receptors in skeletal muscle and by suppression of TNF-α, and can enhance insulin secretion by stimulating both the expression of the insulin gene and exocytosis of insulin granules.[43] Additionally, it works by decreasing hepatic glucose production through AMPK.[44] Adiponectin may activate PPAR-α, leading to increased FA oxidation, and reduced ectopic fat storage through inhibiting lipolysis in adipose tissue, thereby increasing insulin sensitivity.[45]

There is good evidence that adiponectin is lower in pregnancy and in GDM.[46] Downregulation of adiponectin may predict GDM several months before diagnosis, independent of BMI and insulin sensitivity.[47] Hypoadiponectinaemia persists post-partum with GDM and may contribute to progression to T2DM.[46] Thus, it may play a key role in mediating IR and β-cell dysfunction in the pathogenesis of both T2DM and GDM. It is thought that TNF-α and other proinflammatory mediators secreted in GDM suppress the transcription of adiponectin, further aggravating chronic low-grade inflammation.[39]

Adiponectin expression in the placenta is differently regulated by various cytokines.[48] This suggests its significance in adapting energy metabolism at the maternofetal interface. Lower adiponectin DNA methylation levels on the fetal and maternal side of placenta are associated with higher maternal glucose and adiponectin levels.[49] Maternal adiponectin decreases fetal growth by impairing placental insulin signalling and reducing insulin-stimulated amino acid transport;[50] therefore, decreased concentrations may contribute to fetal macrosomia in women with and without GDM.

TNF-α and IL-6

It remains controversial as to whether upregulation of TNF-α in GDM precedes or is a consequence of disease.[39] TNF-α quantified at 11 weeks of gestation was not significantly associated with the risk of developing GDM in a study; however, only 14 cases and 14 controls were included.[51] Placental gene expression of TNF-α, IL-1, and their receptors has been reported to be increased in GDM in some but not all studies.[16,52] Additional analysis is required to clarify the role of TNF-α and other inflammatory cytokines as a predictor of GDM development independent of BMI.

Adipocyte Fatty Acid-Binding Protein

Cross-sectional studies have consistently found increased circulating AFABP concentrations in patients with GDM after adjustment for adiposity, IR, triacylglycerol, C-reactive protein (CRP), and associations with newborn size and adiposity.[53,54] However, no prospective study has assessed whether baseline AFABP concentrations predict the risk of GDM. Furthermore, prospective studies and data for expression of AFABP in the

placenta, visceral, or subcutaneous adipose tissue of patients with GDM have not been published.

Adipokines Probably not Involved in the Pathophysiology of Gestational Diabetes Mellitus

The evidence for visfatin, retinol-binding protein-4, vaspin, resistin, omentin-1, apelin, chemerin, progranulin, fibroblast growth factor 21, lipocalin 2, tissue inhibitor of matrix metalloproteinase-1, and zinc-alpha-2 glycoprotein is contradictory and/or lacking.[55]

Energy Storage

Maternal fat mass increases throughout the pregnancy, with accumulation of fat observed on the trunk.[56] During pregnancy, appropriate expansion of adipose tissue is vital to support nutrient supply to the fetus. However, hypertrophic adipose tissue is associated with excess adiposity followed by elevated adipose tissue inflammation.[7] The relationship between hypertrophic growth of adipose tissue and inflammation causes adipose tissue IR in the third trimester. This situation is exacerbated in obese pregnancies and those with GDM.[57] Adipocyte hypertrophy and reduced adipocyte differentiation in GDM is accompanied by downregulated gene expression of insulin signalling regulators, FA transporters, and key adipogenic transcription factors, such as PPAR.[57] Adipose tissue from obese patients with GDM expresses high levels of ectonucleotide pyrophosphate phosphodiesterase-1, correlating with GLUT4 expression, IRS-1 serine phosphorylation, and induction of adipocyte IR.[58] The combination of IR and reduced adipocyte differentiation hinders the tissue's ability to safely dispose of excess energy, contributing to gluco and lipotoxicity in other peripheral organs.

