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DIABETES

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INSIDE

Review of

EASD 2018

Berlin, Germany

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"The 5-day celebration of the advances made to combat all forms of diabetes proved to be a truly spectacular event."

Spencer Gore, CEO

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Aims and Scope

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

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

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

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

EMJ also publishes 16 therapeutic area journals, which provide concise coverage of salient developments at the leading European congresses. These are published annually, approximately 6 weeks after the relevant congress. Further details can be found on our website: www.europeanmedical-journal.com

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EMJ is supported by various levels of expertise:

- Guidance from an Editorial Board consisting of leading authorities from a wide variety of disciplines.
- Invited contributors are recognised authorities from their respective fields.
- Peer review, which is conducted by EMJ's Peer Review Panel as well as other experts appointed due to their knowledge of a specific topic.
- An experienced team of editors and technical editors.

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This Publication

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Front cover and contents photograph: Berlin, Germany, home of the EASD 2018. © Patryk Kośmider / 123rf.com

EMJ Diabet.

EMJ Respiratory 6.1

EMJ Respiratory 6.1 is sure to showcase fascinating content that will spark countless hours of intense debate and discussion, no doubt leading to further developments...

VIEW ALL JOURNALS ←

Welcome

A very warm welcome to the hotly anticipated 6th edition of *EMJ Diabetes*, a publication dedicated to bringing you the very latest developments and advances from the world of diabetology. As ever, this eJournal contains a selection of high-quality, peer-reviewed articles, the latest developments from the 54th European Association for the Study of Diabetes (EASD) Congress, and fascinating insights from members of the *EMJ Diabetes* Editorial Board.

This year, the Annual Meeting of the EASD, Europe's largest conference for diabetologists, moved to the German capital, Berlin. The 5-day celebration of the advances made to combat all forms of diabetes proved to be a truly spectacular event. With >1,200 abstracts and posters on offer, a selection of which can be found in the Abstract Review section of this journal, there was something for every member of the diabetes community to enjoy and debate. Review the details in full in the comprehensive Congress Review.

Alongside this, the EMJ team has compiled a selection of fascinating articles from leading experts in the field of diabetes. The Editor's Pick for this edition, penned by Saisho, outlines the need for a shift from the current glucose-focussed concept to a more beta cell-focussed understanding of diabetes, a treatment change that could revolutionise the field. Another paper of note is that by Hamasaki. With the rise of 'Pokemon Go' triggering an increase in user exercise and activity time, Hamasaki reviews the growth of wearable technology and its impact on diabetes care and management.

The articles within *EMJ Diabetes 6.1* are complemented perfectly by thought-provoking interviews with two members of the Editorial Board. Both Dr Gijs Goossens and Prof Anne Phillips provide insights into their careers, current projects, hopes for the future of the field, and advice for the next generation of diabetologists.

I am immensely proud of the publication that we have produced. I would like to pass my thanks on to everyone that has contributed to this one-of-a-kind eJournal: our fantastic Editorial Board, dedicated authors, brilliant peer review panel, and, of course, all of the members of the EMJ family. I am sure you will find this edition as fascinating as we do.

Best wishes,

Spencer Gore

Chief Executive Officer, European Medical Group

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Foreword

Dear colleagues and friends,

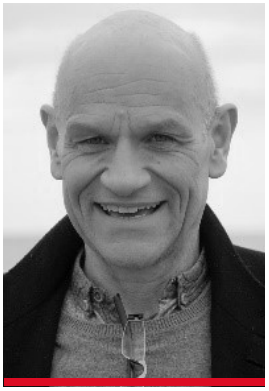
Welcome to the 2018 edition of *EMJ Diabetes*. This issue contains a comprehensive round-up of the European Association for the Study of Diabetes (EASD) Annual Meeting 2018, a selection of fascinating Editorial Board interviews, and a variety of compelling peer-reviewed articles.

The 54th EASD Annual Meeting, which took place in Berlin, Germany, welcomed attendees from around the world who gathered to share their knowledge and research, and hold thought-provoking discussions. This prestigious congress boasted an impressive programme, with >1,200 abstracts chosen for presentation, some of which are summarised within the Abstract Review segment. Complementing the Congress Review section, 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 diabetes field, and where diabetes medicine is headed in the coming years.

As always, *EMJ Diabetes* contains a range of high-quality peer-reviewed articles to keep you at the forefront of diabetes research. The Editor's Pick for this eJournal, written by Saisho, challenges our glucose-centric understanding of diabetes, which is a central focus not only of medics and health professionals but also of diabetes patients' self-care efforts and frequently of family carers. Earlier detection of metabolic disease processes combined with a focus on the pathophysiology of the pancreatic beta cells will create opportunities, so Saisho argues, to develop a more comprehensive understanding of diabetes, hopefully with concomitant benefits for patients and carers. Other fascinating articles of interest include a commentary on the efficacy of wearable devices to promote physical activity in diabetes patients and an evaluation of the use of proprotein convertase subtilisin/kexin type 9 inhibitors for the treatment of hypercholestrolaemia.

Finally, I would like to thank you all for your contributions and efforts to make *EMJ Diabetes 6.1* such a great success. I hope you find this a compelling and enjoyable read, sparking informative discussion and providing direction for your everyday practices.

Best wishes,



Prof Jörg Huber
University of Brighton, UK

Abbott

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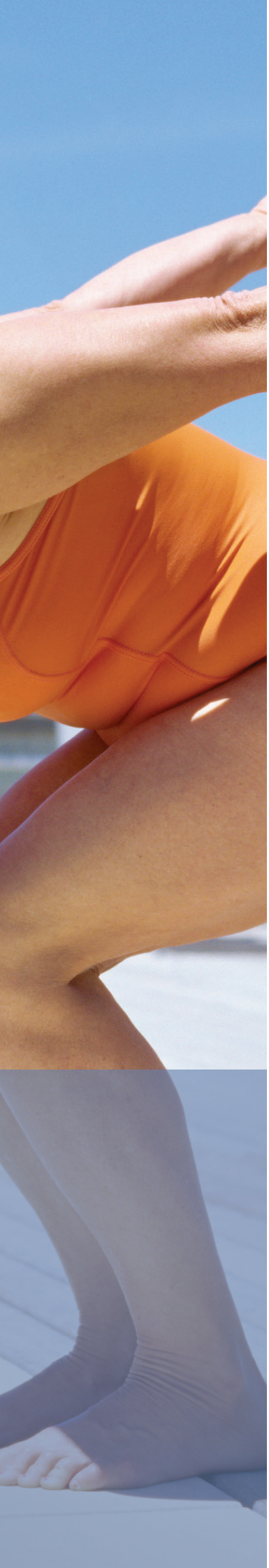

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RESULTS THAT SPEAK FOR THEMSELVES[1]

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1. Patzer KH, Schnell O et al. Journal of Diabetes Science and Technology 2018

Congress Review

Review of the 54th Annual Meeting of the European Association for the Study of Diabetes (EASD)

Location: Berlin, Germany – Messe Berlin

Date: 01.10.18–05.10.18

Citation: EMJ Diabet. 2018;6[1]:12-25. Congress Review.

Held in the beautiful and culturally rich city of Berlin, Germany, this year's European Association for the Study of Diabetes (EASD) congress was set to be a ground-breaking success. With an exceptional scientific programme boasting numerous oral and poster presentations, a vast array of individual lectures by distinguished scientists and Prize Lecturers, poster sessions, and 1,218 abstracts chosen for presentation, there really was something for professionals with all levels of diabetes knowledge over the 5-day event.

The EASD Annual Meeting is the largest international annual congress of diabetes research, positioning the event at the forefront of the field. In line with the EASD's mission to promote excellence in diabetes care through research and education, EASD encourages co-operation and collaboration between industry moguls and research institutions by conducting and funding ground-breaking diabetes research. Offering the perfect platform to present results, EASD welcomed thousands of attendees to its 54th Congress from across the globe to share and build upon their own scientific and medical knowledge.

Following the society's mission to promote diabetes care through education, EASD 2018 saw the launch of the society's new e-Learning programme, which will further expand and develop its postgraduate education activities. The new learning environment will allow students to direct their own learning and takes into consideration demands from current students for active learning, assessments, and feedback. The first three modules of the e-Learning programme were released during the EASD congress and were followed by live demonstrations, giving the audience a chance to test the e-Learning platform and provide their initial feedback.

In the Langerhans hall, Prof Juleen R. Zierath, EASD President, took to the stage to welcome all attendees during the opening ceremony. Prof Zierath swiftly passed

the stage to Prof Joachim Spranger, the Chairman of the Local Organising Committee for EASD 2018. Prof Spranger began by highlighting the fantastic and rapid changes in diabetes care over recent years and reflected on the developments in novel technology, including continuous glucose measurements and nearly closed loop insulin pump systems for Type 1 diabetes mellitus. He also remarked on novel treatment approaches, such as SGLT2 inhibitors, and their impact on Type 2 diabetes mellitus patients, commenting on how these approaches have translated into fewer complications and lower mortality rates.

