EMJ EUROPEAN MEDICAL JOURNAL

DIABETES

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DIABETES 5.1
OCTOBER 2017

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Welcome

Hello, and a wholehearted welcome to all of you joining us for the 2017 edition of *EMJ Diabetes*. Inside you will find a meticulous review of the 53rd European Association for the Study of Diabetes (EASD) Annual Meeting. The event delivered hundreds of presentations from expert diabetologists from all around the world, triggering discussion and promoting collaboration. An array of interviews with our esteemed Editorial Board is also included alongside abstracts from the EASD Annual Meeting and compelling, peer-reviewed articles.

> This edition's peer-reviewed articles provide a variety of topics, all with the ultimate aim of improving life for the diabetic patient.

As well as offering wonderful architecture, enthralling history, and fascinating culture, Lisbon, Portugal, proved a fantastic host for the EASD Annual Meeting. Within *EMJ Diabetes 5.1* you will find reviews from the event, featuring some captivating discoveries into diabetes risk, including your neighbourhood surroundings and even your spouse. Insights into a career in diabetes care is a major topic of discussion in our Editorial Board interviews, in which they share information on their latest research and advice for impeding diabetes development. To spur your interests further, we have provided a selection of abstracts, written by their respective presenters at this year's EASD Annual Meeting. Such abstracts include results from Dr Hills' study, which established the role of connexin-mediated cell communication in fibrosis of tubular epithelial cells within diabetic kidneys, a fascinating enlightenment.

This edition's peer-reviewed articles provide a variety of topics, all with the ultimate aim of improving life for the diabetic patient. Rizvi's study focusses on the relevance and management of hypertension within Type 2 diabetic patients and has been chosen as this issue's Editor's Pick. The paper provides an extensive review into hypertension within this patient group, discussing optimal blood pressure values, and the pathogenesis of cardiovascular disease risk. Additionally, Stewart provides a review regarding future treatments of diabetic retinopathy, with in-depth analysis of drugs currently under development.

We hope you enjoy this edition of *EMJ Diabetes*, and that the topics covered inspire you to strive for further developments within the field. We are confident that the content included will pique the interest of every individual who peeks inside. We look forward to seeing you at the 2018 EASD Annual Meeting, in Berlin, Germany, where we are certain to discover even more fascinating advances within the field, bringing you more and more exciting prospects by the second.

Kind regards,

Spencer Gore

Director, European Medical Journal


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Foreword

Prof Jörg Huber

Research Design Service South East, UK.

Dear Colleagues and Friends,

I would like to wish you all a warm welcome to the 2017 edition of *EMJ Diabetes*. Herein, you will find a detailed round-up of the European Association for the Study of Diabetes (EASD) Annual Meeting 2017, a selection of fascinating Editorial Board interviews, and a number of peer-reviewed articles that I highly recommend to you.

The 53rd Annual Meeting of the EASD welcomed 15,000 attendees from across the world, who gathered to share their knowledge and research, and hold thought-provoking discussions. Held in Lisbon, Portugal, this prestigious congress presented 1,200 research abstracts, a selection of which are summarised within the Abstract Review section, including how voluntary exercise can modify food preferences, as well as the interesting idea that specific genes may lead some people to be 'fat on the outside but thin on the inside'.

> "...I hope you all find this a compelling and enjoyable read, sparking informative discussion and providing direction for your everyday practices."

My colleagues and peers from the *EMJ Diabetes* Editorial Board have kindly given their time to complete insightful interviews detailing their inspirations for choosing careers in diabetes, their current opinions on the field, and where diabetic medicine is heading in the coming years. The Editor's Pick for this eJournal, penned by Rizvi, addresses hypertension in Type 2 diabetes mellitus patients and summarises the approach for treating and identifying hypertension in these patients. In addition, Rizvi explains that patients with these comorbidities are also prone to developing cardiovascular disease. In a second high-quality article, Wehbe and Hawat present the current progress in the use of stem cell therapy to treat Type 2 diabetes mellitus and detail how protocols have been adapted to aid research in this area of proposed diabetes therapy.

Finally, I would like to thank you all for your contributions and I hope you find this a compelling and enjoyable read, sparking informative discussion and providing direction for your everyday practices.

Best wishes,

Jörg Huber

Professor of Health Sciences and Deputy Director, Research Design Service South East; Centre for Health Research, School of Health Sciences, University of Brighton, Brighton, UK.

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Includes a selection of the latest articles for diabetes, interventional cardiology, urology, and more.

FEATURE

Climate Change: What Can Doctors Do?

- Thomas Micklewright

Featured inside:

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State-of-the-Art Advances in Duchenne Muscular Dystrophy

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EASD ANNUAL CONGRESS 2017

FIL - FEIRA INTERNACIONAL DE LISBOA AND MEO ARENA,
11TH–15TH SEPTEMBER 2017
LISBON, PORTUGAL

Welcome to the European Medical Journal review of the 53rd Annual Meeting of the European Association for the Study of Diabetes

Citation: EMJ Diabet. 2017;5[1]:12-26. Congress Review.

Sunny Lisbon played host to this year's European Association for the Study of Diabetes (EASD) 53rd Annual Meeting, welcoming 15,000 attendees from across the world to take part in the sharing of knowledge, research, and discussion. Lisbon was, indeed, a most appropriate location for this congress, being the home of the Portuguese Diabetes Association (APDP), the world's first recorded diabetes association. The APDP is now a world-renowned model for the standard of care in diabetes.

EASD's annual meetings draw attendees, research, and presenters from all over the world. Known internationally as a centre of excellence, the association continually strives to provide attendees with up-to-the-minute information through talks, study groups, poster presentations, late-breaking abstracts, and more. This year, >2,000 abstracts were submitted for consideration by the board, 1,200 of which were selected for presentation at the congress. The poster presentations of these abstracts were available throughout the duration of the congress, allowing attendees to view them at their leisure and ensuring plenty of time to visit as many topics as possible.

EASD President Prof Juleen Zierath, speaking at the opening ceremony, discussed the importance of research, care, and education in achieving the goals of the EASD. She spoke of the 20 study groups within EASD, focussing on research into cardiovascular disease, diabetic foot, nutrition, and other basic research into topics of comorbidities and aspects of diabetes care affecting all patients. Attendees were invited to visit the EASD website for further information on joining the study groups.

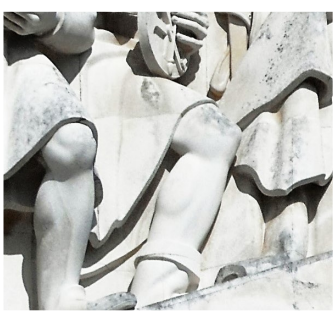
Prof Zierath praised honourary EASD Secretary Prof Francesco Beguinot for his work in assembling the scientific programme for the meeting with the help of other members of the committee. The programme this year was vast and spanned a diverse range of topics sure to interest diabetologists from across the board. Satellite and sponsored symposia kicked off the event, followed by the presidential address and the highly coveted Claude Bernard lecture. This year the prestigious lectureship, which recognises outstanding contributions to the advancement

of knowledge of diabetes and related metabolic diseases, was awarded to Prof Bernard Thorens, Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland. Prof Thorens chose to give his lecture on the topic of a glucose-centric view on diabetes pathogenesis: from islet biology to integrated physiology and precision medicine. The programme went on to feature talks and discussions on the topics of outcome trends, beta cells, hypoglycaemia, genome editing, adipose tissue, and much more, all peppered with poster sessions for both experienced and emerging clinicians to showcase their work.

> “...a number of distinguished researchers were recognised for their outstanding work in advancing knowledge in the sphere of diabetes.”

Alongside the aforementioned Claude Bernard lecture, a number of distinguished researchers were recognised for their outstanding work in advancing knowledge in the sphere of diabetes. This year’s Camillo Golgi prize was awarded to Prof Brian Frier, Queen’s Medical Research Institute, University of Edinburgh, Edinburgh, UK, for his work in the pathophysiology of hypoglycaemia in humans, with particular focus on diabetes. He gave a lecture titled: ‘Recurrent hypoglycaemia in diabetes: the long-term complications’. Prof Jorge Ferrer, Imperial College London, London, UK, was awarded the Albert Reynold prize for his research into the regulation of the genome in pancreatic beta cells, applying this knowledge to advancing understanding of human diabetes.

In the following pages, we have summarised what we believe to be some of the most pertinent topics and stories that were brought forward at this year’s EASD congress. We hope you will enjoy reliving the highlights of the 53rd annual meeting of the EASD as much as our team did, and we look forward to bringing you even more cutting-edge research and innovation in next year’s review of EASD 2018, set to take place in Berlin, Germany.



Study Associates Sodium Intake with Type 2 Diabetes Risk

RISKS of developing Type 2 diabetes mellitus (T2DM) and latent autoimmune diabetes in adults (LADA) has been linked to sodium intake, according to new research from the Institute of Environmental Medicine (IMM), Karolinska Institutet, Stockholm, Sweden, presented at the EASD annual meeting 2017 in Lisbon, Portugal, reported on 15th September, 2017.

> "We confirm an association between sodium intake and T2DM."

Sodium is mainly sourced from salt (sodium chloride) in the diet. LADA is a sub-type of Type 1 diabetes mellitus, in which pathology is the same: insulin-producing cells in the pancreas are destroyed by the body's immune system. However, the onset of LADA occurs much more slowly, sometimes over many years. As a result, LADA is often mistaken for T2DM, as it presents later in adult life.

This population-based study assessed risk factors for developing T2DM and LADA. There were 1,136 T2DM patients involved, 355 LADA patients and 1,379 controls. Each patient was provided with a food questionnaire, assessing dietary intake and calculating daily calorie, nutrient, and sodium intake. The participants were further divided into three groups based on their daily sodium intakes: a) low: <2.3 g (<6.0 g salt equivalent); b) medium: 2.3–2.9 g (6.0–7.3 g salt equivalent); and c) high: >2.9 g (>7.3 g salt equivalent).

Sodium intake was found to increase T2DM development risk by an average of 65%. Those in the high sodium consumption group had a 72% higher risk of developing T2DM compared to the low sodium consumption group. Sodium intake affected the risk of developing LADA even more, with a risk increase of 82% with each gram of sodium consumed each day. The results of this study have great implications for potentially at-risk diabetes patients. "We confirm an association between sodium intake and T2DM," stated the authors, highlighting the very real possibility of a new diabetes prevention method through a change in diet.

Low-Fat Dairy Consumption May Be Associated with Reduced Risk of Cardiometabolic Disease

DISTRIBUTION of fat within the body could explain why the consumption of some dairy products appears to lower the risk of Type 2 diabetes mellitus, reveals a study presented

in a press release dated 14th September, 2017, at the EASD annual meeting 2017 in Lisbon, Portugal.

> “Our preliminary findings suggest a possible mechanism by which total low-fat dairy products and milk may be associated with a lower risk of obesity-related metabolic disorders.”

Researchers in this study, from the Medical Research Council (MRC) Epidemiology Unit, University of Cambridge, Cambridge, UK, examined 12,000 adults aged 30–65 from 2005–2015, recording their daily dairy intake via questionnaires and measuring markers of body composition via X-ray scans and ultrasound. These markers aimed to generate a holistic picture of body composition, including body fat distribution and muscle mass, by recording the ratio of visceral adipose tissue to subcutaneous adipose tissue (VAT/SCAT), total and peripheral body fat mass, and total and appendicular body lean mass.

After correction for confounding factors, such as lifestyle and socio-demographic, the results found total dairy consumption and high-fat dairy consumption to be unrelated to any body composition marker. However, the higher consumption of low-fat dairy products was related to a lower VAT/SCAT ratio. “Our preliminary findings suggest a possible mechanism by which total low-fat dairy products and milk may be associated with a lower risk of obesity-related metabolic disorders. This is via the more favourable distribution of abdominal visceral fat relative to subcutaneous fat and body lean mass”, explained lead researcher Dr Nita Forouhi, University of Cambridge.

Whilst specific subtypes, such as yoghurt, cheese, butter, and ice-cream, were not directly linked to this protective effect, a secondary finding from this study suggested that drinking a glass of low-fat milk every day is significantly associated with higher body lean mass (0.33 kg on average). This may represent the milk’s effect on bone mass, muscle mass, or both.

The researchers point out that this type of study is unable to verify direct causality, but they are hopeful that this new direction of inquiry will bear fruit in future studies. “Our study certainly is hypothesis-generating and should also stimulate future research by others”, concluded Dr Forouhi.

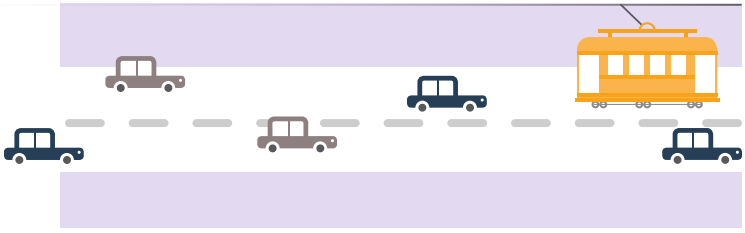
Neighbourhood Design has a Major Impact on the Onset of Prediabetes

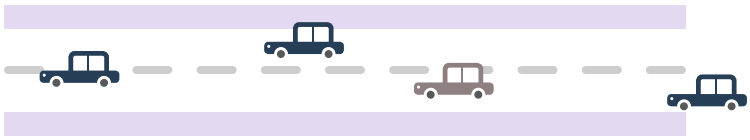
WALKABILITY levels in urban environments have a significant impact on the risk of immigrant populations developing prediabetes, according to research displayed in a EASD press release dated 15th September, 2017.

> We believe further research is required to guide the design of population interventions and policies to target the social and environmental factors perpetuating the development of prediabetes (and subsequent diabetes) among high-risk populations.

The researchers, from St. Michael's Hospital and the Institute for Clinical Evaluative Sciences, Toronto, Canada, built on previous research showing that the development of diabetes is more likely in immigrants living in less walkable areas. The level of walkability is decided by factors such as residential density and availability of shops and services. This study compared the prevalence of prediabetes in different ethnic groups among immigrants living in the highest 20% of walkability areas versus the remaining 80% in four cities in Southern Ontario.

There were 193,899 adults selected for the study, with 20,324 from Sub-Saharan Africa and the Caribbean, 38,441 from South Asia, 18,541 from South-East Asia, and 14,227 from Western Europe. It was discovered that the Western European population had a lower overall incidence of prediabetes than the other ethnic groups, but these differences were much more pronounced in low walkability neighbourhoods and reduced or even eliminated in high walkability areas. For instance, while prediabetes was twice as prevalent in the Sub-Saharan African and Caribbean population than in Western European populations among those residing in low walkability areas, this variation was just 20% in high walkability neighbourhoods. A similar trend was seen in the West Asian/Arab populations, with a 50% higher prevalence rate compared to Western European populations in low walkability neighbourhoods dropping to a statistically insignificant level in the high walkability areas. However, among South Asians, the incidence of prediabetes was around twice as high as Western European populations in both low and high walkability areas.





The authors stated: "The risk of prediabetes development among immigrant populations may be amplified by unexpected factors such as neighbourhood designs. We believe further research is required to guide the design of population interventions and policies to target the social and environmental factors perpetuating the development of prediabetes (and subsequent diabetes) among high-risk populations."

Diabetes Risk Associated with Spousal Obesity

OBESITY or Type 2 diabetes mellitus (T2DM) and their effects on patients' spouses were the subject of two recent studies reported in a EASD press release dated 12th September, 2017, which exposed findings that could lead to increased accuracy in recognising at-risk patients. This is the first time that research has focussed on sex-specific risk of T2DM in relation to spouses. The team, led by Dr Adam Hulman, Department of Public Health, Aarhus University, Aarhus, Denmark, hypothesised that high-risk behaviours were likely to be shared by couples, including poor eating habits and physical inactivity.

The first study enrolled 3,650 men and 3,478 women aged ≥50 years. The participants were selected from the English Longitudinal Study of Ageing (ELSA), which provided a nationally representative sample of participants. Interviews were carried out at 2.5-year intervals from 1998–2015 and T2DM diagnoses were drawn from self-reports or clinical examination. The researchers adjusted results to account for additional contributing factors, such as age, ethnicity, socioeconomic status, and obesity level. At 11.5-year follow-up, the median of new case rates of T2DM for men and women was recorded as 12.6 and 8.6 per 1,000 people per year, respectively.

Results found no statistically significant indication that a diabetic spouse increases a person's risk of developing T2DM, but there were contrasting results for men and women. In the study, a man with an obese wife was found significantly more likely to develop T2DM, with a 21% higher risk for each additional 5 kg/m^2 increase in wife's BMI, with results adjusted to account for the man's own BMI. Women's risk of T2DM did not increase with their husband's obesity; this was solely linked to their own level of obesity.

> "Recognising shared risk between spouses may improve diabetes detection and motivate couples to increase collaborative efforts to eat more healthily and boost their activity levels."

Further to these results, the team investigated the effect of a spouse with T2DM on obesity development with age. In a cohort of 7,187 men and women, it was found that living with a spouse who had T2DM led to much higher levels of obesity in individuals aged ≥55 compared to individuals whose spouse did not have T2DM.

The authors of the study commented: "Recognising shared risk between spouses may improve diabetes detection and motivate couples to increase collaborative efforts to eat more healthily and boost their activity levels. Obesity or T2DM in one spouse may serve as a prompt for diabetes screening and regular weight checks in the other. In particular, men whose wives are obese may benefit from being followed more closely."

New Device Controls Weight Loss and Type 2 Diabetes

CONTROL of Type 2 diabetes mellitus (T2DM) and obesity may become a much easier task, thanks to a new service provided by the UK's National Health Service (NHS), as presented at the EASD Annual Meeting and reported in a press release dated 12th September, 2017.

The new service, known as an 'Endobarrier' device, is endoscopically implanted and so does not require surgery. The device comprises a 60 cm plastic sleeve, which lines the small intestine. This allows the food to pass through the intestine, but prevents it from being absorbed. The device is removed after 1 year and aims to promote healthier living and encourage better habits which aid weight loss.

The study monitored the first 31 patients to receive the treatment (aged 28–62 years), out of a total of 50 who had received it, and 65 who had been accepted for the procedure. All of the patients had had T2DM for an average of 13 years, and 17 of them used insulin to control the condition. Despite having the implant, all patients were still encouraged to make lifestyle changes with regards to improving their diet and increasing exercise. The outcomes were monitored via a secure, online registry.

The study found patients had a significant, average weight loss of 15 kg, in addition to improved blood sugar control, reduced systolic blood pressure and liver fat. Those taking insulin reduced their doses from 100 to 30 units. At the time of analysis, 17 patients had reached 6 months post-treatment and 11 of those (65%) had successfully maintained weight loss improvements and diabetes control. Only two patients had their device removed early, one due to gastrointestinal haemorrhage and one due to liver abscess.

Dr Robert Ryder, City Hospital, Birmingham, UK, concluded: "This first NHS Endobarrier service demonstrates that Endobarrier therapy is highly effective in patients with obesity and diabetes that has been very hard to treat, with high patient satisfaction levels, and an acceptable safety profile." This exciting new treatment allows a surgery-free option for difficult-to-treat Type 2 diabetic, obese patients, with no need for them to remain in hospital (reducing infection risks), while being relatively safe and cost effective for the NHS.

> "This first NHS Endobarrier service demonstrates that Endobarrier therapy is highly effective in patients with obesity and diabetes that has been very hard to treat, with high patient satisfaction levels, and an acceptable safety profile."

Diabetic Patients Benefit from Six Meals a Day Rather Than Three

EATING six meals a day rather than three, whilst retaining the same calorie intake, has been shown to be beneficial for controlling blood sugar in obese patients. This study by Dr Emilia Papakonstantinou, Department of Food Science and Human Nutrition at the Agricultural University of Athens, and colleagues from Athens University Medical School, Attikon University Hospital, and Harokopio University, Athens, Greece, sought to explore the impact of meal frequency on glucose metabolism.

Forty-seven obese patients were divided into three groups; two with prediabetes and one with Type 2 diabetes mellitus. Each group was administered a specially designed weight-maintenance diet for 24 weeks, to be consumed as part of three or six daily meals. Patients followed either the three or six-meal structure for 12 weeks, before swapping to the alternate format for the remaining 12 weeks. Blood tests measuring insulin and glucose levels amongst other factors were taken at the start and end of these periods, and weight was measured every 2 weeks. Interviews assessing hunger, satiety, and desire to eat were also conducted.

Results showed that body weight remained stable throughout the study, but the six-meal group exhibited reduced glycated haemoglobin (HbA1c) and post-oral glucose tolerance test blood glucose levels, suggesting improved blood sugar control. Furthermore, the prediabetes groups showed a decrease in the occurrence of abnormally high insulin levels, as well as a shorter delay in the time taken to reach peak blood glucose following the ingestion of sugars. All three groups reported a decrease in hunger and desire to eat when following the six-meal plan.

> These results suggest that increased frequency of meals, consumed at regular times, may be a useful tool for doctors treating subjects with obesity and diabetes or prediabetes, especially those who are reluctant or unsuccessful dieters."

Dr Emilia Papakonstantinou, Agricultural University of Athens, concluded: "These results suggest that increased frequency of meals, consumed at regular times, may be a useful tool for doctors treating subjects with obesity and diabetes or prediabetes, especially those who are reluctant or unsuccessful dieters."

Lower Risk of Death Among Women with Diabetes Who Drink Caffeine

WOMEN with diabetes who regularly consume caffeine have a lower risk of death than those who do not drink caffeine at all, according to research displayed in a EASD press release, dated 14th September, 2017.

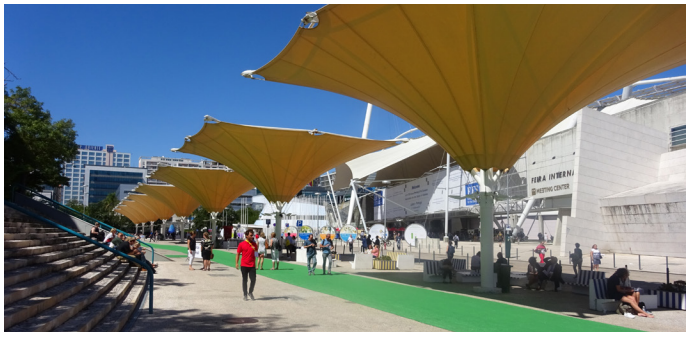
A reduction in the risk of death through consumption of caffeine has been well documented in previous studies, and researchers from the University of Porto, Porto, Portugal, with colleagues from various Portuguese institutions, sought to discover whether a similar effect would be seen in patients with diabetes.

Data relating to levels of caffeine intake and mortality in >3,000 men and women with diabetes were examined from the 1999–2010 National Health Nutrition Examination Survey (NHANES), where patients recorded their caffeine intake from coffee, tea, and soft drinks using dietary recalls. The results showed that among women with diabetes, there was a 51%, 57%, and 66% decreased risk of death in those consuming ≤100 mg, 100–200 mg, and >200 mg of caffeine per day, respectively, compared to non-consumers. However, no such effect was shown in men with diabetes. These findings were independent of factors such as age and race.

Additionally, while caffeine ingested from coffee reduced the risk of death from all causes, it was found that caffeine from tea provided a special protective effect against cancer, with women who had a high consumption of tea having an 80% lower risk of developing cancer compared to non-tea drinkers.

> Our study showed a dose-dependent protective effect of caffeine consumption on all-cause mortality among women.

The authors emphasised the importance of more studies to investigate these findings further: "Our study showed a dose-dependent protective effect of caffeine consumption on all-cause mortality among women. The effect on mortality appears to depend on the source of caffeine, with a protective effect of coffee consumption on all-cause mortality and cardiovascular mortality, and a protective effect of caffeine from tea on cancer mortality among women with diabetes. However, our observational study cannot prove that caffeine reduces the risk of death but only suggests the possibility of such a protective effect."



Transgender Diabetics Require More Specialist Support

ESTIMATES suggest that 1.4 million adults in the USA identified as transgender in 2016 and had been administered hormone therapy for gender confirmation. A study, reported in a EASD press release dated 13th September, 2017, has suggested that transgender individuals suffering from diabetes have a number of modifiable risk factors, including raised levels of triglycerides and low-density lipoproteins, that contribute to increased diabetes severity and complications, possibly as a result of gender reassignment treatment.

> “For both transgender men and women, it is critical to reduce risk factors for diabetes in order to prevent CVD and other complications.”

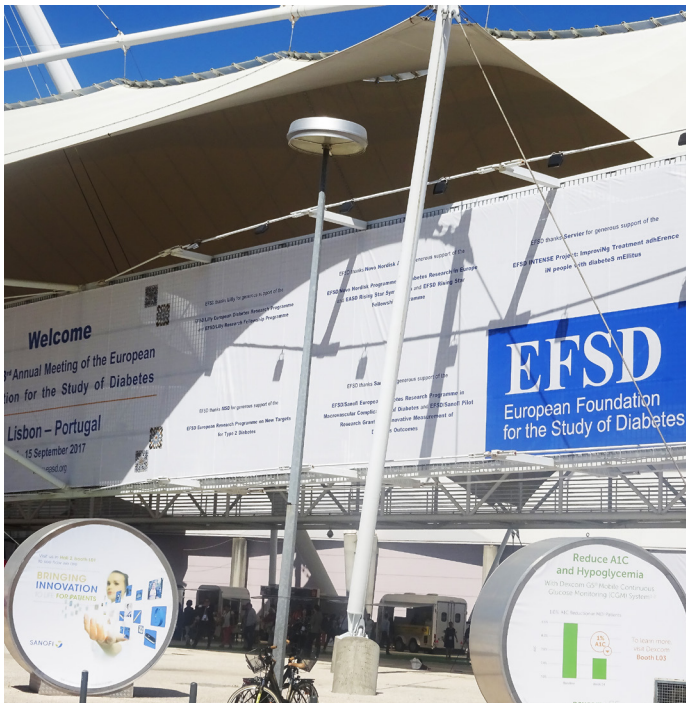
The study, led by Dr Patricia Kapsner, University of New Mexico, Albuquerque, New Mexico, USA, analysed the aforementioned modifiable risk factors of 300 transgender individuals, describing 9 of whom suffered from either Type 1 or 2 diabetes mellitus (T1/2DM). The results showed that diabetic transgender women were more likely to be obese, and exhibit higher levels of both triglycerides and low-density lipoproteins compared to non-diabetic transgender women; this was thought to be caused by the administration of oestrogen. Additionally, vitamin D levels were shown to be reduced, and dysphoria and psychosocial issues, such as substance abuse, contributed to poorer disease management.

Diabetic patients have been shown to be more likely to develop cardiovascular disease (CVD), and the hormone therapy transgender patients undergo has been shown to affect lipid profiles, blood pressure, weight, and blood glucose, possibly exacerbating this risk. “For both transgender men and women, it is critical to reduce risk factors for diabetes in order to prevent CVD and other complications,” explained the authors.

The study is limited by the small sample size, where only 9 of the 300 transgender patients suffered from diabetes (4 with T1DM and 5 with T2DM), but the investigation nonetheless highlighted a key lack of understanding regarding the management of both T1DM and T2DM in transgender patients. “We hope that our research will help boost transgender health and diabetes services to provide effective support and medication to those who need it most,” concluded the research team.

New Associations Between Cardiovascular Disease and Type 2 Diabetes Mellitus

INCREASED risk of developing and dying from cardiovascular diseases (CVD) has been found to be associated with hospital admissions where non-alcoholic fatty liver disease (NAFLD) is present. These new findings from the Scottish Diabetes Research Network were presented at the EASD annual meeting 2017, as reported in a press release from the event.



> “Because non-alcoholic fatty liver independently raises the risk of cardiovascular disease and mortality in people with T2DM, preventing the condition by avoiding unhealthy lifestyles in people with diabetes is vital.”

NAFLD results from the accumulation of fat within liver cells. It characteristically affects approximately three-quarters of obese adults who have Type 2 diabetes mellitus (T2DM). Research has previously determined a link between NAFLD and patients with CVD, but until now it had not been established whether this link was also prevalent among patients with T2DM.

The study, performed by Prof Sarah Wild, University of Edinburgh, Edinburgh, UK, and Prof Christopher Byrne, University of Southampton, Southampton, UK, analysed hospital and death record data in >133,300 adult T2DM patients, specifically looking at possible links between NAFLD and CVD. The patients were all located in Scotland, had been diagnosed with T2DM between 2004 and 2013, and had had at least one hospital admission within this period.

NAFLD was noted in 1,998 patient hospital records over the 4.7-year follow-up. It was found to be associated with an approximately 62% increase in incidence of CVD, including both first-time and current CVD events, compared to patients without NAFLD. Presence of NAFLD was also associated with a 40% increased risk of death from CVD, as well as a doubled risk of death from any cause, and 41-fold increased risk of death from liver cancer.

The authors stated: “Because non-alcoholic fatty liver independently raises the risk of cardiovascular disease and mortality in people with T2DM, preventing the condition by avoiding unhealthy lifestyles in people with diabetes is vital.” The results from this study will hopefully encourage preventative procedures for NAFLD to be enforced, as well as the research and production of new, effective, and safe treatment methods.

Type 2 Diabetes Mellitus May be Associated with Lower Risk of Aortic Aneurism

DECREASED short-term risk of aortic aneurism (AA) and aortic dissection (AD) may be associated with Type 2 diabetes mellitus (T2DM), suggests a new study presented in a press release on the 13th September at the 2017 EASD Annual Meeting in Lisbon, Portugal. The study, performed by Dr Tarik Avdic from the Swedish National Diabetes Register, Gothenburg, Sweden and colleagues from numerous Swedish University Hospitals and the Swedish Vascular Registry (Swedvasc)

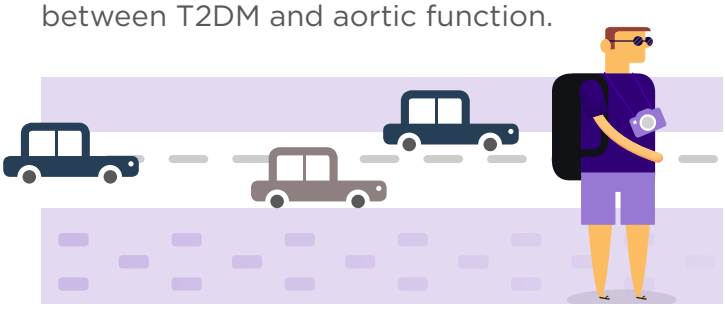
research group, also discovered T2DM patients to have a reduced risk of death following hospitalisation for AA.

> “Glycated cross-links, created by various mechanisms, in aortic tissue among T2DM patients may play a protective role in progression of aortic disease.”

Assessing data from 1998–2015, which included 448,319 patients with T2DM and 2,251,015 healthy controls, 2,878 cases of AA were reported in patients with T2DM versus 16,740 in the control group. Furthermore, cases of AD totalled just 200 in the T2DM group, compared to 2,019 in the control group. Thus, these results indicate that individuals with T2DM have a 28% lower risk of AA, and a 47% lower risk of AD compared to healthy controls.

After adjusting for variables, this study also showed a statistically significant reduction in mortality (12%) up to 2 years after hospitalisation for AA in patients with T2DM. Unadjusted survival rates following hospitalisation for AA in T2DM patients versus the control group were 84.2% versus 80.9% after 3 months; 74.7% versus 71.7% after 1 year; and 66.7% versus 64.2% after 2 years, respectively. Higher survival rates in this group were also noted following AD, but there the results were not statistically significant.

Explaining these results, the authors stated that: “Glycated cross-links, created by various mechanisms, in aortic tissue among T2DM patients may play a protective role in progression of aortic disease.” Whilst more research needs to be completed to fully understand the processes that may lead to this protective quality, researchers are confident that this finding will lead to a more complete understanding of the interaction between T2DM and aortic function.



Certain Individuals Could be Genetically Predisposed to Type 1 Diabetes Mellitus

DEVELOPING Type 1 diabetes mellitus (T1DM) is strongly associated with certain genetic variants, according to research displayed in a EASD press release dated 12th September, 2017. This is the first study to suggest that people can be genetically predisposed to T1DM, and these results could potentially explain why the disease develops at different ages.

While T1DM typically affects younger patients, it can develop in patients >30 years of age, when it is known as late-onset T1DM. In children and young adults, certain groups of genes, in particular the DR3 and DR4 alleles of a group of genes named the HLA complex, are linked to the risk of developing the disease. When these alleles occur in pairs (of either homozygous DR3/DR3 or DR4/DR4] or compound heterozygous [DR3/DR4] genotype) the risk is at its highest. The researchers from the University of Exeter, Exeter, UK, investigated whether a similar link occurs in late-onset T1DM patients.

> “Whilst all three major genotypes greatly increase risk of T1DM throughout life, population analysis has shown for the first time that DR4/DR4 specifically predisposes to T1DM over 30 years of age and carriers of this genotype have the highest risk for development of late-onset T1DM.”

They observed T1DM development in 120,000 people from birth to the age of 60 years from the UK Biobank in those individuals with the highest-risk HLA groups (DR3/DR3, DR4/DR4, and DR3/DR4). It was found that the highest-risk HLA groups made up 61% of all T1DM cases, despite comprising just 6.4% of the UK population.

Following comparison of the DR3/DR3, DR3/DR4, and DR4/DR4 high risk groups, there was a 1.2%, 4.2%, and 3.5% risk of developing T1DM during a lifetime, respectively. The mean age of diagnosis was

also 17, 28, and 38 years of age for the three genotypes, respectively, showing significant differences between these high-risk HLA groups. In the DR4/DR4 group, for example, 71% of cases were in individuals diagnosed after the age of 30 years, in comparison to just 26% in the DR3/DR3 genotype.

"Whilst all three major genotypes greatly increase risk of T1DM throughout life, population analysis has shown for the first time that DR4/DR4 specifically predisposes to T1DM over 30 years of age and carriers of this genotype have the highest risk for development of late-onset T1DM," said the authors.

New Device Improves Type 1 Diabetes Mellitus Management and Birth Outcomes

PREGNANT women with Type 1 diabetes mellitus can better manage their disease and improve birth outcomes through continuous blood sugar level monitoring using a new, implanted device, according to new research presented at the EASD annual meeting 2017, reported in a press release dated 15th September, 2017.

High blood sugar levels in diabetic, pregnant women, cause one in two neonates to experience birth complications. These can be very serious, even resulting in stillbirth. Research has attempted to improve this but with limited progress, and birth outcomes have not improved over the last three to four decades.

The trial analysed the implanted continuous glucose monitoring (CGM) device, which provides 288 glucose readings every day, in comparison to 4–8 using a traditional finger-prick test. A total of 214 pregnant women aged between 18–40 who required daily insulin to manage their condition were included in the study. They were randomly assigned into two groups: one using the CGM device and the other the finger-prick method to monitor glucose levels. Those with the device were required to wear it for approximately 24 weeks.

> "For a long time there has been limited progress in improving birth outcomes for women with Type 1 diabetes mellitus, so we are pleased that our study offers a new option to help pregnant women with diabetes and their children."

The device helped to reduced blood sugar levels by 0.2%, the study found. It helped women to maintain normal blood sugar levels (68% compared to 61% of finger-prick users), and reduce time spent with high blood sugar levels (27% compared to 32%). The birth outcomes of those using the device were improved, with fewer larger-than-average-sized

babies (53% compared to 69%), reduced neonate intensive care admission for >24 hours (27% compared to 43%) and reduced numbers of babies born with low blood sugar (15% compared to 28%).

This study represents an important new treatment option for a vulnerable population facing an unmet clinical need. Dr Denice Feig, University of Toronto and Sinai Health System, Toronto, Canada, said: "For a long time there has been limited progress in improving birth outcomes for women with Type 1 diabetes mellitus, so we are pleased that our study offers a new option to help pregnant women with diabetes and their children."

Further Study Required to Improve Pregnancy Outcomes in Diabetic Mothers

PREGNANCY outcomes remain poor in women with Type 1 diabetes mellitus (T1DM) despite significant advances in diabetes and obstetric care in recent years, suggests a study presented at the EASD 2017 Annual Meeting in Lisbon, Portugal on Friday 15th September.

> "This study provides the important, preliminary results required to spur new investigations into tackling the currently unmet need of this vulnerable demographic."

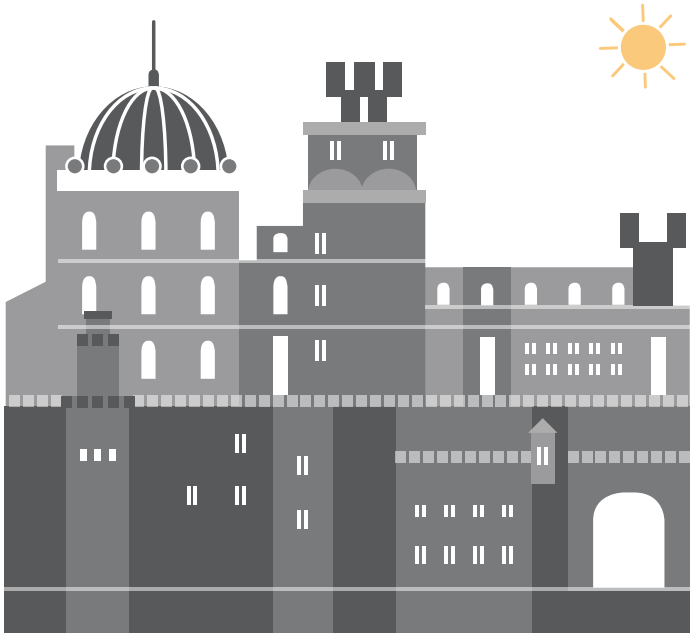
This study, by Dr Lowri Allen of the Diabetes Research Group, Cardiff University, Cardiff, UK and colleagues from Cardiff and Swansea Universities, UK used the Brecon Cohort, an almost complete register of people diagnosed T1DM before the age of 15 in Wales, UK since 1995, to compare women with T1DM aged <35 to healthy controls in terms of pregnancy outcomes. Due to its size, national coverage, and community-based nature, this cohort represents a source of data without many of the typical biases observed in similar studies, thus resulting in more reliable conclusions.

From a pool of nearly 200,000 eligible births between 1995–2013, 330 were to mothers with T1DM. Of this group, 66% gave birth via caesarean section, compared to just 18% in the general population, as well as a 4-week shorter gestation period (35.7 versus 39.7 weeks, respectively). Adverse outcomes, such as pre-eclampsia, stillbirth, and preterm birth were also significantly more common: 3, 10, and 11-times more likely than in women without T1DM, respectively. The babies born to these mothers with childhood-onset T1DM were also more likely to encounter adverse effects, such as low birth weight (twice as likely), have congenital malformations (around three-times more likely), and be admitted to hospital within the first year of life (three-times more likely).

This study formed part of a larger body of work aiming to identify individuals with T1DM who develop early complications and may benefit from new interventions, such as immunotherapy, which would seek to preserve the insulin-producing beta cells in the pancreas. "Measures to preserve beta cell function may improve outcomes and further studies are required to explore this," explained the authors. This study provides the important, preliminary results required to spur new investigations into tackling the currently unmet need of this vulnerable demographic.

Biomarker May be Able to Predict Risk of Developing Pre-Eclampsia

PRE-ECLAMPSIA (PE) risk in pregnant women with Type 1 diabetes mellitus (T1DM) can be predicted through the use of leucine-rich alpha-2-glycoprotein (LRG1) as a biomarker, according to research presented in a EASD press release dated 15th September, 2017.



Delivery of the baby is currently the only treatment for PE, which can cause complications based on the mother's gestational period. Under the NHS, PE care normally consists of careful monitoring of the woman's blood and proteinuria, and if appropriate, blood pressure medicines are administered. Therefore, new methods for early warning and specific treatments for the condition are urgently required.

The researchers, Ms Alice Cheung, Prof Tim Lyons, and Dr Chris Watson, Centre for Experimental Medicine, Queen's University Belfast, Belfast, UK, and colleagues from Australia, Norway, and the USA, aimed to discover whether LRG1, an indicator of both inflammation and angiogenesis, could be used as a predictor of PE in pregnant women with T1DM, as has previously been suggested.

A group of 62 pregnant women from the MAMPED cohort were used for the study; 44 had T1DM of which 23 later developed pre-eclampsia and 21 who did not, as well as a control group of 18 healthy pregnant women. The two groups with T1DM were matched for age, duration of diabetes, glycated haemoglobin levels, and the number of viable pregnancies. The current gold standard for predicting onset of pre-eclampsia, the sFlt enzyme biomarker, had already been measured in the patients, and blood plasma was sampled during the second trimester and analysed for the LRG1 biomarker.

It was found that in women with T1DM who developed PE, LRG1 levels were on average 25% higher than in those women who did not develop PE, which was a statistically significant difference (51 µg/mL versus 41 µg/mL). The researchers commented: "This significant increase preceded the clinical signs and symptoms of pre-eclampsia, whereas sFlt did not predict PE at this gestational age."

They concluded: "LRG1 may have utility as an early predictor of PE, and could provide novel insights into disease mechanisms for PE in diabetic women."

> "LRG1 may have utility as an early predictor of PE, and could provide novel insights into disease mechanisms for PE in diabetic women."

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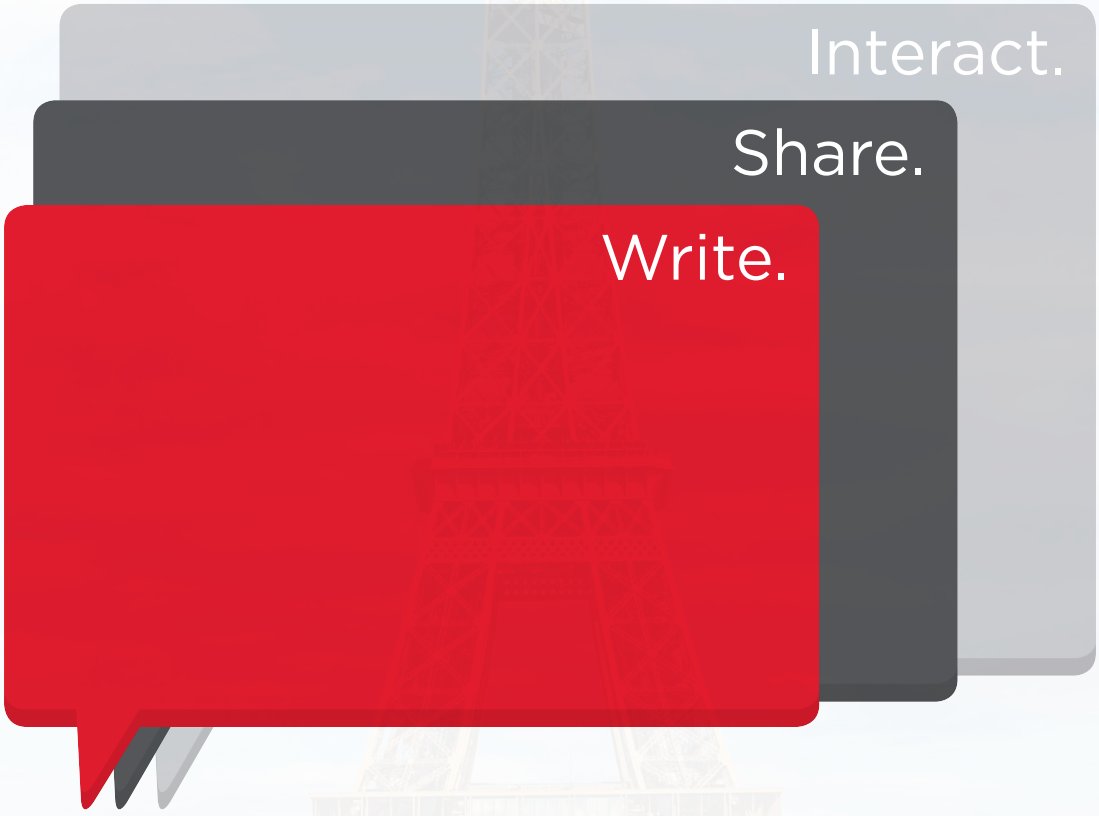

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Martijn Brouwers

Internist-endocrinologist, Department of Internal Medicine, Division Endocrinology, Maastricht University Medical Centre, Maastricht, Netherlands.

Q: What, in your opinion, have been the most exciting developments in endocrinology research in the past year in terms of the impact they have had on clinical practice?