Adipose Tissue Inflammation

Expansion of adipose tissue and increased lipid deposition in adipocytes leads to the development of a more inflammatory adipocyte state, including the secretion of different inflammatory mediators which induce the recruitment of monocytes and/or their differentiation into proinflammatory M1-like macrophages. Once recruited, these macrophages secrete additional chemokines, initiating a feed-forward loop, potentiating the inflammatory response and impairing adipocyte function.[59] Adipose tissue macrophages secrete TNF-α, IL-6, IL-1β, monocyte chemoattractant protein (MCP)-1, and macrophage-inhibitory factor. These factors induce IR either by diminishing insulin receptor tyrosine kinase activity, increasing serine phosphorylation of IRS-1, or through the STAT3–SOCS3 pathway, which degrades IRS-1.[60] Their production is under transcriptional control of two inflammatory pathways: 1) c-Jun-N-terminal kinase (JNK)-activator protein 1 (AP1); and 2) inhibitor of NF-kB kinase (IKK).[60] These pathways are initiated by almost all of the mediators implicated in the development of IR, including oxidative and endoplasmic reticulum stress, saturated FA, and inflammatory cytokines, highlighting their importance in the pathogenesis of disease. TNF-α, IL-1β, and pattern recognition receptors activate JNK and IKKβ/NF-kB through classical receptor-mediated mechanisms.[60] NF-kB and AP-1 transactivate inflammatory genes, which can contribute to IR in a paracrine manner. JNK, a stress kinase that normally phosphorylates the c-Jun component of AP-1 transcription factor, has been shown to promote IR through the phosphorylation of serine residues of insulin receptor.[60] Unlike JNK, IKKβ does not phosphorylate IRS-1 and causes IR through transcriptional activation of NF-κB. Impairment of insulin signalling due to chronic low-grade inflammation in adipose tissue further stimulates expression of genes.[56]

The relationship between pregnancy and inflammation is complex. The widely accepted belief that increased adiposity equates to increased maternal inflammation may not be as evident during pregnancy as in the non-pregnant state. GDM placentas have been shown to secrete fewer proinflammatory cytokines than healthy placentas.[61] This suggests that, while chronic low-grade inflammation appears to be important in the pathogenesis of GDM, the relationship may not be straightforward. The elevation in plasma CRP, MCP-1, IL-6, and IL-1 receptor antagonist levels of overweight or obese women with increasing BMI in early-to-mid pregnancy was not evident towards the end of pregnancy.[62] Therefore, the authors have speculated that increased

adiposity during pregnancy is not associated with enhanced inflammation, as opposed to the widely held belief. Additionally, there is evidence, although still limited, implicating that the association between adipokines and GDM may be independent of adiposity measures and suggesting other pathways linking adipokines to the development of GDM, although BMI is not an accurate measure.[40,41,63] Future studies using objective measures of adiposity, for example, dual-energy X-ray absorptiometry, may help to clarify the adipokines-GDM relations independent of adiposity.

Oxidative Stress

Pathologic pregnancies, including GDM, are associated with heightened oxidative stress due to overproduction of free radicals, leading to abnormal mitochondrial function, and impaired free-radical scavenging mechanisms.[64] Reactive oxygen species inhibit insulin-stimulated glucose uptake by interfering with both IRS-1 and GLUT4. The activation of NADPH oxidase by lipid accumulation in the adipocytes is a potential mechanism shown to increase the production of TNF-α, IL-6, and MCP-1, and decrease the production of adiponectin.[7] Interestingly, iron supplementation in already iron-replete women is associated with GDM, possibly as a result of increased oxidative stress.[65] Homocysteine is also thought to contribute to GDM via oxidative stress. Exposure of β-cells to even small amounts of homocysteine results in impaired insulin secretion.[66] A recent meta-analysis reported significantly higher homocysteine concentrations among women with GDM.[67] Deficiencies and imbalances of B vitamins that are essential for homocysteine homeostasis are associated with GDM.[66]

Adipose Tissue-Derived Exosomal microRNA

Obesity and its related diseases influence the expression of exosomal microRNA, with significant upregulation of microRNA-23-b, microRNA-103-3p, and microRNA-4429.[68] MicroRNA-23-b and microRNA-4429 activate the TGF-β and Wnt/β-catenin signalling pathways, causing obesity-related conditions.[68] MicroRNA-103-3p, known to target the insulin receptor signalling pathway, was previously found to be downregulated in diabetes.[69] Exosomes from hypoxic adipocytes show an enrichment of lipogenic proteins modulating lipogenic pathways in neighbouring adipocytes and pre-adipocytes thereby transferring characteristics of adipocyte dysfunction.[70] In obese pregnancies, adipose tissue-derived exosomes may communicate with the placenta and change its function and therefore contribute to the development of GDM.