"In line with the EASD's mission to promote excellence in diabetes care through research and education, EASD encourages co-operation and collaboration between industry moguls and research institutions by conducting and funding ground-breaking diabetes research."

Prof Spranger went on to emphasise his passion for and his belief that focussing on clinically relevant and patient-orientated outcomes should be standard practice before novel treatments can be considered. This notion was considered novel in recent years but will act as a cornerstone for future research to enable the most effective and worthwhile treatments to reach patients.

As well as looking to the future of diabetes research, EASD 2018 also evaluated current treatments, technologies, and care, along with outstanding scientific and medical research. A selection of the most revolutionary diabetes news presented at EASD is compiled in this Congress Review and offers all those who attended the event a refresher; for those who were unable to make it to Berlin, now is your opportunity to experience the hive of information released during the congress.

Looking to next year, EASD will grace the stage of Fira de Barcelona, Barcelona, Spain, from 17th–20th September 2019 for the society's 55th Annual Meeting. Here at EMJ, we are already eagerly preparing for this much-anticipated event and cannot wait to bring you our independent review of EASD 2019.

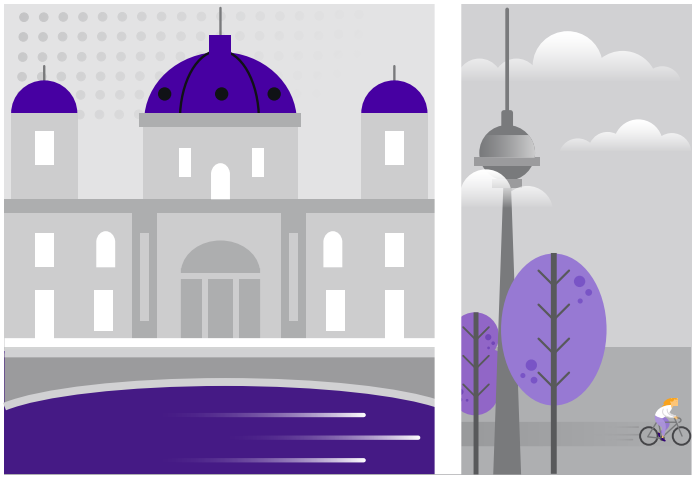
Updated Guidelines for the Management of Hyperglycaemia

IF you were wondering how best to manage hyperglycaemia in patients with Type 2 diabetes mellitus (T2DM), the recent EASD congress has provided answers, as reported in a EASD press release dated 5th October 2018. With the field of diabetes constantly evolving, there have been a number of trials conducted that have expanded the current evidence base in regard to the management of hyperglycaemia in patients with T2DM. Therefore, the EASD and the American Diabetes Association (ADA) conducted a thorough review of the most recent evidence; this review led to an update to the 2015 guidance. The new 2018 EASD–ADA consensus guidelines on how to manage hyperglycaemia in patients with T2DM were published during the EASD congress.

"Patient-centred decision-making and support and consistent efforts to improve diet and exercise remain the foundation of all glycaemic management."

Some of the details contained in these new recommendations can be seen below:

- All individuals with T2DM should be encouraged to increase their physical activity, since an increase in physical activity has been found to improve glycaemic control. Furthermore, any diabetic patients who are overweight or obese should be informed of the health benefits attributable to weight loss. Following this, these patients should also be encouraged to initiate an intensive lifestyle management programme.
- The delivery of patient-centric care should be prioritised by healthcare providers and healthcare systems.
- The recommended first-line therapy for the vast majority of patients with T2DM is metformin. If selecting a medication to add to metformin therapy, there are a number of factors that should be considered, including patient preference and the presence of comorbidities, such as heart failure, kidney disease, and cardiovascular disease.
- A specific priority when determining the choice of glucose-lowering medication should be how to maximise patient medication adherence.



While these guidelines now represent the most up-to-date recommendations for managing hyperglycaemia in patients with T2DM, there are still outstanding research questions, such as what the most efficacious combination of glucose-lowering therapies is. The EASD–ADA panel concluded: "Patient-centred decision-making and support and consistent efforts to improve diet and exercise remain the foundation of all glycaemic management. Initial use of metformin followed by addition of glucose-lowering medications based on patient comorbidities and concerns is recommended as we await answers to the many questions that remain."

Diabetes Diagnosis Up To 20 Years Before Disease Onset

TYPE 2 DIABETES MELLITUS (T2DM) is hallmarked by a number of diagnostic markers, including elevated fasting glucose levels, higher BMI, and impaired insulin sensitivity. A recent Japanese study, reported in a EADV press release dated 5th October 2018, investigated these biomarkers and suggested that T2DM could be predicted 10 years before diagnosis was confirmed.

In total, 27,392 non-diabetic individuals were included in the study that sought to monitor their blood glucose, BMI, and insulin sensitivity until the diagnosis of T2DM or prediabetes, or until 2016, depending on which endpoint came first. Over the course of the study, 1,061 new cases of diabetes were confirmed. Analysing the key biomarkers, the research team identified that all three were elevated over 10 years before T2DM diagnosis was confirmed. For example, the average fasting glucose levels 10 years before diagnosis for patients who developed T2DM was 101.5 mg/dL, compared with 94.5 mg/dL for those who did not develop T2DM. By 1 year before diagnosis, patients who developed T2DM had a mean fasting glucose of 110.0 mg/dL, while those who did not develop T2DM had a mean of 94.0 mg/dL.

"As the vast majority of people with T2DM go through the stage of prediabetes, our findings suggest that elevated metabolic markers for diabetes are detectable >20 years before its diagnosis."

The results of this observational trial are limited by a number of variables, but the data remain of great importance. With the number of patients diagnosed with T2DM continuing to increase each year, early identification of those at greatest risk would allow for the implementation of intervention strategies before the disease takes hold. Study lead Dr Hiroyuki Sagesaka, Aizawa Hospital, Matsumoto, Japan, concluded: "As the vast majority of people with T2DM go through the stage of prediabetes, our findings suggest that elevated metabolic markers for diabetes are detectable >20 years before its diagnosis."

Lorcaserin Reduces the Risk of Developing Diabetes and Helps Control Blood Sugar

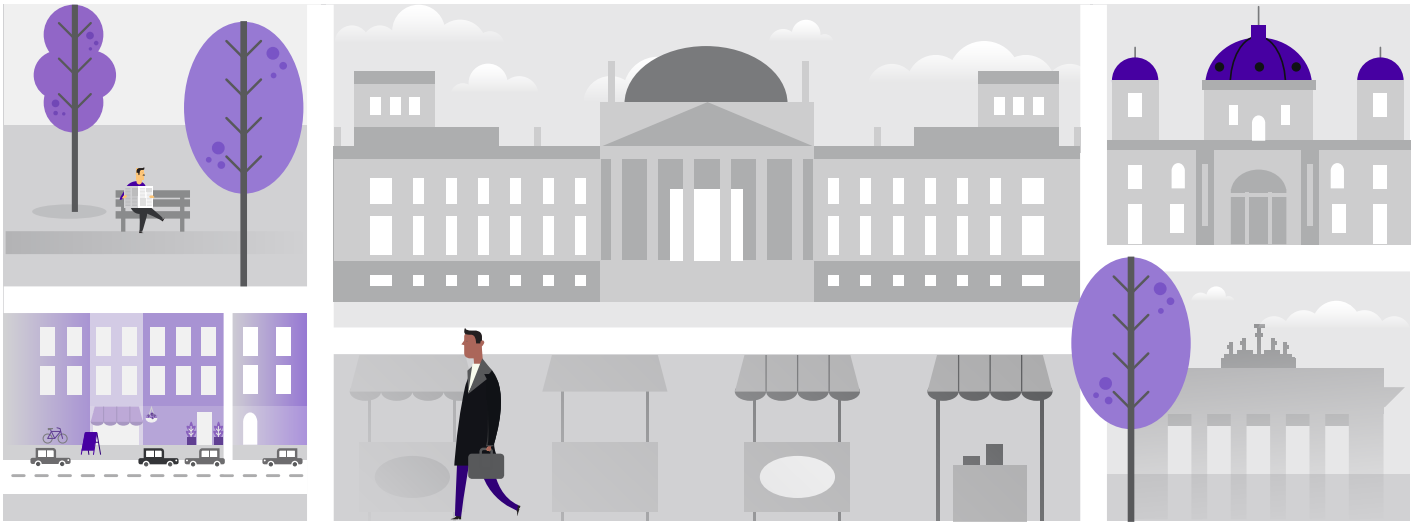
LORCASERIN, a known appetite suppressant, is effective at reducing the risk of developing diabetes and can aid high blood sugar remission in obese and overweight patients at high risk of developing atherosclerotic vascular disease, according to a EASD press release dated 4th October 2018.