A: After the 'thiazolidinedione-disaster' (which now probably deserves some nuancing), many clinicians and scientists were sceptical that new glucose-lowering drugs would be developed that actually reduce cardiovascular risk. Recent results from large randomised controlled trials with GLP1 agonists and SGLT2 inhibitors have demonstrated that these new drugs have positive effects on body weight, renal function, heart failure, and coronary artery disease. These exciting developments, therefore, provide new personalised treatment options for patients with Type 2 diabetes mellitus (T2DM).

Q: Similarly, what are some important research goals that have not yet been achieved in the field? What do you hope to see develop over the coming years?

A: It would be really nice if we were able to prevent Type 1 diabetes mellitus (T1DM).

Q: In your last interview with us, you talked about your research into non-alcoholic fatty liver disease in cardiometabolic disease and how it relates to T2DM, dyslipidaemia, and cardiovascular complications. Can you update us as to your progress with this?

A: Evidence is emerging that accumulation of hepatic fat is central in the development of dyslipidaemia, T2DM, and cardiovascular complications. By applying genetic epidemiology, we have recently demonstrated that not all hepatic fat that accumulates is disadvantageous for vascular health. The metabolic pathway that results in hepatic fat accumulation is likely to account for this phenomenon.

Q: Will you be attending this year's European Association for the Study of Diabetes (EASD) congress? What aspects of the event are you most looking forward to, and why?

A: At the EASD Anual Meeting there has always been a good mix of basic and clinical science. It is always great to meet new people and get new viewpoints.

Q: Do you have any advice for medical students attending the congress on how to make the most of the event?

A: Prepare before you go. Although diabetes mellitus (DM) appears to be one disease (which is already not true) it consists of many facets, such as diagnostic aspects, pathogenesis (with different research angles ranging from genetic, inflammatory, microbiotic, nutritional, lifestyle, psychological, etc.), treatment, and complications. It is prudent to decide on what you would like to learn before you go. Furthermore, it can be very instructive to interact with junior researchers during the poster sessions and learn from their experiences.

Q: In what ways do you think awareness of the risk factors for DM and other metabolic disorders needs to be improved in the general public? Are there any facets of this common condition that are surprisingly little-known by your patients?

A: I think there are still lots of misconceptions on what actually is a healthy diet. Many still believe that fresh orange juice is healthy, but are not aware of the number of calories it contains.

> "These exciting developments, therefore, provide new personalised treatment options for patients with Type 2 diabetes mellitus."

Q: One of your particular interests is in providing more individualised care for T2DM patients. Can you tell us more about your research into this and the impact it is having in clinical practice?

A: Current treatment guidelines are generally written for the 'average' DM patient, who of course does not exist. We are currently investigating whether we can identify patients with different care needs already, at the moment they are diagnosed.

Q: What advice would you give to a medical student who is considering endocrinology as a specialism?

A: Ask an endocrinologist whether it would be possible to join an endocrine practice for a day (or two), so you can really experience what the profession is like.

Q: If you could cure one metabolic disease, which would it be and why?

A: Difficult question. There are many rare, inborn errors of metabolism that, in my view, deserve more attention, but if I really would need to choose I would go for T1DM. This relatively frequent metabolic disease generally develops at a young age. From that moment, patients are confronted daily by their disease when they eat or exercise. A break is not allowed. They are trapped between care providers asking them to do a finger prick four-times a day and warning them about all the horrible complications that can happen if glucose control is not optimal, and the fear of hypoglycaemia as a consequence of this tight glucose control. This should change.

Ellen Blaak

Professor of Physiology of Fat Metabolism, Department of Human Biology, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre, Maastricht, Netherlands.

Q: What first inspired you to pursue a career researching energy and substrate metabolism in the aetiology of chronic metabolic diseases? What aspects particularly interest you within this area?

A: My interest was first raised during my studies into Human Nutrition in Wageningen, Netherlands, when I had to delve into the biochemistry of metabolism and subsequently during my period of practical work in Cambridge, UK. In that period, I studied metabolism during prolonged fasting in lean and obese humans. I noticed that both groups differed greatly in metabolic responses and that textbook knowledge on this issue was very limited and inconsistent with what we found. This inspired me to proceed in metabolic research. So, I continued my research in that direction at Maastricht University, Maastricht, Netherlands. Our research is very much focussed on a detailed understanding of human physiology *in vivo* (gut-adipose tissue-liver-muscle cross-talk) and combining that with more mechanistic *in vitro* and molecular research at tissue level in the areas of substrate metabolism in obesity, obesity-related insulin resistance, and related cardiometabolic diseases. Besides studying aetiology, a main focus is studying the impact of diet and lifestyle in the prevention and treatment of obesity and cardiometabolic diseases. My main drive is to deliver knowledge that can be used for more effective prevention and treatment in the areas of lifestyle and nutrition and nutritional guidelines, but also with respect to pharmacological treatment.

Q: To what extent has our understanding of the physiology of fat metabolism developed since you began your career?

A: In many aspects. At the beginning of my career, for instance, the Randle cycle was the most plausible concept for explaining muscle insulin resistance. During my PhD research, a major finding was that in the obese insulin resistant state, there was a reduced ability to increase fat mobilisation as well as skeletal muscle fat oxidation during

stimulation of the sympathetic nervous system, and our hypothesis was that an impaired capacity to regulate fat oxidation might play a role in the aetiology of insulin resistance. By then, we had a hard time convincing the reviewers for future funding of this idea, but we were saved by the fact that at the same time there came a lot of evidence from the USA on reduced skeletal muscle fat oxidation and metabolic inflexibility as a putative factor in the development of insulin resistance. Since that time (early 1990s), there has been an enormous interest on the concept of ectopic fat accumulation in the aetiology of chronic metabolic diseases.

Also, insight into the fact that it is not adipose tissue mass, per se, but rather a disturbed functionality of adipose tissue, that is of major importance in the aetiology of insulin resistance became more prominent. Thus, adipose tissue was no longer seen as an inert storage depot but as a metabolically active organ in the dynamics of fatty acid metabolism and as an endocrine and inflammatory organ linking obesity to chronic metabolic diseases.

Lifestyle intervention may be effective in the prevention of diabetes mellitus and reduction of cardiometabolic risk. There is increasing insight that we have to study intervention effects, taking factors like the metabolic phenotype and the environment into account. For instance, mechanisms responsible for lipid-induced insulin resistance may depend on dietary fat quality. People with very pronounced liver insulin resistance may benefit from another diet composition or pharmacological intervention compared to individuals with peripheral insulin resistance. We really need prospective studies addressing the response to intervention based on a more personalised approach to optimise the prevention and treatment of chronic metabolic diseases.

Q: You recently co-authored a study investigating the effects of colonic administration of physiologically relevant short-chain fatty acid (SCFA) mixtures on human substrate and energy metabolism. Please could you briefly describe the main study findings and the implications of these results?

A: SCFA are important products of the fermentation of dietary fibres by our gut microbiota. The main findings were that administration of SCFA in the colon has a significant impact on human energy expenditure and fat oxidation, stimulates the satiety hormone PYY, and may reduce low grade inflammation, thus resulting in improved metabolic health when effects translate into the longer term. Of note, these effects were only apparent when these SCFA were administered in the distal part of the colon and not when administered in the proximal colon. When administered distally, the SCFA reached physiologically relevant concentrations (in particular acetate) in the systemic circulation since they bypassed the liver for a larger part as compared to when administrated in the proximal colon. This may have important implications for dietary intervention strategies where we currently focus on combinations of dietary fibres, and possibly proteins, resulting in a very slow fermentation and/or a very high SCFA production in the more distal part of the gut, which may lead to more pronounced improvements in metabolic health.

Q: You have conducted significant research into disturbances in fatty acid metabolism in the aetiology of obesity, insulin resistance, and Type 2 diabetes mellitus. Reflecting on this research, what would you consider your greatest achievements and most influential discoveries to be? What impact are they likely to have for clinicians in the future?

A: I think we were at the forefront of the finding that impairments in the capacity to mobilise and oxidise fat early in the obese state (i.e. metabolic inflexibility) may, on one hand, result in a reduced capacity to adapt to a Western high-fat diet and thus may play a role in the development of obesity. On the other hand, it also may result in ectopic fat accumulation, adversely related to metabolic health. In the years thereafter, we studied these mechanisms in more detail, focussing on tissue specific mechanisms and the inter-organ

crosstalk (gut-adipose, tissue-muscle) in obesity, obesity-related insulin resistance, prediabetes, and Type 2 diabetes mellitus, and studied whether indicated disturbances could be reversed by lifestyle and pharmacological interventions. Among other things, we showed that:

- Lipolysis in subcutaneous adipose tissue is characterised by both catecholamine and atrial natriuretic peptide resistance and that an impaired lipolysis could trigger an impaired adipose tissue mitochondrial function.
- Dysfunctional human adipose tissue may be characterised by hyperoxia rather than by hypoxia, the latter of which has mainly been shown in animal studies.
- The obese insulin resistant muscle is characterised by an increased extraction of liver-derived triacylglycerols, by an imbalance in lipase expression and activity, caused by an altered localisation of bioactive lipid metabolites, and by an impaired lipid turnover, the latter after a high saturated fatty acid meal, but not after a high polyunsaturated fatty acid meal.
- The disturbed muscle fatty acid handling is present in subjects with impaired glucose tolerance but not in subjects with impaired fasting glucose, indicating that these two prediabetic states may represent distinct pathways towards Type 2 diabetes mellitus.
- Bioactive food components, in particular a combination of polyphenols (resveratrol and epigallocatechin gallate), may be effective in increasing fat oxidation and mitochondrial function.

More recently, the gut microbiota has received increasing attention due to its putative role in the aetiology of obesity and diabetes mellitus. We recently showed that pronounced manipulation of our gut microbiota by antibiotics has no clinically relevant impact on energy and substrate metabolism, insulin sensitivity, and metabolic health in prediabetic individuals. This contradicts many rodent studies, illustrating that we have to take care in translating rodent data to the human situation. This does not exclude a role for the gut microbiota during other interventions, such as diet. Indeed, we also recently showed that SCFA formed in the fermentation of indigestible carbohydrates by our gut microbiota may have pronounced effects on metabolic profile. Insight into these mechanisms may provide a target for more effective pharmacological intervention, as well as more targeted lifestyle guidelines.

Q: What lifestyle and dietary advice would you give for curbing the onset of obesity and Type 2 diabetes mellitus?

A: I think a lifestyle according to guidelines of healthy nutrition (currently the Dutch dietary guidelines are to eat more plant based foods, increase dietary fibre, reduce saturated fat, reduce sugary drinks) and increased daily physical activity is a very effective way in reducing diabetes risk and achieving body weight control when people are guided and facilitated to incorporate these changes in their daily lifestyle. Lifestyle intervention studies (Diabetes Prevention Study, European Diabetes Intervention Prevention Study) have been shown to reduce diabetes risk by >50%. This gradual lifestyle change is, in the long term, much more effective than all the currently advocated diets only directed towards weight loss. Although such diets result, most of the time, in a considerable weight loss, this is followed by weight regain in 90% of people. Unfortunately, we are not very successful in incorporating a healthy lifestyle in our lives, since obesity and diabetes mellitus are still on the rise. I think we need joint actions from stakeholders, such as healthcare workers, politicians, and the food industry to reverse this increase, otherwise obesity will become the norm with all the related health consequences.

Within the context of a healthy lifestyle, I think that there is a need for increased movement towards a more personalised approach in the field of nutrition. Not all people respond effectively to lifestyle intervention: around 30% do not respond very well. This may depend on your metabolic phenotype, among other factors. Research in that area may certainly help to optimise the metabolic response to lifestyle interventions resulting in a better compliance. Also, bioactive ingredients like

polyphenols or other functional foods may help in the maintenance of intervention effects. Last but certainly not least, there is an important role for physical activity.

Q: As well as dietary, exercise, and behavioural techniques, pharmacological intervention is another option used to combat obesity. At what point should pharmacological intervention be considered? What is your experience of using pharmacological methods and what impact have these interventions had on patients?

A: Pharmacological intervention may help for body weight control, but this should always be in the context of a simultaneous focus on lifestyle changes. I think lifestyle changes should always be the first priority, but drugs may help in achieving body weight control. There are very few obesity drugs; there may be new developments in the field of gut-related drugs.

We only perform pharmacological studies in an experimental setting and, since I am not a clinician, not in a treatment setting. We have done trials with a GLP1 agonist, liraglutide, with the angiotensin receptor blocker, valsartan, and with the lipolysis inhibitor, acipimox, studying the effect these drugs may have on energy and substrate metabolism, body weight, and insulin sensitivity.

Q: Please describe your role as Secretary at the European Association for the Study of Obesity (EASO). What are the main contributions that this organisation makes, in your view?

A: EASO is a federation of professional membership associations from 32 European countries. It represents scientists, healthcare practitioners, physicians, public health experts, and patients. EASO is in official relations with the World Health Organization (WHO) Regional Office for Europe and is a founding member of the European Union (EU) Platform on Diet, Physical Activity, and Health. My major role within EASO is having responsibility for the organisation of the European Congresses on Obesity. I am also involved in other related meetings (young investigators) and educational activities, scientific advisory boards of EU projects, and a nutrition working group working on guidelines for obesity management. Currently, EASO is expanding rapidly, as well as expanding its education for young scientists and training of healthcare practitioners in obesity management. There is a European network of Centers for Obesity Management with regular meetings, as well as a scientific advisory board, a prevention task force, and a childhood obesity task force.

Q: Are there any different topics that you would be interested in researching in the future?

A: At the moment, we are starting a large project in the field of personalised nutrition. In this project, we have data available from earlier large European dietary intervention studies on macronutrients and metabolic health. These data will be used to design a personalised dietary intervention targeted at the metabolic phenotype. We will investigate the added value of this 'tailor-made' intervention in normalising glucose control, and subsequently test whether we can develop more personalised nutrition advice for people in real-life situations. I hope, and expect, that this project will provide a proof-of-concept of a more personalised lifestyle approach. This will open up opportunities for targeted intervention strategies in the prevention of obesity, diabetes, and cardiovascular diseases. Furthermore, we are interested in sex-specific differences in metabolism, the impact of environmental oxygen tension on metabolism, and the impact of microbial fermentation products on metabolic health and their interaction with diet. Within these projects we will study tissue-specific and inter-organ fat and substrate metabolism to obtain insight in the mechanisms of action.

Q: What do you foresee as the biggest challenges facing the field of diabetes over the next 5 years?

A: As indicated above, one of the challenges may be a more personalised prevention of diabetes, which may improve outcome. But first the evidence for the effectiveness of such an approach must be provided. The biggest challenge may be to achieve a reversal of the obesity epidemic with its positive consequences for diabetes prevention.

> Within the context of a healthy lifestyle, I think that there is a need for increased movement towards a more personalised approach in the field of nutrition.

Q: What is your opinion of the healthcare service's approach to obesity in the Netherlands? How does this compare with other parts of Europe and what could other countries learn from the Dutch experience?

A: In the Netherlands, a lot of initiatives are taken and relevant stakeholders work together at all levels. The Ministry of Health in the Netherlands facilitates several initiatives and many of these initiatives are monitored. There is for instance, a care standard overweight, and a Care 4 Obesity initiative where professionals from healthcare organisations from the area, child care, and schools form a team in treating childhood obesity (integrative care). Also, there is an initiative called 'Young People at Healthy Weight (JOGG)' for an integrated approach in obesity prevention, already implemented in around 100 villages or cities throughout the Netherlands. I think this practice and evidence-based approach can serve as an example for other countries that may not have developed such initiatives yet.

Of note, the prevalence of overweight and obesity is still on the rise worldwide, including in the Netherlands. This raises the question as to whether we have to prioritise these initiatives even more, including financially. In that respect, an evidence based, more personalised approach may help. In addition, more strict measures and regulations may be required, for instance with respect to food marketing (in particular children-directed food marketing) and food taxes, as well as other lifestyle-related measures to really reverse this epidemic.

Nikolaos Tentolouris

Associate Professor in Medicine and Director of the Diabetes Centre, 1st Department of Propaedeutic Internal Medicine, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital, Athens, Greece.

Q: After graduating with your Medical Diploma, you decided to further specialise in internal medicine, more specifically diabetes mellitus. Was there something that initially piqued your interest in the field?

A: During my speciality in internal medicine, I had the opportunity to work on diabetes mellitus because the hospital department had a large diabetes centre. I was struck by the fact that diabetes mellitus patients had, like cardiovascular (CV) diseases at a young age, nephropathy, retinopathy, neuropathy, and problems with the feet, which are all problems a physician may face. At the same time, I started working on obesity and metabolism and I had the opportunity to do research on the role of diet induced thermogenesis on development of obesity and the role of the autonomic nervous system activity in obesity.

Q: Could you describe for us what your duties and responsibilities are as Associate Professor in Medicine and Director of the Diabetes Centre, Athens University Medical School, Laiko General Hospital, Athens, Greece?

A: I am responsible for the management of patients attending the outpatient diabetes clinic, diabetic foot clinic, and obesity clinic. I am also responsible for the training and education of postgraduate doctors and physicians on diabetes mellitus and its complications as well as obesity management. I also participate in the education of undergraduate

medical and dentistry students, as well as the education of residents in internal medicine and diabetes mellitus. Since 2016 I have also been the chief of the master of science in the medical school of our University in diabetes mellitus and obesity.

Q: You have participated in a number of diabetes clinical trials (Phase II–IV) as sub-investigator, co-investigator, and principal investigator. Could you give us an insight into any key factors that must be considered when designing clinical trials, as well as your responsibilities throughout the trial's duration?

A: Key factors in designing clinical trials are the clear definition of the primary and secondary endpoints, clear description of inclusion and exclusion criteria, and correct methodology. The most important thing is to follow the correct methodology throughout the trial because methodological errors cannot be corrected.

The responsibility of the investigators in clinical trials involves response to feasibility questionnaires that start months before the initiation of the clinical trial, corrections in the protocol, submission of the protocol to ethics committees and to national drug organisations, recruitment of patients/participants, close follow-up of the participants according to the protocol needs, entry of the data to the database of the trial, completion of the source documents, prompt reply to queries from the authorities, co-operation with the trial co-ordinators, participation in meetings for the trial and audits by the authorities, and safe keeping of the source data after completion of the trial. It also involves correction of the manuscript and abstracts of the research work to be presented in congresses and to be published in journals.

Q: In your opinion, what are some of the biggest challenges that diabetes researchers will face over the next decade?

A: Challenges in diabetes research include clarification of the mechanisms of newer antidiabetic medications (SGLT2 inhibitors, GLP1 analogues), and reducing CV events and CV mortality. They also include the development of new medications for the management of fatty liver disease (which is very common in patients with diabetes), the role of environmental factors in the epidemic of Type 2 diabetes mellitus, clarification of the mechanisms and potential interventions for the reduction in the high prevalence of cancer in patients with diabetes, and the development of new biomarkers, better than glycated haemoglobin (HbA1c) for the follow-up of patients with the disease as well as genetic biomarkers to know the people with diabetes that are prone to develop specific complications. In addition, the evolution in technology and the potential development of the artificial pancreas will be an exciting area of diabetes research.

Q: How has the field of diabetes changed since you began your career? What are some of the most notable developments you have witnessed?

A: The field of diabetes management has changed completely since I began my career. The most important developments are the role of hyperglycaemia in micro and macro-vascular complications, the knowledge of the natural history of Type 2 diabetes mellitus, the role of incretins and the kidney in the pathogenesis of Type 2 diabetes mellitus, and the developments of new insulins and antidiabetic medications for the management of diabetes. When I was a medical student the only insulins that were available were the isophane and the soluble insulins; now there are long-acting insulin analogues and short-acting insulin analogues that more closely mimic the physiologic insulin secretion and action. In the past the only available antidiabetic medications were metformin, sulfonylureas, and acarbose; now new classes of antidiabetic medications with a unique mode of action are available, including DPP4 inhibitors, glitazones, SGLT2 inhibitors, and GLP1 analogues; today it is easier and safer to achieve good diabetes control with safety.

Q: You currently participate in several national and international scientific societies. What benefits do these organisations offer medical professionals? Could you provide us with a little more information about your responsibilities within the societies?

A: Scientific organisations are very important for continued postgraduate medical education. Both national and international organisations organise congresses, webinars, training courses, and meetings that are very important for the information of the medical community in the developments of science in the field of diabetes mellitus and internal medicine.

In these societies, I participate in the organisation of the scientific programmes and in the selection of the speakers. I also participate actively during the meetings to clarify issues and to answer questions. The scientific organisations I participate in also serve as counsellors to the authorities and the policymakers via the organisation of plans and/or therapeutic protocols for diabetes mellitus.

One of the most important activities we had at the European Association for the Study of Diabetes (EASD) in May 2017 was that we organised a high scientific level event in the European Parliament in Brussels for Diabetes and Technology in diabetes. In addition, we informed the European Parliament of the current situation of diabetes in Europe and the activities the European Union (EU) needs to undertake to prevent diabetes and to fund diabetes research.

Q: One of your most recent publications focusses on the association between anti-diabetic medications and CV safety in patients with Type 2 diabetes mellitus. What key conclusions were drawn from your review of our current knowledge about the CV safety of older and newer anti-diabetic medications?

A: In recent years, one of the most widely discussed topics is the CV safety of anti-diabetic medications. The data for the older anti-diabetic agents are less clear. According to the published literature, metformin is the first-line agent for the treatment of Type 2 diabetes mellitus and seems to have cardio-protective effects. The choice of the second-line agent, when metformin monotherapy fails to achieve HbA1c targets is less clear. In light of the findings of the EMPAREG OUTCOME, the LEADER, and the SUSTAIN 6 trials, empagliflozin, liraglutide, and semaglutide seem reasonable options as second-line agents for patients with CV disease. Sulfonylureas, on the other hand, with the exception of gliclazide, should be avoided in those patients, although CV safety trials are still lacking. In individuals without CV disease, any of the other classes of anti-diabetic medication can be selected on a patient-centred approach. Saxagliptin, alogliptin, sitagliptin, and lixisenatide have been evaluated in CV safety trials and have neutral effects on CV outcomes, while pioglitazone may have some CV benefits. However, saxagliptin and probably alogliptin should be avoided in patients with heart failure, while pioglitazone is contraindicated in this population.

Q: Following on from the previous question, how important is it to disseminate this information to healthcare professionals within the field? Will these findings have an impact on existing evidence-based recommendations for the management of diabetes?

A: The information we have from these large, randomised, multicentre, placebo control trials is that SGLT2 inhibitors and GLP1 analogues not only improve diabetes control, but at the same time reduce CV mortality in patients with Type 2 diabetes mellitus who have established CV disease. It is very important that these findings are adopted by healthcare professionals and to offer these treatments to those patients who need additional treatment. The findings of these trials have changed the clinical practice recommendations by the American Diabetes Association (ADA) and the EASD and suggest that patients with established CV disease can benefit from these new treatments.

Q: Are there any aspects of diabetes research that you have not yet had a chance to explore, or would like to investigate further in the next few years?

A: The areas of diabetes research I would like to work in are the development of genetic biomarkers that will help to identify people prone to develop Type 1 diabetes, and people with diabetes that have the genetic predisposition to develop specific complications from the disease. I would also like to do research on the association of diabetes with cancer, as well as the development of new treatments that help regulate pancreatic islets.

> The new treatments with newer antidiabetic medications and insulin analogues have completely changed diabetes management; therefore, physicians need to know, in depth, the modern management of diabetes mellitus.

Q: What advice would you give to young medical students considering specialising in the field of diabetes?

A: Diabetes is the most common metabolic disease worldwide, affecting 6–10% of the general population. The area of diabetes today is exciting in both basic and clinical research, as well as in clinical practice. There are many areas in the pathogenesis of diabetes and its complications that remain to be explored. The new treatments with newer antidiabetic medications and insulin analogues have completely changed diabetes management; therefore, physicians need to know, in depth, the modern management of diabetes mellitus. I suggest strongly medical students who have an interest in diabetes, metabolism, and research join the diabetes community and to work in the field of diabetes mellitus.

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SESSION 1: BASAL INSULINS: STILL INNOVATING AFTER ALL THESE YEARS

This Sanofi sponsored symposium, titled 'Evolving Standards and Innovation in Diabetes Care', took place on 11th September 2017, as part of the 53rd Annual Meeting of the European Association for the Study of Diabetes (EASD) in Lisbon, Portugal.

Symposium Chair

Elizabeth Seaquist[1]

Session Chair

Robert Ritzel[2]

Speakers

Jeremy Pettus,[3] Kamlesh Khunti[4]

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MEETING SUMMARY

Therapeutic basal insulin has evolved considerably over the past 90 years. A series of landmark innovations has led to the availability of therapies that closely mimic the physiological effects of endogenous insulin and serve as an invaluable addition to the treatment armamentarium for diabetes. Advances in basal insulin have led to the development of the newer basal insulin analogues, namely insulin degludec and insulin glargine 300 U/mL (Gla-300). The desirable pharmacokinetic (PK) and pharmacodynamic (PD) properties of these basal insulins, such as a prolonged duration of action (≥24 hours), may translate into a number of clinical benefits for the patient e.g., a simple, once-daily injection schedule and flexible injection timings.

The technologies supporting patients with diabetes have also evolved considerably in recent years. Continuous glucose monitoring (CGM) can provide insights into some of the challenges faced by patients with diabetes, e.g., glycaemic excursions and the impact of injection time, and may become an alternative

to the current gold standard glycated haemoglobin (HbA1c). Real-world evidence is also providing fresh perspectives on the effectiveness of basal insulins in clinical practice. Today, innovative methods for real-world evidence collection, analysis, and interpretation are helping to generate robust datasets with external validity. Taken together, these innovative approaches are generating an integrated evidence base that is improving our understanding of how basal insulin therapy can be optimised for the benefit of our patients with diabetes.

Symposium Overview

Doctor Elizabeth Seaquist

Diabetes care is evolving. Advances in our understanding of diabetes pathophysiology and treatment now permit individualised therapy based on patient-centred treatment plans that provide the best evidence-based therapies, while minimising personal burden. This personalised approach to treatment requires that therapeutic goals go beyond glycated haemoglobin control to include patient identified outcomes of value such as side effects, cost, and minimal interference with daily living.

Introduction

Professor Robert Ritzel

Landmark innovations in therapeutic basal insulin over the past 90 years, including the development of recombinant human insulin and the introduction of long-acting basal insulin analogues, have led to the availability of therapies that aim to closely mimic the physiological effects of endogenous insulin. Current efforts in diabetes management are looking beyond traditional indicators of glycaemic control and treatment efficacy, to consider the overall patient experience. HbA1c represents the current gold standard for assessment of glycaemic control. However, HbA1c measurement does not take into consideration glucose variability, which may be linked to the pathogenesis of diabetes complications and hyperglycaemia.[1] Furthermore, glucose variability may impact diabetes management and, in turn, patient quality of life.[2] CGM, a method of measuring glucose variability that can provide real-time data, is now a standard of care in the management of patients with Type 1 diabetes mellitus and is increasingly being used by patients with Type 2 diabetes mellitus. Innovation in basal insulins encompasses not only intrinsic improvements in the products themselves, but also how emerging diabetes-related technologies (e.g., CGM) and evidence from real-world studies can together provide an integrated understanding of the effectiveness of existing basal insulin analogues in clinical practice.

Enhancing Confidence with Newer Basal Insulins

Doctor Jeremy Pettus

Key Points

- Innovations in basal insulin have led to the development of the newer basal insulins, namely insulin degludec and Gla-300.
- Clinical studies demonstrate that insulin degludec and Gla-300 are associated with improved PK and PD profiles, and a reduced rate of hypoglycaemia, compared with insulin glargine 100 U/mL (Gla-100).
- CGM profiling and glycaemic variability analyses are providing real-time insights on glycaemic outcomes with basal insulin use in patients with diabetes.
- Taken together, these data should enhance confidence in the use of the newer basal insulins in clinical practice and support appropriate titration for the benefit of our patients.

Innovations and advances in therapeutic basal insulin have led to the development of the newer basal insulins, insulin degludec and Gla-300. Developments in investigational approaches now permit simultaneous and quantitative study of both the PK and PD properties of insulin preparations using the glucose clamp technique (Figure 1).[3]

Preliminary evidence from glucose clamp studies with the newer basal insulins have demonstrated a flatter PK/PD profile, more evenly distributed glucose-lowering effects, and lower between day glucose variability with insulin degludec and Gla-300 versus insulin Gla-100.[4-9]

Continuous Glucose Monitoring Analyses and the Patient Experience

While PK/PD and clinical studies can provide insights into the effect and efficacy of basal insulin analogues in an investigational setting, in the real

world patients with diabetes face many challenges with regard to optimising their therapy, primarily achieving glycaemic control while avoiding hypoglycaemia.[10] Although HbA1c represents the current gold standard for assessment of glycaemic trends in different populations, it is not necessarily an appropriate metric for measuring glucose control at the individual patient level, due to the wide range of glucose concentrations and glucose profiles that are available for a given HbA1c value.[10] As an estimate of mean, HbA1c based on a measurement cannot provide an accurate report of within-day or day-to-day fluctuations in glucose control and may potentially 'mask' episodes of significant dysglycaemia, e.g., hypoglycaemia, which can impact clinical outcomes and patient quality of life. CGM offers an alternative approach for assessing glycaemic control that measures changes in mean glucose concentrations in real time. As daily changes in glucose concentrations vary substantially from one individual to the next, it is important to note that multiple patients with the same HbA1c may exhibit very different CGM profiles.[11] CGM profiling was recently published in a randomised, 16-week, exploratory study to compare glucose control in adults with Type 1 diabetes mellitus receiving either Gla-300 or Gla-100, self-administered in the morning or evening.[12] Analysis of the obtained CGM profiles revealed that mean 24-hour glucose profiles were smoother with Gla-300 versus Gla-100, irrespective of the injection time (morning or evening; Figure 2),[12] findings which were consistent with the known PK/PD profile of Gla-300.[6,7]

Additional analyses demonstrated that Gla-300 was associated with a lower rate of nocturnal, confirmed (<54 mg/dL by self-monitored plasma glucose), or severe hypoglycaemia compared with Gla-100 (four versus nine events per participant-year; rate ratio: 0.45; 95% confidence interval [CI]: 0.24–0.82).[12] In terms of glycaemic variability, all metrics for intra-subject, within, and between-day glucose variability were numerically lower for participants receiving Gla-300 versus Gla-100.

Data from CGM profiling and glycaemic variability studies are providing new and important insights on clinical outcomes with basal insulins in patients with diabetes. These data should enhance confidence in the use of the newer basal insulins in clinical practice by providing physiological context to real-world observations from heterogeneous patient populations.

Translating the Evidence into the Real World: New Perspectives and Old Challenges

Professor Kamlesh Khunti

Key Points

- Well-designed, real-world studies complement randomised controlled trials (RCT) by providing a fresh perspective on the use of basal insulins in the treatment of diabetes.
- Many different sources of real-world data are now available, such as claims databases, electronic medical records, patient registries, and health surveys.
- It is important to be aware of the strengths and limitations associated with each of these datasets.
- Improvements in data collection techniques and analytical methodologies have enabled real-world evidence studies to look beyond pre/post switch analyses and directly compare newer basal insulins in order to guide clinical practice.

Real-world studies offer a different perspective on the evaluation of therapies compared with RCT. While RCT determine the efficacy of therapies in a controlled setting (i.e. can it work?), real-world studies evaluate the effectiveness of therapies in a clinical setting (i.e. does it work?).[13,14] Although RCT have proved essential in establishing the efficacy and safety of pharmaceutical products, translating the results of RCT to a broader patient population remains challenging, in part because RCT are conducted in a highly controlled environment that excludes large proportions of real-world patient populations.

Going Beyond Randomised Controlled Trials Data

Pragmatic trials and observational studies are a vital component in the continuum of clinical research. These real-world studies are conducted under usual-care settings and in broad patient populations to generate clinical data which complements that obtained from efficacy-focussed RCT, such as registration and long-term Phase III studies.[15] As real-world studies can evaluate factors that impact treatment effectiveness in real-life, they provide a means to answer questions that cannot be addressed by RCT. Recent technological advances have led to improvements in analysis techniques for real-world studies, such as approaches for accounting for confounders and minimising bias.[15]

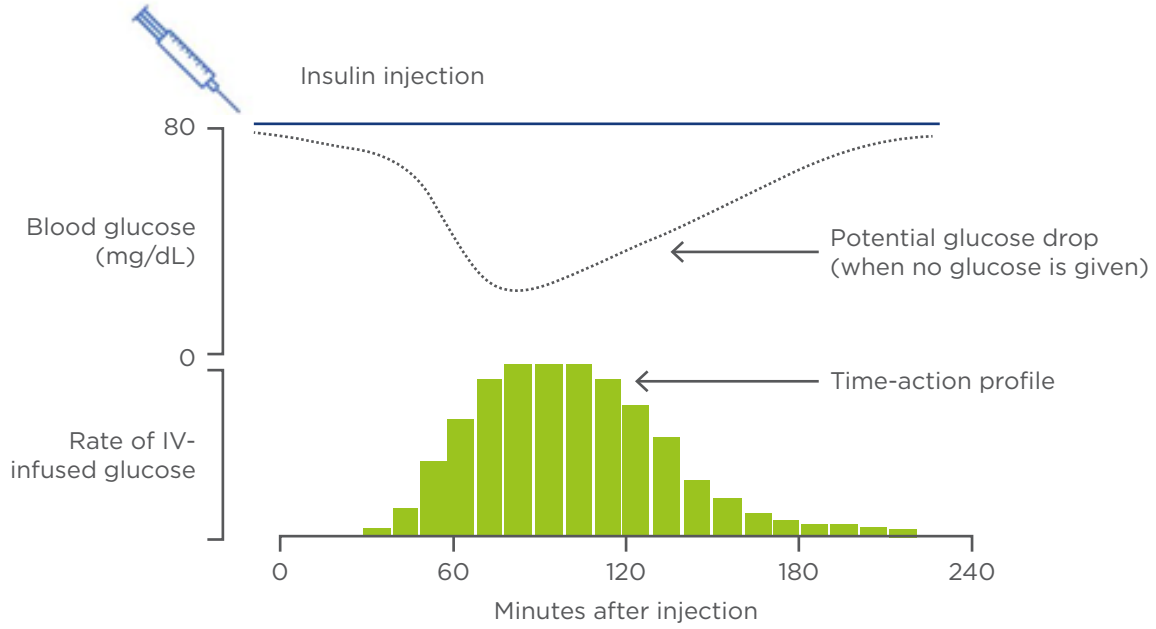

Figure 1: The glucose clamp technique: A means to quantify action of basal insulin.
IV: intravenous.
Adapted from Heinemann and Anderson.[3]

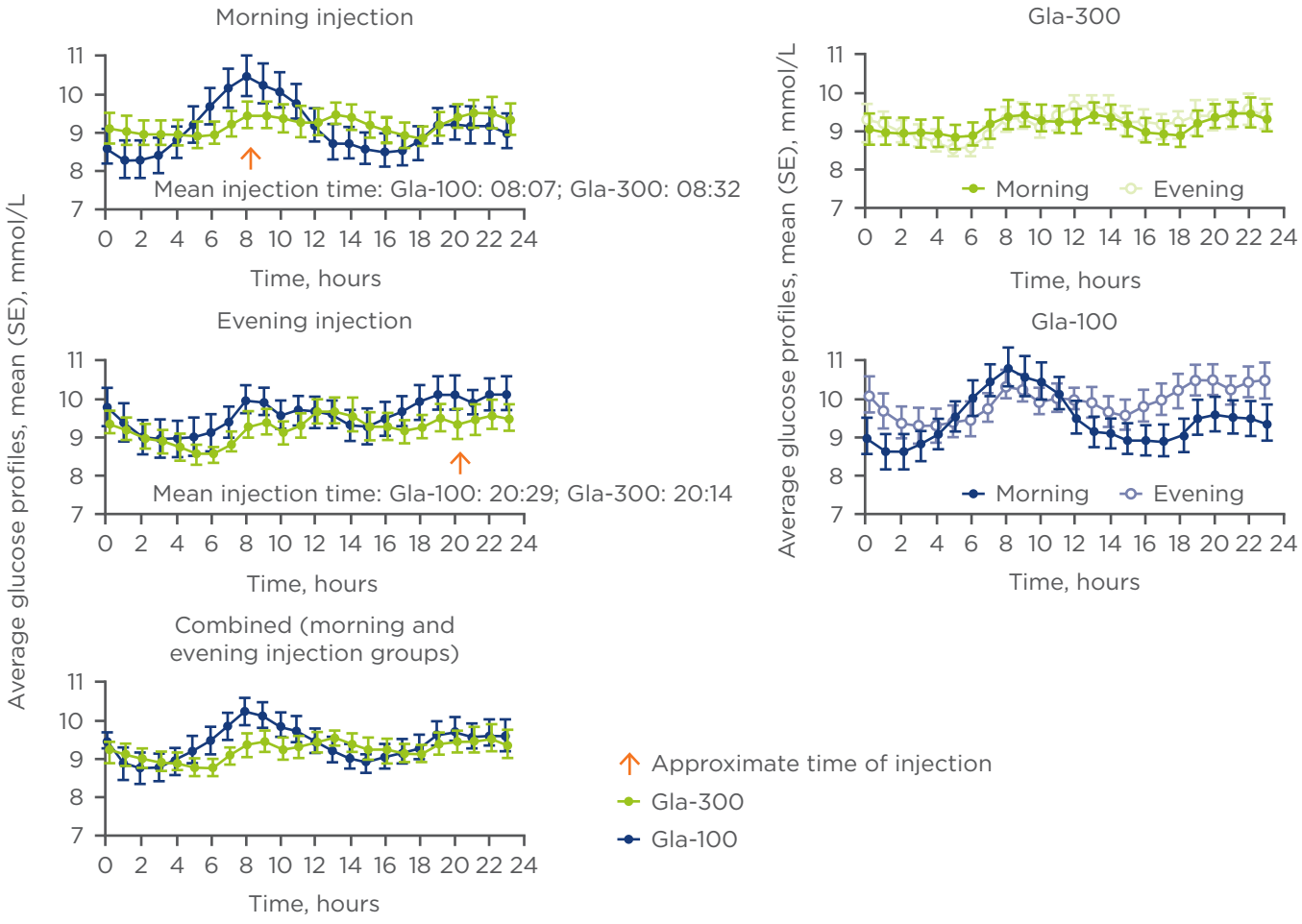

Figure 2: The glucose clamp technique: A means to quantify action of basal insulin.
Gla-100: insulin glargine 100 U/mL; Gla-300: insulin glargine 300 U/mL; SE: standard error.
Adapted from Bergenstal et al.[12]

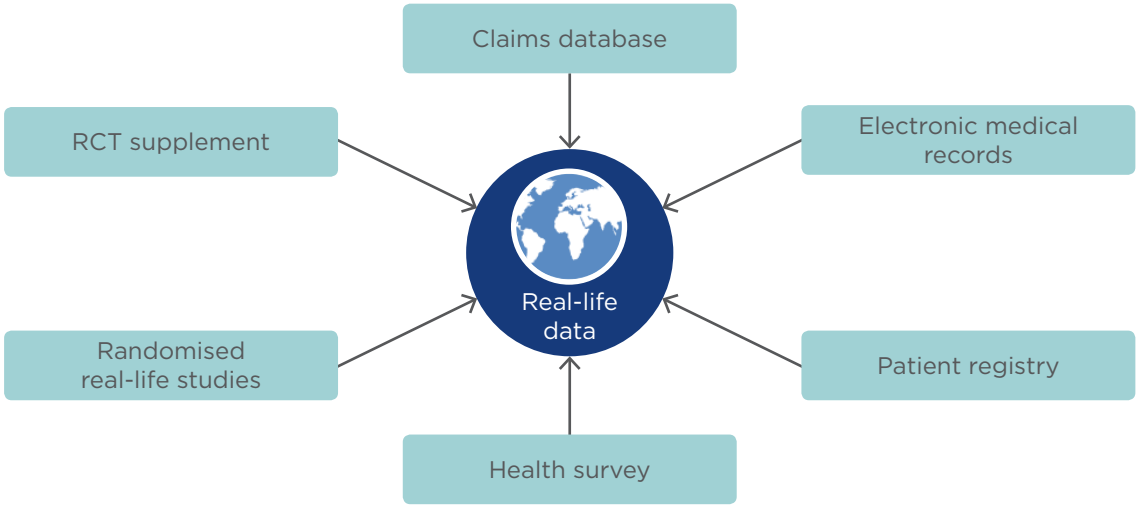

Figure 3: Sources of real-world data.[18–20]
RCT: randomised controlled trial.

Interest in real-world studies and the evidence they can generate is growing among scientific, regulatory, and payer communities in both the USA and Europe. Initiatives to standardise the collection and analysis of real-world data include the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) real-world evidence framework for pharmaceutical industries, the European Medicines Agency's (EMA) Patient Registry Initiative, and the US Food and Drug Administration's (FDA) policy on the use of real-world evidence.[16-18] Real-world data can now be obtained from a diverse array of sources such as claims databases, electronic medical records, patient registries, and health surveys, and can be collected prospectively or retrospectively (Figure 3).[19,20] These data sources typically have broader eligibility criteria than RCT, and may be more reflective of the general patient population and clinical practice. While real-world studies can be utilised to examine clinical endpoints and quality of life measures, these studies also offer a means to investigate factors such as treatment adherence and persistence, psychosocial factors, healthcare utilisation, and financial burden on patients and healthcare systems.

What Does Real-World Evidence Tell Us About Basal Insulins?

RCT provide important insights on the efficacy of basal insulins. Evidence from the pivotal EDITION and BEGIN Phase III programmes has demonstrated that Gla-300 and insulin degludec, respectively, are associated with robust HbA1c-lowering and a reduced risk of hypoglycaemia versus Gla-100.[21,22] A trial-level meta-analysis of clinical outcomes from the EDITION programme demonstrated that the risk of ≥1 confirmed (<54 mg/dL) or severe hypoglycaemic events was lower with Gla-300 compared with Gla-100 at night (00:00–05:59 a.m.), and also at any time (24 hours).[23] Matching analyses of the BEGIN programme showed that insulin degludec compared with Gla-100 was associated with a lower risk of ≥1 confirmed (<56 mg/dL) or severe hypoglycaemic events at night, but comparable risk at any time.[23] However, many real-world patients are under-represented in these types of trials. An analysis of patients with Type 2 diabetes mellitus living in Scotland in 2008 was conducted to describe the proportions of individuals who would meet eligibility criteria for inclusion in landmark RCT of glycaemic control, including ACCORD, ADVANCE, and VADT. The study revealed that, of the patient population surveyed (N=180,590), <36% of individuals were found to meet the inclusion and exclusion criteria of the seven RCT evaluated.[24]

Evidence from observational studies suggests that there is a disparity between data generated from RCT and what happens in the real world. SOLVE, a 24-week observational study involving 10 countries, assessed the safety and effectiveness of initiating once-daily insulin detemir in routine clinical practice among patients with Type 2 diabetes mellitus treated with ≥1 oral antidiabetic drug (OAD).[25] The study demonstrated that prior to insulin initiation, mean HbA1c levels ranged from 8.3% in China to 9.8% in Turkey and the UK. These data indicate

that patients remain poorly controlled on OAD treatment for prolonged periods of time prior to basal insulin initiation.[25] Further analyses of SOLVE demonstrated that patients remained at a relatively low basal insulin dose at study end; the mean daily insulin dose was 0.27 U/kg at Week 24.[25] Treat-to-target trials often report higher insulin doses compared with those recorded in observational trials, such as SOLVE. In one such treat-to-target trial, insulin-naïve patients with Type 2 diabetes mellitus were titrated to receive insulin detemir or Gla-100 once daily. After 52 weeks, the mean daily insulin detemir dose (n=227) was 0.78 U/kg.[26] These differences indicate that in the real world, basal insulin titration is sub-optimal. Further analyses of the SOLVE data evaluated the relationship between mean HbA1c and total insulin dose.