Gut Microbiome

There is emerging evidence that the gut microbiome may contribute to metabolic diseases. The gut microbiota composition of women with GDM, both during and after pregnancy, resembles the aberrant microbiota composition reported in non-pregnant individuals with T2DM and associated intermediary metabolic traits.[71] A study of stool bacteria in women with previous GDM reported a lower proportion of the phylum *Firmicutes* and higher proportion of the family *Prevotellaceae*.[72] *Firmicutes* appear to be relevant to pathogenesis of GDM independent of diet, although the mechanisms underlying this are unknown. *Prevotellaceae* may contribute to increased gut permeability regulated by tight junction proteins, such as zonulin. Increased 'free' serum zonulin is associated with GDM.[73] Increased gut permeability is thought to facilitate the movement of inflammatory mediators from the gut into the circulation, promoting systemic IR.

CONCLUSION AND FUTURE DIRECTIONS

GDM is likely to be a result of a complex and variable interaction of genetic, environmental, maternal, and fetoplacental factors in an integrated manner. The molecular mechanisms by which these factors participate in the pathophysiology of GDM is currently a challenge. The conclusions drawn from most of the trials conducted are limited mainly due to the lack of statistical power and the controversial results obtained. Greater understanding of molecular mechanisms and their contribution to GDM is required to develop effective treatments and prevention strategies.

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Implication of the MAPK Signalling Pathway in the Pathogenesis of Diabetic Nephropathy

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Abstract

Diabetes has become an emerging public health problem because of its serious complications, and high mortality and morbidity rates. Among the most common microvascular complications of diabetes is diabetic nephropathy (DN), which is a major cause of development of end-stage renal disease worldwide. The aetiopathogenesis of DN is not completely elucidated; however, studies have shown that the components of the MAPK signalling pathway play an essential role in the development and progression of the disease. The MAPK family is mainly composed of three subgroups: extracellular signal-regulated kinases 1 and 2, c-Jun N-terminal kinases (JNK) 1–3, and p38 MAPK, all of which are related to several cellular functions, such as cell death, differentiation, proliferation, motility, survival, stress response, and cell growth. In diabetic kidney disease, the MAPK pathway can be activated by processes resulting from hyperglycaemia (polyol pathway products, oxidative stress, and accumulation of advanced glycosylation end-products) and by angiotensin II, and it is related to several renal pathological processes. This review aims to summarise the role of the MAPK signalling pathway in diabetic nephropathy, as well as to link the biological aspects that contribute to clarify the pathological process behind the disease.

INTRODUCTION

Diabetic nephropathy (DN) is considered the most common microvascular complication of diabetes, being a major cause of end-stage renal disease (ESRD) and cardiovascular mortality.[1-3] Data from the United States Renal Data System demonstrate that prevalence of cardiovascular disease is greater in patients with chronic kidney disease, which may present complications, such as acute myocardial infarction and atrial fibrillation.[4] Patients with ESRD require dialysis or kidney transplant;[1] thus, complications could lead to limitations in quality of life, both by the severity of the disease and by the number of hospitalisations.[4] DN contributes to high costs in public healthcare, especially when it progresses to ESRD. Patients with DN have 50% higher annual costs than patients who present with diabetes alone, and patients with ESRD who undergo dialysis have 2.8-times the annual mean

costs compared to those with ESRD and are not receiving dialytic treatment.[5] Due to the severity of complications and socioeconomic factors related to the disease, many mechanisms are being studied to understand the aetiopathogenesis of the DN because it is still not fully elucidated.[6] Factors such as genetic susceptibility, increased products of the polyol pathway, activation of the renin–angiotensin system, and increased production of advanced glycation end products (AGE) have been related to the physiopathology of the disease.[6]