The American study included 12,000 patients followed-up for 3.3 years and randomised to receive either lorcaserin (10 mg twice daily) or placebo. The authors of the study concluded: "Lorcaserin is effective for weight loss, and in contrast to many other obesity medications to date, has proven safety for major adverse cardiovascular events, including CV death, myocardial infarction, or stroke."

The CAMELLIA-TIMI 61 study results showed that after 1 year, a net weight loss of 2.6 kg, 2.8 kg, and 3.3 kg was achieved by patients who received lorcaserin with baseline diabetes (n=6,816, 57%), prediabetes (n=3,991, 33%), and normoglycaemia (n=1,193, 10%), respectively. The results also showed that of the patients who had prediabetes at baseline and who received lorcaserin, 8.5% had a risk of incident diabetes, compared to 10.3% of those who were not treated with lorcaserin.

"Lorcaserin is effective for weight loss, and in contrast to many other obesity medications to date, has proven safety for major adverse cardiovascular events, including CV death, myocardial infarction, or stroke."

Lorcaserin was also found to increase the rate of achieving normoglycaemia in patients with prediabetes and significantly increased the rate of remission of hyperglycaemia in patients with diabetes by 21%. In addition, lorcaserin reduced the risk of microvascular events by 21% in patients with diabetes and reduced HbA1c levels by 0.3% compared with placebo at 1 year from a mean baseline of 7.0%.



The authors of the study commented on the importance of the CAMELLIA-TIMI 61 results: "Now, in addition to proven persistent weight loss efficacy with extended duration use, we report that when added to lifestyle interventions, lorcaserin significantly reduced the incidence of diabetes, tended to increase achievement of normoglycaemia in patients with prediabetes, increased the rate of remission of hyperglycaemia in patients with diabetes, and reduced the risk of diabetic microvascular complications. Taken together, these findings reinforce the notion that modest, durable weight loss can improve cardiometabolic health and supports the role of lorcaserin as an adjunctive therapy in chronic weight management and metabolic health."

Common Misdiagnosis of Diabetes Patients Over 30 Years of Age

PATIENTS diagnosed with Type 2 diabetes mellitus (T2DM) after the age of 30 years are often misdiagnosed and, in fact, have Type 1 diabetes mellitus (T1DM), suggests a new study by researchers at the University of Exeter, Exeter, UK, and reported in a EASD press release dated 5th October 2018.

The study analysed 583 patients with insulin-treated diabetes who had been diagnosed after the age of 30 years, comparing their disease characteristics to those of participants who still produced some insulin and 220 subjects with severe insulin deficiency who had been diagnosed before 30 years of age. The results showed that 21% of the insulin-treated diabetes cohort diagnosed after 30 years had severe insulin deficiency and, thus, T1DM. Of this group, 39% did not receive insulin when first diagnosed and 46% had self-reported T2DM.

"Clinicians should be aware that the majority of patients needing insulin within 3 years of diagnosis will have T1DM, even if they were initially thought to have T2DM and did not need insulin at diagnosis."

Of those patients who became dependent on insulin within 3 years, 44% developed a severe insulin deficiency, and this group was found to have similar clinical, biochemical, and genetic characteristics to those diagnosed with the condition before the age of 30 years. On the other hand, the group that retained some insulin production had lower T1DM genetic risk scores, antibody positivity, and higher BMI. The average age of patients for whom insulin treatment was delayed was higher (48 years) compared to those treated with insulin immediately (41 years); additionally, their rate of self-reporting T1DM was much lower (50% versus 96%). Additionally, oral hyperglycaemic drugs were more commonly prescribed for the delayed diagnosis group (29% versus 7%).

These data revealed the clinical similarities between T1DM diagnosed before and after 30 years of age, thus highlighting the importance of correctly diagnosing the condition as early

as possible. "Clinicians should be aware that the majority of patients needing insulin within 3 years of diagnosis will have T1DM, even if they were initially thought to have T2DM and did not need insulin at diagnosis," highlighted Dr Nick Thomas, University of Exeter.

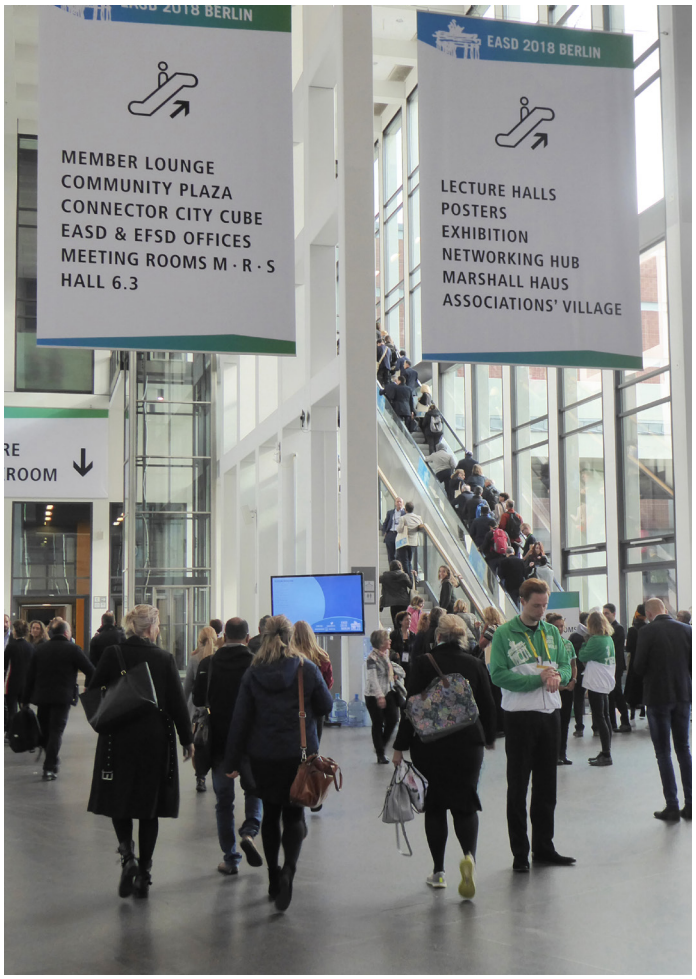
Low-Calorie Sweeteners Negatively Impact the Gut Microbiome

CONSUMING low-calorie sweeteners (LCS) can greatly impact the gut bacteria, suggests new research from the University of Adelaide and Flinders University, Adelaide, Australia and reported in a EASD press release dated 5th October 2018. Previous studies have noted the increased risk of developing Type 2 diabetes mellitus (T2DM) following a high intake of drinks containing LCS, and the authors themselves had recently demonstrated that 2 weeks of consuming a diet augmented with LCS was enough to induce a clinically relevant increase in the body's response to glucose; however, the extent to which gut dysbiosis played a role in this process had yet to be identified.

To explore this topic, the study enrolled 29 non-diabetic subjects with an average age of 30 years and an average BMI of 24 kg/m^2. These subjects were then randomised to placebo (n=15) or an LCS combination (92 mg sucrose and 52 mg acesulfame-K) (n=14) that mirrored the consumption of 1.5 L of diet beverage per day, delivered in the form of capsules taken 3 times per day for 2 weeks.

"Our findings support the concept that such sweeteners worsen blood sugar control in healthy subjects by disrupting the regulation of glucose uptake and disposal, as well as from changes in the balance of gut bacteria."

Stool samples were taken from all subjects before and after the treatment regimen, with results showing a greater variation of microbes present in the LCS-treated group, including a decrease in the good-health-associated bacterium *Eubacterium cylindroides*. Eleven forms of opportunistic gut bacteria were seen to increase, while the number of beneficial bacteria that aid the fermentation of food decreased. "The observed decrease in fermentative bacteria populations and changes in the pathways used by bacteria to harvest energy predicted a deterioration in the body's ability to regulate glucose," explained the authors.



Berliner Dom

Landmark in Berlin, Germany,
home of EASD 2018

This change to intestinal flora can have a direct impact on the metabolism of sucrose and glucose; for example, a decrease in *Butyrivibrio* bacteria was linked to a drop in glucagon-like peptide 1, a hormone that contributes to the control of blood sugar levels. These findings highlight the impact of LCS consumption for metabolism, as well as shedding light on the complex interplay of the gut microbiome and the body's metabolism. "Our findings support the concept that such sweeteners worsen blood sugar control in healthy subjects by disrupting the regulation of glucose uptake and disposal, as well as from changes in the balance of gut bacteria," concluded the authors.

Results of the CARMELINA® Trial Presented

THE SAFETY of linagliptin in regard to cardiovascular and kidney effects has been shown to be approximately equivalent to placebo. More specifically, the results of the CARMELINA® clinical trial, which was designed to examine the effects of linagliptin on cardiovascular and kidney safety in adult patients with Type 2 diabetes mellitus (T2DM) who had a high risk of developing heart and/or kidney disease, were presented at the EASD Annual Meeting 2018 and reported in a EASD press release dated 4th October 2018.