Observational studies are also providing valuable insights on glycaemic goal attainment and maintenance in the real world. In a retrospective analysis of electronic medical records from five European countries and the USA, glycaemic control and hypoglycaemia were evaluated in 40,627 insulin-naïve adults (≥30 years old) initiating basal insulin, with or without OAD. Patients who achieved an HbA1c target ≤7.0% 3 months after basal insulin initiation were more likely to be at HbA1c target at 24 months after basal insulin initiation (odds ratio: 3.70; 95% CI: 3.41–4.00).[27] DUNE, a 12-week observational study, assessed individualised HbA1c target achievement and its association with symptomatic hypoglycaemia (occurrence/frequency) in 3,139 patients with Type 2 diabetes mellitus either newly (at time of enrolment) or recently (<12 months) initiated on basal insulin therapy.[28] The study demonstrated that >25% of all study participants achieved their personalised, physician-set HbA1c target after 12 weeks of any basal insulin treatment, irrespective of whether the patient had been initiated at the time of enrolment or in the previous 12 months.[28] Furthermore, approximately 20% of these patients achieved their target HbA1c without experiencing additional hypoglycaemia.

In addition to providing insights into the effectiveness of basal insulins, real-world studies also provide valuable information on the occurrence of adverse events. The frequency of hypoglycaemic events reported in real-world settings was recently compared with those reported in clinical trials in a pooled analysis of 30 studies (real-world evidence, n=11; RCT, n=19) conducted in patients with Type 1 or Type 2 diabetes mellitus who were treated with basal, premix, or basal-bolus insulin therapy.[29] Patients with Type 1 diabetes mellitus reported rates of hypoglycaemia (confirmed, severe, and nocturnal) were consistently higher in real-world studies compared with RCT. In contrast, analyses from patients with Type 2 diabetes mellitus demonstrated a considerable overlap between real-world and RCT-recorded hypoglycaemia rates.[29] Global hypoglycaemia rates among patients with Type 1 diabetes mellitus were assessed in the HAT study, a 6-month retrospective and 4-week prospective study conducted in 24 countries worldwide. Rates of overall hypoglycaemia were high and varied substantially between geographical regions; rates ranged from 17.5 events per patient-year in South East Asia (n=224) to 93.9 events per patient-year in Latin America (n=427).[30] Further investigation of the factors affecting these geographical differences may help optimise future therapies and reduce the risk of hypoglycaemia.

Real-world data on the newer basal insulin analogues are beginning to emerge from recently completed and soon-to-complete studies, including EU-TREAT (insulin degludec) and DELIVER-2 (Gla-300).[31,32] EU-TREAT was a European, retrospective, non-interventional chart review study in patients with Type 2 diabetes mellitus who switched their basal insulin regimen to insulin degludec at least 6 months prior to data collection.[31] Analyses of the data revealed that insulin degludec was associated with a significant reduction from baseline in mean HbA1c (0.5%; p<0.001) that was sustained at 12 months (p<0.001).[31] Rates of overall hypoglycaemia (0.49; 95% CI: 0.26–0.91), non-severe overall hypoglycaemia (0.51; 95% CI: 0.28–0.92), and non-severe nocturnal hypoglycaemia (0.09; 95% CI: 0.04–0.20) were significantly lower in the 12-month post-switch period versus the pre-switch periods.[31] Taken together, these data indicate that switching patients to insulin degludec substantially improves glycaemic control and reduces the risk of hypoglycaemia in patients with Type 2 diabetes mellitus.

DELIVER-2, a retrospective, observational study in patients with Type 2 diabetes mellitus, collected data on patients switching to Gla-300 from their pre-existing basal insulin regimen.[32] Propensity score matching (1:1 ratio) identified 947 patients who switched to Gla-300 and 947 patients who switched to other basal insulins. At 6 months, Gla-300 was associated with significant reductions from baseline in mean HbA1c (0.6%; p<0.01),

that were consistent with reductions observed with other basal insulin regimens (0.5%).[32] Of note, baseline adjusted mean hypoglycaemia event rates were 25% lower with Gla-300 versus other basal insulin regimens (0.67 versus 0.90 events per patient-year, respectively; p<0.01).[32] Additional analyses of the DELIVER-2 data revealed that the hypoglycaemia event rate associated with hospital inpatient or emergency department visits was 48% lower with Gla-300 versus other basal insulin regimens, a reduction in healthcare resource which could potentially translate to total savings of up to $2,000 per patient per year.[32] A series of prospective, randomised real-life studies have been initiated to further examine Gla-300 versus other basal insulin regimens in the real-world setting. The ongoing ACHIEVE, REACH, and REGAIN studies will evaluate HbA1c reduction, hypoglycaemia rates, persistence, patient reported outcomes, and resource utilisation among insulin-naïve patients treated with Gla-300 versus other basal insulins and will provide additional insights into the effectiveness of Gla-300.[33-35]

In summary, a growing body of real-world evidence is now being generated from numerous sources of data and utilising robust methodologies. These data are providing valuable insights regarding the use of basal insulin in the real world that will ultimately guide clinical practice.

Conclusion

Translating clinical evidence into practice and ensuring it is applicable to the diverse population of patients who are on or initiating insulin therapy remains a challenge in diabetes care. From time-in-range to hypoglycaemia risk, time of basal insulin initiation to treatment adherence, and from prescription to patient education, multiple factors may impact outcomes, patient quality of life, and treatment satisfaction and effectiveness. Innovations in therapeutic basal insulin have been a continuous driver of improving patient care, particularly in recent years. Intrinsic improvements in basal insulin products, as well as new diabetes-related technologies and the availability of robust real-world evidence, are, together, producing an integrated understanding of how the use of basal insulin analogues can be optimised for the benefit of our patients.

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SESSION 2: CHANGING THE TYPE 2 DIABETES MELLITUS MANAGEMENT PARADIGM WITH FIXED-RATIO COMBINATIONS

This Sanofi sponsored symposium, titled 'Evolving Standards and Innovation in Diabetes Care', took place on 11th September 2017, as a part of the 53rd Annual Meeting of the European Association for the Study of Diabetes (EASD) in Lisbon, Portugal

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MEETING SUMMARY

Fixed-ratio combinations, the co-administration of two injectable therapies in a formulation that can be adjusted through titration, are changing the Type 2 diabetes mellitus management paradigm. Current treatment guidelines for glucose control rely heavily on a stepwise approach; however, that can be inconsistently followed and relatively indifferent to the complex pathophysiology of Type 2 diabetes mellitus. Fixed-ratio combinations have targeted actions that complement other treatments. Basal insulin

plus a glucagon-like peptide 1 receptor agonist (GLP-1 RA) represent one such combination that offers an efficacious approach to control both fasting and postprandial glucose, key determinants of glycaemic and clinical outcomes.

Two fixed-ratio combinations, insulin glargine 100 U/mL plus lixisenatide (iGlarLixi) and insulin degludec plus liraglutide (IDegLira), are currently available in the European Union (EU) and USA. Clinical evidence from pivotal, Phase III trials with iGlarLixi and IDegLira have demonstrated their robust glycated haemoglobin (HbA1c)-lowering effects, which are associated with mitigation of side effects commonly experienced with the individual components, including basal insulin-related body weight gain and GLP-1-related gastrointestinal adverse events. The spectrum of clinical benefits associated with these titratable fixed-ratio combinations may offer a more compelling case for earlier and effective use of these therapies that better addresses the complex underlying pathophysiology of Type 2 diabetes mellitus.

Symposium Overview

Doctor Elizabeth Seaquist

Diabetes care is evolving. Advances in our understanding of diabetes pathophysiology and treatment now permit individualised therapy based on patient-centred treatment plans that provide the best evidence-based therapies, while minimising personal burden. This personalised approach to treatment requires that therapeutic goals go beyond glycated haemoglobin control to include patient identified outcomes of value such as side effects, cost, and minimal interference with daily living.

Introduction

Doctor Julio Rosenstock

Fixed-dose oral and fixed-ratio injectable combinations of basal insulin plus a glucagon-like peptide 1 receptor agonist are changing the Type 2 diabetes mellitus management paradigm. Conceptually, a fixed-dose or fixed-ratio combination should exhibit the following characteristics:

- Components should exhibit complementary actions.
- Glycaemic control should be better than with each individual component.
- Combined doses may be lower than each individual component alone.
- Side effects should not be increased and ideally be mitigated.
- Treatment is simplified and may improve adherence and persistence.
- Cost should be lower than the sum of the costs of each individual component.

Fixed-dose combinations represent the co-administration of two oral antihyperglycaemic therapies in the same tablet formulation. Numerous fixed-dose combinations are currently available, including metformin plus sodium-glucose cotransporter 2 (SGLT2) inhibitor formulations. However, the fixed-dose nature of these combinations means that adjustments are limited by tablet options. Fixed-ratio combinations represent the co-administration of two injectable therapies in the same injection, which can be adjusted through titration. These formulations offer the ability to titrate doses in accordance with the individual response and tolerance.

Two approved fixed-ratio combinations, iGlarLixi and IDegLira, are currently available. In Europe, iGlarLixi and IDegLira are indicated for adults with Type 2 diabetes mellitus inadequately controlled with oral antidiabetic drugs (OAD),[1,2] while in the USA, iGlarLixi and IDegLira are indicated for adults with Type 2 diabetes mellitus inadequately controlled with basal insulin.[3,4] Regulatory approval of iGlarLixi and IDegLira in the OAD-failure population was supported by evidence from the pivotal Phase III trials LixiLan-O and DUAL I,[5,6] respectively, while approval in the basal insulin-failure population was supported by evidence from the LixiLan-L and DUAL II trials,[7,8] respectively.

The design of the LixiLan and DUAL programmes was relatively similar, with the exception of a few key differences; the LixiLan trial contained a titration lead-in period, whereas the DUAL trials did not, and fasting plasma glucose targets were modestly higher in the LixiLan versus DUAL trials.[5-8] Data from the LixiLan-O and DUAL I trials revealed study populations with generally comparable characteristics, with the exception that the LixiLan-O population was slightly older and had diabetes for longer.[5,6] Importantly, the studies demonstrated robust and comparable HbA1c-lowering with both iGlarLixi and IDegLira (final HbA1c: 6.5% and 6.4%, respectively). Similarly, LixiLan-L and DUAL II enrolled comparable patient

populations and, despite differences in study design (i.e. the lack of a titration lead-in period in DUAL II), demonstrated robust and comparable reductions in HbA1c (final HbA1c: 6.9% in both trials).[7,8] Taken together, evidence from the LixiLan and DUAL programmes demonstrated that fixed-ratio co-formulations of a basal insulin and GLP-1 RA provide robust glycaemic control with a favourable safety profile, by mitigating side effects of each component, and with no increased regimen complexity.

A Matter of Urgency: Simultaneous Intensification with Fixed Ratio Combinations

Doctor James R. Gavin III

Key Points

- The sequential approach to Type 2 diabetes mellitus management is compounded by substantial clinical inertia at each intensification step.
- Many individuals do not achieve their glycaemic targets despite optimised treatment with multiple OAD and/or injectable therapies.
- Persistent postprandial hyperglycaemia, a predictor of cardiovascular mortality, represents an unmet need in the management of patients with Type 2 diabetes mellitus.
- Fixed-ratio combinations of a basal insulin plus GLP-1 RA provide a means to target both fasting and postprandial glucose levels.
- Basal insulin/GLP-1 RA combinations offer significant clinical benefits to patients, including improved glycaemic control and mitigation of the side effects commonly experienced with the individual components.
- Compared with the sequential approach, simultaneous intensification with a fixed-ratio combination in patients failing oral therapy may serve to maximise the benefits of the fixed-ratio combination and mitigate the risk of clinical inertia.

There is an urgent need for simultaneous treatment intensification in patients with Type 2 diabetes mellitus. Many individuals do not achieve their glycaemic targets despite optimised treatment with multiple OAD and/or insulin or other injectable therapies.[9] Evidence from the European PANORAMA study, a cross-sectional analysis of glycaemic control data collected in 5,817 patients with Type 2 diabetes mellitus aged ≥40 years, showed that up to ~40% of patients were not at HbA1c target (≤7.0%).[9]

Furthermore, the proportion of patients who achieved an HbA1c ≤7.0% decreased with increasing treatment complexity (76.1% in patients receiving one OAD versus 36.1% in patients receiving injectable therapy). This lack of glycaemic control is due, in part, to the sequential treatment approach, which is compounded by substantial clinical inertia at each intensification step. Clinical data indicate that the median time from OAD treatment initiation to the addition of a second OAD is 1.6–2.9 years, while the time to addition of a third OAD is 6.9–7.2 years. A further 6.0–7.1-year delay exists before intensification with insulin.[10] A persistent problem and unmet need in Type 2 diabetes mellitus treatment is how best to manage the postprandial hyperglycaemia that precedes fasting hyperglycaemia during disease progression. Both basal and postprandial elevations contribute to the hyperglycaemic exposure of diabetes. However, current therapies are predominantly effective in controlling the basal component.[11] Findings from prospective, cohort studies show that postprandial hyperglycaemia is an independent predictor of mortality outcomes in patients with pre and overt diabetes,[12,13] while an abundance of studies have reported a link between postprandial blood glucose levels and cardiovascular mortality.[12-15]

Fixed-ratio combinations could potentially offer a number of benefits to patients. These include earlier achievement and greater persistence of glycaemic and other therapeutic goals, and a potential reduction in the risk of side effects with lower doses of the combined drugs versus uptitration of single doses. Fixed-ratio combinations may help to address the multiple physiologic defects associated with Type 2 diabetes mellitus. Furthermore, these formulations may potentially delay underlying disease progression and disease-related vascular complications. The mode of action of basal insulins, to predominantly provide fasting glucose control, is complementary to the postprandial glucose control provided by GLP-1 RA. Together, these anti-hyperglycaemic agents offer a complementary approach to glycaemic control that may help address the postprandial element of hyperglycaemia that persistently limits current diabetes therapies.[16,17] Two basal insulin/GLP-1 RA fixed-ratio combinations have been approved to date: iGlarLixi and IDegLira.

Evidence for Fixed-Ratio Basal Insulin/ Glucagon-like Peptide 1 Receptor Agonist Combination Therapy

The efficacy and safety of iGlarLixi was established in the LixiLan-O trial, which demonstrated that iGlarLixi was associated with a superior HbA1c reduction compared with its individual components, insulin glargine 100 U/mL and lixisenatide (1.6% versus 1.3% and 0.9%, respectively; p<0.0001).[5] In addition, iGlarLixi was associated with greater reductions in 2-hour postprandial glucose levels compared with insulin glargine 100 U/mL or lixisenatide alone.[5] A significantly greater proportion of patients achieved an HbA1c target <7% with iGlarLixi than with insulin glargine 100 U/mL and lixisenatide (74% versus 59% and 33%, respectively; p<0.0001).[5] Modest weight loss was observed with the iGlarLixi arm (0.3 kg), compared with weight gain (1.1 kg) in the insulin glargine 100 U/mL arm, while the incidence of hypoglycaemia was comparable between both arms.[5] In patients with a baseline HbA1c of ≤9% and those who were receiving ≥2 OAD at baseline, iGlarLixi was associated with robust and significantly superior HbA1c-lowering (p≤0.03), and a greater proportion of patients achieving glycaemic goal (HbA1c <7%), compared with its individual components.[18,19]

Together, these data indicate that patients with advanced disease, including those in whom an injectable therapy may be considered, are well suited to the effects of iGlarLixi. In terms of safety and tolerability, the slow titration of the fixed-ratio combination resulted in fewer gastrointestinal (GI) events and a reduced incidence of discontinuation due to GI events with iGlarLixi versus insulin glargine 100 U/mL and lixisenatide given as monocomponents.[5] Evaluation of IDegLira in the DUAL I trial produced comparable results to those observed with iGlarLixi. Analyses of DUAL I showed that IDegLira was associated with superior HbA1c reduction compared with insulin degludec or liraglutide alone (1.9% versus 1.4% and 1.3%, respectively; p<0.0001).[6] In addition, a significantly greater proportion of patients achieved an HbA1c <7% with IDegLira than its individual components (p<0.0001).[6] In terms of body weight change, IDegLira treatment was associated with weight loss (0.5 kg) versus weight gain in the insulin degludec arm (1.6 kg).[6]

Evaluation of iGlarLixi in LixiLan-L showed iGlarLixi versus insulin glargine 100 U/mL was associated with superior HbA1c reduction (1.1% versus 0.6%; p<0.0001), a robust reduction in 2-hour postprandial glucose and fasting plasma glucose levels, a higher proportion of patients at HbA1c targets (p<0.0001), weight loss, and no increased risk of hypoglycaemia.[7] Similarly in DUAL II, IDegLira compared with insulin degludec was associated with superior HbA1c-lowering, a greater proportion of patients at HbA1c targets, and weight loss.[8]

Taken together, these data highlight the numerous clinical benefits that fixed-ratio combinations of a basal insulin and a GLP-1 RA can potentially offer, including simultaneous targeting of both fasting plasma glucose and postprandial glucose, substantial reductions in the side effects of the mono-components, and no increase in the risk of hypoglycaemia compared with basal insulin. For patients who are struggling to manage their disease, there is an urgent need for earlier, intensive glycaemic control. Indeed, post-hoc analyses of 4,119 patients from the ACCORD[20] study demonstrated that early glycaemic goal attainment is predictive of persistent and improved glycaemic control.

Conversely, a global study of 40,627 patients with Type 2 diabetes mellitus initiating basal insulin showed that failure to achieve HbA1c ≤7% at 3 months post initiation was associated with an increased risk of failing to achieve this target at 24 months (odds ratio: 3.70; 95% confidence interval [CI]: 3.41–4.00).[21] In the LixiLan-O trial, patients treated with iGlarLixi were more likely to achieve early HbA1c control; time to target HbA1c <7% was 85 days with iGlarLixi, 166 days with insulin glargine 100 U/mL, and 218 days with lixisenatide.[22]

In summary, fixed-ratio combinations offer significant clinical benefits. Compared with sequential intensification, simultaneous intensification with a fixed-ratio combination in patients failing oral therapy may serve to maximise the benefits of the fixed-ratio combination and mitigate the risk of clinical inertia. iGlarLixi is also associated with earlier achievement of HbA1c targets, a predictor of long-term control.

Who Can Benefit and How to Use: Assessing Clinical Utility

Doctor Neil Skolnik and Ms Lucia Novak

Key Points

- Fixed-ratio combinations offer a simple and efficacious therapeutic approach for advancing therapy in patients with Type 2 diabetes mellitus
- Practical considerations when initiating a patient on a fixed-ratio combination include providing education on the causes and duration of potential side effects, as well as how to minimise the likelihood of these events occurring
- Such practical support will help patients to successfully initiate and persist with their fixed-ratio combination treatment

The body of clinical evidence that supports the efficacy and safety of fixed-ratio combinations indicates that they offer an efficacious therapeutic approach that may reduce treatment complexity.[5-8,10,23]

How to Initiate Fixed-Ratio Combinations

iGlarLixi is available in two dose pens, the 10–40 U pen and the 30–60 U pen, which deliver 10–40 U insulin glargine 100 U/mL plus 5–20 µg/day lixisenatide and 30–60 U insulin glargine 100 U/mL plus 10–20 µg/day lixisenatide, respectively.[1,3] IDegLira is supplied in a single, multiple-dose pen with a maximum permitted dose of 50 U insulin degludec and 1.8 mg liraglutide.[2,4] The starting dose of iGlarLixi or IDegLira is dependent upon the patient's basal insulin experience. For iGlarLixi, patients who are insulin-naïve or receiving basal insulin therapy at a dose of <30 U/day should start treatment on the 10–40 U pen. Patients who are basal insulin experienced and receiving >30 U/day should start treatment on the 30–60 U pen.[1,3] For IDegLira, insulin-naïve patients would initiate treatment at a dose of 10 U, and basal insulin experienced patients (irrespective of their existing insulin dose) should initiate treatment at a dose of 16 U.[2,4] Dosing of iGlarLixi and IDegLira is conducted in accordance with the patient's basal insulin needs. Titration of iGlarLixi and IDegLira doses is based on fasting self-monitored plasma glucose levels and slow uptitration. This slow titration means that increases in the corresponding dose of the GLP-1 RA component are gradual and relatively small.

Patient Education: Practical Considerations

To ensure successful initiation and persistence with fixed-ratio combination therapies, it is important to discuss treatment expectations with patients before beginning treatment to provide them with the tools and understanding they require in order to overcome any potential barriers that they may experience with these medications. Common complications associated with GLP-1 RA treatment are the occurrence of GI events, specifically nausea and vomiting.[5-8] The increased satiety and slowed gastric emptying produced by these agents may lead to an increased sense of fullness that some patients who are new to GLP-1 RA are not accustomed to experiencing. As a result, this could potentially lead to premature treatment discontinuation.[24] In light of this, it is important to highlight to patients that the nausea associated with fixed-ratio combination therapy is usually transient in nature. It is also important to highlight the benefits of fixed-ratio combinations, such as the mitigation of weight gain that can be associated with basal insulin therapy.

Another approach to help patients initiate and persist with their fixed-ratio combination therapy could be to suggest changes to their behaviour.[24] For example, the risk of experiencing GI events can be minimised through slow titration of the dose. Meals containing a high fat content may slow gastric emptying further and contribute to the worsening of nausea symptoms. Therefore, reducing fat intake, mindful eating (i.e. eating slowly and stopping eating when fullness is first sensed), and decreasing portion sizes may also help to reduce the likelihood of experiencing nausea.

Take Home Messages

Fixed-ratio combinations offer a simple and effective therapeutic approach for advancing therapy in patients with Type 2 diabetes mellitus. Efforts to provide patients with supporting education will help patients to successfully initiate and persist with these therapies.

Reflections on Injectables for Type 2 Diabetes Mellitus: Let's Move On!

Doctor Julio Rosenstock

Key Points

- Current clinical guidelines advocate the use of injectable glucose-lowering agents when metformin alone, or in combination with additional OAD, fails to achieve individualised glycaemic goals.

- Injectable therapies, including basal insulin and GLP-1 RA, are well established options for the sequential intensification of metformin treatment in patients unable to achieve glycaemic control.
- However, the effectiveness of traditional, injectable therapies may be hindered by factors such as the fear of weight gain or hypoglycaemia with basal insulin therapy, or concerns regarding treatment complexity.
- The recent introduction of the titratable fixed-ratio combinations iGlarLixi and IDegLira signifies the beginning of a new era for injectable therapies in Type 2 diabetes mellitus.
- Titratable fixed-ratio formulations offer a unique therapeutic approach that can deliver the benefits of both a basal inulin and a GLP-1 RA simultaneously, while mitigating basal insulin-related body weight gain and GLP-1-related GI adverse events, and may potentially replace sequential injectable regimens in the Type 2 diabetes mellitus treatment paradigm.

For many years, the Type 2 diabetes mellitus treatment paradigm has followed a common sequential principle: initiate treatment with metformin and then progressively add therapies according to increasing HbA1c. Indeed, the American Diabetes Association/European Association for the Study of Diabetes joint guidelines advocate metformin as a first-line agent, followed by the potential addition of further oral agents and eventually basal insulin or a GLP-1 RA as a dual or triple therapy, before moving sequentially to basal-bolus insulin.[25] In addition to initial metformin monotherapy, the American Diabetes Association guidelines also suggest using dual therapy as a first-line treatment in patients with HbA1c ≥9%, before sequentially moving to triple therapy and then combination injectable therapy.[26] The American Association of Clinical Endocrinologists guidelines advocate a more aggressive approach, in which dual therapy is recommended as a first-line treatment if HbA1c is ≥7.5%, while monotherapy with either metformin, GLP-1 RA, or SGLT2 is recommended if HbA1c <7.5%.[27] However, the sequential therapeutic approach, as recommended by most clinical guidelines, has failed, mainly due to clinical inertia. Looking forward, it is likely that initial dual therapy will become the standard of care. Furthermore, it is conceivable that initial therapy with a combination of metformin and an SGLT2 inhibitor could become the standard treatment for newly diagnosed Type 2 diabetes mellitus, given the emerging evidence supporting a cardiovascular benefit of the SGLT2 inhibitor class.[28,29]

Choosing a First Injectable in Oral Antidiabetic Drug Failure

In order to select the most appropriate first injectable for patients who are not responding to OAD, it is important to consider key learnings generated from the body of clinical evidence available for basal insulins and GLP-1 RA. Single and pooled analyses of treat-to-target trials with insulin glargine 100 U/mL demonstrate the consistent and robust HbA1c-lowering effect of this therapeutic approach.[30-33] However, these effects are only achievable through the implementation of consistent and systematic basal insulin titration not often followed in clinical practice. Additional limitations of basal insulin therapy include a low, but persistently elevated, increase in the risk of hypoglycaemia, potential weight gain of ~1–3 kg, and low adherence to titration.[30-33] Analyses from a USA retrospective study conducted in 274,102 patients with Type 2 diabetes mellitus also demonstrated that up to 50–60% of patients receiving insulin glargine 100 U/mL discontinued their therapy after 12 months, irrespective of whether they were insulin experienced or new to insulin therapy (<12 months). Neutral protamine Hagedorn insulin was associated with the lowest rates of treatment persistence.[34]

Head-to-head trials among GLP-1 RA have demonstrated the robust glycaemic efficacy of this class, with HbA1c reductions ranging from approximately 0.6–1.9%.[35-40] These studies have also demonstrated substantial body weight reduction associated with GLP-1 RA therapy (ranging from 2.0–2.5 kg).[35-38] However, adherence and persistence with GLP-1 RA is limited by the adverse event profile associated with these therapies. GI adverse events are common with GLP-1 RA, with 18–35% of patients experiencing nausea, 8–12% experiencing vomiting, and 9–14% experiencing diarrhoea. Although nausea and vomiting generally subside in the weeks to months following treatment initiation, a large proportion of patients will discontinue their GLP-1 RA treatment during this preliminary period due to a lack of understanding that these events are transient in nature and the lack of a support system in clinical practice, which is available in randomised clinical trials. Treatment persistence with dulaglutide, exenatide, and liraglutide was evaluated in a 6-month observational study in patients with

Type 2 diabetes mellitus (N=2,470), in which discontinuation was defined as either a 45-day or 60-day gap from the index date of GLP-1 RA initiation to the final day's supply from the last claim of the GLP-1 RA treatment.[39] These analyses showed that higher proportions of patients met the criteria for early discontinuation (no claim for the specified GLP-1 RA within the 45-day gap) compared with delayed discontinuation. Overall, 31–53% of patients discontinued early versus 26–48% who had delayed discontinuation with this trend being present for all three GLP-1 RA evaluated in the study.[39]

Advancing Basal Insulin and Glucagon-like Peptide 1 Receptor Agonists

Guideline recommendations for the sequential intensification of basal insulin permits the addition of prandial insulin (i.e. basal-bolus) or a GLP-1 RA.[25-27] A recent head-to-head study evaluated these prandial treatment options in patients with Type 2 diabetes mellitus inadequately controlled on basal insulin glargine with or without additional OAD. Analyses demonstrated that lixisenatide once daily was associated with similar HbA1c reductions versus insulin glulisine once daily and fairly comparable with thrice daily, when added to insulin glargine as a basal/bolus (final HbA1c: 7.2%, 7.2%, and 7.0%, respectively).[40] Similar findings were demonstrated by a 30-week, randomised, non-inferiority study, which evaluated the addition of a GLP-1 RA (exenatide twice weekly) versus meal-time insulin (lispro three times daily) in patients with Type 2 diabetes mellitus inadequately controlled on basal insulin glargine plus metformin (N=510).[41] At study end, reductions in HbA1c were similar between the exenatide twice weekly and insulin lispro treatment arms (1.1% in both arms), with a final HbA1c of 7.2%.[41] In addition, exenatide twice weekly was associated with substantial body weight reduction (2.5 kg), while meal-time insulin lispro was associated with body weight gain (2.1 kg). Interestingly, evidence from a series of subsequent studies have shown significant reductions in HbA1c and body weight with once-weekly GLP-1 RA; these include once-weekly albiglutide, exenatide, and dulaglutide, which have shown final HbA1c values of 7.7%, 7.6%, and 6.9%, respectively.[41-43]

Simultaneous intensification with a fixed-ratio combination of basal insulin plus a GLP-1 RA offers an alternative therapeutic option to prandial interventions. Clinical evidence from the LixiLan and DUAL clinical programmes with iGlarLixi and IDegLira, respectively, demonstrated that these titratable fixed-ratio combinations produce robust HbA1c-lowering, mitigation of basal insulin-related body weight gain, and mitigation of GLP-1-related GI adverse events.[5-8]

Exploring Sequential Versus Simultaneous Addition of Glucagon-like Peptide 1 Receptor Agonist to Basal Insulin

The differences in efficacy of titratable fixed-ratio combinations and sequential intensification of treatment in accordance with treatment guidelines has been questioned. However, no head-to-head studies comparing these two treatment regimens have yet been carried out. Therefore, propensity score matching was used as a hypothesis-generating, exploratory exercise to investigate if titratable fixed-ratio combinations offer a treatment benefit over correctly executed simultaneous intensification.[44,45] If sequential intensification was performed systematically, and in accordance with guideline recommendations, it is conceivable that outcomes could be improved. Therefore, propensity score matching was used to indirectly compare simultaneous administration of iGlarLixi in the LixiLan-O trial (n=469) with sequential therapy, starting with initial insulin glargine 100 U/mL therapy for 12 weeks, followed by addition of lixisenatide in the GetGoal Duo-1 trial in patients with Type 2 diabetes mellitus who had failed oral therapy but remained on metformin (n=223).[44] At Week 24, data from 87 matched pairs revealed that iGlarLixi was associated with a significantly greater reduction in HbA1c compared with sequential administration of insulin glargine 100 U/mL and then lixisenatide (final HbA1c 6.4% versus 7.0%, respectively; p<0.0001) in patients with Type 2 diabetes mellitus uncontrolled with OAD (Figure 1).[44] Furthermore, a greater proportion of patients achieved the HbA1c target (<7%) with iGlarLixi versus sequential intensification (79% versus 51%; p<0.0001) (Figure 1).[44]

Similar results were generated from a propensity score matching analysis of data from the LixiLan-L (n=367) and GetGoal Duo-2 (n=298) trials in patients with Type 2 diabetes mellitus who had failed basal insulin therapy with or without metformin.[45] At study end, data from 241 matched pairs revealed that iGlarLixi was associated with a significantly greater reduction in HbA1c compared with sequential administration of insulin glargine 100 U/mL and lixisenatide (final HbA1c: 6.8% versus 7.3%, respectively; p<0.0001).[45]

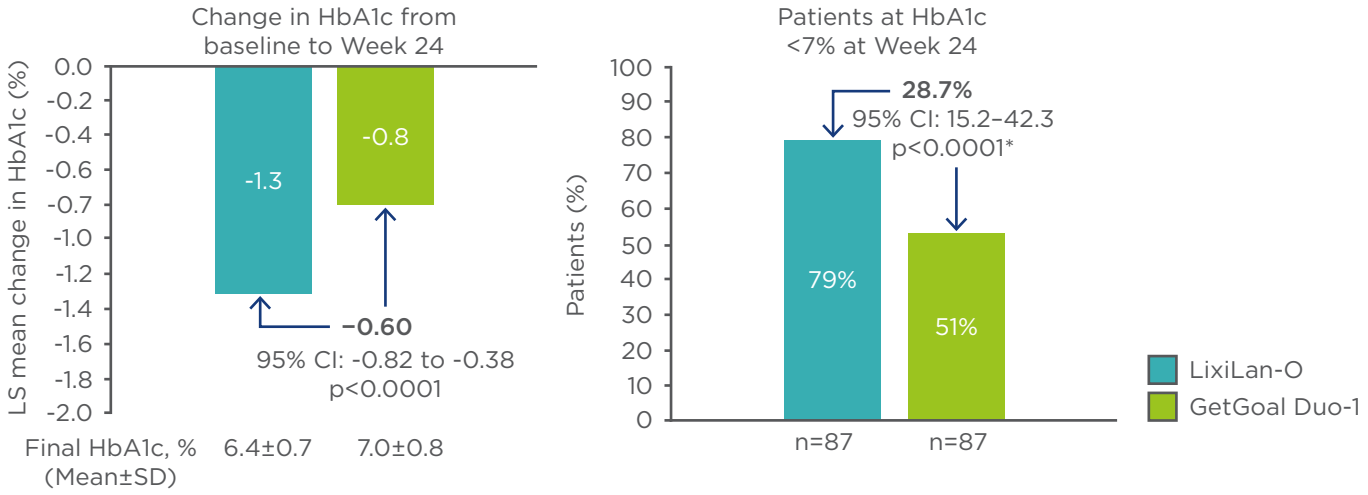

Figure 1: HbA1c changes in propensity scored-matched populations.[44]

*Weighted average of proportion difference between treatment groups from each strata (randomisation strata of HbA1c [<8.0, ≥8.0%]) using Cochran-Mantel-Haenszel weights.

CI: confidence interval; HbA1c: glycated haemoglobin; LS: least squares; SD: standard deviation.

In addition, significantly more patients achieved the HbA1c target (<7%) with iGlarLixi than sequential intensification (62% versus 33%; p<0.0001). These hypothesis-generating, exploratory data are particularly compelling given that this particular patient population is often difficult to treat due to the advanced state of their disease.

Take Home Messages

There is a growing body of clinical evidence supporting the clinical benefits of simultaneous intensification of therapy with a fixed-ratio combination of basal insulin plus a GLP-1 RA in patients with Type 2 diabetes mellitus. Importantly, these titratable fixed-ratio combinations have the potential to ultimately replace the standard, sequential, injectable regimens that, slowly but surely, will become a thing of the past in the management of Type 2 diabetes mellitus.

Conclusions

Titratable fixed-ratio combinations of basal insulin and a GLP-1 RA are changing the Type 2 diabetes mellitus management paradigm. Current guidelines advocate a sequential approach to treatment. However, an abundance of clinical evidence indicates that significant clinical inertia exists at each intensification step. As a result, many patients fail to achieve their personalised glycaemic goals despite optimised treatment with OAD with or without injectable therapy. Fixed-ratio combinations of basal insulin plus a GLP-1 RA represent an efficacious approach to control both fasting and postprandial glucose, key determinants of glycaemic and clinical outcomes. Clinical evidence from pivotal Phase III trials with the two currently available fixed-ratio combinations, iGlarLixi and IDegLira, have demonstrated their robust HbA1c-lowering effects. Furthermore, the titratable nature of these new formulations according to clinical response and tolerance enables patients to reach levels of glycaemic control with mitigated side effects that are unprecedented in the management of Type 2 diabetes mellitus.

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SESSION 3: INNOVATING BEYOND GLUCOSE CONTROL IN DIABETES CARE

This Sanofi sponsored symposium, titled 'Evolving Standards and Innovation in Diabetes Care', took place on 11th September 2017 as part of the 53rd Annual Meeting of the European Association for the Study of Diabetes (EASD) in Lisbon, Portugal

Symposium Chair

Elizabeth Seaquist[1]

Session Chair

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Speakers

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MEETING SUMMARY

Advances in treatment offerings are moving beyond classical considerations around glucose control to focus on other aspects of the disease. Such advances include the development of treatments that address the high cardiovascular (CV) risk in patients with diabetes, or have novel mechanisms of action, and new technologies that will facilitate the future integration of care.

The proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors represent a new therapeutic approach for managing CV risk in patients with diabetes. New clinical data recently generated from dedicated diabetes studies have established PCSK9 inhibitors as an efficacious and well-tolerated treatment option for patients with diabetes and persistently elevated low-density lipoprotein-cholesterol levels, despite optimised lipid-lowering therapy.

Treatments with novel mechanisms of action are also being investigated. Sotagliflozin, a dual inhibitor of the sodium-glucose cotransporter 1 (SGLT1) and sodium-glucose cotransporter 2 (SGLT2), may offer additional clinical benefits beyond those of existing selective SGLT2 inhibitors in patients with Type 1 diabetes mellitus. The sotagliflozin inTandem Phase III programme will provide valuable insights regarding the potential role of dual SGLT1 and SGLT2 inhibitors as an adjunct to insulin therapy in patients with Type 1 diabetes mellitus.

Furthermore, advances in diabetes devices, such as implantable drug delivery systems, non-invasive glucose monitoring, and closed-loop artificial pancreas systems, are fuelling the development of new models of patient care. While there will inevitably be other innovations, three major advances will dramatically change diabetes care over the next 10–20 years: 1) digital diabetes health technologies, 2) artificial intelligence and machine learning, and 3) virtual reality.

Symposium Overview

Doctor Elizabeth Seaquist

Diabetes care is evolving. Advances in our understanding of diabetes pathophysiology and treatment now permit individualised therapy based on patient-centred treatment plans that provide the best evidence-based therapies, while minimising personal burden. This personalised approach to treatment requires that therapeutic goals go beyond glycated haemoglobin control to include patient identified outcomes of value such as side effects, cost, and minimal interference with daily living.

Introduction

Professor Thomas Danne

HbA1c, a useful measure of glycaemic control, represents only a snapshot of a complex dynamic process.[1] Mean HbA1c values cannot provide an accurate overview of day-to-day glycaemic variability,[1] an increasingly important consideration in the management of diabetes and the development of new treatments that minimise the risk of hypoglycaemia. Accordingly, diabetes therapy offerings are evolving. Recent advances include treatments that target the elevated CV risk in patients with diabetes, treatments with novel mechanisms of actions, and new diabetes-related technologies that will be instrumental in revolutionising diabetes management. Such developments include the availability of PCSK9 inhibitors for managing hypercholesterolaemia in diabetes,[2,3] dual inhibition of SGLT1 and SGLT2 as a novel therapeutic target for Type 1 diabetes mellitus,[4] and new devices for improving care, e.g., implantable drug delivery systems, non-invasive glucose monitoring, and closed-loop artificial pancreas systems.

Proprotein Convertase Subtilisin-Kexin Type 9 Inhibition in the Treatment of Hypercholesterolaemia in Diabetes

Professor Dirk Müller-Wieland

Key Points

- Long-term exposure to elevated levels of low-density lipoprotein (LDL) particles is 'toxic' for the arterial wall; reducing LDL-cholesterol (LDL-C) levels should be a key focus of CV disease prevention.
- Individual CV risk represents one determinant of the therapeutic approach adopted for the reduction of LDL-C.

- Preliminary evidence generated from analyses of randomised clinical studies indicate that PCSK9 inhibitors effectively lower atherogenic lipoproteins and are associated with an acceptable safety profile, in both patients with and without diabetes.

An important challenge in the management of patients with diabetes is CV risk. In all individuals, lifelong exposure to raised concentrations of LDL-C increases the risk of experiencing a CV event.[5] This risk is further elevated in patients with diabetes, irrespective of sex or age.[6] Type 2 diabetes mellitus is associated with complex lipid profile aberrations, including elevated levels of very LDL, elevated numbers of LDL particles, and decreased levels of high-density lipoprotein cholesterol (HDL-C). While reduction of LDL-C is a primary goal in CV prevention, an increasing number of clinical guidelines and consensus statements are also incorporating recommendations for non-HDL-C treatment targets.[7,8] Non-HDL-C, which accounts for all atherogenic lipoproteins, may represent a more appropriate predictor of CV risk than LDL-C alone for patients with diabetes and dyslipidaemia.[7,8] Therapeutic approaches for LDL-C lowering in patients with diabetes and atherosclerotic CV disease (ASCVD) vary between clinical guidelines depending on risk categorisation (e.g., very high-risk versus extreme).[8-10] The joint European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) 2017 guidelines recommend an LDL-C goal of <1.8 mmol/L (70 mg/dL) for patients with very high CV risk, while the joint American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) 2017 guidelines recommended a goal of <1.4 mmol/L (55 mg/dL) for patients with extreme CV risk.[8,9] The American Diabetes Association (ADA) recommends consideration of the addition of ezetimibe to a moderate-intensity statin if a patient's LDL-C is ≥1.3 mmol/L (50 mg/dL),[10] guidance which is based on evidence from the IMPROVE-IT.[11] The study demonstrated that in patients with a recent acute coronary syndrome, the combined simvastatin/ezetimibe treatment significantly reduced CV risk compared with simvastatin alone (median time-weighted average LDL-C levels: 1.4 mmol/L [53.7 mg/dL] versus 1.8 mmol/L [69.5 mg/dL], respectively; p<0.001).[11] Furthermore, event rates for the primary endpoint at 7 years were significantly lower in patients with diabetes compared with those without diabetes (40.0% versus 45.5%; hazard ratio [HR]; 0.856; 95% confidence interval [CI]: 0.779–0.939; p=0.023).[11] The relationship between intensive LDL-C lowering and reduced CV risk is well documented. Furthermore, randomised clinical studies have established a correlation between reduced LDL-C levels and regression of atherosclerotic plaque volume.[12] A growing body of clinical evidence suggests that coronary atherosclerosis progression can be slowed by combining statins with additional LDL-C lowering agents. In a placebo-controlled, 78-week randomised study, combined therapy with a PCSK9 inhibitor and statin was associated with significantly greater reductions in absolute LDL-C and atherosclerotic plaque volume versus placebo (p<0.001).[13] Importantly, post-hoc analyses demonstrated that the changes in plaque volume predominantly occurred at LDL-C levels >1.8 mmol/L (70 mg/dL).[13]

Proprotein Convertase Subtilisin-Kexin Type 9 Inhibition for Managing Low-Density Lipoprotein-Cholesterol Levels in Patients with Type 2 Diabetes Mellitus

In patients with Type 2 diabetes mellitus, targeting the LDL-receptor via PCSK9 inhibition represents an innovative approach for the management of LDL-C levels and CV risk.[14] Preliminary insights from meta-analyses and pooled analyses of randomised clinical studies indicate that the PCSK9 inhibitors, evolocumab and alirocumab, markedly reduce atherogenic lipid levels in patients with diabetes, an effect that is consistent with observations in patients without diabetes.[15,16] Furthermore, both evolocumab and alirocumab demonstrated safety and tolerability profiles that were comparable to placebo or active comparators and consistent with those observed in patients without diabetes.[15,16] The effect of lowering LDL-C levels via PCSK9 inhibition on the risk of diabetes has been investigated using Mendelian randomisation approaches. One such study, which analysed data from 14 clinical trials and >112,000 patients, suggested a potential link between PCSK9 variants and an increased risk of diabetes (odds ratio: 1.07; 95% CI: 1.00–1.13).[17] However, it is important to note that PCSK9 inhibitors are monoclonal antibodies that bind extracellular PCSK9 and may not have the same biologic effect as PCSK9 variants that lower LDL-C levels. Interestingly, in a pooled analysis of 10 clinical trials from the ODYSSEY Phase III programme in patients without diabetes at baseline, there was no effect of alirocumab on the incidence of new-onset diabetes or pre-diabetes.[18]

To date, several CV outcomes trials have been initiated to determine whether PCSK9 inhibitors confer any CV benefits, including the recently completed FOURIER trial (evolocumab),[19] the ongoing ODYSSEY Outcome trial (alirocumab),[20] and the discontinued SPIRE-1[21] and SPIRE-2[22] trials (bococizumab). Initial results from FOURIER demonstrate that evolocumab, in combination with statin therapy, significantly reduces the risk of CV events (defined as a composite of CV death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation) compared with placebo (HR: 0.85; 95% CI: 0.79–0.92; p<0.001), in patients with ASCVD.[19] While subtle differences exist between the designs of FOURIER and ODYSSEY (e.g., the primary endpoint in ODYSSEY is a composite of coronary heart disease death, myocardial infarction, ischaemic stroke, and hospitalisation for unstable angina), these trials will provide evidence regarding how to optimise the use of PCSK9 inhibitors in patients with high CV risk.

New Lipid Lowering Strategies in Diabetes: Insights from the ODYSSEY DM Programme

Doctor Lawrence A. Leiter

Key Points

- The ODYSSEY DM programme assessed the efficacy and safety of alirocumab in two groups of very high-risk populations with diabetes: patients on insulin therapy and patients with mixed dyslipidaemia.
- The ODYSSEY DM-INSULIN and ODYSSEY DM-DYLIPIDEMIA studies demonstrated the superior lipid lowering efficacy of alirocumab versus usual care and detected no new safety concerns.
- Together, these data support the use of alirocumab as a treatment option in people with diabetes and high CV risk.