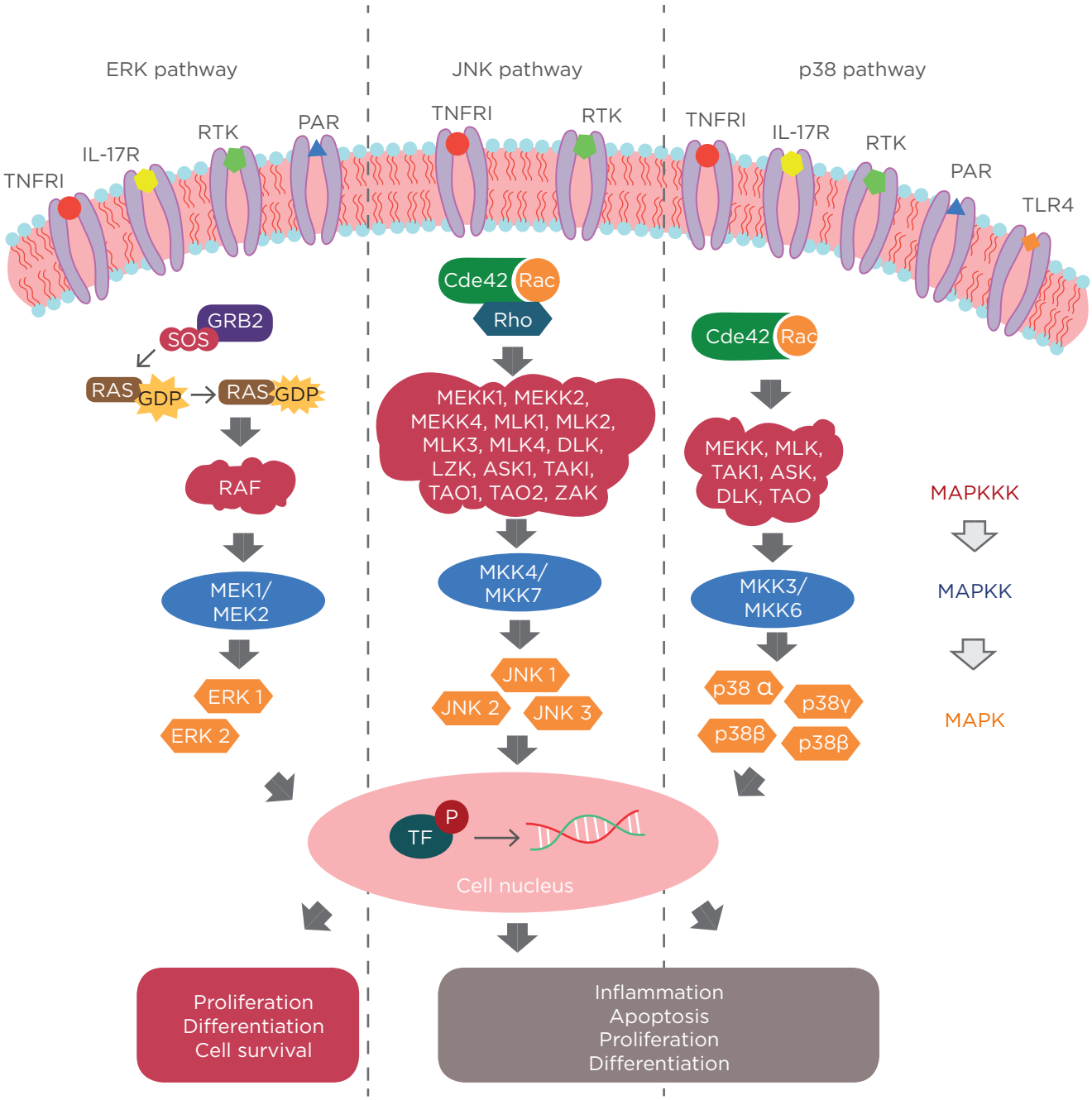

Figure 1: Three major pathways of MAPK: extracellular signal-regulated kinase (ERK) 1 and 2, c-Jun N-terminal kinases (JNK) 1-3 and p38 MAPK.

Cdc42: cell division control protein 42; GDP: guanosine diphosphate; GTP: guanosine triphosphate; GRB2: growth factor receptor-bound protein 2; ERK: extracellular-signal-regulated kinase; JNK: c-Jun N-terminal kinases; MAPK: MAP kinase; MAPKK: MAP kinase kinase; MAPKKK: MAPK kinase kinase kinase; P: phosphorylation; PAR: protease-activated receptor; RTK: tyrosine kinase receptors; SOS: Son of Sevenless; TF: transcription factors; TLR4: toll-like receptors 4; TNFR1: tumour necrosis factor receptor 1.