"The trial confirmed that linagliptin can be used with confidence in this patient population."

The trial's primary endpoint was the time to first occurrence of the three-point major adverse cardiovascular event (3P-MACE); the three points are cardiovascular death, non-fatal stroke, and non-fatal myocardial infarction. The key secondary endpoint was a composite: time to first occurrence of death due to kidney disease, sustained end-stage kidney disease, or a sustained decrease in estimated glomerular filtration rate by ≥40% from baseline compared with placebo.

The trial included 6,979 patients with T2DM who were split into two groups. While both groups received standard care, one group was additionally treated with a once daily dose of linagliptin 5 mg and the other group received placebo. It was found that the cardiovascular events that composed the primary endpoint occurred in 12.4% of the linagliptin group and 12.1% in the placebo group. Furthermore, the key secondary endpoint referring to kidney safety was met in 9.4% of the linagliptin group and 8.8% in the placebo group. Speaking about the results of the trial, Prof Bernard Zinman, Department of Medicine, University of Toronto, Toronto, Canada, one of the study's authors, noted: "CARMELINA adds important new evidence for T2DM patients at high risk of heart and/or kidney disease, a population that has been under-represented in other cardiovascular outcome trials, but whom we see in our daily practice. The trial confirmed that linagliptin can be used with confidence in this patient population."

Two Giant Leaps Forward for Type 2 Diabetes Mellitus Management

EXCITEMENT is widespread in response to the news of multiple new drugs progressing through clinical trials and exhibiting very promising results implicating Type 2 diabetes mellitus (T2DM) care and management, adding to the armoury doctors have at their disposal to combat the disease.

"Complicated treatment regimens that require multiple injections at different times of day can be difficult for patients to adhere to, potentially leading to poor blood sugar control," stated lead investigator Dr Athena Philis-Tsimikas, Scripps Whittier Diabetes Institute, La Jolla, California, USA, when discussing the current management of T2DM. However, the results of a new trial, presented at the EASD Annual Meeting on 2nd October 2018, investigating the efficacy of a once-daily T2DM drug, Ryzodeg® (Novo Nordisk, Bagsværd, Denmark), could revolutionise disease management.

In the 38-week, international, open-label, randomised, treat-to-target Step by Step trial, the safety and efficacy of Ryzodeg was compared with the current standard therapeutic agent, insulin glargine U100 plus insulin aspart, in 532 patients from seven different countries. Ryzodeg is a combination of insulin degludec and insulin aspart (IDegAsp).

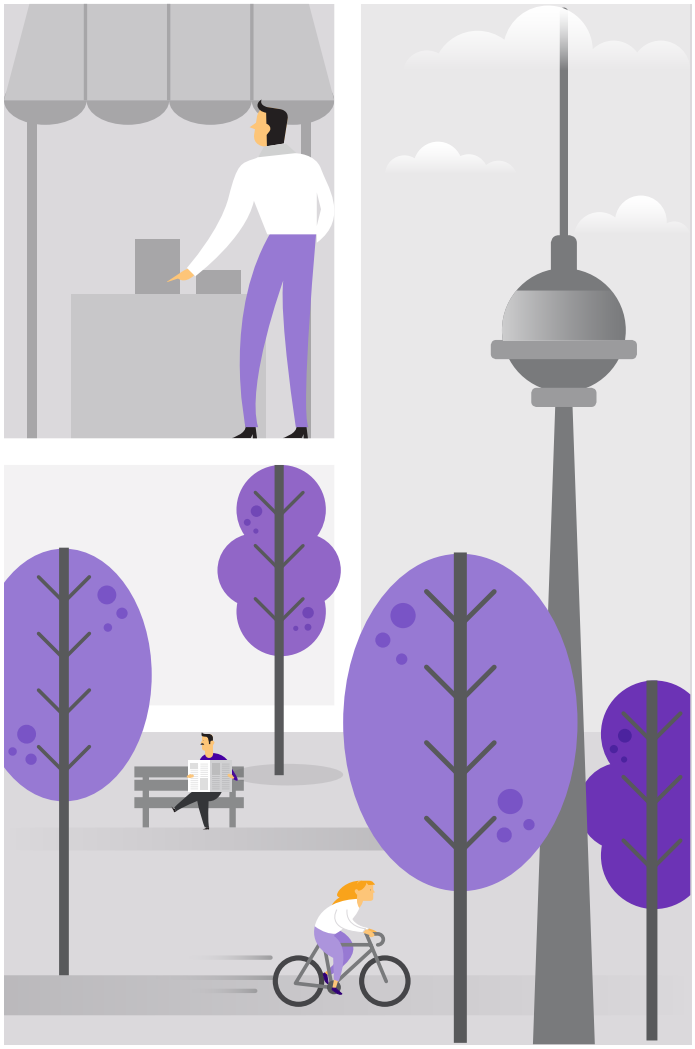
"These trial results show that once-daily IDegAsp [Ryzodeg] can offer people with T2DM a much simpler option with fewer injections compared with insulin glargine U100 plus insulin aspart, to achieve effective blood sugar control."

At the 26-week timepoint, patients in the Ryzodeg arm had received 50% fewer injections and significantly fewer daily insulin units (12%). Furthermore, beyond the 26-week timepoint, Ryzodeg demonstrated a statistically significant 45% lower rate of nocturnal severe or blood glucose-confirmed symptomatic hypoglycaemic episodes compared with insulin glargine U100 plus insulin aspart.

"These trial results show that once-daily IDegAsp [Ryzodeg] can offer people with T2DM a much simpler option with fewer injections compared with insulin glargine U100 plus insulin aspart, to achieve effective blood sugar control," concluded Dr Philis-Tsimikas. The results of the trial offer an exciting new avenue for minimally invasive T2DM management; however, further testing of Ryzodeg is warranted before it replaces current therapeutic standards.

Additionally, the results of a Phase IIb study investigating the effects of a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP)-1 receptor agonist (RA) on blood glucose and weight in T2DM patients were reported at the EASD Annual Meeting on 4th October 2018, showing great promise for future use in T2DM patients.

Aiming to build on the previous success obtained through the use of GLP-1 RA, the 26-week, randomised, placebo-controlled Phase IIb study analysed the effects of four once-weekly doses (1, 5, 10, and 15 mg) of the dual GIP/GLP-1 RA compared with the effects of an active GLP-1 RA, dulaglutide (once-weekly 1.5 mg), and placebo in 300 T2DM patients.



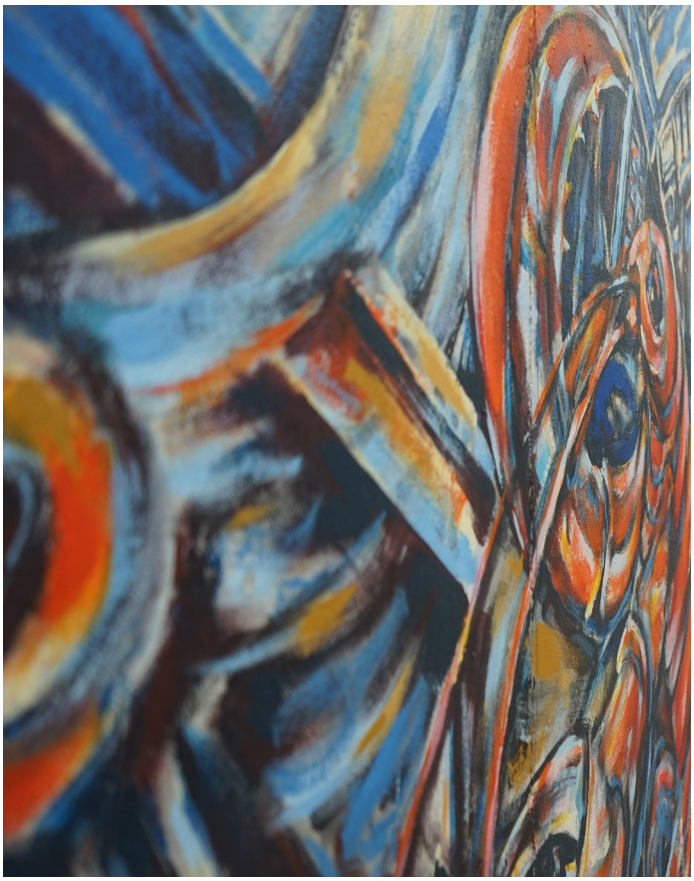
The trial gave rise to a clinically significant decrease in the Hb1Ac levels of patients in the GIP/GLP-1 RA arm, ranging from a 1.6% decrease in those receiving a 5 mg dose to a 2.4% reduction seen in the 15 mg dose group. In comparison, patients administered dulaglutide exhibited a 1.1% reduction in Hb1Ac levels, and in placebo patients a 0.1% reduction was noted. Furthermore, a beneficial effect of GIP/GLP-1 RA on patient weight loss was noted. Average weight loss in the GIP/GLP-1 RA arm ranged from 4.8 kg (5 mg group) to 11.3 kg (15 mg group), compared with 2.7 kg in the dulaglutide arm and 0.4 kg in the placebo group.