The ODYSSEY Phase III programme was designed to evaluate the efficacy and safety of alirocumab in patients with hypercholesterolaemia and high CV risk, of whom approximately 30% had diabetes. Evidence from up to 104 weeks of follow-up in these Phase III trials demonstrated no effect of alirocumab on glycaemic control. The ODYSSEY DM programme was designed to further explore the efficacy and safety of alirocumab in patients with diabetes and comprised two pivotal studies: ODYSSEY DM-INSULIN[23] and ODYSSEY DM-DYSLIPIDEMIA.[24]

ODYSSEY DM-INSULIN: Rationale and Key Clinical Data

Patients with Type 1 diabetes mellitus are often under-represented in lipid-lowering clinical trials and insulin-treated patients with Type 2 diabetes mellitus represent a cohort with long-standing disease and an increased risk of ASCVD. Furthermore, it is important to understand how alirocumab (a monoclonal antibody) behaves when coadministered with the biologic insulin.

DM-INSULIN assessed the efficacy and safety of alirocumab versus placebo in insulin-treated patients with Type 1 or Type 2 diabetes mellitus (plus high CV risk and above-target LDL-C levels despite maximum tolerated doses of statin therapy).[23,25]

DM-INSULIN was a randomised, double-blind, placebo-controlled study.[23] Patients were aged ≥18 years with insulin-treated Type 1 or Type 2 diabetes mellitus (≥12 months), HbA1c levels <10%, LDL-C levels ≥1.81 mmol/L (70 mg/dL), ASCVD and/or at least one additional CV risk factor, and receiving a stable maximum tolerated dose of statin with or without other lipid-lowering therapies.[23] Key exclusion criteria included triglyceride levels >4.5 mmol/L (400 mg/dL) and insulin treatment <6 months in duration or a stable insulin regimen/dose <3 months in duration.[23] After screening, patients were randomised 2:1 to alirocumab (75 mg subcutaneously every 2 weeks [Q2W]) or placebo, stratified by diabetes type, for a 24-week treatment period with an 8-week safety extension. Alirocumab doses were adjusted at Week 12 to 150 mg Q2W if lipid targets (LDL-C levels <1.81 mmol/L [70 mg/dL]) were not achieved at Week 8. Patients remained on a stable diet for glucose and lipid management and received a stable dose regimen of statin and/or other lipid-lowering therapy throughout the study. The primary endpoint was percentage change from baseline in calculated LDL-C at Week 24, and safety up to Week 32.[23]

A total of 517 patients were randomised to treatment, 441 of whom had Type 2 diabetes mellitus. Of these patients, 294 were allocated to alirocumab and 147 to placebo.[2] Baseline characteristics of the Type 2 diabetes mellitus population were generally balanced between treatment arms; the mean age was 64.0 years, mean duration of diabetes was 16.0 years, and mean

HbA1c was 7.5%.[2] Approximately 75% of patients were on statins, the majority of whom were receiving a moderate-intensity dose, and approximately 25% were statin intolerant.[2] Baseline lipid profiles were comparable between treatment arms; calculated mean LDL-C was 2.9 mmol/L (110.8 mg/dL) in the alirocumab arm and 2.8 mmol/L (109.6 mg/dL) in the placebo arm.

At Week 24, alirocumab was associated with a significant reduction from baseline in LDL-C versus placebo (-48.2% versus +0.8%; p<0.0001), an effect that was achieved in most patients with the lower alirocumab dose (79.8% of patients were receiving 75 mg Q2W at Week 12).[2] This finding was consistent with observations from the overall ODYSSEY programme (including pooled analyses) which reported LDL-C lowering ranging from -43.4 to -60.4%.[26-28] Alirocumab also significantly reduced non-HDL-C levels versus placebo (least squares [LS] mean difference: -38.7%; p<0.0001), and produced significant reductions in apolipoprotein B and lipoprotein(a), and elevations in HDL-C levels.[2] Glycaemic-related parameters, including HbA1c, fasting plasma glucose, and total daily insulin dose, were consistent between treatment arms throughout the study.[2] Alirocumab demonstrated an acceptable safety and tolerability profile. The incidence of treatment-emergent adverse events was comparable between alirocumab and placebo arms (66.9% versus 66.2%, respectively). Allergic drug reactions were low in both treatment arms; 3.2% of alirocumab-treated patients had low-titer persistent anti-drug antibodies.

ODYSSEY DM-DYSLIPIDEMIA: Rationale and Key Clinical Data

Individuals with diabetes and mixed dyslipidaemia are at high CV risk, yet alirocumab had not been specifically evaluated in this population prior to the DM-DYSLIPIDEMIA study. Furthermore, no previous trial of a PCSK9 inhibitor has used non-HDL-C as its primary endpoint.[29] This study evaluated alirocumab versus lipid-lowering usual care in patients with Type 2 diabetes mellitus and mixed dyslipidaemia for those at high CV risk with below-target non-HDL-C levels despite maximum tolerated doses of statin therapy.[24]

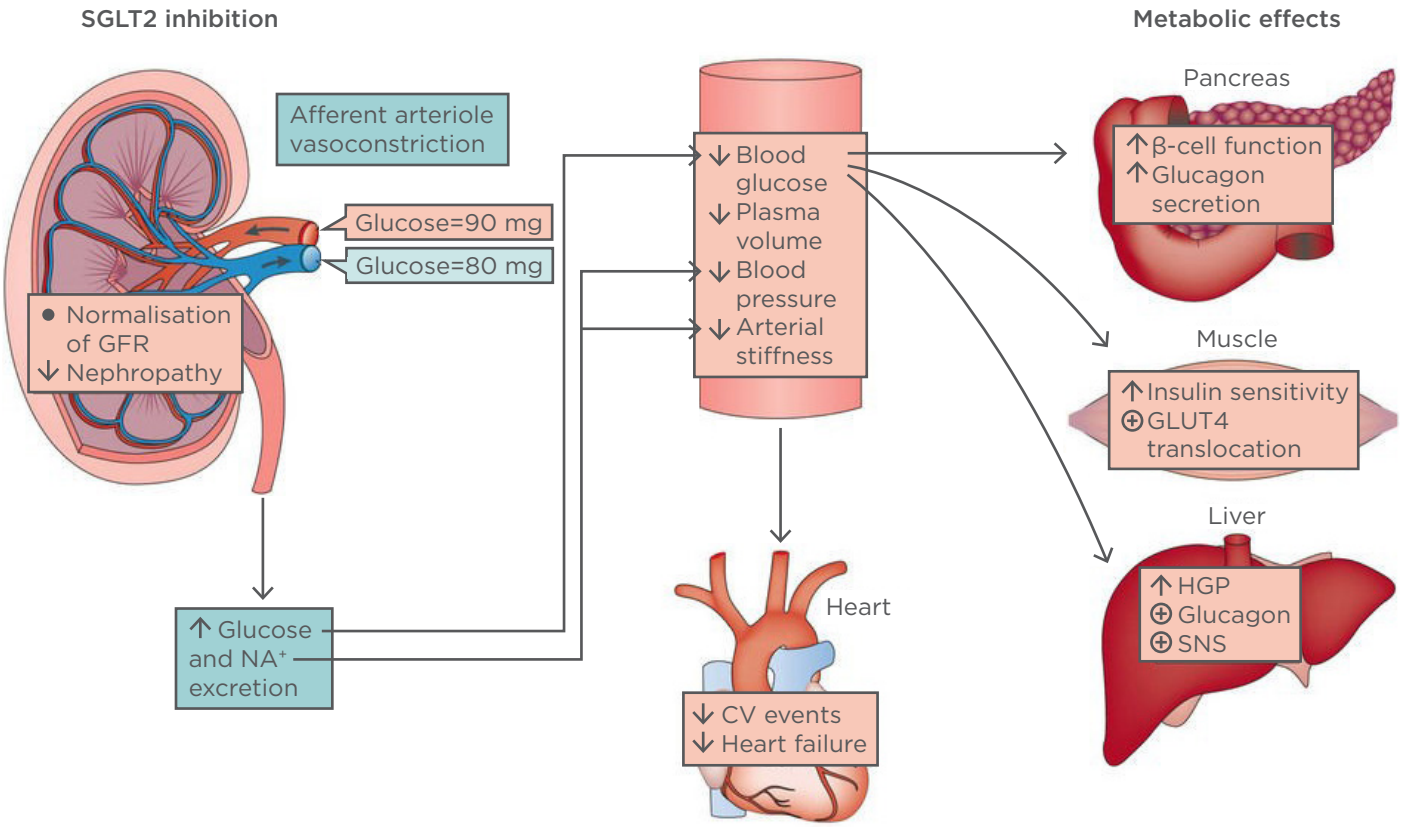

Figure 1: Physiological effects of sodium-glucose cotransporter 2 inhibition.
CV: cardiovascular; GFR: glomerular filtration rate; GLUT4: glucose transporter Type 4; HGP: hepatic glucose production; SGLT2: sodium-glucose cotransporter; SNS: sympathetic nervous system.
Adapted from DeFronzo et al.[31]

ODYSSEY DM-DYSLIPIDEMIA was a randomised, double-blind, placebo-controlled study.[24] Patients had Type 2 diabetes mellitus, non-HDL-C levels ≥2.59 mmol/L (100 mg/dL), triglyceride levels ≥1.70 and <5.65 mmol/L (150–500 mg/dL), and ASCVD or other CV risk factors.[24] Patients were randomised 2:1 to alirocumab treatment (75 mg subcutaneously Q2W) or usual care for 24 weeks followed by an 8-week safety extension.[24] Usual care permitted the optional addition of one of the following to statin therapy, ezetimibe, fenofibrate, omega-3 fatty acids, or nicotinic acid. Alirocumab doses were adjusted at Week 12 to 150 mg Q2W if lipid targets (LDL-C levels <1.81 mmol/L [70 mg/dL]) were not achieved at Week 8. Patients remained on a stable diet for glucose and lipid management, and received a maximum tolerated dose of statin therapy (or no statin if intolerant) throughout the study.[24] The primary endpoint was percentage change from baseline in non-HDL-C at Week 24.[24]

A total of 276 patients were randomised to alirocumab treatment and 137 to usual care.[3] Baseline characteristics were comparable between treatment arms; mean age was 63.5 years and mean HbA1c was 7.1%. Approximately 34% of patients had ASCVD while the remaining 66% had ASCVD plus additional CV risk factors. Lipid profiles were comparable between treatment arms; mean non-HDL-C was 4.0 mmol/L (155.1 mg/dL) with alirocumab and 4.2 mmol/L (161.5 mg/dL) with usual care.[3]

This important clinical trial will illuminate potential mechanisms and treatment strategies in patients with mixed dyslipidaemia or elevated atherogenic remnant cholesterol levels. For example, this trial will explore the clinical value of increasing LDL-receptor activity or hepatic catabolism of atherogenic lipoproteins for the lipoprotein phenotype with alirocumab versus usual care and fenofibrate, the latter mainly inhibiting synthesis of triglyceride-rich lipoproteins.

Details of the EASD scientific session on September 14th reporting new data from the ODYSSEY DM programme in patients with Type 1 and Type 2 diabetes mellitus were announced.[30]

Dual Sodium-Glucose Cotransporter 1 and 2 Inhibition: Of Mechanisms and Men

Professor Thomas Danne

Key Points

- Sotagliflozin is an oral, potent, dual inhibitor of the insulin-independent SGLT1 and SGLT2 transporters.
- Evidence from Phase II studies demonstrate that sotagliflozin, in combination with metformin, lowers HbA1c in patients with Type 2 diabetes mellitus.
- In addition, sotagliflozin therapy provides significant reductions in body weight and systolic blood pressure with an acceptable safety profile.
- Furthermore, the efficacy of sotagliflozin is maintained even in patients with low estimated glomerular filtration rate (eGFR) levels.

The book 'Of Mice and Men', a depiction of the American Dream, was first published by John Steinbeck in 1937. Seventy years later, in 2007, the Nobel Prize in Physiology and Medicine was awarded for creation of the first knockout mouse model. Today, results of emerging novel therapeutic agents for the treatment of Type 1 diabetes mellitus, a dream for many patients since the initial discovery of insulin, are being presented. These novel treatments are also a story of mice and men, as the therapeutic principle has been developed with the help of knockout mouse models and investigational agents have now completed Phase III trials in humans. The original principle was discovered 200 years ago when phlorizin, a glycoside and dual inhibitor of the insulin-independent sodium-glucose cotransporters SGLT1 and SGLT2, was first isolated by French scientists in 1835 from the bark of an apple tree.[31] In subsequent years, understanding of phlorizin's mechanism of action and clinical effects advanced significantly. Although phlorizin was shown to improve glycaemic control in diabetic animals, gastrointestinal (GI) side effects and rapid GI metabolism after oral administration prevented its development as an oral antidiabetic agent.[32,33] Clinical studies have demonstrated the beneficial effects of SGLT2 inhibition on glucose homeostasis (Figure 1).[31]

However, SGLT2 inhibition can be linked with an increased risk of diabetic ketoacidosis

(DKA) and uncharacteristically mild-to-moderate glucose elevations (euglycaemic DKA).[34] Multiple factors can trigger the onset of DKA, including insulin dose reductions and intercurrent illness. However, euglycaemic DKA is detectable and can be managed with proper patient education.[35,36] Preliminary evidence indicates that dual inhibition of both SGLT1 and SGLT2 may serve as a strong target for diabetes management. Indeed, oral glucose tolerance tests have demonstrated reduced glucose excursions in both SGLT1 and SGLT2 knockout mice fed a high-fat diet versus wild-type controls.[37]

Sotagliflozin Mechanism of Action

Sotagliflozin, an investigational oral agent, provides dual inhibition of both SGLT1 and SGLT2 and thus differs from existing therapies which are selective for SGLT2. Sotagliflozin provides potent inhibition of SGLT1 and ~18x more potent inhibition of SGLT2 than canagliflozin.[38] Predominantly expressed in the intestine, SGLT1 acts as the major intestinal glucose and galactose transporter, while SGLT2, which is expressed in the liver, facilitates reabsorption of filtered glucose.[39,40] Therefore, dual SGLT1 and SGLT2 inhibition with sotagliflozin has the potential to lower postprandial glucose, and produce robust reductions in HbA1c with reduced renal glucose excretion that is maintained with reduced kidney function.[41] In patients with Type 2 diabetes mellitus, SGLT1 is overexpressed in the GI tract, similar to the overexpression of SGLT2 in the kidney. Therefore, partial SGLT1 inhibition may provide additional benefits to patients that could not be achieved with SGLT2 inhibition alone.

Insights from Sotagliflozin Phase II Data in Patients with Type 2 Diabetes Mellitus

The safety and efficacy of oral sotagliflozin was evaluated in a Phase IIa, randomised, double-blind, placebo-controlled trial in 36 patients with Type 2 diabetes mellitus.[42] At Week 4, sotagliflozin at doses of 150 mg/day and 300 mg/day were associated with significantly greater reductions from baseline in HbA1c versus placebo (-1.15% and -1.25% versus -0.49%, respectively).[42] In addition, sotagliflozin, at both doses studies, was associated with incremental improvements in postprandial glucose compared with placebo. Furthermore, both doses of sotagliflozin were associated with increased levels of the glucagon-like peptide-1 (GLP-1) as indicated by an increase in total GLP-1 area under the curve.[42] A 12-week, dose-ranging, Phase IIb study evaluated escalating doses of sotagliflozin (75, 200, and 400 mg once-daily; or 200 mg twice-daily) versus placebo in patients with Type 2 diabetes mellitus receiving metformin.[43] Analyses of Week 12 data demonstrated that while HbA1c change from baseline was dose-dependently greater with sotagliflozin versus placebo, urinary glucose/creatinine ratios were not increased with higher sotagliflozin doses. This increased efficacy without increased urinary glucose excretion at 400 mg sotagliflozin was consistent with dose-dependent SGLT-1 inhibition above 200 mg, which differs from observations with selective SGLT2 inhibitors.[43]

Compared with placebo, sotagliflozin was associated with significant reductions in body weight at Week 12 with all doses tested ($p \leq 0.001$). Furthermore, sotagliflozin at higher doses (200–400 mg) significantly reduced systolic blood pressure compared with placebo ($p \leq 0.017$).[43] The incidence of treatment-emergent adverse events was >3% in all sotagliflozin-treated patients, regardless of causality, which was consistent with the placebo arm (57.6–66.7% versus 66.7%, respectively). Nausea events were numerically higher with sotagliflozin 400 mg once-daily versus placebo (6 versus 3, respectively).[43] Genitourinary events were low among both treatment arms, but numerically higher in sotagliflozin-treated patients versus placebo-treated patients (11 events were reported in total; 10 with sotagliflozin and 1 with placebo).[43] In a separate study, the efficacy and safety of sotagliflozin versus placebo was evaluated in a 7-day study of patients with Type 2 diabetes mellitus and renal impairment (defined as an eGFR <60 mL/min/1.73m^2).[44] At Day 7, sotagliflozin treatment was associated with significantly greater postprandial glucose excursions compared with placebo in both the total population ($p=0.003$ versus placebo), and the subgroup of patients with eGFR <45 mL/min/1.73m^2 ($p=0.002$).[44] Furthermore, sotagliflozin compared with placebo significantly lowered systolic blood pressure (LS mean difference: -11.4; $p=0.045$), and numerically lowered diastolic blood pressure (LS mean difference: -4.5; $p=0.08$) in the subgroup of patients with eGFR <60 mL/min/1.73m^2. Taken together, these data indicate that sotagliflozin is efficacious and well-tolerated in patients with Type 2 diabetes mellitus, including those with reduced renal function.

Unmet Needs in Adult Patients with Type 1 Diabetes Mellitus that Could be Addressed with an Oral Agent and the Sotagliflozin Clinical Development Programme

Doctor Anne Peters

Key Points

- Insulin therapy alone is often inadequate in patients with Type 1 diabetes mellitus, who may benefit from adjunctive treatments.
- Measurement of outcomes for adults with Type 1 diabetes mellitus should not be based solely on changes in HbA1c.
- The ongoing inTandem Phase III clinical programme will provide valuable insights regarding the potential role of dual SGLT1 and SGLT2 inhibition in the treatment of Type 1 diabetes mellitus.

Dual inhibitors of SGLT1 and SGLT2 could potentially represent an effective adjunct treatment to insulin therapy in Type 1 diabetes mellitus. Metabolic control varies with advancing age among patients with Type 1 diabetes mellitus. Evidence from the T1D Exchange clinic registry indicates that overall mean HbA1c levels range from 8.1–8.3% in childhood, increasing to >9.0% in adolescents (e.g., 17–20 years), gradually declining to ˜7.5–7.8% in patients aged >30 years, and then modestly decreasing to <7.5% in individuals aged >65 years.[45] Additional analyses from the registry demonstrated that most patients (up to 86%) were unable to achieve their HbA1c targets solely with insulin, an observation that was consistent across age groups.[45] The inadequacy of insulin therapy alone has also been highlighted by other studies. One such study evaluated the effect of intensive versus conventional insulin therapy (≥3 versus 1–2 injections per day, respectively) on the incidence of CV disease over 30 years in patients with Type 1 diabetes mellitus.[46] Analyses revealed that the incidence of hypertension increased with age, irrespective of whether patients received intensive therapy or conventional insulin therapy.[46] Registry data on BMI among patients with Type 1 diabetes mellitus indicate that the proportion of patients with a BMI in the normal range decreases with age, and conversely, the proportion of patients with a BMI in the overweight or obese range increases with age, irrespective of insulin treatment.[45]

Improving Outcomes in Type 1 Diabetes Mellitus Beyond Glycated Haemoglobin

Difficulties in managing diabetes can have serious psychological consequences. Patients may develop diabetes distress, a state in which they can experience feelings of powerlessness (i.e. "my disease is out of control"), physician distress (i.e. disappointment with healthcare providers), and negative social perceptions (i.e. concerns around negative judgement from others).[47] The path to glycaemic control is individual to each patient and more complex than the simple metric of HbA1c can measure. An estimate of mean HbA1c based on a measurement cannot provide an accurate report of daily fluctuations in glucose control and may potentially 'mask' episodes of significant dysglycaemia that can impact clinical outcomes and patient quality of life. In the USA, a number of clinical societies (AACE, American Association of Diabetes Educators [AADE], ADA, Endocrine Society, Pediatric Endocrine Society [PES], JDRF International, Helmsley Charitable Trust, and the T1D Exchange) are currently working together to establish the 'Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes' consensus statement, which will include definitions of standardised measures of outcomes such as hypoglycaemia and hyperglycaemia (by level of severity), time in glycaemic range, and DKA.

Selective Sodium-Glucose Cotransporter 2 Inhibition and Sotagliflozin in Type 1 Diabetes Mellitus

Selective SGLT2 inhibition offers an additional therapeutic option for patients with Type 1 diabetes mellitus; however, SGLT2 inhibitors should be used with caution in those patients who may be susceptible to DKA.[35] A Phase II, placebo-controlled, proof-of-concept study evaluated the effects of dual SGLT1 and SGLT2 inhibition with sotagliflozin over 29 days in patients with Type 1 diabetes mellitus.[48] At the end of the treatment period, change from baseline in HbA1c was significantly lower with sotagliflozin versus placebo (-0.55% versus -0.06%, respectively; p=0.02).[48] Notably, this robust HbA1c-lowering effect of sotagliflozin versus placebo was not accompanied by an increase in hypoglycaemia. Analysis of continuous glucose monitoring data revealed that patients treated with sotagliflozin versus placebo spent a significantly greater proportion of time within the target glycaemic range of 3.8–10 mmol/L

(70–180 mg/dL). In addition, there was no increase in the proportion of time spent in the below target range of <3.8 mmol/L (<70 mg/dL) with sotagliflozin versus placebo (Figure 2).[48]

Sotagliflozin inTandem Clinical Programme

The sotagliflozin inTandem Phase III clinical programme comprised three pivotal trials, inTandem1, inTandem2, and inTandem3.[49,50] inTandem1 and inTandem2 were randomised, placebo-controlled studies that assessed the efficacy and safety of sotagliflozin (200 or 400 mg once-daily) on a background of optimised insulin, in patients with Type 1 diabetes mellitus. inTandem1 enrolled 793 patients from 79 sites in North America, while inTandem2 enrolled 782 patients from 99 sites across Europe and Israel.[49,50] The studies consisted of a 24-week treatment period followed by a 28-week extension. The primary endpoint was change from baseline in HbA1c at Week 24. inTandem3 was a randomised, placebo-controlled trial which evaluated the efficacy and safety of sotagliflozin 400 mg once-daily on a background of standard of care insulin (i.e. not optimised) in 1,405 patients with Type 1 diabetes mellitus from 19 countries worldwide.[51]

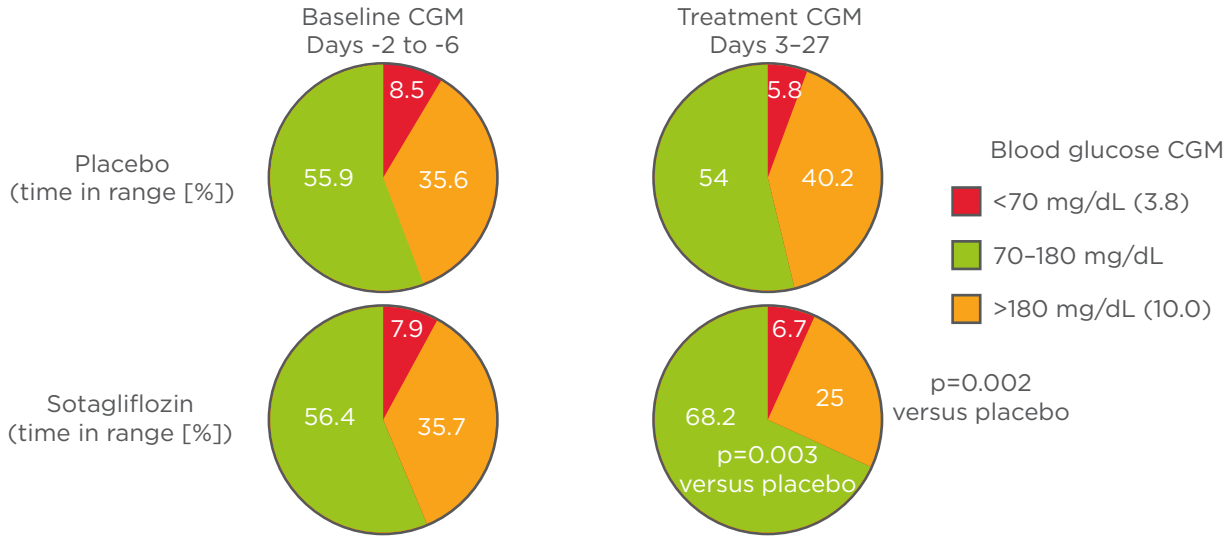

Figure 2: Physiological effects of sodium-glucose cotransporter 2 inhibition.
CGM: continuous glucose monitoring.
Adapted from Sands et al.[48]

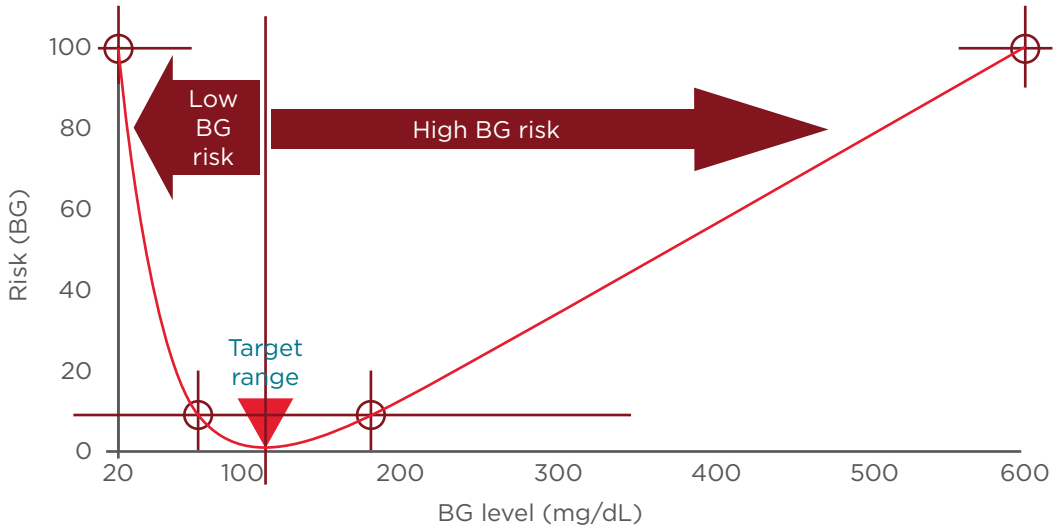

Figure 3: Risk analysis of blood glucose data.
BG: blood glucose.
Adapted from Kovatchev.[54]

The study comprised a 2-week screening period, 2-week run-in, and 24-week treatment period. The primary endpoint was the proportion of patients with HbA1c <7.0% and no episode of severe hypoglycaemia or DKA at Week 24. Results from the sotagliflozin inTandem Phase III clinical programme will provide valuable insights regarding the potential role of dual SGLT1 and SGLT2 inhibition in the treatment of Type 1 diabetes mellitus.

Enriching Diabetes Care: Technology and New Models for Intervention Strategies

Doctor Boris Kovatchev

Key Points

- Innovations in metabolic modelling and technology are revolutionising diabetes care.
- Optimisation of diabetes treatment is dependent upon achieving strict glycaemic control without increasing the risk of hypoglycaemia.
- The development of new diabetes-related technologies, such as closed-loop systems, follows three key steps: 1) formulation of the problem, 2) understand the system, 3) and control diabetes.
- Future integration of patient-level information (e.g., genetic profiling, laboratory results, and real-time monitoring) would create a diabetes treatment ecosystem that could potentially bring precision medicine into the care of people with diabetes.

Since the discovery of insulin in 1921, diabetes-related technology has progressed remarkably. Notable innovations have included the development of insulin pump systems, sensitive glucose monitoring techniques, and advanced metabolic assessment procedures;[52] technological advances that together are helping to advance diabetes treatment. However, clinical optimisation of diabetes therapy (i.e. aiming to achieve and maintain strict glycaemic control without increasing the risk of hypoglycaemia) continues to represent a significant challenge for both physicians and patients.[53] Optimisation of therapy can be achieved by developing new medications or technologies. The development of new diabetes technology follows three key steps: 1) formulate the problem quantitatively, 2) understand the metabolic system, and 3) control diabetes.

Formulate the Problem, Quantitatively

Optimisation of diabetes therapy can only be achieved through lowering glucose variability.[54] A common limitation of traditional glucose variability measures is bias towards hyperglycaemia. This is due to the asymmetric nature of the blood glucose scale and that deviations towards hyperglycaemia occupy a wider range of the scale than deviations towards hypoglycaemia.[54] Furthermore, the clinical risk associated with glycaemic excursions must differentiate between excursions into hyperglycaemia versus acute hypoglycaemia. Risk analyses of blood glucose data provides a means of quantifying glucose variability more accurately. These demonstrate that falling blood glucose levels are associated with a sharp increase in risk, while rising blood glucose values are associated with a gradual increase in risk (Figure 3).[54,55] Accordingly, excursions into the range of extreme hypoglycaemia or hyperglycaemia are allocated progressively increasing risk values. Variance within the optimal euglycaemic range is attenuated, which reduces noise during data analysis.

Understand the System

The development of new medications and technologies is based on an in-depth understanding of the functioning of the human glucose control network in healthy individuals and in patients with Type 1 and Type 2 diabetes mellitus. Glucose homeostasis is regulated by a complex interplay of 'intertissue communication' between the pancreas, liver, gut, brain, and muscle, which is facilitated by glucose and its metabolites and is subject to environmental factors, specifically diet and exercise.[56] In Type 2 diabetes mellitus, altered communication between tissues and an inability to adapt to changing metabolic states both play a critical role in the altered glucose homeostasis that fuels disease progression. The incretin effect represents an example of how glucose homeostasis is perturbed in patients with Type 2 diabetes mellitus. Defined as the difference in insulin secretory response elicited by oral glucose load versus intravenous glucose administration, the incretin effect is substantially diminished in patients with Type 2 diabetes mellitus.[57]

In addition, to a detailed knowledge of the human glucose control network, it is pivotal to fully understand the mechanism and clinical effects of diabetes treatments. Clinical studies provide

quantitative data on the differential effects of various therapeutic approaches (e.g., basal insulin monotherapy versus GLP-1 receptor agonists versus a combination of both) on diabetes outcomes. Taken together, such understanding provides a comprehensive framework for the development of *in silico* metabolic models. These models enable realistic computer simulation of the metabolic manifestations of diabetes and of their treatment. In a multinational study, closed-loop control was compared to state-of-the-art open-loop therapy in adults with Type 1 diabetes mellitus, where the design of the closed-loop control algorithm was done *in silico*.[58] Computer simulated experiments were used to generate data from 300 virtual subjects with Type 1 diabetes mellitus, from three distinct age groups who could be screened, measured, and treated individually. *In silico* modelling resulted in rapid (<6 months compared with the equivalent years of animal trials) and cost-effective system development and testing, leading to regulatory approval in multiple markets.[58] In the USA, the U.S. Food and Drug Administration (FDA) has accepted *in silico* modelling for assessing human glucose and insulin utilisation, interstitial sensor performance, and subcutaneous insulin delivery.[58] Furthermore, *in silico* models are now becoming an accepted alternative to animal trials for the preclinical testing of new insulin treatment strategies and artificial pancreas algorithms.[58]

Control Diabetes

The artificial pancreas represents the ultimate technological treatment of diabetes and has advanced considerably since the first devices were tested around 40 years ago. Early devices were impractical for outpatient use due to the intravenous route of glucose sensing and insulin infusion. However, they validated the feasibility of external glucose control, paving the way for future developments. The subsequent development of minimally invasive subcutaneous glucose sensing technology revolutionised closed-loop control systems. Modern systems comprise a continuous glucose sensor, insulin pump, and a sophisticated control algorithm that uses a mathematical model of the metabolic system to provide automated insulin delivery.[59] The first portable closed-loop control system was introduced by the University of Virginia, Virginia, USA in 2011. The technology, which is controlled by a smart phone, links wirelessly to the glucose sensor and insulin pump to provide optimised, automated insulin delivery.[60] To date, the effectiveness of several closed-loop control systems, including the Medtronic MiniMed 670G System, the Dexcom G4 with Software 505 + Roche insulin pump, and the Dexcom G4 Platinum + two Tandem t:slim insulin pumps have been evaluated in the outpatient setting.[61-63] Time within range analyses demonstrated that closed-loop systems provided effective glycaemic control; patients were within the target glycaemic range of 3.8–10.0 mmol/L (70–180 mg/dL) >70% of the time and were below the target range <3% of the time. Time spent at very low blood glucose levels (<2.8 mmol/L [50 mg/dL]) was negligible (<0.4%).[61-63] In addition, data from a recently completed ski camp study demonstrated that even during challenging winter-sport conditions, overall time within glycaemic range and time within range at night (3.00–7.00 am) was higher with closed-loop systems (71.3% and 84.6%, respectively) versus control (64.7% and 66.2%, respectively). Importantly, time below range was lower with closed-loop systems versus control (1.8% versus 3.2%, respectively).[64]

New Models for Intervention

Future therapeutic interventions could be derived from a diabetes treatment ecosystem. Such an ecosystem would bring together patient-level information, including genetic profiling, laboratory results, real-time monitoring, and predictive analytics, into a comprehensive virtual image of the patient, which would then allow treatment approaches to be tested efficiently *in silico* and tailored to each person.

Integrating Diabetes Care

Professor David Kerr

Key Points

- There is a need for integration of diabetes care and technology (e.g., closed-loop insulin delivery systems and smart insulin pens) in order to improve outcomes for people with diabetes and their families.
- The development of sophisticated algorithms, informed by population-wide data and machine learning, could lead to initiatives that help predict and prevent negative clinical outcomes.
- Achieving integration of care requires new thinking beyond segmenting into Type 1 or Type 2 diabetes mellitus to better reflect personal needs and opportunities based on measurable

metrics of success that are affordable, accessible, and understandable to all users.

Diabetes care needs to change before we are likely to see the introduction of personalised diabetes treatment ecosystems. In the USA alone, >20% of all patients with diabetes have very poor glycaemic control (HbA1c <9%).[65] Registry data from >16,000 patients with Type 1 diabetes mellitus show that the majority of this population (>70%) are above ADA-recommended HbA1c targets, irrespective of age.[45] There is also evidence of a racial divide, in which individuals from minority populations have poorer glycaemic control.[65] Going forward, the concept of value in healthcare when assessing the potential impact of new therapies or devices can be quantitatively defined as the quality of care (i.e. achieving glycaemic targets etc.) plus the experience of care, divided by the cost. Integration of care offers an opportunity to enhance the clinical value of diabetes treatments, but this will require better and more in-depth understandings of the five determinants of health, as they affect individuals with diabetes. These five determinants include 1) genetics (e.g., race and ethnicity-specific effects on drug pharmacology); 2) biology (e.g., intra and inter-individual variations in drug absorption and duration); 3) behaviour (e.g., treatment concordance); 4) psychology (e.g., impact of depression, diabetes distress, and fear of hypoglycaemia); and 5) society (e.g., treatment access, costs, and non-traditional factors, such as environmental temperature and pollution). Current efforts to segment diabetes, e.g., arbitrarily dividing diabetes into Type 1 or Type 2, add little value with regard to clinical care and outcomes. Integrated care provides a means to stratify individuals in a more relevant manner based on their clinical profile, such as hypoglycaemia avoider, diabetes loather, high-cost individual, and insulin user.

Integrated care requires digital diabetes health technologies. Future technological innovation in diabetes care will also include new therapies such as 1) implantable drug delivery systems; 2) automated completely closed-loop systems using a variety of sensors and effectors to maintain physiological homeostasis; and 3) miniaturised, wearable, non-invasive glucose monitoring systems or long-term, implanted continuous glucose sensors. New miniaturised wearable sensors and implanted sensors are already beginning to be used to create systems that links users and their care teams to enable precision management of diabetes.

Preliminary efforts to integrate care are beginning to emerge. In clinical practice, areas exist in which innovation is needed and progression to integration is relatively simple. In an analysis of 2,000 local Latino patients with diabetes, only ˜37% of individuals received two HbA1c tests within 12 months, the minimum number of tests recommended by national and international guidelines. These data highlight that the current process of HbA1c testing (co-ordinating a patient and physician for an appointment, performing a test, and communicating the results to the patient) is proving difficult in clinical practice. One potential approach to overcome this would be to issue a shared service based on geolocation technology that could match a patient with an appointment, when necessary. Integrated systems such as this could potentially contribute to improvements in diabetes management beyond the introduction of new therapies.

Natural progression of technology and the availability of population-wide data could lead to the development of computer systems with the ability to monitor whole diabetes populations and predict the possibility of negative outcomes in individual patients. Similarly, the development of sophisticated algorithms through machine learning may help prevent the occurrence of negative outcomes by alerting clinical teams to individuals who require an appropriate intervention. These data, together with deep learning, automated predictive analytics using blocks of increasing complexity could lead to the prevention, and possibly even cure, of diabetes.

The implementation of integrated care would revolutionise diabetes care; a concept that was illustrated by an animated, hypothetical clinical case. Future developments may permit patients to use virtual reality to learn how to initiate insulin using their smart pen. Furthermore, reminders, support, advice, and education could be provided to patients by a 'home doctor', in which the patient could interact with a virtual physician. The provision of 24-hour care could become a reality through linking smart pens and supporting devices (e.g., smart phones, smart watches) through the 'Internet of Medical Things' to a population-health, centrally located clinician. This individual, with the assistance of robots, would monitor data transmitted between devices and provide support to patients when they are unable to contact their local physician. For example, if a patient experiences an issue outside of their local

physicians' working hours, data can be transmitted to the population-health, centrally located clinician who will consider the information and then send a recommendation to the patient's smart device. This recommendation (e.g., reduce insulin dose) will automatically transmit to the smart insulin pen, which will then prepare the recommended dose.

Achieving integration requires the following, 1) target population must be defined, 2) appropriate metrics of success must be defined, 3) the materials need to be understandable for all users, 4) the benefits of integration need to be sustainable in their return on investment, and 5) the technology needs to be affordable.

Conclusion

Innovations in diabetes care are not exclusive to therapeutic and technologic advances. Increasingly, researchers are looking beyond measures of glucose control to address non-glycaemic outcomes that are relevant to patients with diabetes. Such innovations include the availability of treatments that address the high CV risk that persists in patients with diabetes, despite optimised lipid-lowering therapy, the development of new therapies with novel mechanisms of action for managing Type 1 diabetes mellitus, and new technologies that will facilitate the future integration of care. Advances such as these should help to drive innovation within diabetes management. Furthermore, the integration of these advances into daily clinical practice should help to further evolve and improve patient care in the future.

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A ROLE FOR CONNEXIN MEDIATED CELL COMMUNICATION IN FIBROSIS OF TUBULAR EPITHELIAL CELLS IN THE DIABETIC KIDNEY

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Keywords: Purinergic signalling, gap junctions, extracellular matrix, ATP, inflammation, tubulointerstitial fibrosis, diabetic nephropathy, hemichannels, connexins.

ABSTRACT

Diabetic nephropathy represents the leading cause of end-stage renal disease and is the greatest cause of patient entry into the renal replacement therapy programme.[1] Of the many structural and functional disturbances associated with the disease, tubulointerstitial fibrosis represents the key underlying pathology and occurs in response to a number of phenotypical and morphological changes, culminating in tubular injury.[2] Treatment of fibrosis in nephropathy is an unmet clinical need, and identification of appropriate therapeutic targets is urgently required.

Connexins are involved in the formation of both hemichannels and gap junctions, and multiple secondary complications of diabetes are associated with alterations in the expression or function of these important transmembrane proteins.[3] Previous work from our group suggested that glucose evoked changes in the beta 1 isoform of transforming growth factor (TGF) induced a loss of E-cadherin mediated cell adhesion in human proximal tubule epithelial cells.[4] In the absence of cell–cell adhesion, uncoupled connexins or hemichannels predominate and gap-junctions fail to form. These channels allow cells to signal to each other via local paracrine release of ATP.[5] Interestingly, elevated levels of nucleotides have recently been linked to both increased inflammation and fibrosis in multiple tissue types and various disease states.[6]

Immunohistochemistry of biopsy material isolated from patients with proven diabetic nephropathy confirmed increased expression levels of predominant tubular connexin isoforms: connexin-26 and connexin-43. These data are corroborated by immunoblot analysis of lysates isolated from human primary proximal tubule cells cultured in TGF-β1 (2–10 ng). Using whole-cell paired patch electrophysiology and ATP-biosensing, we observed a switch in gap junction mediated intercellular communication in favour of hemichannel mediated ATP release at both 48-hour (acute) and 7-day (chronic) time periods. Increased ATP levels have been linked to fibrosis and inflammation.[6] Incubation of human primary proximal tubule cells, with either TGF-β1 (2–10 ng/mL) or non-hydrolysable ATPγS (1–100 µM), induced a dose-dependent increase in the expression of candidate proteins, namely collagen I, fibronectin, and interleukin-6, as well as morphological changes towards a fibroblast-like phenotype. The TGF-β1 induced response was partly negated when cells were co-incubated with the nucleotidase, apyrase (5 U/mL), or the purinergic receptor antagonist suramin (10 µM), suggesting that TGF-β1 evoked changes in hemichannel mediated ATP release are driven through activation of downstream purinergic signalling.

In conclusion, our study reports that connexin-26 and connexin-43 expression levels are increased in the diabetic kidney. Increased connexin expression is counterintuitively matched by a loss of direct gap junction mediated cell-to-cell communication as cell-cell tethering decreases and cells move apart. To compensate for this loss of direct intercellular communication, cells of the human proximal tubule increase indirect hemichannel mediated ATP release. Although designed to maintain cell–cell coupling, these changes may actually exacerbate the situation and facilitate loss of epithelial integrity and function through increased fibrosis and inflammation. Targeting connexins in the diabetic kidney therefore represents a viable future therapeutic intervention in diabetic nephropathy.

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SEX DIFFERENCES IN THE DIABETES-ASSOCIATED RISK OF CARDIOVASCULAR EVENTS IN A YOUNG POPULATION

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INTRODUCTION

Incidences of both Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) are increasing among young people.[1] The diabetes-associated excess risk of cardiovascular diseases is known to be higher in women than in men, mostly at peri and post-menopausal ages;[2] however, the risk in a younger population still remains uncertain.[3,4]

To answer this question, we carried out a retrospective observational study over a 6-year follow-up period (1st January 2007–31st December 2012) in Tuscany, Italy, to compare by sex the effect of diabetes on the risk of first hospitalisations for atherosclerotic cardiovascular diseases (ASCVD).

METHODS

Baseline diabetes was identified by a regional diabetes dataset in 2006 and confirmed in the following years over the entire study period. Continuous insulin therapy from the onset was considered as a proxy for T1DM and all other treatments were considered proxies for T2DM. From the regional hospitalisation dataset, outcomes of interest were first hospitalisations for ASCVD, primary or secondary diagnosis of acute myocardial infarction (diagnosis code ICD-9-CM), ischaemic stroke, congestive heart failure, and lower extremity amputation. Patients with at least two prescriptions for angiotensin converting enzyme inhibitors or angiotensin receptor blockers, aspirin, or statins over the study period were traced for further information about primary or secondary prevention therapy. Analysis of proportional incident risk of first hospitalisations for ASCVD, after adjusting for age and comorbidities (Charlson Comorbidity Index), was carried out by the Cox regression analysis model.