It has also been demonstrated that the MAPK signalling pathway plays a crucial role in DN; therefore, it is important to investigate its relationship with the pathogenesis of the disease since this understanding can clarify the pathological process behind the disease and contribute to the development of new therapeutic strategies.[7]

MAPK SIGNALLING PATHWAY AND ITS BIOLOGICAL FUNCTIONS

MAPK are a family of serine/threonine protein kinases (Ser/Thr) responsible for promoting intracellular signal transduction from extracellular stimuli.[8] In this way, they regulate innumerable and important cellular actions, such as cell death, differentiation, proliferation, motility, apoptosis, survival, and stress response.[7,9] These proteins are activated by a series of cascade reactions and are composed of three core kinases that are subsequently phosphorylated: MAPK kinase kinase (MAPKKK), MAPK kinase (MAPKK), and MAPK (Figure 1). This cascade has upstream and downstream elements, known as MAPK kinase kinase kinase (MAPKKKK) and MAPK activated protein kinase (MAPKAPK), respectively.[9] The MAPK group is classified into three major subgroups: extracellular signal-regulated kinase (ERK) 1 and 2, c-Jun N-terminal kinases (JNK) 1–3, and p38 MAPK.[7] ERK are activated by growth factors, while JNK and p38 MAPK are activated by cytokines, cell death receptors, mitogens, and stressors (oxidative stress, hypoxia, thermal shock, and ultraviolet radiation), and therefore also known as stress-activated protein kinases (SAPK) (Figure 1).[10,11] ERK is an essential signalling pathway that controls cellular processes, such as proliferation, survival, and differentiation. Activation of ERK begins with the recruitment of the adapter protein growth factor receptor-bound protein 2 (Grb2) and Son of Sevenless (SOS), which propitiate the exchange of guanosine diphosphate (GDP) of the GTPase RAS protein to a GTP.[12] Activated RAS stimulates the RAF (MAPKKK) by phosphorylation of two residues of Ser active MAPKK (MEK1/MEK2).[9] Phosphorylated MEK1/MEK2 signals to ERK 1 and 2 (MAPK) via threonine and tyrosine residue phosphorylation (Thr and Tyr) in the threonine-glutamine-tyrosine domain (Thr-Glu-Tyr).[9] The subgroups of MAPK act in the cellular nucleus in order to propitiate the activation of transcription factors (Figure 1).[8,10] The different variants of the JNK pathway, 1, 2, and 3, are encoded by the *JNK1, JNK2,* and *JNK3* genes, respectively, and are associated with inflammation, apoptosis, cell differentiation, and proliferation.[11,13,14] After stimulation of this pathway, a series of events occur until the final formation of JNK.[13] The initial step is the action of small GTPases, Cdc42, Rac, and Rho, in MAPKKK, which have 14 different forms capable of activating MAPKK (MKK4 and MKK7). These are MEKK1, MEKK2, MEKK4, MLK1, MLK2, MLK3, MLK4, DLK, LZK, ASK1, TAK1, TAO1, TAO2, and ZAK.[13-15] After activation, MKK4 and MKK7, either separately or in combination, are capable of phosphorylation of the residues Thr and Tyr and all three isoforms of JNK (Figure 1).[14] The p38 MAPK cascade presents a series of components shared with JNK, having similar biological functions, such as inflammation, differentiation, proliferation, and apoptosis (Figure 1).[13] This is related to regulation of the production of proinflammatory cytokines, such as TNF-α and IL-1β, and is therefore of paramount importance for the control of immunological effects.[16] It is of importance that the mammalian p38 pathway presents four different isoforms: α, β, γ, and δ, which are encoded by the *MAPK14, MAPK11, MAPK12,* and *MAPK13* genes, respectively.[17] The α and β isoforms are expressed in several tissues, including in the brain, whereas γ and δ are associated with specific tissues.[16]

p38 MAPK can be activated by cytokines and stressor stimuli which act on small GTPases, Cdc42 and Rac, that are capable of activating one of the different forms of MAKKK (MEKK, MLK, TAK1, ASK, DLK, and TAO).[11,13,15] These phosphorylate MAPKK (MKK 3/6) and transmit the signal to the different isoforms of p38 MAPK.[10] Activation of all three major components of the MAPK pathway is complex and involves several receptors.[10,18] Growth factors activate the MAPK ERK pathway via tyrosine kinase receptors (RTK), while inflammatory cytokines and stressors are activators of these receptors for p38 and JNK, respectively.[18] MAPK function are activated downstream by TNFR1, IL-17 receptor, protease-activated receptor 1 (PAR1) and 4 (PAR4) and toll-like receptors 4 (TLR4) (Figure 1).[10,19-22]

DOES THE MAPK SIGNALLING PATHWAY INFLUENCE THE PATHOGENESIS OF DIABETIC NEPHROPATHY?