The safety profile of GIP/GLP-1 RA was similar to the currently available GLP-1 RA. The most commonly reported adverse effects were gastrointestinal and were dose-dependent; for example, 20% of the 5 mg patients reported nausea, while it was reported in 40% of the 15 mg patients.

These results must be interpreted with caution, considering the large disparity in weekly drug doses between those receiving dulaglutide and GIP/GLP-1 RA. However, with future larger Phase III studies planned in 2019, the results of this novel GIP/GLP-1 RA could mark another revolutionary step in diabetes management. Dr Juan Frias, National Research Institute, Los Angeles, California, USA stated: "These Phase IIb clinical trial results for GIP/GLP-1 RA are unprecedented, and the impressive blood glucose and weight reductions seen may lead to a new treatment option for people with T2DM."

In this age of new and revolutionary medicines, the advancements made with the degludec analogue, Ryzodeg, and the novel GIP/GLP-1 RA offer new strategies for T2DM management, tackling the disease on multiple fronts.

"These Phase IIb clinical trial results for GIP/GLP-1 RA are unprecedented, and the impressive blood glucose and weight reductions seen may lead to a new treatment option for people with T2DM."



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Interviews

How do the experts approach diabetes care and research? Find out in the following interviews with two of the renowned Editorial Board members of *EMJ Diabetes*

Featuring: Dr Gijs Goossens and Prof Anne Phillips

Dr Gijs Goossens @LinkedIn

Maastricht University Medical Centre, Netherlands

You have always been quite a sporty person, enjoying playing football, running, and cycling. Did your passion for exercise play a part in your career choice?

Since a very young age I have been quite active, playing football with friends and at the sports club. In fact, I grew up in a physically active family. My father enjoyed cycling and badminton, my mother played volleyball and went for a run on a regular basis, and my older sister played hockey. I think it is very important that young children are stimulated to play outside and join sports clubs. This will provide an important basis for healthy behaviour in later life. Nowadays, I enjoy running and cycling, and I do resistance exercise training during the winter months.

I find it is rather surprising that many scientists and clinicians working in the field of obesity and diabetes do not engage in regular physical exercise. This perhaps illustrates that it can be very difficult to implement physical exercise into our daily routines. I became more and more interested in health and disease in general during my time at secondary school, so for me it was a logical next step to move to Maastricht, Netherlands, to study health sciences, specialising in movement sciences; indeed, this was partly because of my passion for exercise. During this period, I decided that my future career should be in the area of chronic cardiometabolic diseases, rather than elite sports.

Who has been your greatest inspiration throughout your career and why?

It is difficult for me to mention just one person, I learned a lot from many people over the years. During my first internship at the Department of Human Biology, Maastricht University, Maastricht, I was involved in a project that investigated the importance of intramyocellular lipids in glucose homeostasis in humans. My role in this study was to perform many oral glucose tolerance tests, conduct maximal aerobic exercise capacity

tests, and quantify the amount of lipids in the muscle cells using non-invasive proton magnetic resonance spectroscopy. Prof Ellen Blaak, my fellow *EMJ Diabetes* Editorial Board member, who later invited me to complete a PhD in the same department, supervised this project, which fuelled my interest in metabolic research. Before the start of my PhD, I first wanted to acquire more research experience abroad. I was fortunate enough to work together with two excellent scientists, Prof Keith Frayn and Prof Fredrik Karpe from the Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK, for about 6 months. I really had a great time in Oxford and was inspired by the innovative methodology used and the many discussions I had with leading scientists in the field. So, when I came back to Maastricht, I was very motivated to continue with metabolic *in vivo* studies in humans during my PhD project, supervised by Prof Marleen van Baak, Prof Ellen Blaak, and Prof Wim Saris. These people have been great mentors, from whom I learned a lot about scientific research in many different ways. Furthermore, I very much appreciate that they gave me a lot of freedom to develop my own research ideas, which I could also bring into practice.

A lot of your research has focussed on the underlying mechanisms surrounding obesity and Type 2 diabetes mellitus. What question or challenge were you setting out to address when you started this work?

The objective of my PhD project was to investigate the role of the renin-angiotensin system (RAS) in the metabolic and haemodynamic impairments in obese humans. More specifically, we performed several studies to investigate the effects of angiotensin II, the main effector molecule of the RAS, on adipose tissue and skeletal muscle lipolysis and blood flow, using state-of-the-art methodology. In addition, we examined the effects of pharmacological interference with the RAS on substrate utilisation and insulin sensitivity in obese individuals. During these years, I became even more fascinated by the adipose tissue, which is a complex, metabolically active endocrine organ that exerts marked effects on whole-body physiology. In follow-up studies that I performed as a post-doctoral fellow, we demonstrated that long-term inhibition of the RAS, using the angiotensin II type 1 receptor blocker valsartan, improves both insulin sensitivity and beta cell function in humans. Interestingly, this seemed to be mediated, at least partly, via effects on adipose tissue, since valsartan treatment decreased fat cell size, reduced macrophage infiltration, and increased adipose tissue blood flow. Thereafter, I continued my work with a focus on adipose tissue biology.

"I believe that unexpected findings are the most interesting, and that scientists should not aim to be on the side of the majority, but rather should try to think out-of-the-box."

What are the key discoveries that have led you to pursue your current work? How did you come up with these hypotheses?

It is currently recognised that adipose tissue dysfunction in obesity, rather than excess fat mass per se, is a key factor in the pathophysiology of obesity-related chronic diseases. It has previously been demonstrated by our group and others that adipocyte hypertrophy, impairments in lipid metabolism, a decreased blood flow, and a proinflammatory phenotype are characteristics of dysfunctional adipose tissue in obesity. However, it is still not fully understood what triggers an impaired functioning of this tissue, and why different fat depots seem to have distinct functions that also relate to interindividual differences in disease risk.

Based on earlier findings of impaired adipose tissue angiogenesis and blood flow in obesity, I hypothesised that the oxygen availability in adipose tissue may be reduced in obese compared to lean individuals. There was some *in vitro* evidence that an altered microenvironmental oxygen availability in adipose tissue may contribute to the metabolic and endocrine impairments as seen in obese adipose tissue. As a result, we established and applied an accurate optochemical measurement system for the continuous monitoring of tissue

oxygenation in humans to be able to link this to metabolic and inflammatory processes. Whilst we set out to address this hypothesis in humans, it was shown by others that hypoxia was indeed present in adipose tissue in obese rodent models. Contrary to our expectations, we found that adipose tissue oxygen partial pressure was higher rather than lower in obese humans with impaired glucose homeostasis, despite lower adipose tissue blood flow. Although mice and humans are not alike, which also holds true for the rate and extent of fat mass gain in mouse models of obesity compared with humans, this finding still came as a big surprise. There is now evidence to suggest that a higher oxygenation of obese adipose tissue may be due to a lower metabolic rate (i.e., lower oxygen consumption) in obese versus lean adipose tissue. These exciting findings provided the basis for a series of follow-up studies to investigate the interplay between tissue oxygenation, inflammation, and metabolism in humans, some of which are currently in progress.

"...I think that one performs much better when there is a healthy balance between work and private lives."

How did these completely unexpected results shape your research thereafter?

Our discovery that obese adipose tissue was characterised by increased oxygen tension rather than hypoxia has evoked major interest and discussion throughout the scientific community. Our findings challenged the widely held concept of hypoxic adipose tissue in human obesity. Of note, it is rather surprising to me that the concept of adipose tissue hypoxia in obesity is often taken for granted, since to date very few human studies have been performed to formally address this. Of course, follow-up studies were needed. In agreement with our initial findings, we have recently shown that diet-induced weight loss decreased adipose tissue oxygen tension in obese individuals, which was accompanied by improved insulin sensitivity. Earlier this year, we published data indicating that adipose tissue oxygen tension is positively associated with insulin resistance, independently of adiposity. Mechanistically, we further showed that prolonged exposure to low rather than high physiological oxygen tension decreases gene expression of several proinflammatory markers in differentiated human adipocytes.

The German philosopher Arthur Schopenhauer once said: "A truth passes through three stages. First, it is ridiculed. Second, it is violently opposed. Third, it is accepted as being self-evident." We are certainly not at the final stage yet. To be honest, I believe that unexpected findings are the most interesting, and that scientists should not aim to be on the side of the majority, but rather should try to think out-of-the-box. This will contribute to new discoveries in science.