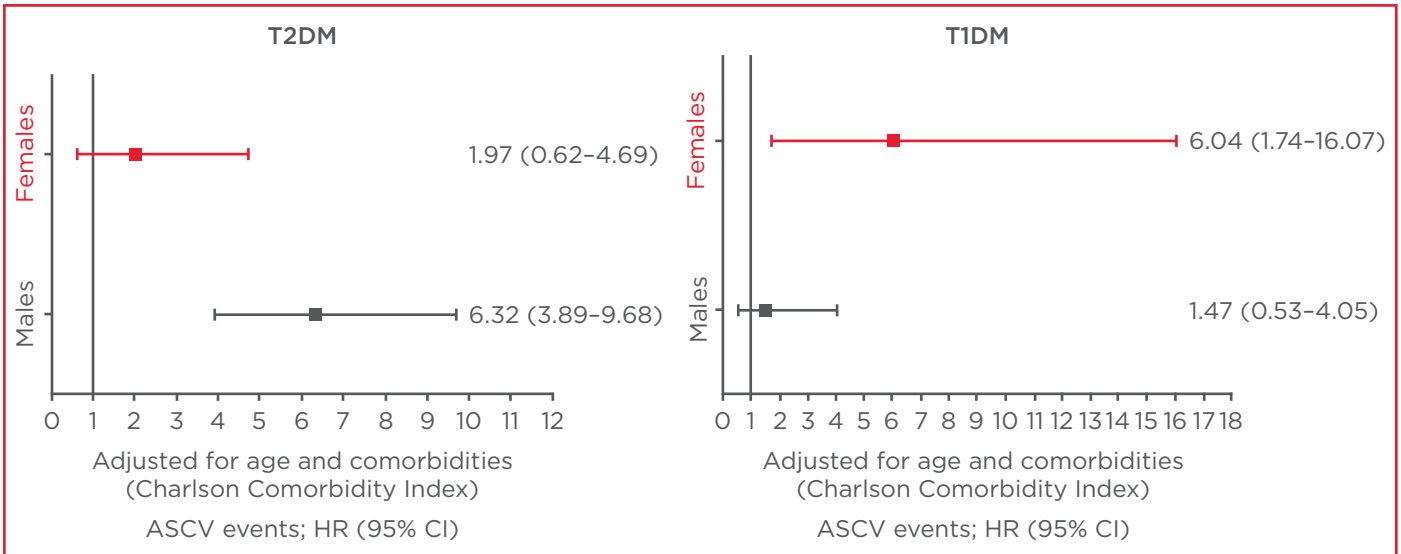

Figure 1: Risk of ASCVD events in subjects with T2DM or T1DM compared to those without diabetes, stratified by sex.
ASCVD: atherosclerotic cardiovascular diseases; CI: confidence interval; HR: hazard ratio; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

RESULTS

The population without diabetes comprised 514,732 males and 515,799 females, and there were 2,052 males and 2,598 females with diabetes who had a mean age of 32±7 years (934 T1DM/1,664 T2DM among females and 1,256 T1DM/796 T2DM among males). Hospitalisation rates for ASCVD (per year per 100,000) were much higher in those with diabetes in both sexes (32 per year in people without diabetes versus 209 per year for T1DM and versus 510 per year in T2DM among males, and 14 per year versus 194 per year in T1DM and versus 48 per year for T2DM among females). In the T1DM group the hazard ratio of hospitalisations for ASCVD, adjusted for age and comorbidities, as compared with those without diabetes, was 6-times higher in women, although the ASCVD incidence rate in diabetic people was similar in both sexes. On the contrary, in T2DM patients the excess risk was 6-fold higher in men but not in women (Figure 1).

Furthermore, within the diabetic populations, the risk of hospitalisation for ASCVD was higher in men with T2DM and similar between sexes in the T1DM group. ASCVD risk was higher in T1DM than in T2DM for males, while no significant difference between diabetes type was observed in females. Prescription of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, aspirin, or statins was similar between sexes in T1DM patients and much greater among males with T2DM. No sex difference in all-cause mortality was observed, comparing people with or without diabetes.

CONCLUSION

In conclusion, whether these differences are due to a real sex-linked dimorphism, different characteristics of T1DM or T2DM in the youth, or a difference in the the presence of other modifiable ASCVD risk factors, as suggested by the sex inequality in drug prescription among people with T2DM, needs further investigation.

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SHORT-TERM RENAL EFFECTS OF VILDAGLIPTIN ADDITION AND THEIR CLINICAL AND LABORATORY PREDICTORS IN INSULIN-TREATED TYPE 2 DIABETES MELLITUS PATIENTS: A RANDOMISED, COMPARATIVE, PROSPECTIVE CLINICAL STUDY

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Keywords: Vildagliptin, Type 2 diabetes mellitus (T2DM), renal function, renoprotection, urinary collagen Type IV (uColIV), serum cystatin C, urinary L-Type fatty acid binding protein (L-FABP), estimated glomerular filtration rate using cystatin C (eGFRcys), estimated glomerular filtration rate using serum creatinine and cystatin C (eGFRcr-cys), randomised.

AIMS

Positive renal effects of vildagliptin have been shown by several experimental studies.[1,2] Nonetheless, clinical evidence for its renoprotective potential is limited and predictive determinants are unknown.[3] To assess the renal effects of vildagliptin and identify their clinical and laboratory predictors, 47 insulin-treated male and female Caucasians, aged 49–70 years, with satisfactorally controlled Type 2 diabetes mellitus (T2DM) and blood pressure (BP) were enrolled. Patients had no overt chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR]: ≥60 mL/min; and the absence of proteinuria), morbid obesity, severe vascular diabetic complications, non-diabetic renal impairment, liver failure, or systemic autoimmune disorders. Patients were randomised either to continue insulin therapy (control) or to receive vildagliptin in a daily dose of 50 mg added-on insulin (V+ group). At baseline and after 6 months of treatment, we assessed eGFR (with the CKD Epidemiology Collaboration creatinine equation) using serum creatinine (eGFRcr), cystatin C (eGFRcys), both (eGFRcr-cys), and creatinine-adjusted urinary markers of glomerular (urine albumin-to-creatinine ratio, collagen Type IV [uColIV]) and tubular injury (L-Type fatty acid binding protein [L-FABP]), as well as metabolic control parameters.

Table 1: Clinical and laboratory parameters of patients with T2DM in the studied groups at baseline and after 6 months of the treatment.

Study groups / Variable	Insulin-treated group (control) (n=21)			Insulin-vildagliptin-treated (V+) group (n=23)			p*
	0 months	6 months	p-value	0 months	6 months	p-value	
BMI (kg/m^2)	31.5 [28.0; 35.4]	31.2 [28.2; 35.7]	0.06	31.6 [30.3; 34.9]	31.8 [29.7; 34.1]	0.72	0.71
HbA1c (%)	7.2 [6.6; 7.6]	7.3 [6.8; 7.7]	0.81	7.3 [6.9; 7.6]	7.0 [6.8; 7.4]	0.002	0.83
Daily insulin dose (units/kg)	0.44 [0.37; 0.63]	0.46 [0.31; 0.62]	0.43	0.43 [0.37; 0.54]	0.39 [0.33; 0.50]	0.001	0.40
Monthly frequency of hypoglycaemic episodes	1.0 [0.3; 2.0]	1.0 [0.5; 1.6]	0.19	1.0 [0.5; 2.0]	0.7 [0.2; 1.2]	0.001	0.43
Total cholesterol (mmol/L)	5.4 [4.8; 6.3]	5.7 [4.7; 6.1]	0.24	5.5 [4.8; 6.1]	5.4 [4.8; 5.9]	0.46	0.62
Systolic blood pressure (mmHg)	132.0 [125.0; 139.0]	131.0 [125.0; 142.5]	0.23	133.0 [128; 138]	134.0 [127.0; 140.0]	0.32	0.78
Diastolic blood pressure (mmHg)	78.0 [73.0; 84.0]	78.0 [73.0; 86.0]	0.49	81.0 [75.0; 85.0]	74.0 [71.0; 82.0]	0.001	0.84
eGFRcr (mL/min/1.73m^2)	77.0 [67.5; 84.4]	78.2 [65.3; 88.3]	0.43	69.8 [62.7; 95.0]	72.8 [61.8; 94.7]	0.22	0.86
Serum cystatin C (mg/L)	0.87 [0.81; 1.01]	0.86 [0.79; 0.99]	0.27	0.84 [0.76; 0.93]	0.75 [0.69; 0.82]	<0.001	0.01
eGFRcys (mL/min/1.73m^2)	89.9 [73.8; 100.8]	94.6 [71.5; 100.1]	0.27	90.6 [81.9; 104.1]	100.9 [95.1; 107.6]	<0.001	0.049
eGFRcr-cys (mL/min/1.73 m^2)	80.0 [73.0; 91.0]	79.0 [66.5; 93.5]	0.68	79.0 [75.0; 101.0]	90.0 [77.0; 104.0]	0.001	0.18
UACR (mg/g) Cr.	26.7 [20.1; 70.4]	27.2 [12.6; 89.1]	0.88	28.6 [15.0; 61.4]	24.0 [16.4; 47.3]	0.14	0.63
uCollV (µg/g) Cr.	3.8 [2.4; 7.2]	4.3 [2.5; 6.0]	0.69	3.3 [1.7; 6.9]	1.7 [1.4; 4.1]	<0.001	0.21
uL-FABP (µg/g) Cr.	2.4 [1.8; 4.0]	2.9 [1.7; 4.2]	0.43	2.6 [1.4; 4.3]	2.0 [1.3; 4.1]	0.45	0.73

The median [25th percentile; 75th percentile] are shown. p-values at 0 months versus 6 months at the same group (the Wilcoxon signed-rank test). p*: comparisons between both measurements of studied groups (repeated measures in the general linear models). Nonsignificant differences between baseline values in the study groups (Mann-Whitney U-test) are not shown.
Cr: creatinine-adjusted; eGFRcr: estimated glomerular filtration rate using serum creatinine; eGFRcr-cys: estimated glomerular filtration rate using serum creatinine and cystatin C; eGFRcys: estimated glomerular filtration rate using cystatin C; HbA1c: glycated haemoglobin; T2DM: Type 2 diabetes mellitus; UACR: urine albumin-to-creatinine ratio; uCollV: urine collagen Type IV; uL-FABP: urinary L-Type fatty acid binding protein.

RESULTS

Forty-four patients completed the study. The groups were comparable on the basis of sex (42.9% male in control group and 39.1% in V+ group), age (median value control group: 60.0 years [25th percentile: 54.0; 75th percentile: 66.0] versus 62.0 years [58.0; 63.0] in the V+ group), and known T2DM duration (≥10.0 [6.0; 13.0] years versus 8.0 [7.0; 12.0] years, respectively) (p>0.05 for each). A2 category of CKD was detected in 47.6% of control patients and in 52.2% in the V+ group (p=0.76). Arterial hypertension was observed in 81.0% and 86.9% of patients in the control group and V+ group, respectively (p=0.59), and clinically manifested atherosclerosis in 52.4% and

47.8%, respectively (p=0.76). Renin-angiotensin-modulating therapy was received by 76.2% and 82.6% of patients, respectively (p=0.6).

As shown in Table 1, at baseline there were no significant differences in assessed laboratory parameters between the two groups. In the control group, no parameter changed significantly after 6 months of the treatment. Compared to the dynamics in the control group, patients from the V+ group demonstrated a significant decrease in glycated haemoglobin (HbA1c) and insulin requirement as well as the frequency of hypoglycaemia. Furthermore, a significant reduction in diastolic BP, serum cystatin C, and excretion of uColIV was documented in the V+ group, as well as an increase in eGFRcys and eGFRcr-cys. When we compared the repeated measurements of the study markers, only the changes in serum cystatin C and eGFRcys in the V+ group differed significantly compared to the control. Correlation analysis showed that neither changes of serum cystatin C, eGFRcys, and eGFRcr-cys, nor changes of uColIV in the V+ group, were significantly related to the dynamics of HbA1c (r: -0.31, 0.21, 0.19, and 0.13, respectively; p>0.05 each). We found an inverse association between the changes in systolic BP and eGFRcr-cys (β: -0.47; R^2: 0.22; p=0.02), suggesting that haemodynamic mechanisms at least partially contribute to the renal action of vildagliptin. Stepwise regression analysis showed that lower levels of baseline eGFRcys were independent predictors of both eGFRcys and eGFRcr-cys increase (β: -0.61; R^2: 0.37 and β: -0.45; R^2: 0.20, respectively; p<0.05 each). Reduction of uColIV excretion was more pronounced in older patients (β: -0.74) with lower levels of diastolic BP (β: 0.57; R^2: 0.46; p=0.002).

CONCLUSION

Vildagliptin administration to insulin-treated T2DM patients was associated with a reduction of the glomerular injury marker, uColIV excretion, along with an increase of eGFRcr-cys and eGFRcys, independent of glycaemic control. Older age and lower baseline values of diastolic BP were predictive of a better uColIV-response in the V+ group. Since eGFR improvement could result from temporary hyperfiltration,[4] long-term studies of the renal effects of vildagliptin with isotope clearance eGFR measurement are required.

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ACUTE ENDOTHELIAL BENEFITS OF FAT RESTRICTION OVER CARBOHYDRATE RESTRICTION IN TYPE 2 DIABETES MELLITUS

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Keywords: Endothelial function, low fat (LF) diet, low carbohydrate diet, Type 2 diabetes mellitus (T2DM).

ABSTRACT

The current 'Western cluster' of non-communicable disorders could be redefined as a dysfunction of the heterogenic, complex, and bidirectional metabolic network, which often affects not one, but several tissues simultaneously leading to Type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and non-alcoholic fatty liver disease. These masts of the pathologic network share a combination of various common risk factors, as well as an advantageous imbalance between energy expenditure and energy intake. In this context, gradual and sustained nutritional changes have become the cornerstone for prevention and treatment of metabolic pathologies. Most common strategies entail either restriction of carbohydrates or fats; nevertheless, previous studies have shown conflicting results addressing which of these diets leads to greater reductions regarding these risk factors.[1,2]

For this reason, the department of Clinical Nutrition at the German Institute of Human Nutrition, Nuthetal, Germany is interested to disclose the role of nutrient-dependent factors in this still-abstract pathologic network.

A total of 55 subjects were recruited within a subgroup of an ongoing intervention study. All study participants gave their written informed consent and were randomly selected to undertake either a very low carbohydrate (VLC) or a low fat (LF) diet. During the intervention, subjects were guided by a professional nutrition specialist and took part in the examination at baseline and after 3 weeks of diet. Both examinations included magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI) scans and assessment of endothelial function, among others.

The design of both dietary interventions was focussed on calorie restriction by limiting the amount of the respective macronutrients. The VLC diet (1,200–1,500 kcal/d) provided 5–10% of total energy from carbohydrates. The LF diet was characterised by a fat intake <30% of the total energy intake by an even stronger calorie restriction compared to VLC diet (1,000–1,200 kcal/d).

By making use of a highly innovative computerised system, which allowed the motioned identification of the arterial intima media complex, we were able to assess the endothelial function as an independent risk marker for CVD. The endothelial function was assessed by a non-invasive method, which triggers the endothelium-dependent relaxation of the right brachial artery in response to ischaemia. This so-called flow-mediated dilation investigation technique was developed following the guidelines of the International Brachial Artery Reactivity Task Force.[3]

Interestingly, results of the flow-mediated dilation data showed that, after 3 weeks, the endothelial function significantly improved in the LF group only. This acute effect was also observed in the visceral adipose tissue, which was significantly reduced in the LF diet group. In contrast, the intrahepatic lipids decreased similarly in both groups.

Previous studies have highlighted the potential negative effect of a VLC diet on endothelial function and CVD.[4] This is based on the assumption that a VLC diet implicates a high fat intake, especially saturated fats; indeed, in this study the aim was to increase fat by 60–70%.

To conclude, it is worth mentioning that both LF and VLC diets have different properties when performed for a longer period of time. Consequently, according to our results, patients at high CVD risk with T2DM and non-alcoholic fatty liver disease may experience greater benefits from following a LF hypocaloric diet for the first treatment weeks, in order to change endothelial function.

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DURATION-8 RANDOMISED CONTROLLED TRIAL 1-YEAR RESULTS: EFFICACY AND SAFETY OF ONCE-WEEKLY EXENATIDE PLUS ONCE-DAILY DAPAGLIFLOZIN VERSUS EXENATIDE OR DAPAGLIFLOZIN ALONE

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Keywords: Glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, exenatide, dapagliflozin (DAPA), Type 2 diabetes mellitus, DURATION-8.

Glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors have complementary mechanisms of action: both lower blood glucose with the advantages of weight loss, a low risk of hypoglycaemia, and a favourable cardiovascular profile. DURATION-8 was a Phase III, multicentre, double-blind, randomised, active-controlled, 28-week study with a 24-week (and subsequent 52-week) extension study. DURATION-8 tested the efficacy and safety of combining exenatide once weekly (ExQW), a glucagon-like peptide-1 receptor agonist, and dapagliflozin (DAPA), a sodium-glucose cotransporter-2 inhibitor, for the treatment of patients with Type 2 diabetes mellitus uncontrolled by metformin alone (baseline glycated haemoglobin [HbA1c]: 8.0–12.0%; mean: 9.3%).[1] During 28 weeks of treatment, the combination of ExQW plus DAPA reduced HbA1c, fasting plasma glucose (FPG), postprandial glucose, weight, and systolic blood pressure (SBP) significantly better than ExQW plus placebo

(PBO) or DAPA plus PBO, with no unexpected safety signals.[1] During the EASD 2017 meeting in Lisbon, Portugal, we presented the results for the same study endpoints after a further 24 weeks of treatment, totalling 52 weeks of double-blind therapy.[2]

From 8–28 weeks, patients received rescue therapy with added basal insulin based on progressively stricter FPG criteria (from >270 mg/dL to >200 mg/dL). From 36–52 weeks, patients were rescued if their HbA1c was >8.0%. Efficacy analyses excluded measurements after the initiation of rescue therapy. Of 695 randomised patients, 564 (81.2%) completed the study and 523 (75.3%) completed treatment. The most common reasons for discontinuation of treatment or study withdrawal were withdrawals by the patient, adverse events (AE), or being lost to follow-up. All endpoints at 52 weeks were considered exploratory; therefore, no significance can be claimed.

At Week 52, we obtained greater reductions with ExQW plus DAPA compared to ExQW plus PBO or DAPA plus PBO for HbA1c (1.75% versus 1.38% versus 1.23%, respectively), FPG (63.0 versus 45.7 versus 39.7 mg/dL, respectively), 2-hour postprandial glucose (82.4 versus 64.0 versus 59.6 mg/dL, respectively), body weight (3.3 versus 1.5 versus 2.3 kg, respectively), and SBP (4.5 versus 0.7 versus 2.8 mmHg, respectively). Overall, the reductions of these endpoints at Week 52 were comparable with those recorded at Week 28, while treatment differences were maintained.

Over 52 weeks, the combination of ExQW plus DAPA was well tolerated by participants, with comparable rates of AE and serious AE between the three study groups. As expected, the most frequent AE were gastrointestinal and injection-site nodules in ExQW-treated patients and urinary tract infections in DAPA-treated patients. We recorded no episodes of major hypoglycaemia, while minor hypoglycaemia occurred in 1.3%, 0.0%, and 0.4% of patients, respectively. No deaths were recorded in the 28–52-week extension.

In conclusion, over 52 weeks of treatment the combination of ExQW plus DAPA was more effective compared with either treatment alone in patients with Type 2 diabetes mellitus poorly controlled by metformin alone. The improvements observed at Week 28 for glycaemic parameters, body weight, and SBP were maintained over 52 weeks, indicating the durability of the effect of this combination treatment. In addition, treatment with ExQW plus DAPA was well tolerated, with an expected safety profile. Overall, the data indicate the 1-year efficacy and safety of the ExQW plus DAPA combination; however, further studies are required to assess its effects on long-term outcomes and cardiovascular safety/benefit, as well as cost-effectiveness.

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'FAVOURABLE ADIPOSITY' GENES PROVIDE EVIDENCE THAT SOME PEOPLE ARE FAT ON THE OUTSIDE BUT THIN ON THE INSIDE

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Keywords: Favourable adiposity, genetics, cardiometabolic disease.

Higher BMI is associated with an adverse metabolic effect and a higher risk of Type 2 diabetes mellitus (T2DM), heart disease, and hypertension. However, there are some obese individuals who will not develop T2DM throughout their lives. Age, sex, ethnicity, and physical activity are factors that make two people of the same BMI have different risks of T2DM. Another important factor is genetics; recent genetic studies have identified seven genetic variants associated with 'favourable adiposity', which refers to alleles associated with higher body fat percentage but lower risk of T2DM, hypertension, and heart disease.[1-4] Examples of these variants are in *PPARG* and *IRS1*. We aimed to identify more of these genetic variants and use genetics to understand the underlying mechanism of favourable adiposity.

We designed a three-step study to identify genetic variants associated with 'favourable adiposity'. First, we used data from the UK Biobank, a single cohort of 500,000 men and women. These individuals were sourced from different study centres within the UK and were aged between 40 and 69 years at baseline. We identified genetic variants associated with adiposity (as measured by body fat percentage using a Tanita analyser). Secondly, we tested genetic variants associated with adiposity against a multivariate metabolic outcome using data from published genome-wide association studies (GWAS). We identified favourable adiposity variants as those with a favourable effect on metabolic biomarkers; alleles associated with higher adiposity are associated with higher high density lipoprotein cholesterol (n=99,900),[5] higher adiponectin (n=29,400),[6] higher sex hormone binding globulin (n=21,800),[7] lower triglycerides (n=96,600),[5] lower fasting insulin (n=51,800),[8] and lower alanine transaminase (n=55,500).[9] We used data from the UK Biobank to find the impact of favourable adiposity on metabolic diseases and used the published GWAS of subcutaneous and visceral fat distribution, as measured by computed tomography (CT) or magnetic resonance imaging (MRI),[10] to understand the underlying mechanism.

We identified 15 genetic variants associated with 'favourable adiposity', including seven known variants in or near *PPARG, LYPLAL1, GRB14, IRS1, PEPD, FAM13A,* and *ANKRD55*. Carrying additional 'favourable adiposity' alleles was associated with a higher BMI (n=382,902), but a lower risk of T2DM (12,333 cases versus 370,112 controls), a lower risk of hypertension (79,586 cases versus 307,602 controls), and a lower risk of heart disease (32,105 cases versus 275,037 controls). These effects were similar when we removed the seven known 'favourable adiposity' variants from the analysis. Carrying more 'favourable adiposity' alleles was associated with a favourable body shape in women (associated with a lower waist but a higher hip circumference). However, in men, 'favourable adiposity' alleles were associated with fat all over the body (associated with a higher hip and waist circumference). 'Favourable adiposity' alleles were associated with higher levels of subcutaneous adipose tissue and a lower visceral-to-subcutaneous adipose tissue ratio in both men and women. The p-values in all the analyses were $<1x10^{-10}$.

Our genetic study suggests that the underlying mechanism is through better ability to store fat in a suitable location within the body (subcutaneous adipose tissue).

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SOCS2-/- MOUSE AS A POTENTIAL MODEL OF MACROSOMIA AND GESTATIONAL DIABETES

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Keywords: Macrosomia, gestational diabetes, suppressor of cytokine signalling 2 (SOCS2).

BACKGROUND AND AIMS

Fetal macrosomia, a complication of gestational diabetes (GD), is associated with negative maternal and neonatal outcomes. Macrosomic newborns have increased risks of respiratory distress and neonatal hypoglycaemia, and are at a high risk of developing obesity and diabetes. Factors associated with macrosomia include maternal obesity/being overweight, high lipid and glucose concentrations, and older maternal age. Its prevalence is increasing worldwide simultaneously with the rates of obesity and diabetes, but its lifelong impact is not yet fully understood.[1,2] Animal models of GD and macrosomia are necessary to study both conditions. Very few transgenic strains mimic GD and only diabetes (db)-/-strains show the poor fetal outcome of macrosomia.[3] We have observed apparent macrosomia in the offspring of suppressor of cytokine signalling 2 (SOCS2) knockout mice (SOCS2-/-). SOCS2, through the janus kinase and signal transducers and activators of transcription (JAK/STAT) pathway, acts by mediating cytokine responses to control growth, development, metabolism, and immunity.[4] The SOCS2-/- mouse, a model of gigantism, shows normal size at birth, and a progressive, proportional increase after weaning, without fat accumulation.[5]

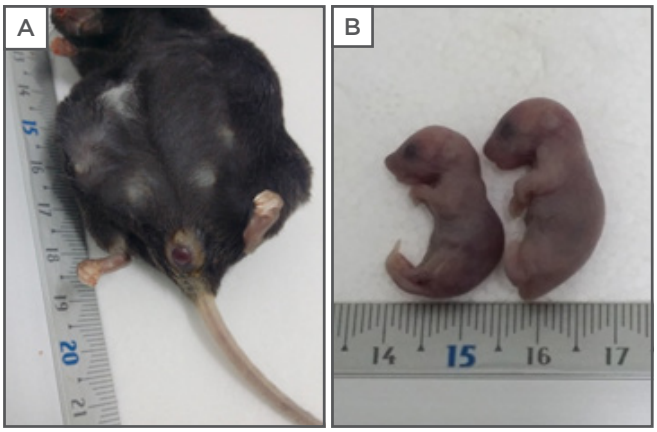

Figure 1: SOCS2-/- macrosomic phenotype.
A) A SOCS2-/- mother with delivery problems due to a severe fetal dystocia; B) Evident differences between the delivered and undelivered SOCS2-/- neonate littermates were noted.
SOCS2: suppressor of cytokine signalling 2.

Glucose impairment has also been described, although there are discrepancies among authors.[6,7] To our knowledge, macrosomia and delivery problems have not been previously reported in the SOCS2-/- model before. Therefore, we aimed to evaluate the SOCS2-/- mouse as a potential model for fetal macrosomia.

MATERIAL AND METHODS

As part of routine colony management, pregnant SOCS2-/- mice were monitored. If an inability to give birth was detected, the mice were humanely euthanised. Mothers' age and body weight (BW) were obtained. BW, head length, lateral height, dorsolateral diameter, abdomen width, and body length were measured in undelivered and delivered (control group) neonates. The mouse colony archive (May 2015–July 2017) was also reviewed. To compare groups, Mann-Whitney U tests and Student's t-tests were assessed and bivariate correlations (Spearman) were performed. A two-tailed $p<0.05$ was considered significant.

RESULTS

A total of 21 pregnant females and their 126 (120 undelivered, 6 delivered) offspring were analysed. Evident dystocia was observed in all mothers (Figure 1A) and all litters seemed to be at an immature stage. Undelivered neonates were 40% heavier than delivered neonates (1.53 ± 0.18 g versus 1.08 ± 0.14 g; $p<0.01$) and had longer heads (1.41 [0.9–2.0] cm versus 1.17 [1.0–1.4] cm; $p<0.024$) (Figure 1B). No significant differences were obtained for abdomen width. Aberrant forms, like malformations and extremely big fetuses, were identified in 13% of the necropsied mothers. A total of 154 pregnancies were analysed from the mouse archive. Low rates of successful pregnancies (39%) and high rates of perinatal (19%) and maternal mortalities (56%) were identified. An age dependent role was observed for the rate of successful pregnancies (R: -0.47; $p<0.001$) and maternal mortality (R: 0.74; $p<0.001$).

CONCLUSION

Undelivered neonates were bigger than their delivered littermates and their size caused their mothers' inability to give birth. Older females had higher maternal mortalities and lower birth success rates. We hypothesise that macrosomia and mothers' maturity is associated with subsequent gestational diabetes. Further studies will be performed to evaluate the presence of diabetes and the role of SOCS2 in this macrosomia model.

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VOLUNTARY EXERCISE CAN MODIFY THE PREFERENCE FOR PALATABLE FOOD THROUGH THE MODULATION OF CENTRAL REWARD CIRCUIT BY PERIPHERAL GHRELIN SIGNAL

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Keywords: Voluntary exercise, food preference, palatable food, ghrelin, reward circuit, dopamine (DA), microdialysis.

BACKGROUND

In obese human subjects, hedonic eating is often present due to palatable foods perhaps promoting addiction in a similar way to drugs.[1] It has been reported that voluntary exercise, such as wheel running, reduces the preference to palatable food such as that comprising a high-fat diet (HFD), although the mechanisms behind this are unclear.[2] We previously reported that voluntary exercise contributed to an amelioration of abnormal feeding behaviour, with a concomitant restoration of ghrelin production in a HFD-induced obese model.[3] It is known that hedonic eating is related to the activation of the central reward circuit via the ghrelin receptor in the ventral tegmental area (VTA) of the brain;[4] therefore, we investigated whether voluntary exercise could modify food preference in relation to peripheral ghrelin and central dopamine systems in rats.

METHODS

Four-week-old, male Sprague-Dawley rats were housed as either a sedentary group (Se) (in ordinary cages throughout the experiment) or an exercise group (Ex) (in ordinary cages from Monday to Thursday and in special acrylic chambers equipped with a running wheel from Friday to Sunday). All rats were allowed free access to either the control, chow diet (CD; 10 kcal fat percentage) or HFD (60 kcal fat percentage); the choice of consumption was therefore their own preference. Food preference was measured each Monday morning until the rats reached 10 weeks old. After 10 weeks, dopaminergic activity within the nucleus accumbens in either Ex or Se was measured using microdialysis. Dopamine (DA) measurements were performed together with food consumption for 20 minutes after 24 hours of food deprivation. Furthermore, synthesised rat ghrelin (3 nmol/2 mL) was administered intravenously to Se at 10 weeks old, with microdialysis procedures performed thereafter.

RESULTS

Body weight and visceral fat volume in the Se group was significantly higher than those in the Ex group at 10 weeks old. In Se, most of the consumed food was HFD throughout the experiment. In contrast, the preference for HFD was attenuated by the induction of voluntary exercise, and around 40% of food consumption was substituted for CD after 5 weeks old to the end of the experimental period.

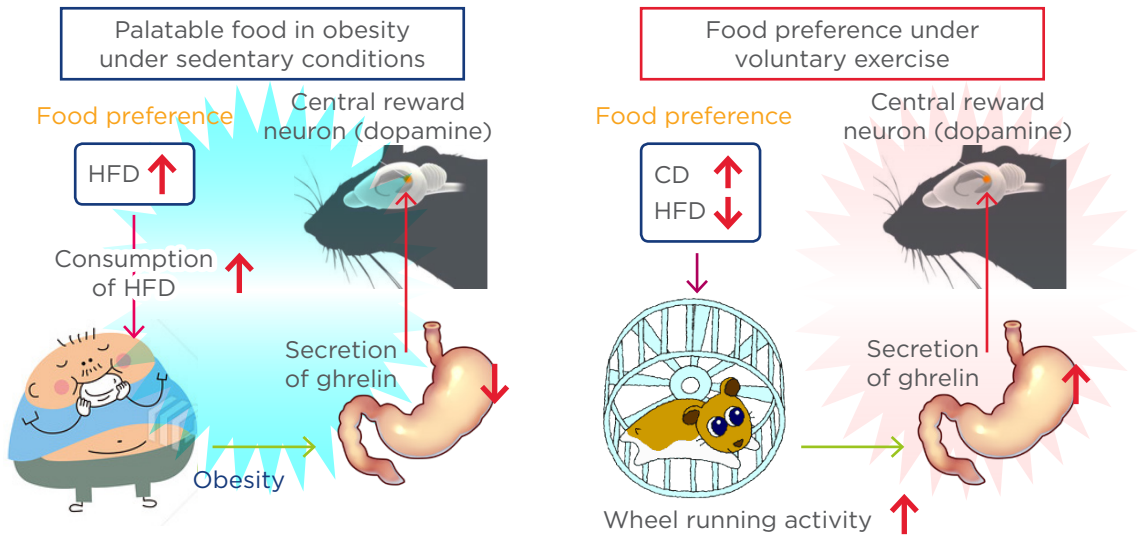

Figure 1: Putative mechanisms for the modification of food preference by voluntary exercise in relation to the central reward circuit and peripheral ghrelin signals.
Ghrelin secretion is increased in response to voluntary exercise, and subsequently suppresses dopamine release due to HFD consumption. Voluntary exercise, therefore, may reduce the palatability for HFD.
CD: chow diet; HDF: high fat diet.

In Se, DA level in the nucleus accumbens was increased in response to either CD or HFD fed for 20 minutes by 50% of basal levels. Voluntary exercise abolished the HFD-induced DA surge in spite of having no effect on CD-induced DA. Systemic ghrelin administration to Se abolished HFD-induced DA surge with no effect on CD-induced DA in the same manner as voluntary exercise did.

CONCLUSION

It was reported that systemic ghrelin administration brought about the inhibition of a DA surge associated with HFD through the activation of the dynorphin A/kappa opioid receptor pathway of DA neurons in VTA.[5] As in our previous report,[3] ghrelin secretion is enhanced by voluntary exercise and then suppresses DA response to HFD selectively in the VTA. Thus, it is fair to assume that voluntary exercise could attenuate the preference for palatable HFD, through the modulation of the central DA system together with peripheral ghrelin signals (Figure 1). Exercise is thus an essential strategy for the treatment of obesity from the aspect of the central reward circuit.

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EDITOR'S PICK

The Editor's Pick for this issue is an informative review from Ali A. Rizvi on hypertension in patients with Type 2 diabetes mellitus and considers the pathogenesis, goals, and therapeutic approaches to managing this comorbidity. There have been many clinical trials in this area and this paper discusses the outcomes of these trials and the implications for patients with diabetes. Efforts are needed to translate the knowledge already gained into population-based implementation while further research is required to understand the pathogenetic mechanisms and to expand the therapeutic armamentarium.

Samantha Warne

ADDRESSING HYPERTENSION IN THE PATIENT WITH TYPE 2 DIABETES MELLITUS: PATHOGENESIS, GOALS, AND THERAPEUTIC APPROACH

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ABSTRACT

Hypertension is considered a powerful cardiovascular risk factor and is present in up to two-thirds of patients who suffer from diabetes. In the background of an established epidemiological association between lower blood pressure (BP) and improvement in long-term clinical outcomes, several large landmark trials and analyses have attempted to examine the possible benefit of tighter BP control in patients with Type 2 diabetes mellitus. Although aggressive BP targets in patients with diabetes have been advocated for a long time, currently accepted evidence from these studies has led to a general recommendation of systolic BP <140 mmHg and diastolic BP <90 mmHg. Therapy consists of lifestyle management, including weight loss if overweight or obese, a Dietary Approaches to Stop Hypertension (DASH)-style based nutrition counselling, and reduced sodium intake. Timely initiation and subsequent titration of antihypertensive medications to achieve individualised BP goals is recommended. A therapeutic agent that acts on the renin-angiotensin-aldosterone pathway, such as an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, should generally be included in the pharmacologic therapy for hypertension in patients with Type 2 diabetes mellitus. A multi-drug combination, particularly including a thiazide diuretic, is very often necessary and should be started early in the course of management. Finally, an accurate and standardised method of BP measurement in the outpatient setting is essential to ensure proper monitoring and gauge the effectiveness of treatment.

Keywords: Type 2 diabetes mellitus (T2DM), hypertension, blood pressure (BP), cardiovascular risk.

INTRODUCTION

Patients with diabetes mellitus (DM) are at risk of adverse cardiovascular (CV) outcomes, including microvascular and atherosclerotic complications. In Type 2 diabetes mellitus (T2DM), a clustering of CV risk factors, very often with underlying insulin resistance, leads to a propensity for increased morbidity and mortality. The American Diabetes Association (ADA) has revised its general blood

pressure (BP) goals in persons with DM to <140/90 mmHg, additionally advising that "lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals with DM, such as younger patients, those with albuminuria, and/or those with hypertension and one or more additional atherosclerotic CV disease risk factors, if they can be achieved without undue treatment burden."[1] The optimal therapeutic approach involves both lifestyle measures, consisting mainly of dietary modification, weight loss, and restricting salt ingestion, and the evidence-based use of an individualised regimen of antihypertensive drug treatment. Close follow-up, timely modification of therapy, and active BP management in patients with DM has been shown to be beneficial; however, treatment can be challenging in the long run. In the clinical setting, healthcare professionals are frequently faced with the key question of what approach would be best to reduce the possibility of future CV events, morbidity, and mortality. Herein is a review of the significance and management of hypertension in individuals with T2DM.

PATHOGENESIS OF INCREASED CARDIOVASCULAR RISK IN TYPE 2 DIABETES MELLITUS AND HYPERTENSION: ROLE OF THE KIDNEYS AND ENDOTHELIUM

The presence of hypertension in individuals with DM is a strong determinant of atherosclerotic disease, endothelial inflammation, and vascular damage. Statistics show that almost 40% of individuals with T2DM are already hypertensive at diagnosis, a situation that is very often accompanied by obesity and a higher risk of developing CV disease.[2] In contrast, most patients with Type 1 diabetes mellitus (T1DM) do not have hypertension when diagnosed with DM.[3] The development of essential hypertension and complications from target organ damage, in particular nephropathy, is thought to be responsible for the increase in prevalence with longer duration of DM.

The kidneys and the cardiovascular system are inextricably intertwined as determinants of ambient BP levels in both normal and diseased conditions. The earliest detectable pathologic increase in urinary albumin excretion, termed 'moderately increased albuminuria' (urinary albumin loss of 30–300 mg/24 hours),[4] results from DM as well as hypertension, and the presence of both conditions is multiplicative in its emergence. In a bidirectional manner, the incidence and severity of hypertension increases with the emergence and progression of nephropathy. The complex interplay of hypertension and renal disease appears to be especially evident in persons with DM, who are inherently at high risk for progressive glomerular damage (Figure 1). Eighty-five percent of patients with overt diabetic nephropathy have hypertension.[5] Additionally, increased extracellular volume results from sodium retention secondary to hyperfiltration of glucose; the reabsorption of both is increased because of upregulation of the sodium-glucose cotransporter enzyme in the proximal tubule.[3,6] The resultant elevation in BP due to volume expansion tends to be exacerbated by salt intake and is responsive to sodium restriction. Advanced glycosylated end-products have a direct correlation with chronic hyperglycaemia and, together with atherosclerotic manifestations, contribute to reduced arterial pliability.[7] The ensuing changes in blood vessels increase vascular stiffness, particularly resulting in a rise in the systolic BP. Endothelial dysfunction and increased oxidative stress are believed to play a pathologic role in both hypertension and diabetes early in their natural history, increasing the risk of atherothrombosis.[8] Central sympathoadrenal activation is especially evident in hypertensive states. The roles of adipose tissue as a proinflammatory organ and the characteristic 'diabetic dyslipidaemia' further contribute to endovascular toxicity in a vicious cycle. In summary, the coexistence of both DM and hypertension combine to multiply the risk of the development, as well as progression, of nephropathy, while concurrently instigating endothelial damage and elevating the risk for adverse CV outcomes through multiple mechanisms.

BLOOD PRESSURE CONTROL IN INDIVIDUALS WITH DIABETES MELLITUS: A REVIEW OF THE EVIDENCE

Insights into the significance of BP management in subjects with DM have been derived from trials designed primarily to examine glycaemic control, and from analysis of CV outcomes in subsets of DM subjects in hypertension studies. The data concerning BP management in patients with DM are notable for their heterogeneity and lack of uniformity. In general, the preponderance of evidence demonstrates that patients treated to lower BP targets have a reduced propensity to vascular events and lower rates of development and progression of microvascular complications,

such as diabetic nephropathy. The benefits, although clinically important, were achieved with combination therapy with multiple medications, and were accompanied with increased risk of drug-induced side effects. Major trials pertaining to the significance of BP in patients with DM are summarised in Table 1, and what follows is a brief description of the prominent clinical studies that have contributed to our current understanding of the subject.

In the HOT trial,[9] the diastolic pressures in almost 19,000 participants were targeted to ≤90, ≤85, or ≤80 mmHg; the achieved average values were 144/85, 141/83, and 140/81 mmHg, respectively. In the subset of 3,000 patients with DM, but not in other patients, the relative risk (RR) of a CV event was significantly reduced in the ≤80 mmHg group compared to the ≤90 mmHg group (RR: 0.49; 95% confidence interval [CI]: 0.29–0.81).

The landmark UKPDS[10] studied 1,148 patients with T2DM with a mean baseline BP of 160/94 mmHg. Compared to the standard arm (<180/105, achieved BP 154/87 mmHg), patients assigned to a lower BP target (<150/85, achieved BP 144/82 mmHg) had a 32% reduction in DM-related mortality (24% versus 35%), a 44% reduction in stroke, and a 24% reduction in microvascular disease after >8 years. There was no difference in outcomes between captopril and atenolol as the primary therapy. The benefits were not sustained and were lost within 2 years of post-trial observational monitoring.[11] Follow-up a decade later indicated that each 10 mmHg reduction in systolic pressure was associated with a 12% risk reduction; the lowest risk occurred at a systolic pressure <120 mmHg.[12] However, since the UKPDS was not designed to assess the usefulness of systolic BP <140 mmHg, cause-and-effect conclusions could not be made.

The normotensive ABCD trial[13] enrolled close to 500 patients with T2DM into a moderate control (placebo) arm or an intensive arm with a target diastolic BP 10 mmHg below the initial baseline level, using either enalapril or nisoldipine. At 5 years, mean attained BP for the moderate and intensive control groups were 137/81 and 128/75 mmHg, respectively. Glomerular filtration rates showed no difference, whereas intensive BP control slowed progression of retinopathy and albuminuria. Apart from a significant reduction in stroke, there was no difference in composite CV events with more aggressive antihypertensive therapy.

An important study was the ADVANCE trial,[14] comparing the use of a perindopril/indapamide fixed combination as antihypertensive treatment in patients with T2DM of long duration who were at high risk of vascular complications.

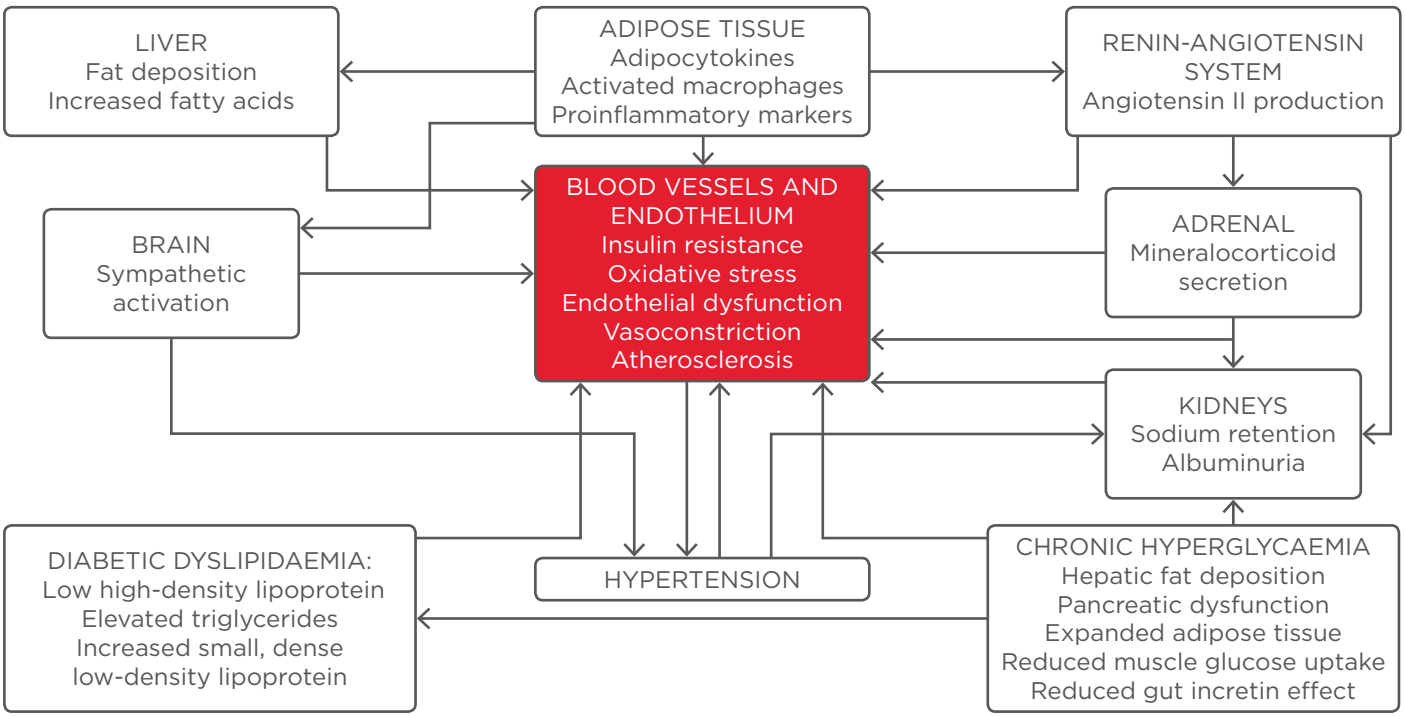

Figure 1: Multiple, interlinked pathophysiologic mechanisms that increase the risk of cardiovascular complications in hypertension and diabetes.

Table 1: A summary of the clinical trial data on blood pressure and diabetes mellitus.