MAPK signalling pathway is related to inflammatory, oxidative, and apoptotic processes and therefore has a crucial role in DN development.[8] Among mechanisms proposed to explain the activation of MAPK components in DN are insulin, high glucose levels, oxidative stress, inflammation, and angiotensin II.[8,22-25] It is well known that diabetes promotes glucose cell deficiency, which is associated with insulin resistance and compensatory hyperinsulinaemia.[26] Moreover, iatrogenic hyperinsulinaemia may occur in Type 1 and Type 2 diabetes mellitus by insulin treatment, one of the most effective strategies to delay the disease.[23] The presence of insulin in both situations can lead to kidney damage through MAPK pathway activation.[27]

Insulin directly activates all three MAPK pathways and could also indirectly produce an excess of H_2O_2 in podocytes, a compound related to oxidative stress and therefore associated with activation of the MAPK pathway.[23,24,27] Although ERK, JNK, and p38 MAPK are phosphorylated in response to insulin, the pathway that mediates this process is only well established for ERK1 and ERK2.[27] This mechanism has a series of reactions that begins with the binding of insulin to its cognate receptor. The phosphorylation of the insulin receptor substrate (IRS) 1 and 2, which is an important adapter for Grb2 and SOS, results in ERK activation.[27]

Alongside hyperinsulinaemia, high glucose levels activate the MAPK cascade via many approaches, such as the polyol pathway, oxidative stress, and accumulation of AGE.[28] It has been demonstrated that renal tubular epithelial cells (NRK-52E) exposed to a high glucose medium activated ERK, JNK, and p38 MAPK and that renal proximal tubular epithelial cells (HK-2) incubated in high glucose concentration caused activation of the p38 MAPK pathway, which was associated with increased cell apoptosis.[7,29] Activation of MAPK components is also mediated by inflammation, and vice versa.[8,30] Inflammatory cytokines and growth factors, such as IL-1 and TNF-α are associated with interstitial fibrosis in diabetic patients and experimental models.[21] TNF-α activates all three groups of MAPK signalling pathways, JNK and p38-MAPK are also stimulated by IL-1.[10,30,31] Studies have shown that p38 MAPK and ERK are activated in human podocyte cells by IL-17RA and that p38 MAPK is phosphorylated in the kidney of diabetic rats and in rat mesangial cells (HBZY-1) by TLR4.[19,22]

Additional studies have revealed that angiotensin II activates ERK1 and ERK2 from proximal tubule cells *in vitro* through processes that include angiotensin II receptors.[25,32,33] A model performed in the human embryonic kidney (293 cells) identified the fundamental role of angiotensin II and its receptor angiotensin Type II 1a receptor (AT1aR) in ERK1 and ERK2 activation. Stimulation of the receptor AT1aR by angiotensin II mediates downstream ERK phosphorylation by two distinct mechanisms: heterotrimeric guanine nucleotide-binding protein (G protein) and β-arrestin. The G protein (Gαq/11) stimulates protein kinase C (PKC) and downstream signalling that promotes activation of RAF-1, MEK, and ERK.[34]

Many other receptors with different functions are related to phosphorylation of the MAPK pathway in DN.[19-21,35] In an *in vitro* study with mesangial cells, ERK 1 and ERK2 activation was PAR-1 dependent, related to fibronectin production by increasing TGF-β signalling.[20] It has also been shown that the production of AGE stimulated the synthesis of kallikrein and activated PAR-4, promoting stimulation of the p38 MAPK pathway, which led to C-C Motif Chemokine Ligand 2 (CCL2), IL-8, and IL-6 production.[21]

The interaction of AGE with its cognate receptor (RAGE) promoted the production of reactive oxygen species in mesangial cells, which in turn stimulated the non-receptor Tyr kinases (NRTK) of the Src family. Consequently, Src/NRTK phosphorylated phosphatidylinositol 3-kinase (PI3K) to activate RAS, RAF, MEK, ERK1, and ERK2, leading the expression of insulin-like growth factor 1 (IGF-1), fibronectin, collagen, and TGF-β.[35]

MAPK phosphorylation is an event that promotes a series of reactions. The classical mechanism of action of MAPK is divided into two steps: firstly, its phosphorylation occurs in the cellular cytoplasm, and then it is translocated to the nucleus, where it activates several transcription factors through the phosphorylation of its Ser and Thr residues.[8]

Among the transcription factors stimulated by MAPK that mediate inflammation in DN is NF-κB.[8] This protein is associated with increased extracellular matrix (ECM) accumulation and renal fibrosis through the production of TGF-β1;[36] furthermore, NF-κB plays an important role in the production of inflammatory cytokines, such as TNF-α and IL-6, which are associated with the pathogenesis of DN.[8]

MAPK pathway inactivation contributes to reduced expression of inflammatory (TNF-α, NF-κB, and IL-6) and apoptotic elements (Bax and caspase-3) in DN, its phosphorylation is also related to the increase of adhesion molecules, which, in association with cytokines, promotes cell death.[8]

Table 1: Possible therapeutic strategies for inhibition of MAPK cascade in DN.