Is there any research currently ongoing that you are not involved with that you are keen to know the outcomes of?

The overarching goal of our translational research is to provide an evidence-base for future interventions to prevent and treat obesity-related chronic metabolic and cardiovascular diseases. We investigated the effects of different interventions (i.e., dietary, exercise, and pharmacological interventions) to improve cardiometabolic health in overweight and obese humans, with healthy ageing as the ultimate goal. As such, I am very interested in the outcomes of several large clinical endpoint trials, but at the same time I look forward to hearing about the results of mechanistic human metabolic studies. For example, we still do not understand the mechanisms responsible for depot-specific adipose tissue expansion in humans. I think this would be an important step towards a better understanding of interindividual differences in the pathophysiology of obesity-related cardiometabolic diseases.

You have been the President of The Netherlands Association for the Study of Obesity (NASO) since 2014. What made you want to be involved with this organisation, and what is your favourite aspect of your presidential role?

My motivation to become a board member of the NASO stems from my continued involvement in scientific NASO meetings. I have always

appreciated the rather informal setting of the annual scientific meetings, allowing investigators to meet, interact, and discuss ideas with colleagues. I feel this is of particular importance for new investigators in the field. After serving on the NASO board as the Secretary of the association for several years, I was asked to become the President of the association a few years ago. What I very much enjoy about my role as President is that I meet interesting people, learn from other people, I am challenged in my thinking and actions, and have a voice that can help make a difference, for example within the European Association for the Study of Obesity (EASO). Moreover, I appreciate that our members are actively involved in the association and support the work that is done by the members of the board.

With such a busy life, how do you strike a balance between your work and personal commitments?

Indeed, maintaining a good balance between work and private life it is not always easy. It can be rather busy when combining a scientific career, raising two lovely daughters (Saar and Fem, who are now 5 and 3 years old, respectively) together with my wife Lieke, finding time to exercise, and having a social life as well. I am happy that I can say that we have managed quite well so far. To be honest, I think that one performs much better when there is a healthy balance between work and private lives. At least, that certainly holds true for myself.

If money was no object, what diabetic disease/disorder would you cure and why?

Obesity is a major risk factor for the development of Type 2 diabetes mellitus. In my opinion, we do not pay sufficient attention to reversing the obesity epidemic. It is alarming that the prevalence of obesity is still on the rise, not only in adults but also in children. I think governments should invest much more in this.

What advice would you give to a young researcher or medical student aiming to pursue a career like yours?

Of course, we all have different skills, interests, and expectations. I would advise new researchers to make up their mind about what really interests them, what skills that have acquired, and where they get energy from. Then choose a path that feels right at that moment, talk to people that may be able to help you, show that you are eager to learn, do your utmost to achieve your goals, and never regret a decision. Finally, realise that you may change your mind in the future, and that it is always possible to redirect your career.

Prof Anne Phillips

Birmingham City University, UK

You hold a number of professional and volunteer positions; please could you describe what your typical working week entails?

I have a busy, dynamic, and varied role as an Associate Professor in Diabetes Care. This involves research, teaching, scholarship activities, consultancy, clinical work, and academic supervision and publications. I volunteer for Diabetes UK and contribute to several national and international committees in diabetes care. I really enjoy my role and never have a day the same. I am fortunate to also be a Queen's Nurse and so focus very much on the interface between primary and specialist services in diabetes care.

What was it that first drew you to teaching?

I have always enjoyed working with people and facilitating the learning of individuals and

families in their own experiences of diabetes. While I was working as a diabetes specialist nurse, I had the opportunity to teach at a local university; this soon developed into a module leader role as a lecturer/practitioner and then on to a senior lecturer role in diabetes care. Translating my clinical knowledge into effective and meaningful teaching of healthcare professionals seemed a natural step.

"Every healthcare professional is really important because they are the catalyst for increasing the reach of information to so many people with diabetes and their families."

Are there any guiding principles underpinning your teaching style?

Every healthcare professional is really important because they are the catalyst for increasing the reach of information to so many people with diabetes and their families. Like the analogy of a pebble being thrown into a pool of water, by reaching one healthcare professional with increased diabetes knowledge, this then escalates like the ripples from the pebble hitting the water's surface. So, this new knowledge can reach so many more people with diabetes and their families. To me, this is the real value and true impact of teaching health professionals, as their influence is vital and so far-reaching into the wider populations of people living with diabetes.

Could you tell us more about the innovative diabetes care programmes for which you received a National Teaching Fellowship?

I am fortunate enough to work with really innovative and enabling diabetes clinical colleagues. Together we have created and provided a wide-reaching and highly successful portfolio of clinical and empowering diabetes education programmes. The education portfolio was flexible and far-reaching, and included conferences, master classes, modules, degree and postgraduate programmes, and international outreach and consultancy topics. These all gathered the common threads in diabetes care together and inspired progress and innovation in clinical practice. I have been really very privileged to work alongside many inspirational clinical colleagues; examples include Dr Fiona Campbell and Ms Carole Gelder from Leeds Children's Hospital, Leeds, UK. Their drive and passion to develop diabetes care is so motivating and underpins my approach to healthcare professional education.

I was awarded The National Teaching Fellowship in 2016 for my own personal pedagogical philosophy of engagement in interdisciplinary health professional diabetes education. My focus has always been on practice-changing education for a wide range of diabetes care delivery methods across the UK and internationally. I consider reflecting on converting learning into practice and practice into learning to be the the catalyst for increasing education, and hence enabling diabetes practice development.

Are there any medical specialities, or indeed other professions, that you believe diabetologists could learn from?

I always aspire to teach practitioners at every level to work as a team and to recognise their individual role within that team. Working to recognise and be flexible with each individual and their experience of diabetes is the key. As a team, all practitioners can work successfully in a patient-centric way. Interdisciplinary teamwork is the essence of diabetes care and is also the granite foundation of effective diabetes care delivery in both primary and specialist services worldwide.

How can medical educators prepare their students for the increasing pressures faced by those in the medical profession today?

Medical educators can prepare their students by being flexible, in terms of being able to change with the times, regularly reviewing their working practices, being open to change when needed, and, most of all, supporting one another. This creates at atmosphere of synergy in the workplace. Ineffective leadership breeds discontent and cynicism. The most effective leaders are the ones who inspire and transform,

even in the most difficult of times, as they encourage others. All healthcare departments are under increasing scrutiny and pressure currently, and, thus, having a united vision with effective and enabling leadership is essential; it is not just about financial resources, because perhaps the most important element is the supportive human resources we have within diabetes care.

It was recently highlighted that the general public do not take diabetes very seriously as a condition. Why do you think this is and what would you like to see done about it?

I think this is certainly a changing position, especially since so much media attention has been focussed on the increased incidence of diabetes worldwide. Communities are now engaging in innovative programmes, like in Leicestershire, UK with the Global Cities Changing Diabetes Programme. These programmes encourage other cities to follow suit and mean community-wide education about diabetes, particularly Type 2 diabetes mellitus prevention, is available and accelerated. Also, the IDEAL group, which I am part of, has just launched their first white paper, which is focussed on working with Clinical Commissioning Groups to provide consistent delivery of diabetes care across England.

What is it that you enjoy about your role as a volunteer for Diabetes UK?

Volunteering for Diabetes UK opens doors to reach out to so many different communities. The opportunity to support and contribute to Diabetes UK has been part of my work for many years. These opportunities are also echoed by Chris Askew, Chief Executive of Diabetes UK, who said that: "Diabetes is a crisis for the health of the nation. But if we work together we can realise our vision of a world where diabetes can do no harm." This is vital and strategically underpins the aims of the IDEAL Project.

Have there been any developments in the field of diabetes that have particularly excited you over the last few years?

It is a really good time to take stock and reflect on just how far diabetes care has progressed over the last few years. Many people are living long and healthy lives alongside their diabetes, which is just as it should be. Research is developing wonderful technologies in self-management potentials for Type 1 and Type 2 diabetes mellitus. Obviously, if these can be made more cost-effective then they can and will reach millions of individuals and their families. An obvious example is the current funding position with flash glucose monitoring.

If, however, we can reflect on the recurrent issues we face in the workforce, like succession planning in a consistent way, this then can strengthen our diabetes-aware workforce. Also, by increasing our outreach of person-centred, structured education and prevention, we can endeavour to be so much more effective in diabetes prevention and care.

What plans do you have for the next 5 years?

To keep doing what I enjoy and, by embracing opportunities, to develop and extend diabetes health professional education. I am also shortly going to become a grandmother, so am very much looking forward to that too!

"I always aspire to teach practitioners at every level to work as a team and to recognise their individual role within that team."