RESULTS OF CLINICAL STUDIES	
Clinical Trial	**Results**
HOT[9]	Significant reduction in CV events in DM subjects with systolic goal <80 versus <90 mmHg
UKPDS[10]	Lower BP resulted in lower DM-related mortality, stroke, and microvascular complications
ABCD[13]	A significant reduction in stroke, but no difference in composite CV events with more aggressive antihypertensive therapy
ADVANCE[14]	Decreased microvascular and CV events and all-cause mortality in the lower BP group
SANDS[15]	No difference in clinical CV events between the standard and intensive treatment groups
ACCORD BP[16]	Reduction in stroke and more side effects in the intensive arm versus the standard arm
HOPE-3[18]	Statin use, but not BP lowering, was associated with CV risk reduction
ACCORDION[17]	Observational 9-year follow-up showed that the difference in BP and stroke risk was no longer sustained
CONCLUSIONS FROM LARGE META-ANALYSES	
Study	**Results**
McBrien et al.[19]	BP lowering in patients with diabetes significantly lowered the incidence of stroke
Emdin et al.[20]	Antihypertensive therapy significantly reduced the rates of mortality, total CV disease, myocardial infarction, and stroke compared with placebo
Xie et al.[21]	Significant reduction in major CV events with more intensive as compared with less intensive BP lowering

BP: blood pressure; CV: cardiovascular; DM: diabetes mellitus.

The baseline BP was 145/81 mmHg and no BP goal was aimed for. Over 11,000 patients were studied and a placebo arm was included. The mean BP values were 134.5/74 versus 140/76 mmHg after 4 years. The intensively treated group had fewer macro and microvascular events and decreased CV mortality (3.8% versus 4.6%), as well as all-cause mortality (7.3% versus 8.5%). Taking into account a post-trial observational phase of 6 years, all-cause mortality was significantly lower among those in the lower BP group.

Aggressive BP lowering seems to have a beneficial effect on surrogate markers of morbidity and end-organ changes. In this respect, the SANDS trial[15] was conducted on 499 Native American men and women with T2DM without prior history of CV disease, who were randomised to either a standard arm or an intensively-treated arm with regard to BP and low-density lipoprotein (LDL) cholesterol. At 3 years, the mean attained systolic BP was 117 and 129 mmHg in the aggressive and standard groups, respectively, with more adverse events related to antihypertensive drugs in the former. Although there was no difference in clinical events (1.6 versus 1.5 per 100 person-years), intensive therapy was associated with slower progression of atherosclerosis and a greater reduction in left ventricular mass.

The unresolved issue of safety and benefits of lowering the systolic BP to <120 mmHg were specifically addressed in the ACCORD BP trial.[16] The results of this trial were destined to impact the formulation of BP guidelines in DM subjects. Patients with T2DM (n=4,733) who had established CV disease or at least two additional CV risk factors were randomly assigned to either a goal systolic BP <120 mmHg or <140 mmHg. The mean attained BPs in the two groups after 4.7 years of follow-up were 119.3 and 133.5 mmHg, respectively, compared to 139/76 mmHg at baseline. The primary composite outcome of non-fatal myocardial infarction, non-fatal stroke, or death from CV causes was comparable between the intensive versus standard therapy groups (1.87% versus 2.09%; hazard ratio [HR]: 0.88; 95% CI: 0.73–1.06), as was the annual all-cause mortality rate between intensive and standard therapy groups (1.28% versus 1.19%) and the rate of death from CV causes (0.52% versus 0.49%). Interestingly, intensive therapy was associated with significant reductions in the annual rates of total stroke and nonfatal stroke (0.32% versus 0.53%; HR: 0.59; 95% CI: 0.39–0.89, for total

stroke; and 0.3% versus 0.47%; HR: 0.63; 95% CI: 0.41–0.96, for nonfatal stroke). The intensive group experienced more serious adverse events, including hypotension, syncope, bradycardia or arrhythmia, hyperkalaemia, angioedema, and renal failure, and an increase in serum creatinine >1.5 mg/dL. In summary, ACCORD studied BP management in patients with T2DM at high CV risk, essentially revealing a reduction in cerebrovascular events and more drug side effects in the intensive versus the standard treatment group. A subsequent 9-year follow-up of the ACCORD BP subjects, termed ACCORDION,[17] demonstrated a significant interaction between glucose and BP control. The intensive treatment group had a significant 21% reduction in the primary endpoints compared to the standard group. Interestingly, the initial favourable reduction in stroke rate in the intensive-treatment group in ACCORD was absent in ACCORDION; it is worth noting that the original BP difference between the two groups no longer remained.

The HOPE-3 study[18] was a primary CV prevention trial in 12,705 intermediate-risk individuals. While not specifically a trial of DM, a major finding was that lowering LDL cholesterol by approximately 35 mg/dL with rosuvastatin significantly decreased the primary outcome (CV related death, non-fatal stroke, or non-fatal myocardial infarction) in comparison to placebo. The combination of candesartan/hydrochlorothiazide, which lowered BP by 6 mmHg systolic and 3 mmHg diastolic compared to placebo, did not significantly lower the primary outcome measure. The largest benefit (4.8% versus 6.5%) was observed in the subgroup with the highest systolic BP measuring 143 mmHg at baseline.

A combined analysis of three of the previously mentioned trials (ACCORD BP, ABCD, and HOT) suggested that intensive BP lowering in patients with DM significantly lowered the incidence of stroke (2.0% versus 3.1%), but not mortality (5.5% versus 6.3%) or myocardial infarction (7.9% versus 8.5%).[19] A recent meta-analysis of 40 trials examined the effects of antihypertensive therapy in studies that ranged in duration from 6 months to 8 years. In >100,000 subjects with DM, antihypertensive therapy significantly reduced the rates of mortality, total CV disease, myocardial infarction, and stroke compared with placebo.[20] However, the benefit was seen only in those with initial systolic pressures >140 mmHg; in these subjects, a 10 mmHg reduction was associated with a HR for death of 0.87 (95% CI: 0.78–0.96) and for total CV disease of 0.89 (95% CI: 0.83–0.95). Among those with lower initial systolic pressures, therapy reduced the risk of stroke only. Whereas beta-blocker use was associated with an increased the risk of stroke compared with other agents (RR: 1.25; 95% CI: 1.05–1.50), calcium channel blockers decreased it in comparison with other agents (RR: 0.86; 95% CI: 0.97–0.77). It is noteworthy that, in general, no single class of drugs showed clear advantages over others for most clinical outcomes.

Finally, a meta-analysis of 19 BP trials, including 5 that included patients with DM, with a combined 44,989 individuals, found a significant reduction in major CV events with more intensive as compared to less intensive BP lowering (RR: 0.86; 95% CI: 0.78–0.96).[21] The effect of intensive BP lowering in the five trials of DM patients was similar (RR: 0.83; 95% CI: 0.71–0.96) to other trials. All-cause mortality was also lower with intensive treatment, although it was not statistically significant (RR: 0.91; 95% CI: 0.81–1.03).

WHAT SHOULD BE THE BLOOD PRESSURE GOALS IN PATIENTS WITH DIABETES?

For many years, the recommended BP goal in persons with diabetes was <130/80 mmHg,[22,23] based on the assumption that lower goals may slow the rate of progression of diabetic nephropathy and proteinuria.[24] The treatment of hypertension in DM patients was associated with significant clinical benefits in the HOT,[9] UKPDS,[10] and ADVANCE trials,[14] as detailed previously. However, although these observations support a goal BP for DM patients of <140/90 mmHg, as recommended in the majority of patients with hypertension in general, lower targets of <130/80 mmHg were not clearly justified by available data. In fact, the results from ACCORD BP argue against the presumption that 'lower is better'.[16,17] The SPRINT[25] findings suggest that, in non-DM patients, early use of lower goals may result in benefits, despite the increased risk of side effects and adverse events. Individualisation of therapy, taking into account the risks and benefits and using clinical judgement, is sensible.[26]

Table 2: Recommendations for management of hypertension in patients with diabetes, based on the recommendations from the American Diabetes Association (ADA) Standards of Medical Care.[1]

BP Goals	Patients with DM and hypertension should be treated to systolic and diastolic BP goals of 140 mmHg and <90 mmHg, respectively. Lower targets, such as <130/<80 mmHg, may be appropriate in younger patients, those with albuminuria, and/or those with hypertension and one or more additional atherosclerotic CV disease risk factors, provided this can be achieved without undue treatment burden and side-effects.
Caution in older adults	Pharmacologic therapy to achieve treatment goals of <130/70 mmHg is not recommended; treating to systolic BP <130 mmHg has not been shown to improve CV outcomes and treating to diastolic BP <70 mmHg has been associated with higher mortality.
Non-pharmacologic Interventions	Lifestyle therapy for elevated BP consists of weight loss, if overweight or obese; a DASH-style dietary pattern, including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity.
Drug therapy	Patients with confirmed office-based BP >140/90 mmHg should, in addition to lifestyle therapy, have early initiation and timely subsequent titration of pharmacologic therapy to achieve BP goals.
Choice of antihypertensive agents	Pharmacologic therapy for patients with DM and hypertension should comprise a regimen that includes either an ACE-I or an ARB, but not both. If one class is not tolerated, the other should be substituted. These two classes of drugs should be especially considered in patients with evidence of nephropathy and/or heart failure.
Multi-drug therapy	A combination of a thiazide diuretic and ACE-I/ARB at maximal doses, a calcium-channel blocker, or a beta-blocker is generally required to achieve BP targets.
Individualisation of treatment	The choice of initial agent as well as subsequent combinations should be based on individual patient characteristics, preferences, potential side-effects, and cost.

ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BP: blood pressure; CV: cardiovascular; DASH: Dietary Approaches to Stop Hypertension; DM: diabetes mellitus.

BLOOD PRESSURE MANAGEMENT IN INDIVIDUALS WITH DIABETES MELLITUS: A RATIONAL THERAPEUTIC APPROACH

Lifestyle-based interventions as the pillar of early, as well as ongoing, treatment of hypertension is particularly important in patients with DM, both to prevent CV disease and to minimise progression of nephropathy and retinopathy.[27,28] Non-pharmacologic methods include weight reduction; dietary modifications that increase consumption of fresh fruits, vegetables, and low-fat dairy products; physical activity; avoidance of processed foods that are high in sodium content; and avoidance of tobacco and excess alcohol intake. The ADA guidelines advise that among patients with a systolic BP of 120–139 mmHg, or a diastolic pressure of 80–89 mmHg, lifestyle changes and primarily non-drug modalities should be introduced to reduce BP (Table 2).[1]

Based on available evidence, patients with DM and persistent BP readings >140/90 mmHg should be started on antihypertensive drug therapy.[29,30] These data are clear that drug therapy in hypertensive DM patients is effective in reducing mortality; preventing adverse CV events, such as myocardial infarction, stroke, and heart failure; and slowing the progression of existing kidney disease.[31,32] It is important to keep in mind that the degree of BP reduction is the major determinant of reduction in CV risk, superseding the choice of antihypertensive drug; a dictum that is valid in patients with DM.[10]

The choice of initial agent is based on the individual clinical situation. Monotherapy can attain goal BP in some patients with DM and hypertension, especially when the BP is only modestly elevated. However, combination therapy is eventually required in most patients.

In patients with DM nephropathy, angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) may slow kidney disease progression more effectively than other antihypertensive drugs. These medications may have CV benefits in high-risk patients that exceed those of other agents.[33,34] In randomised trials comparing ACE-I or ARB with placebo in patients at increased CV risk who had a baseline systolic BP >130 mmHg, the outcomes were similar in patients with or without DM.[35-37] Results of a meta-analysis comprising 48 trials found that ACE-I significantly reduced mortality compared with

placebo (9.3% versus 10.5%), whereas ARB did not (5% versus 5%), the caveat being that many trials included low-risk patients.[38] However, both ACE-I and ARB were superior to other antihypertensive drugs (10.2% versus 11.9% and 8.5% versus 10.5%, respectively), and had significant benefits on heart failure; ACE-I significantly reduced the risk of myocardial infarction and ARB significantly reduced the risk of stroke. Other meta-analyses found that both classes had comparable beneficial effects on mortality and end-stage renal disease,[39] and, in patients with and without DM, on mortality and CV events.[40] Combining agents from both classes, however, does not yield additional benefit and is, in fact, contraindicated.

In patients without increased albuminuria, initial monotherapy can consist of an ACE-I, ARB, thiazide diuretic, or calcium channel blocker. Thiazide diuretics and beta-blockers have the disadvantage of worsening glucose metabolism and potentially aggravating hyperglycaemia. In the ALLHAT trial,[41] chlorthalidone was associated with a mild rise in the plasma glucose; in non-DM patients, an elevation in fasting glucose into the DM range (≥126 mg/dL) occurred significantly more often with chlorthalidone (11.6% versus 9.8% and 8.1% with amlodipine and lisinopril, respectively). Although the IDNT[42] and RENAAL trial[43] found that patients treated with an ARB had achieved renal protection and had significant reductions in hospitalisations for heart failure, neither trial showed a significant CV mortality reduction. A loop diuretic is likely to be required in patients with renal disease or heart failure who have a propensity to fluid retention.

Beta-blockers have a reputation as unsuitable agents for patients with DM, a notion that is grounded in earlier findings that suggested aggravation of insulin resistance and masking of the warning symptoms of hypoglycaemia. The LIFE reduction in hypertension DM parallel study[44] showed that the ARB agent losartan provided significantly more protection from adverse CV outcomes than atenolol (18% versus 23% at a mean follow-up of 4.7 years), CV mortality (6% versus 10%), and total mortality (11% versus 17%). Regression in left ventricular hypertrophy induced by losartan administration may have conferred a beneficial action. Interestingly, however, in the UKPDS, atenolol was found to be as effective as captopril in terms of both BP lowering and protection against microvascular disease in patients with T2DM.[45] The beta-blocker carvedilol has combined non-selective beta and alpha-1 adrenergic antagonist actions; it improves survival in patients with heart failure and may not be as deleterious for glucose control.[46,47]

In patients who require more than one drug for BP control, a combination of an ACE-I or ARB and a dihydropyridine calcium channel blocker (e.g., amlodipine) is appropriate.[48] Amlodipine may provide better protection against CV events than hydrochlorothiazide in this setting. Better efficacy and lack of adverse effects on lipid or carbohydrate metabolism also apply to the non-dihydropyridine calcium channel blockers (diltiazem and verapamil).[49] Low-dose thiazides in combination with other agents work at least in part by countering volume expansion.[50] ACE-I may minimise or prevent some of the metabolic complications associated with diuretic therapy, such as hypokalaemia and hyperuricaemia.[51] The ACCOMPLISH trial[52] evaluated combination therapy in 11,506 hypertensive patients with hypertension, 60% of whom had DM, showing that an ACE-I/calcium channel blocker regimen was superior to an ACE-I/diuretic combination. Of note, the evidence for a role of aldosterone blockade by selective and non-selective mineralocorticoid receptor antagonists, such as spironolactone or eplerenone, in patients with T2DM is limited; however, they may be considered in resistant cases as long as careful monitoring of renal function and serum potassium is maintained.[53]

To summarise, the weight of currently available evidence suggests that lifestyle and pharmacologic therapies in hypertensive persons with DM that reduces BP levels to <140/90 mmHg are associated with clinically significant lowering of vascular complications.[20] The higher the BP level, the greater the benefit accrued from decreasing it. Although a combination of multiple medications, most frequently either an ACE-I or an ARB with one or more agents is necessary, such an approach is successful in attaining BP goals in the majority of patients with DM. It would be expected, therefore, that the patient with T2DM would optimally benefit from a combination of antihypertensive agents, one of which would act on the renin-angiotensin-aldosterone pathway (i.e. ACE-I or ARB).

CONCLUSIONS

Patients with coexisting DM and hypertension appear to be especially prone to CV disease and DM hypertensive microvascular complications.

Recent data from several randomised clinical trials have led to the recommendation of target systolic BP of <140 mmHg and diastolic of <90 mmHg. In clinical practice, these goals necessitate the use of two or more antihypertensive medications, most often combining an ACE-1 or ARB with one or more agents from other drug classes. Individualisation of targets, choice of pharmacotherapeutic agents, and attention to cost and side effect profile are important considerations in management. Lifestyle modifications to reduce weight, improve diet, restrict salt intake, and incorporate physical activity have beneficial actions not only on BP, but also on glycaemic control, lipid profile, and overall CV risk. Efforts are needed to translate the knowledge already gained into population-based implementation while conducting further research into understanding pathogenetic mechanisms and expanding the therapeutic armamentarium.

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FUTURE TREATMENTS OF DIABETIC RETINOPATHY: PHARMACOTHERAPEUTIC PRODUCTS UNDER DEVELOPMENT

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ABSTRACT

Diabetic macular oedema (DMO) is the leading cause of vision loss in working aged individuals. Macular laser photocoagulation was the primary DMO treatment for several decades, but has recently been replaced by intravitreal injections of corticosteroids and drugs that inhibit the actions of vascular endothelial growth factor (VEGF). In Phase III trials, anti-VEGF drugs improve best corrected visual acuity by a mean of +12 letters, but up to 40% of patients have sub-optimal responses to therapy. The new anti-VEGF drugs abicipar and brolucizumab may possess extended durations of action in Phase III neovascular age-related macular degeneration trials, and DMO trials are being planned. Angiopoietin-2 inhibitors, both as co-formulations with anti-VEGF drugs and as bispecific antibodies, are in Phase II trials for DMO. Drugs that stimulate the Tie2 receptor are administered via subcutaneous injections. Intravenously administered antibodies that decrease diabetes-mediated inflammation, such as tocilizumab and teprotumumab, are entering early phase studies. Other drugs with topical (mecamylamine) and oral (minocycline) delivery routes are being developed. Several of these drugs may become available to patients within the next 5–10 years.

Keywords: Angiopoietin, blood retinal barrier, diabetic macular oedema (DMO), pharmacotherapy, angiopoietin-1 (Tie2) inhibition, vascular endothelial growth factor (VEGF).

INTRODUCTION

Diabetic retinopathy (DR) is the leading cause of blindness in working-aged individuals in industrialised nations[1] and 75% of these cases are the result of diabetic macular oedema (DMO).[2] Chronic hyperglycaemia dysregulates several biochemical pathways (hexosamine, aldose reductase, advanced glycation end-products, and protein kinase C) and leads to the accumulation of abnormal by-products that interfere with electron transfer through the cytochrome chain within the mitochondria.[3] The resultant superoxides induce chronic inflammation by upregulating several chemokines and cytokines, including interleukin (IL)-1β, IL-6, interferon-inducible protein 10, intercellular adhesion protein-1, monocyte chemotactic protein-1, placental growth factor, and vascular endothelial growth factor (VEGF).[4] Chronic inflammation activates retinal glial cells; damages capillary endothelial cells[5] and pericytes,[6,7] thereby producing neurodegeneration;[8] and, together with advanced glycation end-products, thickens vascular basement membranes.[9] Blood-retinal barrier breakdown enables albumin and water to pass into the retinal interstitium, resulting in the formation of DMO.[10]

Laser photocoagulation of microaneurysms and leaking retinal capillary beds had been the standard treatment of DMO for three decades[11] but drugs that inhibit VEGF have recently become first-line therapy for centre-involving DMO.[12,13] They improve mean best corrected visual acuity (BCVA) by ≤13 letters and decrease macular thickness;[12-14] however, 20–40% of patients respond poorly to repeated intravitreal injections.[15]

The most potent DMO treatments require repeated intravitreal injections, but compliance with these

regimens can be challenging. Drugs that can be administered topically, subconjunctivally, subcutaneously, and orally may be easier to administer, but questions regarding ocular penetration, efficacy, and systemic safety must be addressed. New medications that work synergistically with existing drugs, or serve as salvage therapy when eyes fail to respond sufficiently to first-line therapies, are needed to improve overall efficacy.

DRUGS UNDER DEVELOPMENT

VEGF plays a central role in blood-retinal-barrier breakdown in most eyes with DMO. Modulation of other molecular targets, however, may also produce important clinical responses. Drugs that are being evaluated in both preclinical studies and early phase clinical trials are detailed in the following sections.

Vascular Endothelial Growth Factor Inhibitors (Table 1)

Abicipar pegol

Abicipar pegol (Allergan, Irvine, California, USA), a designed ankyrin repeating protein, is currently being developed for the treatment of oncologic, inflammatory, and chorioretinal vascular conditions.[16] Abicipar binds all isoforms of VEGF-A with a high affinity (K_D=2 pM for $VEGF_{165}$) and, because of its polyethylene glycol moiety, possesses a long intravitreal half-life in rabbits (6 days). A Phase I/II, multicentre, open-label, dose-escalation trial determined that singular 1 mg injections produced excellent reductions in DMO-related macular thickness and improvements in mean BCVA (+10 letters) at 12 weeks.[17] Pharmacokinetic analyses of anterior chamber drug concentrations suggested that abicipar has a long intraocular half-life (13.4 days) in humans. A recently completed Phase II DMO trial with once every 8 weeks and once every 12 weeks dosing met its primary (BCVA improvements of +7.1 and +7.2 letters) and secondary (central retinal thickness improvements of -158.8 µm and -162.0 µm) endpoints.[18] Data from the Phase II trial supports progression to Phase III.[19]

Brolucizumab

Brolucizumab (RTH258, Alcon, Fort Worth, Texas, USA) is a single-chain, VEGF-binding, antibody fragment being developed for the treatment of neovascular age-related macular degeneration (nAMD). Its small molecular weight allows large drug quantities to be injected; as such, developers hope that brolucizumab will have a longer duration of action than currently available anti-VEGF drugs.

A Phase II trial compared 6 mg brolucizumab to 2 mg aflibercept in patients with nAMD.[20] At the study's 12-week primary endpoint, brolucizumab produced BCVA gains that were non-inferior to aflibercept and with a greater reduction in macular fluid. Patients treated at 12-week intervals improved, suggesting that the drug possesses a long duration of action.[20]

Conbercept

Conbercept (KH902, Chengdu Kanghong Biotech, Sichuan, China) is a 143 kDa, recombinant, fusion protein that contains the second immunoglobulin (Ig) binding domain from VEGF receptor 1 (VEGFR1), the third and fourth binding domains from VEGFR2, and the fragment crystallisable region of human IgG.[21] The fourth Ig domain of VEGFR2 enhances the association rate of VEGF to the receptor and is essential for receptor dimerisation. Conbercept possesses a high affinity for VEGF. Conbercept mimics aflibercept by acting as a soluble receptor that binds all isoforms of VEGF-A, VEGF-B, and placental growth factor. Conbercept has already been approved for the treatment of nAMD in China and a Phase III trial evaluating its efficacy for the treatment of DMO is currently enrolling patients.[22]

Implantable drug delivery pump

The Posterior MicroPump Drug Delivery System (PMP, Replenish Inc., Pasadena, California, USA) uses a microelectromechanical system technology (the same technology used in insulin pumps) to deliver drugs into the eye. The PMP can reliably deliver 100 programmed doses of an anti-VEGF drug (equivalent to >8 years of therapy) into animal eyes and long-term safety has been demonstrated.[23] The PMP was well tolerated for 3 months by 11 patients with DMO, with no cases of endophthalmitis or strabismus.[24]

PAN-90806

A low molecular weight VEGF receptor blocker (PAN-90806, PanOptica, London, UK) produces excellent drug concentrations in the central retina and choroid up to 17 hours after topical administration, but with minimal systemic exposure. Decreased leakage and bleeding from choroidal neovascular membranes, comparable to that

achieved with intravitreal anti-VEGF antibodies, have been seen in animal studies. Patients in each of the four monotherapy arms in a Phase I/II nAMD trial experienced improved visual acuity.[25] A Phase I trial for proliferative DR has been completed but the results have not been reported.[26]

Ranibizumab sustained release reservoir

A refillable ranibizumab port delivery system continuously releases ranibizumab into the vitreous to reduce the need for repeated intravitreal injections. The preloaded implant is surgically implanted through a 3.2 mm pars plana incision and the port, which is covered with conjunctiva, can be accessed and refilled in the office.

In a Phase I nAMD trial,[27] the reservoir was implanted and eyes were injected with 0.5 mg ranibizumab: 0.25 mg into the vitreous and 0.25 mg into the reservoir. Additional injections were given according to optical coherence tomography-based assessment of disease activity. Four of the 20 patients had significant or serious adverse events (endophthalmitis [n=1], vitreous haemorrhage [n=2], and traumatic cataract [n=1]), but 3 of these 4 had improved BCVA by the study's 12-month endpoint. The average BCVA gains for the cohort were +10 letters, with 10 eyes (50%) gaining at least 3 lines and 2 (10%) losing at least 3 lines. The mean number of refills was 4.8 per patient.

Table 1: Vascular endothelial growth factor inhibitory drugs being evaluated for the treatment of diabetic macular oedema.

Drug	Clinical phase	Important characteristics
Abicipar pegol	Phase II	• Designed ankyrin repeat protein (DARPin). • Currently in Phase III trial for nAMD. • In Phase I/II trial of 18 patients with DMO: a) Estimated half-life of 13.4 days. b) BCVA improvement of +10 letters at 12 weeks after single injection.
Brolucizumab	Currently in Phase III trial for nAMD	• High-affinity, single-chain antibody fragment. • Large quantity of drug (6 mg/0.05 mL) may produce extended duration of action. • Phase II nAMD trial showed comparable efficacy to aflibercept. Extended duration of action suggests every 3-month dosing.
Conbercept	Phase III	• Fusion protein with native receptor-binding sequences attached to Fc fragment of IgG. • High-binding affinity (K_D=0.75 pM for $VEGF_{165}$). • Binds VEGF-A, VEGF-B, and placental growth factor. • Approved for treatment of nAMD in China.
Implantable drug delivery pump	Phase I completed	• Miniature pump delivers drug to retina. • Long-term safety seen in animals. • Phase I trial of 11 patients with DMO treated for 3 months; no cases of endophthalmitis or strabismus.
PAN-90806	Phase II trial underway	• Low molecular weight, topical anti-VEGF medication. • Excellent retinal drug concentrations 17 hours after administration. • Animal studies show CNVM control comparable to antibodies. • Phase I proliferative diabetic retinopathy trial underway.
Ranibizumab sustained release reservoir	Currently in Phase II trial for nAMD	• A refillable port delivery system that is implanted through the pars plana. • 1-year Phase I nAMD trial of 20 patients found: a) Mean of 4.8 reinjections. b) BCVA improvement of +10 letters. c) 4 implant-related serious adverse effects.
Ziv-aflibercept	Off-label intravitreal use in DMO	• Intravenous formulation of aflibercept (Zaltrap®), indicated for treatment of advanced solid tumours. • Two DMO patients had significant improvements in BCVA and macular thickness. • Ongoing off-label treatment continues.

BCVA: best corrected visual acuity; CNVM: choroidal neovascular membrane; DMO: diabetic macular oedema; Ig: immunoglobulin; nAMD: neovascular age-related macular degeneration; VEGF: vascular endothelial growth factor.

The ongoing Phase II trial is using 0.75 mg injections in an attempt to extend the treatment intervals to 4 months.[28]

Ziv-aflibercept

Ziv-aflibercept (Zaltrap®, Regeneron, Tarrytown, New York, USA) is the intravenous formulation of Eylea® (a VEGF-A, VEGF-B, and placental growth factor blocker) that is used to treat advanced colorectal carcinoma. Small cohorts of nAMD patients that received single injections of ziv-aflibercept experienced improvements in thickness and BCVA at 1 month without evidence of toxicity.[29] Two patients with DMO experienced improved BCVA (20/800 to 20/100, and 20/800 to 20/200, for each patient, respectively) and macular thickness (central subfield thickness [CST]: -65 µm and -352 µm, respectively) 1 week after intravitreal injections.[30] Investigational ziv-aflibercept treatment of patients with nAMD, DMO, and retinal vein occlusions continues.

Table 2: Drugs not in the previously identified categories being evaluated for the treatment of diabetic macular oedema.

Drug	Clinical phase	Important characteristics
Adenosine kinase inhibitor (ABT-702)	Preclinical	• Adenosine helps regulate anti-inflammatory actions, angiogenesis, and oxygen supply and demand. • Adenosine is a major source of stored energy (ATP). • Intraperitoneal ABT-702 in rats decreased signs of inflammation in experimental diabetes.
Angiopoietin-2 (Ang2) inhibition	Phase II trials underway (AVENUE, BOULEVARD)	• Competes with Ang-1 for Tie2 receptor. • Bi-specific antibody (VEGF and Ang2) and co-formulation currently being studied.
Anti-oxidants	Phase II trials completed	• Failed in most trials to prevent the development of macular oedema.
ASP8232	Phase II trial underway	• Inhibitor of vascular adhesion protein-1. • VIDI trial is evaluating ASP8232 monotherapy and in combination with ranibizumab.
Darapladib	Phase II trial underway	• Inhibits lipoprotein-associated phospholipase CA2. • Protects against atherogenesis and vascular leakage in animal models.
Fasudil	Phase I trial completed	• Rho-kinase inhibitor used to treat cerebral vasospasm. • Can suppress leukocyte adhesion and prevent neutrophil-mediated capillary endothelial cell damage. • In a small prospective study, fasudil with bevacizumab improved BCVA and CRT at 4 weeks.
Gene therapy (VEGF receptor)	Phase IIa (nAMD)	• Improved BCVA results and fewer anti-VEGF injections compared to monotherapy. • DMO trials not yet announced.
iCo-007	Phase II trial completed	• iCo-007 and iCo-007 plus ranibizumab were compared to laser (iDEAL study). No difference among groups for proportion of patients with 15-letter BCVA loss.
Luminate (ALG-1001)	Phase IIb trial underway	• Integrin receptor antagonist. • May be effective for VMT and DMO. Promotes vitreolysis and interferes with angiogenesis. • Phase I trial in patients with DMO that were refractory to standard care. At 150 days: a) BCVA improved from 20/200 to 20/125. b) CMT improved from 519 µm to 387 µm.
Mecamylamine	Phase I/II trial completed	• Antagonist of n-acetyl choline receptors. • 23 patients with DMO were treated with twice daily drops for 12 weeks. At 16 weeks: a) BCVA improved by +3.1 letters. b) No change in foveal thickness.
Microspheres	Preclinical	• Local administration of sustained release particles that can be loaded with several molecules. • Subconjunctival injections of sustained release, celecoxib-loaded microspheres decreased VEGF production and blood-barrier breakdown in a rat model of diabetes.

Table 2 continued.

Drug	Clinical phase	Important characteristics
Minocycline	Phase I/II trial completed	• Has an anti-inflammatory effect against glial activation. • Six-month oral administration in prospective, open-label study resulted in: a) BCVA improvement of +5.8 letters. b) CST improvement of 8.1%.
Non-steroidal anti-inflammatory drugs	Phase IIa trial completed	• Low dose aspirin (81 mg daily) is ineffective. Need trial with anti-inflammatory dose (650 mg daily). • Single intravitreal injections of diclofenac versus bevacizumab. At 12 weeks diclofenac produced: a) Better improvement in BCVA (-0.08 LogMAR versus +0.04 LogMAR; p=0.033). b) Less improvement in oedema.
Plasma kallikrein inhibitor	Phase II trials planned	• A serine protease that is part of the body's inflammatory response. Increases levels of bradykinin. • Increased kallekrein activity seen in DMO, hereditary angioedema, and cerebral haemorrhage. • In a Phase I study, 14 patients received single injections of 3 doses. At day 84: a) BCVA improved by +4 letters. b) CST improved by -40 µm.
Sirolimus	Phase II trials underway	• mTOR inhibitor that modulates HIF-1α-mediated activation of growth factors • In Phase I trial, single subconjunctival or intravitreal injections were given to 50 eyes. At Day 45, median improvements in subconjunctival and intravitreal eyes were: a) BCVA: +4 letters in both groups. b) Decrease in retinal thickness: -23.7 µm and -52 µm.
Tie2 agonist (AKB-9778)	Phase IIa trial completed	• Tie2 is a trans-membrane receptor that stabilises vasculature and decreases leakage. • 12-week randomised trial evaluated AKB-9778 monotherapy and in combination with ranibizumab: a) AKB-9778 monotherapy was not effective. b) Compared to ranibizumab monotherapy, combination therapy: - Improved CST (-164 µm versus -110 µm; p=0.008). - Improved the BCVA (+6.3 letters versus +5.7 letters).
Tocilizumab	Phase II trial underway	• Inhibits IL-6. • READ-4 trial randomises patients to ranibizumab, tocilizumab, or combination therapy.
Teprotumumab	Phase I trial underway	• Insulin-like growth factor inhibitor. • Intravenous administration for DMO.

BCVA: best corrected visual acuity; CMT: central macular thickness; CRT: central retinal thickness; CST: central subfield thickness; DMO: diabetic macular oedema; IL: interleukin; logMAR: Logarithm of the Minimum Angle of Resolution; mTOR: mechanistic target of rapamycin; VEGF: vascular endothelial growth factor; VMT: vitreomacular traction.

OTHER TREATMENTS (TABLE 2)

Adenosine Kinase Inhibitor

The selective adenosine kinase inhibitor, ABT-702, was injected twice-weekly into streptozotocin-induced diabetic mice[31] and retinal inflammation was evaluated using a Western blot, real-time polymerase chain reaction, and immuno-staining analyses. The role of A2A adenosine receptor signalling was analysed in amadori-glycated-albumin-treated microglial cells. At 16 weeks, when diabetic mice usually exhibit significant signs of retinal inflammation, including upregulation of oxidative/nitrosative stress, A2AAR, ENT1, Iba1, tumour necrosis factor (TNF)-α, ICAM-1, retinal cell death, and downregulation of adenosine kinase, the ABT-702 treated group showed decreased signs of inflammation compared to control animals receiving the vehicle.

Angiopoietin-2 Inhibition

Angiopoietin-2 (Ang2) promotes angiogenesis and vascular leakage in the presence of VEGF

and proinflammatory cytokines, but facilitates vascular regression in the absence of VEGF.[32] Ang2 sensitises endothelial cells to TNF-α induced expression of ICAM-1, the critical player in the pathogenesis of inflammation-induced retinopathy.[33] Intravitreal injection of Ang2 into non-diabetic rats increases retinal vascular permeability.[34] Pharmacologic blockade of Ang2 might also prevent pericyte dropout in DR.[35]

Elevated vitreous concentrations of Ang2 have been found in patients with DMO.[36] A bispecific-anti-VEGF and anti-Ang2 antibody is currently in Phase II testing for patients with DMO (BOULEVARD trial, Hoffman-La Roche, Basel, Switzerland)[37] and an anti-Ang2 antibody is being injected with aflibercept (AVENUE Trial, Regeneron).[38]

Anti-Oxidants

Evidence from animal studies both supports and refutes the use of antioxidants to prevent experimental diabetic retinopathy,[39,40] but this use of antioxidants has not been supported by clinical trials in humans.[41]

ASP8232

ASP8232 belongs to a novel class of orally administered vascular adhesion protein-1 inhibitors that is being evaluated in a Phase II, multicentre, randomised controlled trial (the VIDI study) for the treatment of DMO. The safety and efficacy of ASP8232 plus sham are being compared to ASP8232 plus ranibizumab and placebo plus ranibizumab. Enrolment (84 patients) was completed in 2016, but results have yet to be posted.[42]

Darapladib

Darapladib, a lipoprotein-associated phospholipase CA2 (Lp-PLA2) inhibitor, protects against atherogenesis and vascular leakage in diabetic and hypercholesterolaemic animal models. It suppresses blood-retina barrier (BRB) breakdown in streptozotocin-diabetic Brown Norway rats, comparable to that achieved with intravitreal anti-VEGF therapy.[43] In a Phase IIa study, patients receiving darapladib experienced improvements in BCVA (+4.1 letters) and CST (-57 µm) compared to the placebo group.[44]

Fasudil

Fasudil (Asahi Kasei Pharma Corporation, Tokyo, Japan), a rho-kinase inhibitor used to treat cerebral vasospasm after aneurysm rupture and stroke, primary pulmonary hypertension, and memory deficits in patients with Alzheimer's disease suppresses leukocyte adhesion, prevents neutrophil-induced retinal capillary endothelial cell damage,[45] and may directly protect vascular endothelial cells by reversing endothelial cell nitric oxide synthase activity.

In a small, prospective study, patients with DMO received single intravitreal injections of bevacizumab combined with fasudil (0.025 mg). Compared to baseline, patients had significant improvements in mean BCVA (0.84 Logarithm of the Minimum Angle of Resolution [logMAR] to 0.49 logMAR; p=0.003) and mean central retinal thickness (448 µm to 347 µm; p=0.001) at 4 weeks.[46]

Gene Therapy

Management of DR with gene therapy has been proposed for several years; it is thought that effective therapies may improve efficacy, decrease the need for frequent injections and clinic visits, improve patient compliance, decrease side effects, and allow intervention to be performed earlier in the disease process (i.e. during retinal neurodegeneration). Unfortunately, advances in research have been slow and therapies are not yet available. Gene therapy for inherited retinal disorders, such as Leber's congenital amaurosis, Stargardt's disease, X-linked retinoschisis, and choroideremia, is underway. The most important biochemical target in patients with DMO is VEGF, and single injections of a gene coding for a soluble VEGF receptor have produced encouraging results in patients with nAMD,[47] but DMO trials have not yet been performed.

Other chemokines and cytokines (endostatin, pigment epithelium derived factor, hypoxia inducible factor-1α, angiostatin) have been targeted in animal models, but few studies have been performed in humans. Significant efforts have been made to identify other genetic factors that predispose to DR, but few consistent findings have emerged.[48]

iCo-007

The anti-sense oligonucleotide iCo-007 inhibits c-Raf expression and blocks mitogen-activated protein kinase signalling. iCo-007 has a favourable ocular pharmacokinetic profile with an intraocular half-life of 6–8 weeks in rabbits and monkeys after intravitreal injection.[49]

In a Phase I, dose-escalation study (doses ranging between 110 µg and 1,000 µg), 15 patients with diffuse DMO received single, intravitreal injections of iC0-007. At the 24-week secondary endpoint, mean reduction of excess retinal thickness was 40%, and 69% of patients experienced improved BCVA.[50] A multicentre, Phase II trial evaluated iCo-007 monotherapy and combination therapy with ranibizumab or laser for centre-involving DMO (the iDEAL Study). At 8 months, BCVA improved by 15 letters in 64% (700 µg monotherapy arm), 33% (350 µg monotherapy arm), 33% (350 µg plus laser arm), and 41% (350 µg plus ranibizumab arm) of patients, whereas at 4 months the results were 29%, 9%, 9%, and 14%, respectively.[51]

Luminate (ALG-1001)

Luminate (ALG-1001, Allegro Ophthalmics, San Juan Capistrano, California, USA) is a first-in-class therapy that targets integrin receptors involved in cell signalling and regulation, and in the formation of new blood vessels. ALG-1001 exhibits prolonged binding to all integrin receptors involved with retinal angiogenesis.[52] Luminate may be useful to treat both vitreomacular traction (by promoting vitreolysis) and macular vascular diseases (by interfering with angiogenesis).

A Phase I study evaluated the safety and efficacy of luminate in 15 subjects with advanced DMO. Patients received three 2.5 mg intravitreal luminate injections at monthly intervals, with 3 months follow-up after the last injection. No subjects lost BCVA or experienced an increase in CST, and no significant adverse events were seen during follow-up. Mean BCVA improved from 20/200 at baseline to 20/125 at 60 days (last treatment) and remained stable throughout 150 days. The mean central macular thickness decreased from 519 µm to 387 µm at 150 days.[53] Luminate is being evaluated in a Phase IIb DMO clinical trial against bevacizumab and focal laser. The enrolment goal (150 patients) was met in late 2015.[54]

Mecamylamine

In a multicentre, Phase I/II DMO trial, the safety and bioactivity of topical 1% mecamylamine, an antagonist of nicotinic acetylcholine receptors, was tested in 23 patients.[55] Mecamylamine 1% drops were well tolerated when administered twice-daily and there were no drug-related safety problems. Mean improvements in BCVA at 1, 4, 8, 12, and 16 weeks were +2.8, +1.9, +2.4, +0.8, and +3.1 letters, respectively. There was little change in mean excess foveal thickness, but there was substantial heterogeneity in response since 8 patients had improved BCVA, foveal thickness, or both, 9 patients experienced no significant changes, and 4 patients worsened. The study suggested that the effects of topical mecamylamine are heterogeneous in patients with DMO.

Microspheres

Administration of biodegradable microspheres may be an attractive alternative to frequently repeated injections since they can deliver drugs in a controlled way. Most treatable retinal diseases are the result of several biochemical abnormalities, and as such microspheres represent a promising treatment platform that can be filled with several active substances. Microsphere carriers have been loaded with budesonide and celecoxib to treat experimental DR in rats.[56] A posterior subconjunctival injection (0.05 mL) of the celecoxib-microsphere suspension inhibited diabetes-induced VEGF elevations and BRB leakage in rat eyes.[57]

Minocycline

Neuroretinal inflammation usually precedes the microvascular findings in DR and activates microglia.[58] Tetracycline reduces inflammation-mediated connective tissue breakdown, protein glycation, and excessive collagen synthesis, and limits microglial-mediated cell death, retinal cell apoptosis, and capillary damage by inhibiting caspase.[59] Minocycline, a commonly used second-generation tetracycline, has anti-inflammatory properties that are independent of its antibacterial property.[59] Oral minocycline (100 mg twice-daily for 6 months) was studied in a single-centre, prospective, open-label, Phase I/II clinical trial of 5 participants with fovea-involving DMO.[60] Mean BCVA improved continuously from baseline through 1, 2, 4, and 6 months by +1.0, +4.0, +4.0, and +5.8 letters, respectively, while CST decreased by 2.9%, 5.7%, 13.9, and 8.1%, respectively, at the same time points. At 6 months, the mean area of late leakage on fluorescein angiography decreased by 34.4% in study eyes. Two trials with oral doxycycline, however, produced conflicting results.[61,62]

Non-Steroidal Anti-Inflammatory Drugs

In clinical studies, low-dose aspirin (81 mg) has shown little or no benefit in preventing DR. Further work is still needed, however, to determine if high-dose aspirin (650 mg), which has a greater anti-inflammatory effect, can prevent the

development of DR. In a randomised trial, 57 eyes with treatment naïve DMO received single intravitreal injections of either diclofenac (500 µg/0.1 ml) or bevacizumab.[63] At the 12-week endpoint, eyes receiving diclofenac had better mean improvements in BCVA compared to bevacizumab (Δ -0.08 LogMAR versus Δ +0.04 LogMAR; p=0.033), but bevacizumab improved macular oedema slightly better.

Plasma Kallikrein Inhibitor

Plasma kallikrein activity is upregulated in many diseases, including DMO, hereditary angioedema, and cerebral haemorrhage; several components of the kallikrein-kinin system, including plasma kallikrein, factor XII, and kininogen, have been found in the vitreous of patients with advanced DR.[64] Rodent studies have shown that activated intravitreal plasma kallikrein increases retinal vascular permeability, whereas kallikrein inhibition reduces diabetes and hypertension-induced retinal vascular leakage.[65]

A low molecular weight, plasma kallikrein inhibitor (KVD001) to treat DMO and hereditary angioedema is currently being developed. A 5-site, Phase I DMO study treated three cohorts (a total of 14 patients) that had previously received anti-VEGF injections. Single injections of 1, 3, and 10 µg KVD001 improved mean BCVA and CST by +4 letters and -40 µm, respectively, at Day 84.[66] Two Phase II trials are being planned, one combining a plasma kallikrein inhibitor with an anti-VEGF drug, and the other evaluating plasma kallikrein inhibitor monotherapy in eyes with anti-VEGF resistant DMO.[67]

Sirolimus

The mechanistic target of rapamycin (mTOR) inhibitors may delay or prevent breakdown of the BRB and progression of retinal microangiopathies by modulating HIF-1α-mediated downstream activation of growth factors.[68] As DR progresses and proliferative lesions develop, PI3K/Akt/mTOR pathway inhibition may promote neovascular regression by downregulating pro-survival growth factors, modulating the inflammatory cascade, preventing angiogenesis, and promoting apoptosis of newly formed vessels.[69]

A randomised, open-label, dose-escalating, Phase I study evaluated the safety and tolerability of sirolimus (Perceiva, Macusight, Union City, California, USA) for the treatment of DMO.[70] Single subconjunctival (220, 440, 880, 1320, or 1760 µg) or intravitreal (44, 110, 176, 264, or 352 µg) injections were given to 50 eyes of 50 patients.