Pathway related to diabetic nephropathy development	Possible therapeutic strategy	Results	Reference
MAPK/ACE/Ang II/TGF- β1	C66, a curcumin analogue already related to anti-inflammatory effects.	C66 treatment promoted inhibition of ERK, JNK, and p38 MAPK in renal tubular epithelial cells (NRK-52E) and in diabetic mice kidneys. As a consequence, there was a reduction in gene and protein expression of ACE, Ang II, and TGF-β1, which was associated with the kidney injury improvement in the *in vivo* model.	Pan et al.[7]
MAPK/NF-κB/TGF-β1 and TGF-β1/MAPK/fibronectin	Apigenin, a flavonoid abundant in fruits and vegetables that has antioxidant anti-inflammatory, antiapoptotic, antimutagenic biological activities.	Apigenin administration reduced oxidative stress, apoptosis, inflammation, and fibrosis in streptozotocin-induced diabetic nephropathy rats via inhibition of MAPK/ NF-κB/ TGF-β1 and TGF-β1/MAPK/fibronectin pathways.	Malik et al.[8]
TLR4/p38-MAPK	Oridonin, a compound isolated from the Chinese medicinal herb *Rabdosia rubescens* already associated with anti-tumour, anti-inflammatory, immunoregulatory, antioxidant, and antibacterial properties.	Oridonin reduced inflammatory cell infiltration and inflammatory cytokine production in T2DM rat model and HG-treated rat mesangial cells by suppressing the TLR4/p38-MAPK pathway.	Li et al.[22]
ERK1/2	Astragaloside IV, one active ingredient of *Radix Astragali*, which has antioxidant, anti-inflammatory, and immunoregulatory effects.	Astragaloside IV prevented kidney damage in iatrogenic hyperinsulinaemic diabetic rats by downregulating ERK1/2 activation.	He et al.[23]
ROS/ERK1/2	Recombinant human EC-SOD (rhEC-SOD), a synthetic compound that has anti-inflammatory activities.	rhEC-SOD administration improved streptozotocin-induced diabetic nephropathy, promoting reduction in death rates, kidney weight/body weight ratio and fibrosis change through the suppression of ROS/ERK1/2 signalling pathway.	Kuo et al.[24]

Table 1 continued.

p38 MAPK	Pentosan polysulfate, a semisynthetic sulfated polysaccharide that is used for the treatment of interstitial cystitis.	Pentosan polysulfate attenuated apoptosis and inflammation by downregulating activation of the p38 MAPK pathway in high glucose treated human renal proximal tubular epithelial cells (HK 2).	Chen et al.[29]
p38 MAPK	Fangchinoline, an alkaloid isolated from *Stephania tetrandra* Radix (Stephania) that possess anti-inflammatory, anti-oxidant, anti-hyperglycaemic, and anti-cancer activities	Treatment with fangchinoline inhibited p38 MAPK in streptozotocin-induced diabetic nephropathy, with consequent reduction of the expression of TNF-α, MMP-9, and COX-2.	Jiang et al.[30]
TGF-β/MAPK/PPAR-γ	Huangqi decoction, a therapeutic element comprising *Poria, Trichosanthes, Ophiopogon, Schisandra*, Licorice, and *Renmannia* that is used for treatment of diabetes in China.	Huangqi decoction alleviated streptozotocin-Induced rat diabetic nephropathy by suppressing TGF-β/MAPK/PPAR-γ signalling.	Han et al.[42]
ROS/MAPK/NF-κB	Gigantol, a compound derived from medicinal orchids that has anti-osmotic, antioxidant, antispasmodic, antinociceptive, and anti-inflammatory bioactivities.	Gigantol was able to improve high glucose-evoked nephrotoxicity in mouse glomerulus mesangial cells (MES) by inhibiting the ROS/MAPK/NF-κB signalling pathway.	Chen et al.[43]

ACE: Angiotensin-converting enzyme; Ang II: Angiontesin II; C66: (2E,6E)-2,6-bis(2-(trifluoromethyl) benzylidene) cyclohexanone; DN: diabetic nephropathy; ERK: extracellular signal-regulated kinase; JNK: c-Jun N-terminal kinase; PPAR-γ: receptor peroxisome proliferator-activated receptor-γ; ROS: reactive oxygen species; TGF-β1: transforming growth factor beta 1; TLR4: toll-like receptors 4.