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Abstract Reviews

A selection of insightful, hand-picked EASD 2018 abstract reviews from the presenters themselves

Implementation of an Aggressive Management of Insulin Therapy and Carbohydrates Intake During a Trail-Running Endurance Competition in Athletes with Type 1 Diabetes Mellitus

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Keywords: Aggressive management, endurance, implementation, performed-based carbs strategy, Type 1 diabetes mellitus (T1DM).

Citation: EMJ Diabet. 2018;6[1]:35-37. Abstract Review No. AR1.

BACKGROUND

The idea to test the implementation of an aggressive insulin and carbohydrate intervention strategy approach to Type 1 diabetes mellitus (T1DM) athletes in a real-life trail-running endurance competition, was developed by a group of T1DM amateur athletes and members of Diabete No Limits (DNL), an Italian, nonprofit organisation, that enrolled a team of volunteers, selected by doctors, trainers, and DNL fellows, to take part in this project.

The starting points of the study were the recommendations and guidelines given to T1DM patients completing exercise, focussing almost exclusively on blood glucose (BG) levels and hypoglycaemia risk, through a conservative reduction of insulin and/or by assuming carbohydrates were consumed on a

defensive eating basis. On the other hand, for non-T1DM endurance athletes a high carbohydrate supplementation strategy is strongly suggested to maximise patient response.[1,2] Since the physiology of energetic substrate metabolism is the same regardless of the presence of T1DM, we asked the question: "What if a similar approach were applied to a T1DM endurance athletes?"

MATERIALS AND METHODS

In 2017, DNL enrolled eight T1DM athletes (seven males, one female), well trained in endurance sports, six receiving multiple daily dose insulin injections and two receiving continuous subcutaneous insulin infusion therapy. The mean diabetes duration in the patients was 20 years (range: 9–37 years), insulin requirements low-to-moderate (0.26–0.59; mean: 0.46 U/Kg), and good glycaemic control (HbA1c range: 6.7–7.8; mean: 7.3%).

The day before competing, the athletes completed functional tests to assess aerobic heart rate (HR); threshold and VO_2 max (55–64.3; mean: 59.2), and a briefing was held focussing on metabolism, physiology, and on the scheduled collecting data protocol for the race day.

The task for athletes was to maximise running performance without reducing the insulin basal rate and boluses before, during, and after the competition, through regular supply of carbohydrates.

At the end of each lap runners had a quick stop in a dedicated transition area to check BG, lactates, HR, carbohydrate intake, and Borg scale, as well as to verify pace and lap time, to consider further carbohydrate consumption or insulin integrations, basing primarily on athlete experience and medical staff advice. Available carbohydrates were fast-acting gels, long-acting maltodextrin gels, and moderate-to-long-acting bars and isotonic beverages.

RESULTS

Bad weather conditions made the 6 km circuit, with an elevation gain of 300 m (300d+), track very tough, but all athletes completed 3–4 laps within the race limit time of 3 hours. All subjects maintained their insulin doses and carbohydrate integration ranged from 30–83 g/hour, with 50% athletes taking >60 g/hour and the other 50% taking slightly less than that.

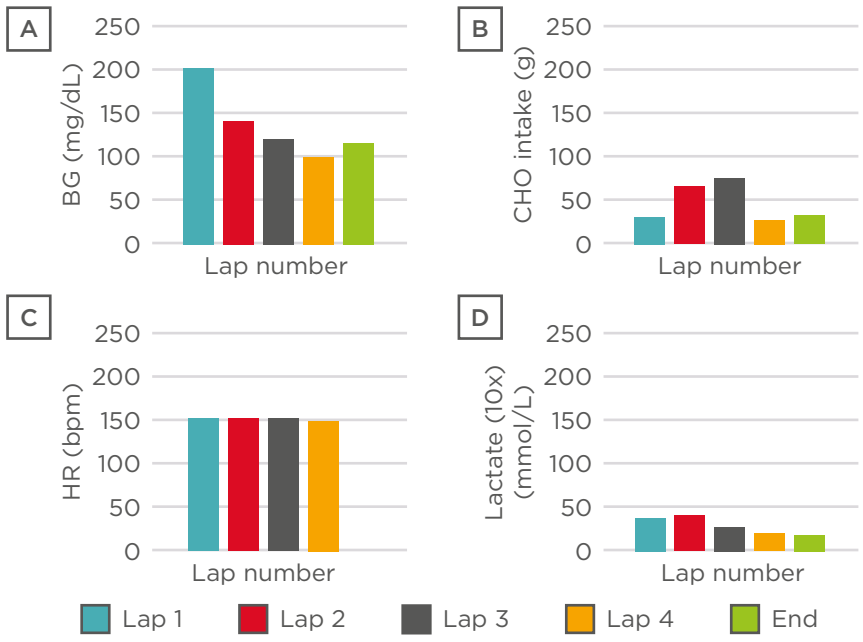

Figure 1: Mean (A) blood glucose, (B) carbohydrate intake, (C) heart rate, and (D) lactate levels measured after the completion of a 6 km endurance trail running circuit.

BG: blood glucose; CHO: carbohydrate; HR: heart rate.

HR was maintained in Zone 2 and 3, rising to Zone 4 occasionally for very short time periods. Lactate levels profile confirmed that energy supply was supported by aerobic metabolism (lactate peak value range: 1.7–9.6 mmol/L; mean: 3.5 mmol/L). Despite a mean carbohydrate integration of 57 g/hour, we observed a mean BG reduction of 83 mg/dL, which dropped from a mean of 201 mg/dL to 118 mg/dL, without any severe hypo or hyperglycaemic effects (range of BG: 62–242 mg/dL) (Figure 1). None of the athletes suffered nausea or gastrointestinal discomforts.

CONCLUSIONS

To maximise their performance, T1DM athletes completing an endurance competition should not exclusively focus on BG levels, risk of hypo or hyperglycaemia, and 'defensive eating-based' carbohydrate intake. Instead, T1DM athletes should consider a 'performance-based' carbohydrate intake strategy. Throughout the decision-making process, balancing peculiarities of T1DM with exercise physiology, including athletic goals, duration, intensity of the effort, fitness level, and nutritional demands, must be considered.

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Abdominal Subcutaneous Adipose Tissue Gene Expression in Relation to Tissue-Specific Insulin Resistance in Human Obesity

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Acknowledgements: †co-first authors. ‡co-last authors.

Keywords: Adipose tissue, hepatic insulin sensitivity, insulin resistance, low-grade inflammation, muscle insulin sensitivity, obesity, transcriptomics.

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Obesity and being overweight are major risk factors for several diseases, including cardiovascular disease and Type 2 diabetes mellitus.[1] Adipose tissue dysfunction, rather than excess fat mass per se, is frequently associated with the progression towards insulin resistance (IR).[2] IR can develop simultaneously in multiple organs, but the severity may vary between organs. For instance, impaired fasting glucose and impaired glucose tolerance may represent distinct prediabetic phenotypes, which are characterised by more pronounced hepatic or muscle IR, respectively.[3] Identification and quantification of metabolic anomalies in different IR phenotypes are important because they can provide directions for more personalised lifestyle or pharmacological interventions in the prevention and control of cardiometabolic diseases. Indeed, there is evidence from a post-hoc analysis that the response to nutritional intervention may depend on IR phenotype (e.g., being more insulin resistant at the level of the liver or skeletal muscle).[4] Analysis of gene expression in subcutaneous adipose tissue (ScAT) may help to elucidate the pathways and mechanisms that link adipose tissue function to tissue-specific IR. Therefore, the presented study aimed to identify distinct transcriptome profiles of abdominal ScAT in relation to muscle or liver IR.

In this study, we identified abdominal ScAT transcriptome profiles in relation to liver or muscle IR by RNA sequencing in overweight and obese non-diabetic participants of the DiOGenes study (BMI >27 kg/m^2; n=368). The tissue-specific IR phenotype was based on tertiles of the muscle insulin sensitivity index (MISI) and the hepatic IR index (HIRI), derived from a 5-point oral glucose tolerance test.[5] Subsequently, the participants were classified at baseline into 4 groups: no-IR (n=186), muscle-IR (n=69), liver-IR (n=53), and muscle/ liver-IR (n=60). ScAT RNA sequencing data were compared between groups using differential gene expression analysis (DESeq)2 and were adjusted for study centre, sex, BMI, and waist-to-hip ratio. We found that ScAT extracellular matrix organisation genes (e.g., collagens) were significantly upregulated in the liver-IR versus no-IR comparison (fold change [FC] >1.2; p<0.05). In muscle-IR versus no-IR comparison, inflammatory pathways were significantly changed with pronounced upregulation of chemokine and complement genes (FC >1.2; p<0.05).