No dose-limiting toxicities were observed and ocular adverse events were mild and transient. For the subconjunctival group, median increases in BCVA at Days 7, 14, 45, and 90 were +5, +3, +4, and +4 letters, respectively. Median decrease in retinal thickness was -23.7 µm at Day 45. For the intravitreal group, median increase in BCVA was +2 letters, which was maintained throughout the 90 days (+4.0 letters); the median decrease in retinal thickness was -52.0 µm at Day 45. These findings support advancing the present sirolimus formulation into Phase II studies.

Tie2 Agonist (AKB-9778)

Tyrosine kinase with Ig-like and EGF-like domains 2 (Tie2) is a transmembrane receptor that regulates vascular permeability.[71] Activation of Tie2 stabilises vasculature and decreases leakage. Angiopoietin-1 stimulates Tie2 phosphorylation,[72] whereas angiopoietin-2 only partially stimulates Tie2 phosphorylation and, therefore, competes with angiopoietin-1 to suppress Tie2 phosphorylation.[73]

A randomised, placebo and sham injection-controlled, double-masked, Phase IIa DMO trial assessed the effect of the Tie2 agonist AKB-9778 (administered subcutaneously twice-daily) alone or in combination with ranibizumab in 144 patients. At 12 weeks, the mean change in CST was significantly greater in the combination group compared with the ranibizumab monotherapy group (-164 µm versus -110 µm; p=0.008) but was only -6 µm in the AKB-9778 monotherapy group. The mean change in BCVA was +6.3 letters in the combination group, +5.7 in the ranibizumab monotherapy group, and +1.5 in the AKB-9778 monotherapy group. Improvements in DR severity scores were similar across groups and the percentage of qualified fellow eyes with a ≥2-step improvement was 11.4% in all AKB-9778-treated patients compared with 4.2% in the ranibizumab monotherapy group. The authors concluded that activation of Tie2 by subcutaneous injections of AKB-9778 combined with VEGF suppression reduces DMO greater than with anti-VEGF monotherapy.[74]

Tocilizumab

The READ-4 study will compare ranibizumab and tocilizumab, an IL-6 inhibitor, in the treatment of DMO. The study will randomise patients to receive ranibizumab, tocilizumab, or a combination

with the primary endpoint analysis at 6 months. Enrolment for the study is expected to begin in the final quarter of 2017.[75]

Teprotumumab

Currently the intravenously administrated insulin-like growth factor-1 inhibitor teprotumumab (RV001) is being evaluated in an open-label Phase I study at three centres.[76]

CONCLUSION

A robust pipeline features numerous DMO-treating drugs in various stages of development. Drugs are being evaluated both as monotherapy and in combination with anti-VEGF therapy. Regardless of the successes of these new drugs, however, anti-VEGF treatment will likely remain an important component of DMO therapy for many years.

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ROLE OF PROBIOTICS IN DIABETES: A REVIEW OF THEIR RATIONALE AND EFFICACY

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ABSTRACT

The commensal bacteria that are present in our body since infancy are known to play a role in metabolism, in health as well as disease. Diabetes is a growing epidemic, and a long-term solution that targets the disease at the molecular level is yet to be developed. In this article, we have reviewed the link between the body's microbiota and disturbed glucose metabolism, as well as the reasons for bacterial dysbiosis and the mechanisms by which it causes inflammation. The link between dysbiosis and diabetes is convincing, particularly since probiotics have been shown to be of some benefit in normalising disturbed metabolism in diabetes patients. Probiotics have recently been found to have a wide application in diseases such as autoimmune, inflammatory, and allergic conditions. The efficacy of probiotics in diabetes has been proven by their ability to lower fasting glucose and insulin levels in a preclinical setting as well as in human trials. However, there is heterogeneity in these studies, including the species used, probiotic dosage, and the magnitude of efficacy. Based on the robust understanding of the benefits of probiotics in diabetes at the cellular level, in both animal studies and clinical trials, combined with their excellent tolerability, probiotics should be explored for their application in clinics.

Keywords: Diabetes, commensals, probiotics, gut flora, insulin resistance.

INTRODUCTION

Bacteria enter the body at the time of birth, growing in diversity and numbers to resemble the adult composition by around 2–3 years of age.[1] They are not just commensals but are mutualistic, since both humans and the bacteria benefit from each other. The number of bacteria equals the number of human cells, at a ratio of 1:1 (previously thought to be 10:1).[2] From the perspective of this vast number, the flora can be referred to as a separate endocrine organ. This flora, which we gradually build from birth, influences the body's functions. Nearly all organs that come into contact with the external environment harbour commensal bacteria, such as the gastrointestinal tract, skin, saliva, oral mucosa, and conjunctiva, with the colon harbouring the largest number of bacteria.[2] Some of the well-known physiological roles of these bacteria are the production of vitamins in the gut,[3] maintaining an acidic pH in the vagina,[4] and preventing outgrowth of pathogenic bacteria. Metabolomic studies have shown the significant influence of these bacteria on important biochemical reactions and metabolic pathways. Research has also suggested the role of the microbiome in a vast array of diseases, such as diarrhoea,[5] bacterial vaginosis,[4] and allergic[6] and autoimmune inflammatory conditions, including Crohn's disease, ulcerative colitis, and irritable bowel disease.[7] The gut has also been linked via these bacteria to the central nervous system in conditions such as depression, stress, and anxiety.[8]

Metabolic syndrome and diabetes are conditions that now deserve to be recognised as being of high importance. The widespread use of antibiotics, improved sanitation, and the transition to a highly processed diet lacking fibre and other prebiotics, have altered our natural flora.[9] There are several observations that have led us to believe that this altered flora, or dysbiosis, is linked to metabolic diseases such as diabetes, obesity, hypertension, and dyslipidaemia.

The objective of this review was to first understand the reason behind an altered flora in these patients, followed by a review of how dysbiosis affects carbohydrate metabolism. In the second part of this article, the beneficial role of probiotics in modulating glycaemic parameters has been explored, at the *in vitro* level as well as in animal and human studies.

Evidence was searched for using PubMed and Google Scholar, by entering key words such as 'altered flora', 'dysbiosis', 'obesity', 'diabetes', and 'probiotics'. Original research articles detailing animal and human studies, review articles, and meta-analyses were reviewed, and finally all relevant data were compiled.

UNDERSTANDING THE LINK BETWEEN ALTERED GUT FLORA AND DIABETES

Altered Gut Flora in Obese People with Diabetes

Data from animal and human models suggest that obesity and Type 2 diabetes mellitus (T2DM) are associated with a profound dysbiosis.[10] Gut bacteria is an important determinant of susceptibility to obesity and related metabolic diseases. Gut bacteria could also affect obesity by promoting a chronic inflammatory status.[11]

Animal models of obesity have made connections between an altered microbiota composition and the development of obesity, insulin resistance, and diabetes in the host through several mechanisms, such as increased energy harvest from the diet, altered fatty acid metabolism and composition in adipose tissue and the liver, modulation of gut peptide YY and glucagon-like peptide 1 secretion, activation of the lipopolysaccharide toll-like receptor-4 axis, and modulation of intestinal barrier integrity by glucagon-like peptide 2.[12]

Differences Between Gut Flora in People with and Without Diabetes

The relationship between the gut microbiota and human health is becoming increasingly recognised. It is now well-established that a healthy gut flora is largely responsible for overall health of the host. The normal gut microbiota has specific functions in host nutrient metabolism, xenobiotic and drug metabolism, maintenance of structural integrity of the gut mucosal barrier, immunomodulation, and protection against pathogens.[13]

It is reported that the gut microbiota between adults with T2DM and nondiabetic adults is quite different.[14] In landmark research from a European Union (EU) supported research team with European and Chinese researchers, MetaHIT clearly showed that specific imbalances in the composition and function of the intestinal bacteria led to insulin resistance and thereby increased the risk of developing T2DM.[15] Gut microbial dysbiosis and an increase in opportunistic pathogens, along with a reduction of butyrate producing bacteria, were seen in patients with T2DM.[16]

Connections Between Gut Leakage, Inflammation, and Glucose and Insulin Metabolism

Whole bacteria, as well as their products and metabolites, undergo increased translocation through the gut epithelium to the circulation, due to degraded tight junctions and the consequent increase in intestinal permeability that culminates in inflammation and insulin resistance.[17] Lipopolysaccharides (LPS) from the membranes of gram-negative bacteria penetrate into the blood stream via impaired permeability of the intestinal mucosa, which induces metabolic endotoxemia, inflammation, impaired glucose metabolism, insulin resistance, obesity, and contributes to the development of metabolic syndrome, T2DM, and other conditions.[18]

Dietary intolerance (excessive fat, refined carbohydrate, or fructose) alters the gastrointestinal microbiota. This initiates an immune response when bacteria migrate into the general circulation, as a result of increased intestinal permeability. Increased insulin resistance in the hypothalamus increases food intake by decreasing satiety, thus increasing body weight. Consequential inflammation and immune cell infiltration of insulin sensitive organs induces insulin resistance, supporting the obese phenotype.[19]

Dysbiosis and the resulting increased LPS levels induce chronic inflammation.[20] The mechanism involved alters the commensal bacteria proportions in the gut and reduces the expression of adhesion proteins and tight junction proteins in the intestinal mucosa, which leads to increased permeability and translocation of LPS.[21] Type 1 diabetes mellitus (T1DM) patients were found to have an altered thickness of microvilli and the space between microvilli, as well as a reduced thickness of tight junctions.[22] In addition to LPS,

bacterial fragments also diffuse through the intestinal barrier and bind to pattern recognition and toll-like receptors that regulate innate and adaptive immunity.[23] In a separate study, it was observed that in mice with high-fat diet-induced diabetes, live bacteria, originating in the intestine, translocated to the blood and adipose tissue where low-grade inflammation was initiated.[24] In another study, it was revealed that metabolic endotoxaemia due to bacterial LPS caused hyperglycaemia, hyperinsulinaemia, and insulin resistance, and this action of LPS was mediated through CD-14 receptors.[25]

A study of women with T2DM identified that these patients had a different gut metagenome compared to those with normal glucose control; this implied that the metagenome can be used as a risk factor to predicting T2DM.[14] Apelin, a molecule with the potential to restore insulin sensitivity, can induce glucose lowering by enhancing glucose uptake into the skeletal muscles and adipose tissue (Figure 1).[26]

Conditions Predisposing to Altered Gut Flora

High dietary fat, obesity, and diabetes all predispose individuals to an altered microbiota. It was found that in rats given a high-fat diet, the proportions of *Bacteroides*, *Clostridium*, and *Enterobacteriaceae* species increased, whereas the total bacterial density was reduced.[27] Gut microbial dysbiosis and an increase in opportunistic pathogens, along with a reduction of butyrate producing bacteria, were seen in patients with T2DM.[16] One of the reasons for an altered gut flora associated with a high-fat diet can be an altered bacterial adhesion to the gut mucosa.[28] In another discovery, the fasting and fed states in mice correlated with a reduction and an increase in metabolic endotoxaemia, respectively.

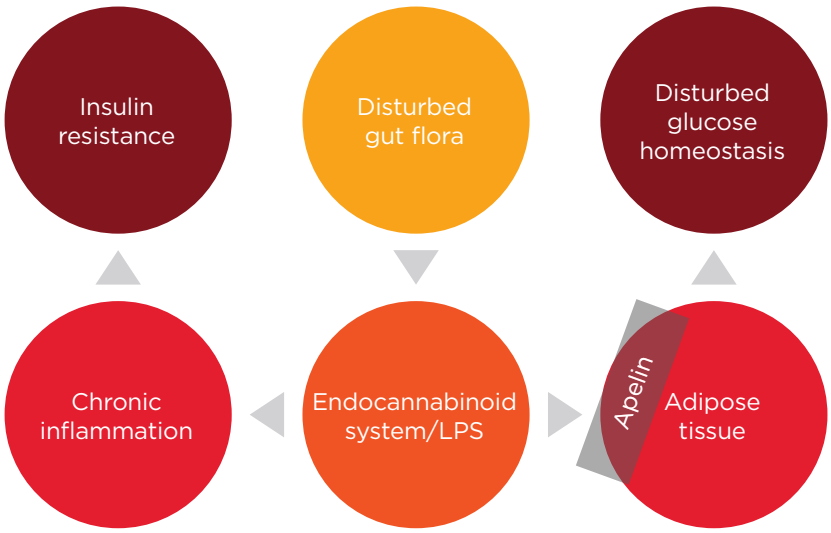

Figure 1: A possible mechanism of regulation of glucose homeostasis by gut bacteria.
LPS: lipopolysaccharide.

Table 1: A list of commonly used probiotic organisms.

Genus	Species
Lactobacillus	*Acidophilus, reuteri, sporogenes, rhamnosus, johnsonii, bulgaricus, bifidum, casei*
Saccharomyces	*Boulardii*
Bacillus	*Clausii, coagulans, subtilis*
Clostridium	*Butyricum*
Streptococcus	*Faecalis*
Bifidobacterium	*Lactis, infantis, adolescentis, animalis, bifidum, longum, breve*

Adapted from Fijan.[32]

Furthermore, when the mice were given a high-fat diet for 4 weeks, the levels of LPS-containing bacteria in the gut increased chronically.[25]

The Gut-Adipose-Glucose Axis

Dysbiosis can increase the endocannabinoid, anandamide, levels in the adipose tissue, as studied in an obese diabetic mouse model. Also, dysbiosis leads to increased LPS levels, which induce low-grade inflammation in the gut.[29] These two factors, endocannabinoid tone and LPS, regulate the expression of apelin, which is secreted by the adipose tissue.[30]

Chronic Inflammation Due to Altered Bacterial Flora and Diabetes

Chronic inflammation has been recognised as an important factor in the pathogenesis of diabetes and obesity. This finding is supported by a vast amount of research. Inflammatory cytokines cause resistance to leptin and insulin. The mechanisms that link inflammation with insulin resistance include the activation of IκB kinase complex (inhibitor of kappa beta, a kinase which activates inflammation), extracellular signal-regulated protein kinases 1 and 2 (ERK1/2), and c-Jun N-terminal kinases. These changes cause insulin resistance by decreasing tyrosine phosphorylation of the insulin receptor substrate proteins.[23] The expression of genes encoding insulin receptor substrate-1, GLUT4, and PPAR-α are affected by cytokines produced in the adipose tissue, such as tumour necrosis factor (TNF)-α or interleukin (IL)-1β.[31]

Preclinical Evidence Supporting the Role of Probiotics in Diabetes

As defined by the World Health Organization (WHO), probiotics are live microorganisms, which, when administered in adequate amounts, confer a health benefit on the host. Immense research has been conducted on probiotics in recent decades, with several bacterial and some fungal organisms being used as probiotics. As well as varied applications in human health, probiotics hold a strong place in veterinary science, being used as feed supplements. Strains like *Enterococcus faecium* can cause opportunistic diseases in humans and are only used as probiotics in animals. The majority of the probiotic strains belong to the lactic acid bacteria that can convert sugars to lactic acid, thus inhibiting pathogen growth by creating an acidic environment. Some commonly used probiotic strains with health benefits have been compiled in Table 1.[32] The role of probiotics in glucose homeostasis and diabetes is reviewed hereafter.

Probiotics Improve Epithelial Barrier Function

In an epithelial cell model, *Lactobacilli* were found to reinforce the barrier function of epithelial cells by increasing the levels of adhesion proteins, including beta-catenin and E-cadherin. They also stabilised the junctional E-cadherin/ beta-catenin complex by stimulating a protein kinase.[33]

Probiotics Reduce Pathogen Adherence in the Intestine and Translocation to Adipose Tissue

In a model of high-fat diet-induced diabetes in mice, after 4 weeks of a high-fat diet, the counts of *Escherichia coli* increased in the intestine. As the strain was radiolabelled, tracing of the same bacterial species also showed translocation from the intestine to the blood and mesenteric adipose tissue. One month of daily probiotic treatment with *Bifidobacterium animalis* reduced the counts of *Enterobacteriaceae* species present in both the small intestine mucosa and the adipose tissue.[24] In another study, it was found that 12 different probiotic strains were all effective in displacing *Bacteroides*, *Clostridium*, *Staphylococcus*, and *Enterobacteriaceae* from immobilised human mucus.[34]

Probiotics Modulate Immune Differentiation

Lactobacillus johnsonii was found to induce T helper (Th)17 cell differentiation in mesenteric lymph nodes, and thereby provided immunity to the development of T1DM in diabetes prone rats. Another group treated with *Lactobacillus reuteri* did not develop Th17 differentiation and, thereafter, developed T1DM.[35] One month of daily probiotic treatment with *B. animalis* was found to reduce the expression of proinflammatory cytokines, such as TNF-α, IL-1β, plasminogen activator inhibitor-1, and IL-6, in the mesenteric adipose tissue, liver, and muscle (as determined by the concentration of coding messenger RNA).[24] However, in a clinical study of patients with T2DM, probiotic supplementation failed to reduce markers of inflammation when given for 4 weeks.[36]

Probiotics Normalise Insulin Sensitivity

Probiotic administration of *Bifidobacterium* for 1 month in mice with high-fat diet-induced diabetes normalised the glucose metabolism. This was documented by the lowering of fasting insulin

levels, blunting of glucose excursions on the intraperitoneal glucose tolerance test, and increase in the glucose turnover rate.[24] In a genetic mouse model of T2DM, administration of the *Lactobacillus gasseri* probiotic twice a day orally for 12 weeks resulted in a significant fall in fasting and post-prandial glucose levels.[37]

Clinical Evidence Supporting the Role of Probiotics in Diabetes

Effect on glycaemic parameters

Clinical trials of probiotic use in patients with diabetes, as well as healthy individuals, are summarised in Table 2. Probiotics were found to lower fasting blood glucose, insulin levels, and improve glycosylated haemoglobin (HbA1c) and insulin resistance (as measured by lowering of HOMA-IR [Homeostatic model assessment for insulin resistance] values).

A meta-analysis of 12 randomised controlled trials (RCT) with reported lipid profiles (n=508), fasting blood glucose (n=520), HOMA-IR (n=368), and HbA1c (n=380) concluded that probiotics could reduce fasting blood glucose levels by around 15 mg/dL (0.8325 mmol/L) and HbA1c by 0.54% (3.6000 mmol/mol), along with a significant improvement of 0.98 in HOMA-IR values, indicating a modest effect on glycaemic control. This analysis elucidated that probiotics may improve glycaemic control and lipid metabolism in T2DM.[38]

Another meta-analysis of 11 RCT with 614 subjects concluded that the glucose reduction was 9.36 mg/dL (0.52 mmol/L; 95% confidence interval [CI]: -0.92–[-0.11] mmol/L; p=0·01) and the HbA1c reduction was 0.32% (1.1 mmol/L; 95% CI: -0·57–[-0·07%]; p=0·01). The reduction in insulin levels and improvement in HOMA-IR was significant in patients with diabetes. This suggested that probiotics may be used as an important dietary supplement in reducing the glucose-related metabolic factors associated with diabetes.[39] Overall, there was a modest effect on glycaemic control in both meta-analyses in patients with diabetes.

A recent meta-analysis of 12 RCT involving 770 patients with T2DM showed that probiotics could significantly reduce fasting blood glucose by 11.27 mg/dL (95% CI: -21.76–[-0.79]; p<0.001) and serum insulin concentration by 2.36 µU/mL (95% CI: -4.01–[-0.72]; p=0.005), but with no significant reduction in HbA1c (-0.19%; 95% CI: -0.49–0.12; p=0.230). Probiotics could significantly reduce HOMA-IR in T2DM patients (-1.05; 95% CI: -1.52–[-0.59]; p<0.001).[40]

Non-alcoholic fatty liver disease (NAFLD) is thought to be a hepatic manifestation of metabolic syndrome and could share its pathology with diabetes. A meta-analysis evaluated the effect of probiotics in patients with NAFLD. It reported that there was a significant reduction in the HOMA-IR values by 0.46 (95% CI: -0.73–[-0.19]; p=0.0008).[41] A HOMA-IR value >2 is generally present in patients with metabolic syndrome.[42]

Effects on oxidative stress and inflammatory parameters

Probiotics improve antioxidant status in patients of T2DM. In a study, improvement of the antioxidant enzyme levels, such as glutathione peroxidase and erythrocyte superoxide dismutase, were noted.[43] In a study of 72 patients with T2DM and NAFLD, probiotics given for 30 days were found to significantly reduce the levels of IL-6, IL-8, IL-1, interferon-gamma, and TNF-α.[44] Synbiotics (probiotics and prebiotics) were found to significantly reduce the levels of high-sensitivity C-reactive protein in a clinical study on T2DM patients.[45]

Effects on lipid parameters

It has been documented that probiotics increase high-density lipoprotein.[46] The widely reported mechanism suggests that cholesterol is lowered due to the prevention of bile salt recycling, since probiotics deconjugate the bile salts, which are then not able to be reabsorbed and are excreted.[47]

Tolerability

In the clinical trials previously discussed, no adverse events were reported with probiotics in patients with T2DM. Probiotics were found to be safe to use in healthy pregnant women, who did not report any adverse effects. No adverse events were seen in their children either.[48] Use of probiotics in immunocompromised individuals is known to cause concern.

DISCUSSION AND CONCLUSION

Probiotics have been proven to be effective in diseases such as infective diarrhoea, chronic inflammatory bowel diseases, lactose intolerance, and allergy, and we have reviewed their role in diabetes. The link between pathogenic bacteria and chronic low-grade inflammation is established.

Table 2: Overview of important clinical studies demonstrating the effect of probiotics on metabolic profiles in patients with Type 2 diabetes mellitus.

Study	Probiotics used	Participant age in years (N)	Design	Duration	Outcome
Mazloom et al.[49]	*L. acidophilus, L. bulgaricus, L. bifidum, L.* casei	25–65 (34)	Single-blind, PC	6 weeks	Non-significant declining trend in the level of TG, MDA, and IL-6 and insulin resistance
Ejtahed et al.[43]	Yogurt containing *L. acidophilus La5, B. lactis Bb12*	30–60 (64)	Double-blind	6 weeks	Improved fasting blood glucose and antioxidant status
Moroti et al.[46]	*L. acidophilus, B. bifidum,* fructooligosaccharides	50–60 (20)	Double-blind, PC	30 days	Significant increase in HDL and a significant decrease of glycaemia
Andreasen et al.[36]	*L. acidophilus*	55-62 (45)	Double-blind, PC	4 weeks	Preserved insulin sensitivity, but did not affect the systemic inflammatory response
Asemi et al.[45]	*L. sporogenes* and inulin as prebiotic	35-70 (62)	Double-blind, PC	6 weeks	Significant effects on serum insulin, hs-CRP, uric acid, and plasma total GSH levels
Tonucci et al.[50]	*L. acidophilus La-5, B. animalis subsp lactis BB-12*	35-60 (50)	Double-blind, PC	6 weeks	Improved glycaemic control, decrease in inflammatory cytokines (TNF-α and resistin) and increase in acetic acid
Firouzi et al.[51]	*Lactobacillus and Bifidobacterium*	30–70 (136)	Double-blind, PC	12 weeks	Modest improvement in HbA1c and fasting insulin

B. species: *Bifidobacterium*; GSH: glutathione; HbA1c: glycated haemoglobin; HDL: high-density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; IL: interleukin; *L.* species: *Lactobacillus*; MDA: malondialdehyde; PC: placebo controlled; TG: triglyceride; TNF: tumour necrosis factor.

The mechanisms by which inflammation leads to insulin resistance are also well-defined. Intervention to restore normality of the gut flora by means of probiotics has led to improvement in glycaemic parameters, as shown in clinical trials. *Lactobacillus* and *Bifidobacterium* species have been the most commonly used probiotics in these trials. Since all bacteria have a different mode of action, the use of multiple species is preferable until trials localise a specific strain. The efficacy was improved when probiotics were used for a moderate to long duration (around 8 weeks). However, conflicting results were revealed in some trials where probiotics did not have any effect on glycaemic parameters. This could be because of sub-therapeutic doses or insufficient study duration.

Although evidence is limited, the use of probiotics as add-on agents is advocated, keeping in mind the strong preclinical evidence as well as clinical evidence in improving diabetes, along with their excellent tolerability profile. Further research needs to be performed on selecting the exact strain and therapeutic dose, as well as study duration, for optimum effect.

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TYPE 2 DIABETES MELLITUS AND STEM CELL THERAPY: A REVIEW

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ABSTRACT

Most public health statistics outline the rapidly exploding burden of Type 2 diabetes mellitus as a chronic endemic disease related to sedentary lifestyle and obesity. Tremendous efforts and resources are being invested in finding new medical treatments and alternative therapies through cell-based replacement strategies among other methods. Several types of cells continue to be under active research, including autologous islet cells, allogeneic cadaveric islet cells, embryonic and induced pluripotent stem cells, bone marrow-derived hematopoietic and mononuclear cells, and mesenchymal stem cells of different sources. The objective of this review is to bring the reader up to speed on the efforts being spent in this field with a clear and critical approach to the difficult and sometimes futile methodology undermining the results obtained.

Keywords: Type 2 diabetes mellitus (T2DM), stem cells, glycated haemoglobin (HbA1c), mesenchymal stem cells (MSC), bone marrow derived cells, induced pluripotent stem cells (IPC).

INTRODUCTION

Over the past decade, the potential of stem cells has been explored with amazement, myths, and many more questions than answers. The dream was that we might be able to repair almost any malfunction inflicting our bodies. The promise of taking off-the-shelf cells or even body parts, making better targeted pharmaceutical agents, and even defying death, all fired our imagination. Along that evolving field, the regulatory authorities proceeded shyly. The biggest hurdle was the challenge to the scientific method, which served us well for >200 years; however, questions have arisen regarding its adaptability to new clinical research requirements. As a result, data that were felt to provide overly weak evidence, lack the proper statistical weight, and be poorly designed and executed, inundated the scientific arena and split the scientific community for and against stem cell research.[1,2]

Diabetes has become a major endemic problem around the world with a very expensive price tag. Its incidence is on the rise, fuelled by our digital lifestyle and the growing endemic of obesity. The International Diabetes Federation (IDF) estimates that in 2015, there were 415 million diabetic adults aged 20–79 years worldwide, including 193 million undiagnosed subjects. Another 318 million adults are estimated to have pre-diabetes or impaired glucose tolerance and insulin resistance. The cost of diabetes care is estimated at $673 billion per year. The American Diabetes Association (ADA) estimates that roughly 9.3% of the American population is diabetic with about 2–3-times as many possibly having pre-diabetes.[3,4]

The pancreatic islets of Langerhans are tiny clusters of cells scattered throughout the pancreas consisting of several groups of specialised cells, including insulin-producing beta cells. The pathology of Type 2 diabetes mellitus (T2DM) combines an inflammatory–autoimmune microenvironment affecting the insulin-production units, which become unresponsive to demand. More importantly, a dysfunction of the insulin receptors ensues, leading

to peripheral insulin resistance. Another component of the pathobiology is widespread microvascular disease, which leads to many of the clinical manifestations and complications accompanying T2DM, including limb ischaemia and ulcers, retinal damage, impotence, neuropathies, nephropathies, and cardiovascular and cerebral-vascular diseases.[5-8]

Cellular therapy for diabetes has adapted different protocols and methods due to uncertainty regarding the best cells to use, optimal cell number, route of administration, and schedule. Many cells remain under investigation, including embryonic reprogrammed cells, pancreatic islet-derived replacement cells, reprogrammed induced pluripotent stem cells (IPC), mesenchymal stem cells (MSC), bone marrow mononuclear cells (BM-MNC), and others.

PRIMARY ISLET CELL REPLACEMENT

Allo and autotransplantation of islet cells were two of the earliest methods used to replace damaged beta cells. The allotransplantation, consisting mainly of infusion of cadaveric islet cells into the hepatic artery, is used mostly for Type I diabetes mellitus, but major drawbacks existed as patients had to be on lifelong immune suppression to prevent immune rejection. Allografting was mostly carried out between 1999 and 2013 and documented by the Collaborative Islet Transplant Registry (CITR). One thousand and eleven allogeneic islet transplants were carried out by 2013, mostly in North America. Autologous islet transplant is performed following total pancreatectomy in cases of severe, chronic pancreatitis. The islets are infused back into the hepatic artery or directly into muscle to reimplant and regain function in a new, less aggressive microenvironment.[9]

INDUCED ISLET BETA CELLS

The lack of sufficient sources of islet cells, need for immune-suppression when performing allotransplants, and the high mortality and morbidities associated with islet cell transplantation led to the need for new sources to replace the damaged beta cells in diabetes.

Different cells, including embryonic, MSC, IPC, hepatocytes, fibroblasts, and neurons were shown to be transformable into beta islet cells using sequential expression of one or several differentiation genes leading ultimately to the beta-cell phenotypes capable of releasing insulin on demand.[10] Using the IPC technology on autologous cells, several factors and media were shown to promote this transformation. Oct4, Nanog, and Pdx1 are differentiation factors expressed early in pancreatic embryogenesis. Other factors, including Sox17, FoxA2, Pdx1, Nkx6.1, and Ngn3, may be used to induce transformation into functional beta cells. Factors like Pax4 have been shown to induce alpha cell transformation into beta cells *in vitro*. Pdx1, Ngn3, and MafA were shown to transform acinar cells into beta cells.[11-13]

Ramiya et al.[14] isolated pancreatic ductal epithelial cells from prediabetic, adult, and non-obese mice and allowed them to proliferate in long-term cultures. The group then induced the production of functional islets that responded *in vitro* to a glucose challenge, and reversed insulin-dependent diabetes in mice.[14] Xu et al.[15] used MSC *in vitro* to produce insulin-secreting beta-like cells using recombinant adenoviruses carrying Pdx1 or Pdx1 along with Pax4. Mihara et al.[16] showed that induced expression of Pdx1 and Nkx6.1 factors could result in insulin producing cells, on demand, using a three-dimensional suspension bioreactor system and stage-specific growth factors. Another approach used was the addition of bone morphogenetic protein inhibitors and protein kinase C activators to produce beta cells from embryonic stem cells.[17,18]

Another innovative approach used specific micro-RNA (miRNA) to overexpress in umbilical cord-derived MSC. miR-375 and miR-26a have been shown to have the capability to induce differentiation into insulin-producing cells.[19] Chandra et al.[20] generated IPC from murine adipose tissue-derived stem cells, and restored glycaemic control within 2 weeks in mice.

Both the bone marrow and the Warton's jelly stem cells were shown to form islet-like clusters in a medium containing nicotinamide, activin, hepatocyte growth factor, exendin-4, and pentagastrin.[21] Neuron-conditioned medium was also shown to have the ability to differentiate IPC into normal functioning beta cells *in vivo* using a stepwise culturing approach.[22]

While all these advances bring a lot of hope to the field, only preclinical data are available and the clinical exploitation of each of these techniques remains a few years and many trials away before the clinical safety, efficacy, and usefulness become evident.

Table 1: Clinical trials using bone marrow hematopoietic and mononuclear cells to treat Type 2 diabetes mellitus.

Author	Route of cell delivery	Dose per kg	Follow-up
Bhansali et al.[24]	BM-MNC locally (pancreas feeding arteries)	$3.2x10^8$	12 months
Hu et al.[36]	BM-MNC locally	$2.8x10^9$	33 months
Estrada et al.[60]	BM-MNC locally		12 months
Sood et al.[49]	BM-MNC locally or systemically	$5–7x10^8$	12 months
Wang et al.[33]	BM-MNC locally	$3.8x10^9$	12 months
Wu et al.[25]	BM-MNC locally	$3.8x10^9$	12 months
Bhansali et al.[47]	BM-MNC locally	10^9 total vs MSC	12 months
Wehbe et al.[23]	BM-MNC locally	$2x10^6$	24 months
Zhao et al.[61]	Cord blood; IV		12 months
Tong et al.[62]	Cord blood; locally	$2.88x10^6$	

BM-MNC: bone marrow mononuclear cells; IV: intravenous; MSC: mesenchymal stem cells.

HAEMATOPOETIC AND BONE MARROW CELLS

There are about a dozen studies using peripheral and bone marrow derived CD34+ haematopoietic cells claiming effective diabetes control in human studies. The injection of the prepared cells into the arteries feeding the pancreas was used in most studies. The side effects were mild, including abdominal pain, nausea, and discomfort. The efficacy was again shown in several studies using glycated haemoglobin (HbA1c), C-peptide levels, and the need for fewer medications and insulin.[23] (Table 1).

Autologous bone marrow contains hematopoietic stem cells, a mixture of mononuclear cells, a few mesenchymal cells, and other cells. Peripheral blood stem cells are mainly selected by their CD34 antigen positivity. Different preparations of the hematopoietic cells have been claimed to be effective in correcting hyperglycaemia, improvement of endogenous insulin production, and diminishing or eliminating the need for insulin and other diabetes controlling treatments.[23-26] There is no evidence of *in vivo* BM-MNC differentiation into pancreatic beta cells;[27] there are other potential mechanisms to explain this improvement, including neovascularisation, endothelial repair, inflammatory environment modulation, and endogenous stem cell stimulation through paracrine mediators.[28,29] The hematopoietic cells were shown to stimulate angiogenesis and vascularisation in ischaemic areas;[30] their interaction with the microenvironment was also shown to stimulate the tissue's own endogenous stem cells to replace the injured cells resulting in repair.[29] By virtue of these processes, an anti-fibrosis effect was often observed.

The bone marrow can be separated by centrifugation with or without Ficoll-Paque density gradient into different sections. The bone marrow stem cells move to the injured areas where they secrete different growth factors and interact with the microenvironment.[30,31] No significant adverse events or safety issues have been reported to hinder the administration of these cells, except for procedure-related pain, minor bleeding, or haematomas.[23-33] Wang et al.[33] used autologous bone marrow to treat 31 patients with stem cell infusion into the major arteries feeding the pancreas. The HbA1c dropped by >1.5% within 30 days and the C-peptide increased at the 3-month follow-up mark. All patients were reported to have had a significant reduction of their anti-diabetic medications.[25]

BM-MNC were used by Bhansali et al.[24] in a prospective, randomised, placebo-controlled trial designed to treat 11 patients. Altogether, 9 of the 11 patients (82%) achieved 50% reduction of the insulin requirements and 10 (91%) achieved a HbA1c <7% in the intervention group. The C-peptide elevation is the surrogate used to demonstrate activation of the endogenous insulin production.[34] Wu et al.[25] reported treating 80 patients with BM-MNC with or without hyperbaric oxygen. The bone marrow was shown to help control the

diabetes, partially or completely in some cases, with no effect of the hyperbaric therapy.[35] Hu et al.[36] treated 118 patients with BM-MNC or insulin only. The BM-MNC were infused into the pancreas feeding arteries. The HbA1c and C-peptide levels improved significantly.[36]

Finally, two recent meta-analysis of published trials concluded that both BM-MNC and peripheral blood mononuclear cell infusion may result in improvement of the HbA1C, fasting plasma glucose, C-peptide levels, and endogenous insulin production at 12 months in the majority of treated patients. These two publications compiled several studies differing in terms of the number of cells used and routes of infusions, lacking the statistical significance and the proper randomisation design. Nevertheless, these data were exploited to support powerful conclusions and claims of safety and effectiveness.[11,37,38] Again, the duration of response varied between 6 months and 2 years as assessed by the HbA1C.

UNDIFFERENTIATED MESENCHYMAL STEM CELLS

MSC are pluripotent progenitor cells with proven regenerative, angiogenic, anti-fibrosis, immunomodulatory, and growth-stimulating properties. The MSC can be isolated from different tissues in culture, including the placenta, bone marrow, adipose tissue, and fetal cord, among others. In T2DM, the MSC may achieve more than one goal, including endothelial blood vessel repair, balancing of the immune environment, stimulation of the endogenous stem cells, and ultimately islet cell repair and replacement. The MSC can be allogeneic or autologous and have to be sequentially cultured in specially defined conditions exploiting the property of attachment to the culture dishes.[39,40]

Even the conditioned medium where the MSC are cultured were found to have similar capacity and properties to regulate glucose in diabetic mice, indicating a major paracrine contribution.[41] The MSC create a microenvironment that promotes the endogenous cells to proliferate and regain function.[40] Some paracrine factors have been identified, like the vascular endothelial growth factor alpha, platelet-derived growth factor, angiopoietin-1, and insulin-like growth factor.[41]

The known immune regulatory and immune privileged properties of MSC with a low expression of Class II major histocompatibility complex and co-stimulatory molecules allow them to suppress the proliferation of T and B lymphocytes and modulate their immune responses, including antibody formation, cytotoxicity of T and natural killer cells, B cell maturation by promotion of the T cell tolerance, and induction of the proliferation of regulatory T cell populations.[42,43] The sum of these processes may lead to the sparing of the pancreatic cells from the ongoing destruction. MSC have been claimed to induce autophagy as well and by this mechanism promote cellular repair and wound healing.[43,44] Several studies provided evidence that MSC may help alleviate the insulin resistance encountered in T2DM. The reversal or attenuation of the insulin resistance may be mediated by the cytokines released and possibly their effects on the macrophages, but the exact mechanisms remain far from understood. No significant acute allergic or immunologic events have been reported but occasional mild nausea, vomiting, headaches, abdominal pain at the puncture site, haemorrhage, or haematoma may occur (Table 2).[45-52]

Table 2: Clinical trials using mesenchymal stem cells to treat Type 2 diabetes mellitus.

Author	Route of cell delivery	Dose per kg	Follow-up
Bhansali et al.[46]	Locally	$3.2x10^8$	12 months
Liu et al.[48]	Locally and IV	$1x10^6$	12 months
Jiang et al.[50]	Locally	$1.35x10^6$	6 months
Kong et al.[51]	Systemically		12 months
Skyler et al.[54]	Locally	$0.3–2x10^6$	24 months
Li et al.[53]	Locally		12 months

IV: intravenous.

The fate of the infused cells was explored by Sood et al.[49] who gave radio-labelled fluorodeoxyglucose bone marrow MSC (BM-MSC) to mice intravenously or into the superior pancreatico-duodenal and splenic arteries. Positron emission tomography tracking showed that the MSC given through the intravenous route homed to the lungs before spreading through the systemic circulation. The locally injected cells partially migrated to the pancreas. The HbA1c reduction and insulin requirements were proven to be superior when the cells were injected directly into the pancreas feeding arteries.[49]

Bhansali et al.[46] infused BM-MSC to treat 10 patients and showed reduction of the insulin requirements; in addition, 3 patients were able to discontinue insulin completely. Wang et al.[43] reported a reduction in the HbA1C levels as early as 1 month. The same phenomenon was also observed in two other clinical trials carried out by other researchers; HbA1C was found to diminish starting at 3 months and lasting 1 year on average.[50-52] The effect of the cells was shown to persist between 9 months and 2 years.[43,50-52]

Multiple MSC injections were used in some trials in an attempt to prolong their effects, but no clear results have been reached on the best schedule of injection and there is no consensus on the optimal time or interval of MSC infusion in diabetic patients. What is clear from different reports is that the effect is typically limited to several months, although it may persist up to 2 years.[49,51,52]

Another important issue to consider is the best dose of the effector cells. While most studies used a cell number dependent on the weight, on average 10^6–2.6×10^7cells/kg are being used.[38] The response has been reported to be dose-dependent in some, but not all, studies.[53] The effects on hyperglycaemia were observed early on in some studies but the C-peptide followed later, peaking at 6 months. The effects, on average, lasted about 12 months following MSC implantation. Hu et al.[52] reported that the normalisation of the C-peptide peaked at 1 year and declined over the following 2 years.[48,50,51]

Skyler et al.[54] published a milestone Phase III, placebo-controlled, multicentre clinical study in July 2015 using allogeneic MSC at an escalating dose. The target HbA1c of ≤7% was achieved by 33% (5 of 15) of the subjects who received the 2.0×10^6 cells/kg dose and 50% of those receiving 1.0×10^6 cells/kg. The source of the MSC was adult allogeneic bone-marrow precursor cells. Only one dose of MSC was given intravenously with no significant side effects reported. No patients discontinued the study because of an adverse event.[54]

Finally, Domouky et al.[55] transplanted 40 rats with BM-MSC or IPC with differentiated insulin producing cells. Both groups showed improvement of diabetic control but the IPC group displayed normal regeneration and distribution of the beta cells in the pancreas and resumption of endogenous insulin production to a more significant degree.[55]

DIABETIC COMPLICATIONS

The pathobiology of diabetic complications is closely related to the diabetic vasculopathies and the inflammatory microenvironment. On the clinical platform impotence, neuropathies, wound healing, renal failure, retinal damages, cardiac failure, and leg ulcers, among other complications, can make life exceedingly challenging for T2DM patients. Several trials have shown efficacy, or at least improvement, of the diabetic complications. Cao et al.[56] used BM-MSC to show improved healing of diabetic foot ulcers. Packham et al.[57] showed that the infusion of allogeneic mesenchymal precursor cells in patients suffering from diabetic nephropathy using a commercially available allogeneic MSC (Rexlemestrocel-L®, Mesoblast, New York City, New York, USA) is safe and tolerable for human use and may stabilise or improve diabetic nephropathy.[57] Xiang et al.[58] showed that rats treated with BM-MSC conditioned medium had enhanced vascular remodelling after an induced stroke. Zhang et al.[59] reported restoration of vision in diabetic retinopathy in rats after intra-vitreal injection of neural stem cells originating from human umbilical cord-derived MSC. Treatment of diabetic rats prevented the decline in brain-derived neurotrophic factor levels usually caused by diabetes.[59] Intralesional BM-MNC injections into skin ulcers and its surroundings have been shown to improve the limb perfusion and ulcer healing in patients with critical limb ischaemia.[31]

CONCLUSION AND FUTURE DIRECTIONS

There are about 50 ongoing studies on stem cell use in T2DM that are registered at www.clinicaltrials.gov. There has been a large number of small published studies that indeed do not constitute a solid scientific proof of the efficacy

of different stem cells being tried. Due to most published data lacking statistical significance and a blinded randomisation scheme, we feel that it is futile to employ meta-analytical methods to draw useful conclusions. One big issue is whether cells are comparable between laboratories. In other words, we do not have enough data to assume each study is not reporting on a different cell subtype, due to missing flow cytometric identification in most studies. The introduction of pre-prepared or frozen cells, like the MSC of umbilical or bone marrow origin, by different pharmaceutical companies has proven extremely expensive at this point and definitely out of reach to the vast majority of individuals. Larger studies are needed to advance the field and understand the best way to realise its potential. We believe stem cell therapy should only be used within clinical trials at this time, until enough evaluable data becomes available. Caution has to be exerted to expand the regulatory work necessary to frame this new field and help it enhance our armamentarium against T2DM. The laboratory methods, like culture conditions and methods of cell numbering, have to be better thought of and more uniformly standardised, and the interpretation of the results should be done critically. Many biases have to be excluded by adopting better double blinded randomisation, statistical methods, and large enough sample sizes. Most researchers in the field are working through the preclinical phases of experimenting with the differentiation of different stem cells into insulin-producing beta cells while another group is exploiting the anti-inflammatory properties of the bone marrow and MSC. The future of stem cells may be heading towards restoring and executing both strategies at the same time.

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ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY IN DIABETIC MACULAR OEDEMA: IS IT EFFECTIVE?

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ABSTRACT

Diabetic macular oedema (DMO) is a common ocular problem among patients with diabetic retinopathy, which is sight-threatening and leads to blindness. The gold standard treatment for DMO had been focal/grid laser photocoagulation that achieved stabilisation of disease progression. However, newer pharmacological treatment options have gradually been favoured, as studies demonstrate their superior efficacy with regard to significant visual improvements. In particular, use of anti-vascular endothelial growth factor (anti-VEGF) has become very popular, with promising evidence emerging from numerous trials regarding efficacy and safety. Based on the 2014 American Society of Retina Specialists (ASRS) Preferences and Trends survey, the current preferred first-line therapy for DMO is in fact an anti-VEGF agent. Studies have shown that VEGF plays a critical role in both the angiogenesis and inflammation processes that occur during development of DMO. Hence, this allows anti-VEGF agents to specifically target and treat the underlying pathology, signifying its importance, and possibly accounting for its efficacy. We evaluate the available literature documenting the efficacy of anti-VEGF treatment in DMO. A key clinical finding was that anti-VEGF, as a drug class, achieved superior resolution of macular oedema and visual improvements that were consistently sustainable over 3 years, with some evidence pointing towards 5-year sustainability too. Hence, with intravitreal anti-VEGF treatments increasingly available, better long-term prognosis and, crucially, reduced likelihood of progression to blindness can be expected in patients with DMO.