MAPK phosphorylation promotes apoptosis, infiltration of inflammatory cells, ECM synthesis, and renal inflammation and dysfunction, and is therefore important for kidney disease pathogenesis.[7,8]

A significant reduction of the fibrotic area of glomeruli and renal tubules occurred in a Type 1 diabetic mouse model through the use of JNK inhibitor SP600125, ERK inhibitor PD98059, and p38 inhibitor SB203850. Gene expression of TNF-α, IL-6, and iNOS was also decreased in renal tissues after treatment with these MAPK inhibitors.[37] Though phosphorylated ERK and phosphorylated p38 were detected in various renal components of kidneys specimens of individuals with DN, such as podocytes, tubular epithelial cells, mesangial cells, and endothelial cells, only phosphorylated ERK correlated with the progression of glomerular lesions.[38]

In DN, ERK pathway elements (MEK 1, MEK 2, ERK 1 and ERK 2) were expressed more in the glomerular mesangial and epithelial renal cells of kidney tissues.[39] In the context of hyperglycaemia, the JNK pathway is associated with mesangial cell proliferation and fibronectin expression, whereas p38 MAPK is predominantly expressed in diabetic tubules and therefore related to tubular lesions.[29,40] TGF-β is located in this same p38 MAPK region, which indicates a correlation between p38 MAPK in TGF-β-mediated renal fibrosis.[29]

p38 MAPK induce renal tubular cell apoptosis and their suppression promotes a reduction in apoptosis and improves renal dysfunction.[29] Phosphorylated p38 MAPK also increases levels of TNF-α, IL-1, IL-6, and IL-8, promoting glomerulonephritis and DN development;[41] thus, inhibition of the p38 MAPK pathway promotes the reduction of inflammation and fibrosis, improving manifestations of kidney disease.[30,37]

The MAPK pathway directly promotes the renin–angiotensin–aldosterone system (RAAS), which contributes to the pathogenesis of DN.[7,37] ERK1, ERK2, JNK, and the p38 MAPK pathway were directly involved in angiotensin-converting enzyme (ACE) production in a study *in vitro* with renal tubular epithelial cells (NRK-52E).[7] Similarly, administration of MAPK inhibitors promoted reduced gene expression of angiotensinogen or renin in renal tissues, and JNK signalling was especially associated with downregulation of the ACE/angiotensin II pathway.[37]

Several studies about possible therapeutic strategies for inhibition of MAPK cascade in DN have been developed in recent years (Table 1).[7,8,42,43] It was demonstrated that two drugs, metformin and glucagon-like peptide-1–based therapies (GLP-1), already effective in treating diabetes, also corroborate the improvement of DN by inhibiting components of the MAPK pathway.[44-47] A study *in vitro* showed that metformin inhibits ERK1, ERK2, and p38 MAPK phosphorylation in mouse mesangial cells exposed to high glucose levels, while a streptozotocin-induced diabetic nephropathy rat model provided evidence that GLP-1 inhibited p38 MAPK activity via GLP1-receptor, which improves inflammation and fibrosis in the kidneys.[44-45]

CONCLUSION

DN is a serious complication of diabetes and directly contributes to the development of chronic kidney disease. This is associated with high mortality, morbidity, and high costs in public healthcare; therefore, it is important to understand its aetiopathogenesis because this is not yet completely elucidated. It has been demonstrated that the pathogenesis of DN is complex and involves several interactions and mechanisms, such as the MAPK signalling pathway. The MAPK signalling pathway is crucial for cellular responses and in DN it can be affected by many factors that are closely associated with the pathophysiology of the disease. Stimulation of the pathway promotes deregulation of renal tissue function, which in turn promotes a pathological process that leads to kidney fibrosis, contributing to the development of ESRD. Understanding the association of this biological pathway with DN is fundamental for better clarification of the aetiopathogenesis of the disease and for the development of new therapeutic strategies for prevention, improved quality of life, and the reduction of costs for public health.

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