Keywords: Anti-vascular endothelial growth factor (anti-VEGF), ranibizumab, bevacizumab, aflibercept, pegaptanib, laser, diabetic macular oedema (DMO), diabetic retinopathy (DR), efficacy, READ-2, BOLT, DA VINCI, DRCR, protocol T.

INTRODUCTION

Diabetic macular oedema (DMO) is a common ocular problem among patients with diabetic retinopathy that is sight-threatening and leads to blindness. Being the leading cause of legal blindness in diabetics,[1] effective management is crucial. Diagnosis is first made clinically, followed by quantification using optical coherence tomography and fundus fluorescein angiography for monitoring disease progression and treatment response.[2] Currently, various treatments targeting different pathways in the pathogenesis of DMO exist, albeit with varying efficacy. In particular, anti-vascular endothelial growth factor (anti-VEGF) is fast becoming a popular treatment option over focal/grid laser photocoagulation (hereafter referred to as 'laser'), the gold standard treatment for DMO over the past decade. Unlike laser that stabilises disease progression, anti-VEGF agents are reported to improve vision significantly.[3] As VEGF is a critical molecule in the pathogenesis of DMO, this allows anti-VEGF agents to specifically target and treat the underlying pathology,[4] signifying its importance. Hence, this review is focussed on discussing the effectiveness of anti-VEGF therapy in DMO, while associated safety and real-world cost concerns are discussed elsewhere.[5]

Table 1: Summary of molecular differences between anti-VEGF agents.

Anti-VEGF agent	Molecular weight (kDa)	Molecular characteristics	K_D for $VEGF_{165}$ (pM)
Ranibizumab	48	Fab fragment	46–192
Bevacizumab	149	Full-length mAB	58–1,100
Aflibercept	115	Fusion protein	0.45
Pegaptanib	50	RNA aptamer	50

Fab: antigen binding fragment; K_D: dissociation constant; mAB: monoclonal antibody; pM: picomolar; VEGF: vascular endothelial growth factor.

METHODS

A comprehensive literature search was conducted on Medline, PubMed®, and Cochrane® databases using the keywords: 'anti-VEGF', 'bevacizumab', 'ranibizumab', 'aflibercept', 'trap-eye', 'pegaptanib', 'diabetic macular edema'. Only studies with abstracts and full-texts published in English between 2004 and 2016 were included. This time period was chosen to include seminal papers and landmark trials documenting the use of anti-VEGF in treating DMO. Selection of relevant articles was initially performed based on their titles and abstracts, followed by detailed review of their full-texts. In total, 28 clinical trials, 3 systematic reviews, 14 review articles, 5 retrospective studies, and 3 prospective studies were selected.

RATIONALE FOR ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR IN DIABETIC MACULAR OEDEMA

The associated vision loss in DMO occurs due to the breakdown of the blood-retinal barrier. Increase in vascular permeability results in plasma protein leakage and retinal swelling/thickening.[4] Multiple studies have identified several growth factors and inflammatory mediators to be responsible for this breakdown, especially VEGF. Although the exact pathogenic mechanism is not completely understood, independent analysis by Fogli et al.[4] supports the theory that VEGF plays a critical role in both the angiogenesis and inflammation processes that occur during the development of DMO, justifying the use of anti-VEGF in treatment. Currently, four different intravitreal anti-VEGF agents are used: namely, ranibizumab (RBZ), bevacizumab (BVZ), aflibercept, and pegaptanib. Their properties are summarised in Table 1. Their superior clinical efficacy reported in randomised controlled trials (RCT) (summarised in Table 2 and 3) and other studies, support a shift in treatment paradigm towards anti-VEGF.

Ranibizumab

RBZ (Lucentis™, Genentech, San Francisco, California, USA/Roche™, Basel, Switzerland) is a recombinant, humanised, monoclonal antibody fragment that binds all isoforms of VEGF-A. Currently, it is approved for treating age-related macular degeneration (AMD), retinal vein occlusion and diabetic retinopathy with or without DMO, in the USA and European Union (EU). Treatment regimens in DMO typically vary between practices.

Herein, we discussed five important RCT studying RBZ in DMO. Additionally, DRCR.net (Protocol T), comparing the efficacy of RBZ against two other anti-VEGF agents, will be separately discussed.

READ-2

A Phase II, 14-site, investigator-initiated clinical trial comparing 0.5 mg RBZ, laser, and 0.5 mg RBZ combined with laser over 6, 24, and 36 months. Six-month results demonstrated short-term visual and anatomical benefits of RBZ monotherapy, with mean best-corrected visual acuity (BCVA) improving significantly from baseline by +7.24 ETDRS (Early Treatment Diabetic Retinopathy Study) letters (versus -0.43 letters in laser), and 50% of this group experienced a reduction in foveal thickness (versus 33% in laser). Also, significantly more patients gained ≥15 letters with RBZ monotherapy (22%) than laser (0%).[6] After 6 months (primary endpoint), most patients fulfilled the retreatment criteria and were retreated with RBZ monotherapy. Subsequent results revealed sustained benefits after 24 months in the monotherapy arm, while retreated patients experienced improved vision and reduction of

residual oedema (Table 2).[7] Despite improvements after 24 months, many patients continued to have persistent oedema, defined as central subfield thickness (CST) ≥250 µm, suggesting possible under-treatment. Consequently, treatment regimen was intensified from bimonthly to monthly, which saw significant improvements in both mean BCVA and CST (Table 2). Hence, suggesting that outcomes can be improved with more aggressive therapy.[8]

RESOLVE

A Phase II, multicentre, sham-controlled trial assessing the efficacy and safety of two doses of RBZ (0.3 mg and 0.5 mg) against placebo over 12 months. Dose effect was difficult to assess, due to study design allowing doubled doses of RBZ or rescue laser to be administered when needed (91.8% in placebo arm; 68.6% in RBZ arm). Hence, data reported was pooled from all RBZ-treated patients (regardless of dose) instead. Overall, RBZ-treated patients once again show improved outcomes compared to placebo (Table 2).[9]

RESTORE

A Phase III, multicentre trial comparing 0.5 mg RBZ, combination with laser, and laser over 12 and 36 months. Results after 12 months were similar to READ-2 and RESOLVE, demonstrating superiority of RBZ treatment over laser (Table 2).[10]

Table 2: Summary of main anatomical and functional outcomes in randomised controlled trials for ranibizumab, bevacizumab, and aflibercept.

	Study duration (months)	Study eyes (N)	Mean BCVA gains from baseline (ETDRS letters)		Mean CRT/CMT/CST reduction from baseline (µm)		Eyes gaining ≥15 letters from baseline (%)	
			Mono	Control	Mono	Control	Mono	Control
Ranibizumab								
READ-2	6	126	7.24	-0.43	106.3	82.8	22	0
	24	101	7.7◊	5.1◊	80.1◊	153.6◊	24◊	18◊
	36	74	10.3◊	1.4◊	132.0◊	193.0◊	32◊	9◊
RESOLVE	12	151	10.3	-1.4	194.2	48.4	32.4	10.2
RESTORE	12	345	6.1	0.8	118.7	61.3	22.6	8.2
	36	240	8.0	6.0	142.1	142.7	27.7	21.6
RISE#	24	377	11.9–12.5	2.6	250.6–253.1	133.4	39.2–44.8	18.1
	36	377	11.0–14.2	4.3	261.2–269.1	200.1	41.6–51.2	22.0
RIDE#	24	382	10.9–12.0	2.3	259.8–270.7	125.8	33.6–45.7	12.3
	36	382	10.6–11.4	4.7	261.8–266.7	213.2	36.8–40.2	19.2
Protocol I	12	854	9	3	131.0–137.0	102.0	28–30	15
	24	628	7–9	3	141.0–150.0	138.0	28–29*	18*
Bevacizumab								
DRCR.net	3	109	0-7◊	-1◊	5.0-56.0◊	40.0◊	9-15◊	5◊
BOLT	12	80	5.6	-4.6	129	68	11.9*	5.3*
	24	80	8.6	-0.5	146*	118*	32	4
Aflibercept								
DA VINCI	6	221	8.5–11.4	2.5	127.3–194.5	67.9	17–34*	21*
	12	221	9.7–13.1	-1.3	165.4–227.4	58.4	23.8–45.5*	11.4*

◊Statistical analysis not available for results; *results not statistically significant (p>0.05); #results of open-label 2-year extension not included, because results were derived from pooled data across RISE/RIDE, making direct comparison with 24 and 36-week results reported in the Table meaningless.
BCVA: best-corrected visual acuity; CMT: central macular thickness; CRT: central retinal thickness; CST: central subfield thickness; ETDRS: Early Treatment Diabetic Retinopathy Study; Mono: anti-VEGF monotherapy.

After 12 months, all remaining patients were treated with RBZ. Results after 36 months reported that visual and anatomical gains were sustained in the original RBZ arm, while previously laser-treated patients improved to similar levels as the original RBZ arm despite RBZ being delayed for a year (Table 2).[11]

RISE/RIDE

RISE/RIDE were two parallel, methodologically identical, Phase III, multicentre trials randomising patients into three groups (0.3 mg RBZ, 0.5 mg RBZ, and sham injections) to assess efficacy and safety of RBZ compared to sham over 3 years with an additional 2-year extension. Similar to RESTORE, all patients were changed onto RBZ therapy after 24 months. The 24 and 36-month results were very similar to RESTORE, with superior and sustainable ocular benefits reported in the RBZ arm after 3 years, and up to 54 months. However, among the originally laser-treated patients, delayed RBZ treatment never achieved a similar extent of visual improvements as the original RBZ arm after 36 and 54 months. This data therefore contradicts the extent of benefits seen in RESTORE (Table 2).[12-14]

DRCR.net (Protocol I)

The DRCR.net (Protocol I) study compared the efficacy of both steroid and RBZ treatment against laser over 5 years. Participants were divided into four groups (0.5 mg RBZ and prompt laser, 0.5 mg RBZ and deferred laser, 4 mg intravitreal triamcinolone and prompt laser, laser only). Of relevance, 1 and 2-year results demonstrated significant improvements in mean BCVA and CST reductions in both RBZ-treated groups compared to laser (Table 2) that was maintained through 5 years. Interestingly, both 3 and 5-year results reported reduced mean BCVA gains when laser was started at RBZ initiation (RBZ and prompt laser versus RBZ and deferred laser: +6.8 versus +9.7 letters [p=0.02, 3 years]; +7.2 versus +9.8 [p=0.09, 5 years]).[15-18]

Bevacizumab

BVZ (Avastin™, Genentech; Roche™) is a recombinant, humanised, full-length monoclonal antibody that binds all isoforms of VEGF-A. BVZ is currently US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved for systemic treatment of several different cancers only, and its use for ocular diseases is off-label. Despite its off-label status, doctors commonly use it for wet AMD and DMO[19] due to its low cost and efficacy demonstrated in various trials. Currently, no consensus on treatment regimen is available, with the most common being 1.25 mg monthly until oedema is stabilised before using an 'as needed' regimen.[20]

DRCR.net

The first Phase II, multicentre trial comparing various BVZ treatment regimens against laser identified several key findings.[21] Firstly, eyes treated with intravitreal BVZ achieved significant BCVA improvement that persisted over 12 weeks, and greater CST reduction at 3 weeks compared to laser. Secondly, results identified no significant difference between the tested doses (1.25 mg, 2.5 mg). Thirdly, BVZ treatment achieved significantly greater BCVA improvements in DMO-treatment naïve eyes. Similar findings were also reported in a RCT conducted by Lam et al.[22]

BOLT

A Phase II, single-centre RCT, comparing 1.25 mg intravitreal BVZ and laser, provided further evidence supporting the benefits of BVZ. After 12 months, BVZ-treated patients gained a median of +8 letters (versus -0.5 letters in laser, p=0.0002) and mean central macular thickness (CMT) reduction of -129 µm (versus -68 µm in laser, p=0.02). Similar functional and anatomical improvements were also reported at 24 months (Table 2).[23,24]

PACORES

A recently published 5-year result from a multicentre retrospective study conducted in Latin America and Spain seemed to disagree about the sustainability of visual gains after 5 years.[20] The study included eyes treated with at least one injection of 1.25/2.5 mg of intravitreal BVZ with an 'as needed' regimen. Results showed that mean BCVA ultimately returned to baseline after 60 months, despite significant improvements at 36 months. Subgroup analysis showed that after 60 months about 75% of BVZ-treated patients had at least stable BCVA, even though only 29% achieved visual gains. Notably, significant anatomical improvements were observed 6 months after treatment and remained relatively constant throughout the 60 months.

Other studies

A review of intravitreal BVZ in DMO looked at several smaller studies with different study parameters, and similarly concluded its general

efficacy.[19] Two noteworthy points not seen in RCT, due to their strict exclusion criteria, are that BVZ seemed to achieve visual and anatomical improvements even in cases that were unresponsive to other DMO treatments,[25,26] but not in cases with macular ischaemia.[27] However, these respective studies are inconclusive due to short follow-up periods.

Aflibercept

Aflibercept (Eylea™, Regeneron, Tarrytown, New York, USA, formerly VEGF trap-eye) is a high affinity, recombinant fusion protein, with VEGF-binding domains of human VEGF receptors 1 and 2 fused to fragment crystallisable domain of human immunoglobulin-G1, which binds all circulating VEGF isoforms and placental growth factor. It is currently approved in the USA, EU, Japan, and Australia for several different vascular ocular diseases, including DMO.[28] The recommended dose is 2 mg every 8 weeks after 5 initial monthly loading injections.[28] Three landmark trials were conducted with convincing results supporting intravitreal aflibercept in DMO.

DA VINCI

A multicentre, active-controlled RCT, compared four different aflibercept regimens to laser, and each regimen achieved statistically significant improvements. The 24-week results showed aflibercept subgroups achieving mean BCVA gains between +8.5 and +11.4 letters (versus +2.5 letters in laser, p≤0.0085 for each subgroup), and mean CRT reduction between -127.3 µm and -194.5 µm (versus -67.9 µm with laser, p=0.0066 for each subgroup).[29,30] The superiority of aflibercept over laser remained statistically significant even after 1 year (Table 2).[31]

VISTA/VIVID

Two similarly designed Phase III, active-controlled RCT, comparing two aflibercept regimens (2 mg every 4 weeks and 2 mg every 8 weeks after 5 initial monthly doses) to laser were carried out. The 52, 100, and 148-week results are summarised in Table 3. Results after 1 year were very similar to those reported in the DA VINCI trial for three outcome measures. Additionally, the reported 100 and 148-week results provided strong significant evidence of the sustainability of visual benefits with aflibercept over laser even in the longer term. Additionally, the study design allowed all patients who met retreatment criteria to be given rescue treatment after Week 24. Aflibercept-treated eyes consistently required significantly less rescue treatment compared to laser-treated eyes from 24 to 148 weeks. Overall, no significant differences in efficacy were found between the two aflibercept regimens.[32-34]

Pegaptanib

Pegaptanib sodium (Macugen™, Eyetech™, New York City, New York, USA) is a ribonucleic acid aptamer that specifically blocks the ocular angiogenic activity of the $VEGF_{165}$ isoform. Although it is approved only for the treatment of wet AMD in USA and Europe,[35] results from Phase II and III trials are highly supportive of its application in treating DMO. Both trials recommend a dosage regimen of 0.3 mg every 6 weeks followed by an 'as needed' regimen.

A Phase II RCT reported both functional and anatomical improvements with 0.3 mg compared to sham. Median BCVA at Week 36 was significantly better, with 0.3 mg (20/50) compared to sham (20/63) (p=0.04), and significantly more patients gained VA of ≥10 letters with 0.3 mg (34%) compared to sham (10%) (p=0.003). Treatment reduced mean central retinal thickness (CRT) by -68 µm, while sham resulted in +4 µm thickening (p=0.02).[36]

Findings drawn from 2-year data collated from another Phase II/III trial confirmed the short term clinical benefits and suggested continued long-term visual improvements. After Week 54, 36.8% of patients treated with pegaptanib gained BCVA of ≥10 letters compared to 19.7% with sham (p=0.0047). At Week 102, the same BCVA improvement was higher in the treatment group (38.3%) compared to sham (30.0%), albeit not statistically significant (p=0.1729). Additionally, the trial showed statistically superior improvements in mean VA from baseline after treatment compared with sham (p<0.05) at both Weeks 54 and 102. However, CRT improvements between both groups at Weeks 54 and 102 were 'numerically different but not statistically significant' suggesting that benefits of pegaptanib might be more functional rather than anatomical.[37]

A separate meta-analysis combined data from both of these trials and demonstrated a statistically significant greater percentage of treated patients gained VA of ≥15 letters over sham.[38] Also, two smaller studies (one prospective and one retrospective) both reported significant

improvements in mean BCVA and mean CRT with pegaptanib too,[39,40] indicating effectiveness across a wider population.

COMPARISON BETWEEN ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR AGENTS

DRCR.net (Protocol T) is the first and only RCT directly comparing more than two different anti-VEGF agents, enabling relative efficacy to be studied. This multicentre RCT randomised patients into three groups (0.3 mg RBZ, 1.25 mg BVZ and 2 mg aflibercept) with BCVA gains as the primary outcome measure. Mean BCVA gains from baseline were +11.2, +9.7, and +13.3 letters for RBZ, BVZ, and aflibercept, respectively, after 1 year, and +12.3, +10.0, +12.8, respectively, after 2 years. Overall, all three anti-VEGF agents were efficacious in DMO. Subgroup analysis identified that in eyes with better baseline BCVA (between 20/32 and 20/40), 1-year and 2-year BCVA gains were similar across the three agents. However, in eyes with poorer baseline VA (20/50 or worse), aflibercept performed significantly better than BVZ and RBZ after 1 year, but only superiority over BVZ was maintained after 2 years. Notably, no significant difference in BCVA improvements was found between RBZ and BVZ over the 2 years.[28,41,42]

DISCUSSION

The use of anti-VEGF agents in DMO has popularised over the last few years. Before that, the gold standard treatment was laser that reduces the 3-year risk of moderate vision loss by 50%, compared to observation in the landmark ETDRS study.[43] However, as the disease may progress to blindness, settling for a treatment that slows DMO progression is suboptimal. Ideally, treatment should improve visual outcomes early on and persist in the long run to be considered effective, due to disease chronicity requiring prolonged repeated treatments.

Unfortunately, laser only improved vision by three lines in 11% and 16% of patients after 1 and 3 years, respectively.[43] Comparatively, results from the aforementioned landmark studies clearly highlight the superior therapeutic benefits of anti-VEGF agents in achieving both visual improvements and resolution of DMO. Overall, as a drug class, early clinical benefits are observed as early as 1 month.[20]

Table 3: Summary of 52 and 100-week results from VISTA/VIVID study.[32-34]

		VISTA			VIVID		
		2q4	2q8	Laser	2q4	2q8	Laser
Mean BCVA gains (ETDRS letters)	52 weeks	12.5	10.7	0.2	10.5	10.7	1.2
	100 weeks	11.5	11.1	0.9	11.4	9.4	0.7
	148 weeks	10.4	10.5	1.4	10.3	11.7	1.6
Mean CRT reduction (µm)	52 weeks	185.9	183.1	73.3	195.0	192.4	66.2
	100 weeks	191.4	191.1	83.9	211.8	195.8	85.7
	148 weeks	200.4	190.1	109.8	215.2	202.8	122.6
Eyes gaining ≥15 letters from baseline (%)	52 weeks	41.6	31.1	7.8	32.4	33.3	9.1
	100 weeks	38.3	33.1	13.0	38.2	31.1	12.1
	148 weeks	42.9	35.8	13.6	41.2	42.2	18.9
Eyes requiring rescue treatment after 24 weeks* (%)	52 weeks	2.6	0.7	31.2	4.4	8.1	24.1
	100 weeks	3.2	8.6	40.9	7.4	11.1	34.6
	148 weeks	4.5	10.5	40.9	7.4	11.9	35.3

All results were clinically significant ($p \leq 0.0001$).

*Rescue treatment refers to the treatment modality that patient was not randomised to and have not received before (e.g., patients in the laser-treated group received rescue aflibercept of 5 doses 2q4 followed by 2q8 until end of study).

BCVA: best-corrected visual acuity; CRT: central retinal thickness; ETDRS: Early Treatment Diabetic Retinopathy Study; 2q4: 2 mg every 4 weeks after 5 initial monthly doses; 2q8: 2 mg every 8 weeks after 5 initial monthly doses.

Furthermore, current evidence strongly supports the sustainability of clinical benefits for at least 3 years, with several RCT, like RISE/RIDE and Protocol I, even reporting persistent improvements after 5 years. However, two retrospective studies presenting 5-year data, the PACORES study and Wecker et al.,[44] both reported mean BCVA returning to baseline with no significant improvements after 5 years.[20,44] These conflicting conclusions in 5-year sustainability might possibly be accounted for by differences in study population characteristics. Is the heterogeneous sample in these retrospective studies a better reflection of real-world patient characteristics? Or is there an inherent selection bias affecting how we should interpret long-term results from these retrospective studies?[44] Hence, we believe that 5-year benefits are likely to be sustainable in most patients, but not necessarily in patients with resistant/recurrent DMO. Nonetheless, in such patients, anti-VEGF treatment is likely to be non-inferior to laser after 5 years, as further deterioration towards blindness is avoided; hence, making anti-VEGF therapy superior and more popular than laser.

Additionally, encouraging retreatment results show that patients can still benefit from anti-VEGF therapy, even if initiation was delayed. However, whether delayed anti-VEGF therapy can achieve levels of improvement seen in early treatment is still debatable. Chung et al.[27] suggested avoiding BVZ treatment in patients with macular ischaemia as it led to worse visual outcomes. This is particularly interesting as it would constitute a contraindication for anti-VEGF treatment. A possible explanation could be that the downregulation of VEGF below physiological levels induces excessive vasoconstriction, that further disrupts the already compromised chorioretinal circulation in diabetics, causing macular ischaemia and poorer visual outcomes.[27,45] Though such data is limited, another review suggests the rare possibility of anti-VEGF compromising retinal circulation,[45] thereby causing macular ischaemia. Hence, extra precautions, such as frequent follow-ups or alternative treatments, should be considered in such patients until conclusive evidence is found.

In terms of the drug class effect among anti-VEGF agents, two articles reviewed both reported visual and anatomical improvements after converting from RBZ/BVZ to aflibercept treatment.[46,47] Hence, it is worth switching between anti-VEGF agents if response is suboptimal. This makes close monitoring early on after initiation especially important. Nonetheless, more studies are required to fully understand whether similar improvements are achieved when converting to other anti-VEGF agents besides aflibercept.

CONCLUSION

In conclusion, intravitreal anti-VEGF agents have definitely revolutionised the management of DMO. The reported superior visual improvements and resolution of macular oedema create a strong case for it to be the new standard of care. Nonetheless, caution should be taken when treating patients with macular ischaemia or persistent DMO. Hopefully, with long-term clinical benefits of anti-VEGF therapy generally sustainable, prevalence of DMO can be effectively lowered to reduce blindness.

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ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY IN DIABETIC MACULAR OEDEMA: IS IT SAFE?

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ABSTRACT

Over the last decade, intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents have been increasingly used in the management of various retinal diseases, especially diabetic macular oedema. Diabetic macular oedema is one of the leading causes of legal blindness among patients with diabetic retinopathy, meaning these patients are eligible for associated medical benefits. It is essential that diabetic macular oedema is managed with an effective and safe treatment for good long-term prognosis. Over the past decade, focal/grid laser photocoagulation has been the gold standard treatment. However, evidence supporting the superior clinical benefits and relative safety of anti-VEGF agents has driven a recent shift in treatment paradigm, favouring anti-VEGF over laser treatment. Previous studies involving systemic anti-VEGF treatment in cancers have identified an associated increased risk of arteriothrombotic events, such as myocardial infarction and stroke, which are potentially fatal. Hence, it is important to evaluate whether such risks, which will significantly alter the safety profile, persist with intravitreal administration. A comprehensive literature review was performed and concluded that no significant increase in risk of ocular or non-ocular adverse events, particularly arteriothrombotic events, were associated with anti-VEGF agents, predicting an overall favourable safety profile. A summary of some of the possible adverse events recorded in the various studies, albeit at relatively low rates, are also included. Additionally, it is briefly discussed how real-world concerns of cost and affordability can influence treatment choice, thereby affecting how clinical evidence is transferred into practice.

Keywords: Anti-vascular endothelial growth factor (anti-VEGF), ranibizumab (RBZ), bevacizumab (BVZ), aflibercept, pegaptanib, laser, diabetic macular oedema (DMO), safety, adverse events (AE), READ-2, BOLT, DA VINCI, DRCR, protocol T.

INTRODUCTION

Over the last decade, intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents have been increasingly used in the management of various retinal diseases, especially diabetic macular oedema (DMO). DMO is one of the leading causes of legal blindness among patients with diabetic retinopathy, meaning these patients are eligible for associated medical benefits.[1] Hence, choosing an effective and safe treatment is crucial for long-term prognosis. Over the past decade, focal/grid laser photocoagulation (hereafter referred to as 'laser') has been the gold standard treatment for DMO. Recent evidence from multiple trials reporting the superior clinical benefits and relative safety[2] of anti-VEGF agents has driven a shift in the treatment paradigm towards their usage. In terms of safety, previous studies involving systemic anti-VEGF treatment in cancers have identified an associated increased risk of arteriothrombotic events (ATE), such as myocardial infarction (MI) and stroke,[3] that are potentially fatal. Consequently, the ocular and systemic safety profile of intravitreal anti-VEGF agents should be well evaluated to determine if they are safer compared to other available treatments for DMO. An example is intravitreal corticosteroid injections or implants,

which are effective but associated with increased risks of elevated intraocular pressure (IOP) and premature cataracts.[4,5] The efficacy of anti-VEGF agents is presented elsewhere;[6] hence, this review discusses the safety profile and real-world cost concerns of anti-VEGF therapy to aid the selection of treatment.

METHODS

Using Medline, PubMed, and Cochrane databases, a comprehensive literature review was performed to identify relevant studies on anti-VEGF treatment in DMO. Search terms included anti-VEGF, bevacizumab, ranibizumab, aflibercept, trap-eye, pegaptanib, diabetic macular edema, effectiveness, efficacy, safety, and cost. Studies published in English from 2004–2016 were selected, after reading their abstracts and full-texts, to include seminal papers and landmark trials. Eventually, 52 studies were collated, comprising 26 clinical trials, 3 systematic reviews, 20 review articles, 2 retrospective studies, and 1 case series/report.

A BRIEF HISTORY OF INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR USE

The use of intravitreal anti-VEGF for treatment of ocular neovascularisation arose when studies identified the pivotal role VEGF had in the pathogenesis of wet age-related macular degeneration (AMD). Trials testing pegaptanib (anti-VEGF) in patients with wet AMD demonstrated a safe reduction in the associated visual loss, resulting in US Food and Drug Administration (FDA) approval in late 2004.[7] This marked the first approval of an anti-VEGF for the treatment of a disease due to ocular neovascularisation.[7]

In early 2004, bevacizumab (BVZ) was the first anti-VEGF to be FDA approved for the systemic treatment of colon cancer, following successful trials. Yet, there were concerns over BVZ structure, diminishing the drug properties of penetration, efficacy, and safety during intravitreal use.[8] This led to ranibizumab (RBZ), a small truncated variant of BVZ, being created. Contrary to these concerns, off-label use of intravitreal BVZ proved to be effective too,[7] although the treatment was never approved by the FDA for intraocular use. Instead, it was the smaller molecule, RBZ, which attained FDA approval in 2006, following pegaptanib, for the treatment of wet AMD after large trials proved its efficacy and safety.[7]

Aflibercept was marketed as an alternative agent, with a lower dosing frequency and better pharmacokinetics of VEGF binding; compared to RBZ or BVZ, the VEGF binding affinity of aflibercept is 100-fold stronger. Results from these trials demonstrated non-inferiority, despite its lower dosing frequency, culminating in aflibercept approval by the FDA in 2011.[7] A comparison between the molecular properties of the four anti-VEGF agents has previously been summarised.[6]

PATHOGENESIS OF DIABETIC MACULAR OEDEMA

In diabetes, pathophysiological mechanisms such as synthesis of advanced glycation end-products and protein kinase C activation contribute to many diabetes-related microvascular complications,[9] including DMO. These biochemical abnormalities cause intracellular hypoxia and increased VEGF expression,[10] resulting in an imbalance of pro-angiogenic and normally expressed VEGF-A isoforms. Several other growth factors and inflammatory mediators also contribute to the pathogenic process of DMO, leading to breakdown of the blood-retinal barrier.[11] Consequently, retinal vascular permeability increases and plasma proteins leak into the neural interstitium, resulting in an oedematous retinal layer. This affects visual processing and thereby visual acuity. Intravitreal anti-VEGF therapy achieves its therapeutic effect by downregulating circulating VEGF, a critical molecule in the angiogenesis and inflammatory processes that occur in DMO.[3,11] Hence, it is possible that consequent lower levels of VEGF may interfere with its normal physiological role of stimulating vasculogenesis and angiogenesis in hypoxic conditions, resulting in an increased risk of systemic adverse events (AE), such as ATE and hypertension,[3] which have been reported with systemic anti-VEGF use. Currently, four intravitreal anti-VEGF agents are available to treat DMO: namely, RBZ, BVZ, aflibercept, and pegaptanib. Herein, we discuss their safety profiles with a focus on landmark trials.

SAFETY OF ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR AGENTS

Ranibizumab

RBZ (Lucentis™, Genentech, Francisco, California, USA; Roche™, Basel, Switzerland) is a recombinant, humanised, monoclonal antibody fragment that has

only antigen binding domains specific to all isoforms of VEGF-A. It is approved by the FDA and European Medicines Agency (EMA) for the treatment of AMD, retinal vein occlusion, and diabetic retinopathy. Among the four agents, RBZ is well-studied with extensive Level I evidence supporting its efficacy and safety.[9] We reviewed and summarised its safety profile in Table 1, based on five important randomised controlled trials (RCT). Additionally, DRCR.net (Protocol T), which compares the relative safety of RBZ and two other anti-VEGF agents in patients with DMO, will be discussed separately.

READ-2

This clinical trial was a Phase II, 14-site, investigator-initiated study that randomised 126 patients into three groups (0.5 mg RBZ, laser, and combination of RBZ with laser) and reported results at three intervals (6, 24, and 36 months); however, safety data were only reported at the 6-month interval. Systemically, one death from stroke occurred in the combination arm, but was judged to be unrelated to RBZ treatment. Notably, vitreous haemorrhage occurred in all three arms with no significant difference in incidence.[12]

RESOLVE

RESOLVE, a Phase II, multicentre, sham-controlled trial studying the effects of two doses of RBZ (0.3 mg and 0.5 mg) against placebo in 151 patients, found no significant differences in the incidence of ocular and systemic serious AE (SAE) or AE between RBZ and sham. However, an episode of MI (1%) within the study group was suspected to be related to RBZ. Also, two RBZ-treated patients (2%) were discontinued due to endophthalmitis. Common ocular AE reported included conjunctival haemorrhage, elevated IOP, and eye pain.[13]

RESTORE

RESTORE was a Phase III, multicentre (across 13 countries) trial that studied efficacy and safety of 0.5 mg RBZ against laser only and RBZ combination with laser, and involved 345 patients assessed over a 12 to 36-month period. In terms of ocular SAE, cataract was most common with no statistically significant difference between groups, while endophthalmitis did not occur. Several non-ocular SAE were suspected, including pulmonary embolism and arterial thrombosis in the limb. Overall, there were 14 deaths over 3 years, but none were related to RBZ or the procedure. Common ocular AE included eye pain, while reported non-ocular AE included nasopharyngitis.[14,15]

Table 1: Summary of adverse events with ranibizumab treatment in DMO patients in RCT.

Study	Study eyes	Study duration (months)	SE in treatment arm	
			Ocular	Systemic
READ-2	126	6, 24, 36*	Vitreous haemorrhage	
RESOLVE	151	12	Endophthalmitis Elevated IOP Eye pain Conjunctival haemorrhage	MI Infections
RESTORE	345	12, 36	Cataract Eye pain Elevated IOP Conjunctival haemorrhage	Nasopharyngitis PE Arterial thrombosis limb Hypertension
RISE/RIDE	377/382	24, 36, 54	Endophthalmitis Vitreous haemorrhage Traumatic cataract Rhegmatogenous RD Elevated IOP	MI Pneumonia CHF
DRCR.net (Protocol I)	854	12, 24, 36, 60	Endophthalmitis Tractional RD Elevated IOP	CHF Nasopharyngitis

*Safety data was only reported at 6-month intervals in READ-2.
CHF: congestive heart failure; DMO: diabetic macular oedema; IOP: intraocular pressure; MI: myocardial infarction; PE: pulmonary embolism; RCT: randomised clinical trial; RD: retinal detachment; SE: side effects.

RISE/RIDE

RISE/RIDE were two parallel, methodologically identical, Phase III, multicentre trials that compared the efficacy and safety of RBZ with sham at 2, 3, and 5-year intervals by randomising patients into three groups (0.3 mg RBZ, 0.5 mg RBZ, or sham injections). RBZ was generally safe over 5 years, with relatively low rates of ocular and non-ocular AE. Ocular SAE were uncommon but included vitreous haemorrhage, endophthalmitis, and traumatic cataract. Common ocular AE reported were similar to those in the aforementioned trials. Systemically, the most common SAE were MI and congestive heart failure, but these events were related to the disease rather than RBZ. Additionally, the incidence of Anti-Platelet Trialists' Collaboration (APTC) events at 24 months in all RBZ-treated patients was 2.4–8.8% (versus 4.9% [RISE] and 5.5% [RIDE] in sham). Despite this difference in incidence between RBZ and control, no associated increase in risk was found.[16-18]

DRCR.net (Protocol I)

This study was designed to compare both RBZ and intravitreal steroid treatment against laser over 5 years at four intervals (1, 2, 3, and 5 years). Of relevance, there were no associated differences in systemic or ocular events between RBZ-treated eyes and control over the 5-year period. Systemically, in terms of APTC events, lower rates were observed in the RBZ group than sham group. Locally, the 5-year safety data reported four cases of endophthalmitis in RBZ-treated patients, which was not significantly different from laser-treated patients.[19-22]

Bevacizumab

BVZ (Avastin™, Genentech; Roche™) is a recombinant, humanised, full-length monoclonal antibody that binds the same targets as RBZ, since both are derived from the same parent mouse antibody. Unlike RBZ, BVZ is licensed for the treatment of several different cancers only in the USA and the European Union (EU). Despite this, off-label usage is common in the management of wet AMD and DMO.[23]

DRCR.net

This trial was the first Phase II, multicentre RCT comparing intravitreal BVZ treatment against laser in 109 DMO patients for 24 weeks. Its small sample size and short follow-up time limit its suitability for drawing conclusions regarding BVZ's safety profile. Nonetheless, the safety data are still useful as an indication of some of the ocular and systemic AE or SAE that might be expected with BVZ treatment. In terms of ocular complications, a case of both endophthalmitis and transient elevated IOP was reported following BVZ. Additionally, although two cases of MI and three cases of hypertension occurred in the study group, the authors judged them to be unrelated to the study drug, because the involved patients had pre-existing comorbidities predisposing to susceptibility.[24]

BOLT

This study was a Phase II, single-centre RCT, designed to compare intravitreal BVZ and laser at 12 and 24-month endpoints among 80 patients. At 12 months, no cases of endophthalmitis or retinal detachment were reported with BVZ treatment, while most ocular AE were ocular surface disturbances related to the injection procedure, including eye pain, watering, and subconjunctival haemorrhage. Although evidence showed that BVZ was not associated with an increased risk for hypertension or ATE, it is worth noting that severe hypertension developed in one patient following BVZ treatment.[25] Findings reported after 24 months were largely similar, with notable occurrence of one case of ocular hypertension (2.7%) and two cases of MI (5.4%). Nonetheless, no trends in systemic safety events related to BVZ were observed.[26]

PACORES

The PACORES study was a multicentre retrospective study that offers 5-year safety data, the longest available, on BVZ treatment in 201 patients with DMO (296 study eyes). Similar low rates of ocular and non-ocular SAE or AE were reported, consistent with other studies. Notable ocular complications included tractional retinal detachment (8 eyes; 2.7%), glaucoma (6 eyes; 2.0%), uveitis (4 eyes; 1.4%), rhegmatogenous retinal detachment (3 eyes; 1.0%), vitreous haemorrhage (2 eyes; 0.7%), and endophthalmitis (1 eye; 0.3%), while non-ocular complications included stroke (10 eyes; 3.4%), and MI (5 eyes; 1.7%).[27]

Aflibercept

Aflibercept (Eylea™, Regeneron, Tarrytown, New York, USA; formerly known as VEGF trap-eye) is a high affinity, recombinant fusion protein capable of binding multiple signal proteins involved in angiogenesis, specifically all isoforms of circulating

VEGF-A, VEGF-B, and placental growth factor. It contains VEGF-binding domains of human VEGF receptors 1 and 2, fused to the Fc domain of human immunoglobulin-G1. Currently, aflibercept is licensed in the USA, EU, Japan, Switzerland, and Australia for several different vascular retinal diseases, including DMO.[28]

DA VINCI

DA VINCI was a multicentre, active-controlled RCT designed to compare four different aflibercept regimens to laser at 24 and 52-week intervals involving 221 patients. The most common ocular AE were 33 cases of conjunctival haemorrhage (18.9%), 17 cases of increased IOP (9.7%), and 15 cases of eye pain (8.6%). Two cases of endophthalmitis (1.1%), and one case of uveitis and retinal tear (0.6%) were reported with aflibercept treatment. However, no significant difference in the incidence of ocular SAE or AE was identified between aflibercept and laser. Notably, several cases of hypertension, MI, and cerebrovascular accident (CVA) occurred with aflibercept treatment, but were unlikely to be attributable to the study drug because all had significant underlying comorbidities that increased their cardiovascular risk.[29] After 52 weeks, seven aflibercept-treated patients died, but this was unrelated to the study drug or procedures.[30]

VISTA/VIVID

VISTA (USA) and VIVID (Europe, Japan, Australia) are similarly designed Phase III, multicentre, active-controlled RCT comparing two aflibercept regimens to laser. Generally, the 52 and 100-week results were very similar, with similar incidences of ocular and non-ocular SAE or AE between aflibercept and laser. No cases of endophthalmitis were reported, while several cases of intraocular inflammation occurred. Additionally, there was no obvious trend in non-ocular serious AE, especially ATE, despite some slight imbalances in the incidence of various events between aflibercept and laser.[31,32] Overall, the safety profile remained consistent after 148 weeks, with no new associated increased risk of any AE. Notably, three (0.5%) new cases of endophthalmitis occurred between 100 and 148 weeks in the original RBZ arms.[33]

Table 2: Possible ocular and systemic, adverse, and serious adverse events with anti-VEGF as occurred across the RCT.

Ocular	Systemic
Adverse events	
Eye pain	Nephropathy
Visual disturbances	Dyspnoea
Conjunctival haemorrhage	Angina
Transient IOP increase	CHF
Vitreous floaters	
Foreign body sensation	
Tearing	
Serious adverse events	
Endophthalmitis	Death
Uveitis	MI
Retinal detachment/tear	CVA/TIA
Retinal/vitreous haemorrhage	Haemorrhage
Cataract	Hypertension
Macular ischaemia	Ischaemia
IOP hypertension	
Glaucoma	

CHF: congestive heart failure; CVA: cerebrovascular accident; IOP: intraocular pressure; MI: myocardial infarction; RCT: randomised clinical trial; TIA: transient ischaemic attack; VEGF: vascular endothelial growth factor.

Pegaptanib

Pegaptanib sodium (Macugen™, Eyetech™, New York City, New York, USA) is a ribonucleic acid aptamer licensed for wet AMD only in the USA and Europe.[34] It specifically binds to the $VEGF_{165}$ isoform to reduce ocular angiogenesis. Two main trials that studied pegaptanib in DMO patients produced results suggesting there was no significant difference in the incidence of AE between treatment and sham. Most ocular AE that occurred were mild-to-moderate, injection-procedure related, and expected. Notably, a case of endophthalmitis (0.8% per patient) was reported by Cunningham et al.,[35] 25 cases of increased IOP (17.4%) were reported by Sultan et al.,[36] and no retinal detachment was reported. Systemically, no evidence of increased risk of ATE related to pegaptanib was noted, despite incidences of SAE like CVA/coronary artery disease/angina pectoris (1.40% each) and hypertension (0.07%).[36]

COMPARISON OF ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR AGENTS

DRCR.net (Protocol T) was the first and only RCT that published results directly comparing more than two different anti-VEGF agents, allowing us to understand their relative safety. This multicentre RCT was carried out over 2 years and randomised patients into three groups (0.3 mg RBZ, 1.25 mg BVZ, 2 mg aflibercept). Incidence of all AE over 2 years was similar across all groups except for APTC events, with incidence of 12%, 8%, and 5% in RBZ, BVZ, and aflibercept, respectively. Pairwise comparisons showed significant differences, which disappeared after accounting for potential baseline confounders, between RBZ and aflibercept only. Hence, caution should be taken to observe for APTC events when using RBZ.[37]

DISCUSSION

The shift in treatment paradigm from laser to intravitreal anti-VEGF as first-line therapy in DMO makes it paramount that they are safe with minimal side effects. Concerns over the safety profile of intravitreal use are understandable, considering how systemic usage is associated with an increased risk of ATE.[3] Hence, it is essential that sufficient evidence shows that the risk of ATE is not increased with intravitreal anti-VEGF.

Overall, intravitreal anti-VEGF agents in DMO have been shown to be generally well-tolerated and safe,[38] with a safety profile similar to results from trials evaluating their usage in other retinal diseases. No significant trend relating to the occurrence of ocular and non-ocular SAE or AE was specifically identified for any anti-VEGF agents. However, the caveat lies in that these trials are not powered to demonstrate safety, and more large-scale safety trials are needed before being certain about its safety. Table 2 shows a short summary of possible AE. Notably, most ocular AE are mild and injection-procedure related, making it possible to reduce occurrences by taking extra precaution during the procedure using aseptic technique for preparation and injection. This is particularly relevant to off-label BVZ use, as the need for individual repackaging/compounding makes sterile preparation especially crucial to avoid foreign body deposition, as described in a case report.[39] Although systemic AE were reported, most are likely attributable to the patient's pre-existing comorbidities. A meta-analysis by Avery et al.[3] interestingly suggests that prolonged treatment with anti-VEGF might increase risk of CVA, vascular, and non-vascular death. Hence, precaution might be warranted when treating patients with significant cardiac and stroke history, or those with persistent DMO requiring repeated intravitreal anti-VEGF injections.

A Cochrane review also concluded that anti-VEGF agents are generally safe, apart from in high-risk patients, in whom their use still requires more research.[2] Despite this, some differences do exist between individual agents as established in Protocol T, with results suggesting that aflibercept is relatively safer compared to the other two agents.[37,40] However, this is not reflected in real life due to cost concerns. According to the 2015 American Society of Retina Specialists (ASRS) Preferences and Trends survey, BVZ is the most commonly used intravitreal anti-VEGF agent in the USA. Huge price differences exist between BVZ, RBZ, and aflibercept ($60, $1,170, and $1,850 per dose, respectively).[41-44] Considering that diabetes maculopathy is a chronic disease and treatment of DMO requires multiple repeated injections, these cost differences can be significant. With raising medical costs and limited healthcare budgets, there is pressure on doctors to choose the most cost-effective option, especially in public-funded health systems. Several independent reviews have agreed that BVZ is indeed the most cost-effective

option, even after using an analytical model to account for the raised concerns of increased risk of endophthalmitis or vascular complications.[41]

CONCLUSION

This review has consistently identified results across pivotal studies to support a favourable long-term safety profile among intravitreal anti-VEGF, with no significant increased risk of ATE. Though we agree that more large-scale safety trials are needed to be conclusive, doctors can still recommend anti-VEGF treatment to most patients, as clinical benefits of visual improvement and resolution of macular oedema outweigh the possible ocular risks. Notable cases where greater consideration should be given before starting anti-VEGF therapy include patients with significant comorbidities that increase their overall cardiovascular risk, as well as chronic persistent DMO. Lastly, besides considering the clinical evidence of efficacy and safety, cost practicality can be a huge influencing factor when choosing treatment in practice.

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