Following up on the DiOGenes outcomes, the relationship between systemic low-grade inflammation and IR phenotype was studied in overweight and obese non-diabetic individuals of the Cohort on Diabetes and Atherosclerosis Maastricht (CODAM) (BMI >25 kg/m^2 [n=325]) and Maastricht study (BMI >27 kg/m^2 [n=792]), using linear regression analyses. The plasma low-grade inflammation score was inversely associated with MISI (CODAM: standardised-ß: -0.108, 95% confidence interval [CI]: 0.205; -0.011; p=0.028; Maastricht Study: standardised-ß: -0.131, 95% CI: 0.193; 0.068; p<0.001), while no association was observed with HIRI (CODAM: standardised-ß: 0.066; 95% CI: -0.032; 0.165; p=0.184; Maastricht Study: standardised-ß: 0.000, 95% CI: 0.064; 0.064; p=0.995). Importantly, the association between low-grade inflammation and MISI was adjusted for HIRI, and vice versa. We showed in these two independent cohorts that an increased systemic low-grade inflammation profile was specifically related to muscle IR.

In conclusion, we showed that hepatic and muscle IR were characterised by distinct abdominal ScAT transcriptome profiles. Extracellular matrix remodelling genes were upregulated in individuals with primarily hepatic IR, while inflammatory genes were significantly upregulated in primarily muscle IR individuals. An increased systemic low-grade inflammation profile was specifically related to muscle IR. We propose that increased ScAT inflammatory gene expression may

translate into an increased systemic inflammatory profile, linking ScAT inflammation to the muscle IR phenotype. These distinct IR phenotypes may provide leads for personalised nutritional or lifestyle prevention strategies.

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Variants in Genes (*DHCR7*, *CYP2R1*, and *GC*) Regulating Vitamin D Metabolism Determine Low Vitamin D Levels in Type 2 Diabetic Patients

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Keywords: 7-dehydrocholesterol reductase (*DHCR7*), cytochrome P450 family 2 subfamily R member 1 (*CYP2R1*), genetic risk score, SUMMER study in diabetes, vitamin D binding protein (*GC*).

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Hypovitaminosis D is associated with an increased prevalence and incidence of metabolic syndrome and Type 2 diabetes mellitus (T2DM).[1] Moreover, meta-analyses of observational studies have consistently found that vitamin D deficiency is associated with an increased risk of cardiovascular mortality and morbidity.[2,3] Although vitamin D levels are influenced by modifiable determinants, such as diet and sun exposure, classical twin studies showed that vitamin D levels are heritable in 50–80% of cases,[4] thus implying the central role of genetic determinants.

Genes modulating vitamin D metabolism are likely candidates for the control of vitamin D levels. A large meta-analysis of a genome-wide association study of serum 25-hydroxyvitamin D identified variants in three genes involved in vitamin D metabolism: *DHCR7*, *CYP2R1*, and *GC*.[5] *DHCR7* encodes the enzyme 7-dehydrocholesterol reductase, thereby affecting vitamin D synthesis;[6] *CYP2R1* encodes a hepatic microsomal enzyme responsible for vitamin D 25-hydroxylation;[7] and *GC* encodes for a multifunctional serum glycoprotein that binds and transports vitamin D.[8] All genetic associations between these three genes and vitamin D levels were only observed in the general population and never in T2DM populations.

Our aim was to investigate the role of *DHCR7*, *CYP2R1*, and *GC* gene variants on serum vitamin D concentrations in a large and very homogeneous cohort of Italian patients with T2DM. *DHCR7*, *CYP2R1*, and *GC* genes were studied in 2,163 consecutive study subjects from the Sapienza University Mortality and Morbidity Event Rate (SUMMER) study, which was conducted in a cohort of patients with diabetes.[9]

Table 1: Vitamin D levels of all participants in the SUMMER study across *DHCR7*, *CYP2R1*, and *GC* genotypes.

	Genotypes	Vitamin D (ng/mL)
DHCR7 rs12785878 T>G	TT (n=1,099)	23.8±10.2
	TG (n=854)	22.6±10.1
	GG (n=210)	21.1±9.5
	p value	0.000038
CYP2R1 rs10741657 G>A	GG (n=1,069)	22.7±9.4
	GA (n=894)	23.2±10.8
	AA (n=200)	24.7±12.2
	p value	0.11
GC rs4588 G>T	GG (n=1,140)	24.0±10.7
	GT (n=845)	22.3±9.5
	TT (n=178)	20.9±8.7
	p value	0.0000058

A: adenosine; C: cytosine; G: guanine; T: thymine.

Adapted from Barchetta et al.[9]

The three genes were significantly associated with lower vitamin D levels, with a mean reduction of 4 ng/mL in carriers of the risk genotypes compared to wild-type carriers (Table 1). The allelic risk (OR) for vitamin D insufficiency (i.e., having a vitamin D level of <30 ng/mL) was 1.28 (p=0.003) for *DHCR7*, 1.36 (p=0.00047) for *GC*, and 1.18 (p=0.042) for *CYP2R1*.

A weighted genotype risk score was then calculated by summing the risk alleles of the three single nucleotide polymorphisms in each individual, weighted with the effect size for risk of hypovitaminosis D (<30 ng/mL). We observed a strong association with vitamin D levels, which decreased significantly from the first to the last category (24.3±11, 24.8±11.5, 22±8.9, and 21±9 ng/mL, respectively [p=0.0000001]), with an OR for the subgroup with ≥3 risk alleles (versus 0 alleles carriers) of 1.24 (p=0.000011).

In summary, we observed a significant association between variants in the *DHCR7*, *CYP2R1*, and *GC* genes and lower vitamin D levels in T2DM patients. The weighted genotype risk score with the three variants together resulted in highly significant associations with vitamin D levels and with the risk of hypovitaminosis. Of note, we observed a mean difference between genotypes of 4 ng/dL in vitamin D levels. Although it is reasonable to believe that this difference between genotypes in vitamin D level may not be clinically relevant, it is conceivable that in diabetic subjects who are already affected by low vitamin D levels, a further genetically induced decrease may have detrimental consequences in the long term.

In conclusion, these results provide strong evidence of the effects of variations in genes coding for proteins involved in vitamin D metabolism on vitamin D levels in T2DM patients. Hence, we now have a genetic marker of vitamin D levels in diabetes that can be used in longitudinal studies to address whether the reported association between vitamin D and mortality rate[10] in T2DM is sustained by a cause–effect relationship.

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High Low-Density Lipoprotein Cholesterol Levels and Risk of Peripheral Vascular Diseases: A Mendelian Randomisation Study Including 116,419 Individuals From The General Population

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Keywords: Chronic kidney disease (CKD), low-density lipoprotein (LDL) cholesterol, Mendelian randomisation, peripheral arterial disease (PAD), retinopathy.

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BACKGROUND AND AIMS

High low-density lipoprotein (LDL) cholesterol levels are causally involved in the pathogenesis of atherosclerosis and are related to an increased risk of cardiovascular disease.[1] It is unknown whether high LDL cholesterol levels are causally related to an increased risk of microvascular diseases, such as retinopathy and neuropathy, and peripheral vascular diseases also involving larger arteries, such as chronic kidney disease (CKD) and peripheral arterial disease (PAD). We hypothesised that high LDL cholesterol levels are causally related to the risk of retinopathy, neuropathy, CKD, and PAD in the general population.

MATERIALS AND METHODS

We included 116,419 individuals from the Copenhagen City Heart Study and the Copenhagen General Population Study and used Mendelian randomisation to examine causality between high LDL cholesterol levels and peripheral vascular endpoints. We selected and genotyped 11 variants in the *LDLR, APOB, HMGCR, NPC1L1,* and *PCSK9* genes and calculated a weighted genetic risk score. Peripheral vascular endpoints were based on International Statistical Classification of Diseases and Related Health Problems codes

collected from all hospital admissions and outpatient clinic visits in the national Danish Patient Registry and the national Danish Registry of Causes of Death. To test whether the findings could be replicated in another general population cohort, we performed a two-sample Mendelian randomisation analysis using genetic variants associated with high LDL cholesterol levels in the Global Lipid Genetic Consortium, and peripheral vascular endpoints from the UK Biobank.

RESULTS

Observationally, we found no association between high LDL cholesterol levels and risk of retinopathy (p=0.12) or neuropathy (p=0.005). We found a stepwise increase in the hazard rate of CKD and PAD with higher LDL cholesterol levels, with a hazard ratio of 1.06 (95% confidence interval [CI]: 0.99–1.14) for CKD and 1.37 (95% CI: 1.20–1.57) for PAD in individuals with LDL cholesterol levels above the 95th percentile versus those below the 50th percentile. In the genetic, causal analyses, the risk ratio of disease for a 1 mmol/L higher LDL cholesterol level was 1.06 (95% CI: 0.24–4.58) for retinopathy, 1.05 (95% CI: 0.25–1.72) for neuropathy, 3.10 (95% CI: 1.79–5.39) for CKD, and 1.96 (95% CI: 1.26–3.06) for PAD. Summary level data from the UK Biobank using the weighted median of instrumental variable estimates Mendelian randomisation gave a risk ratio of 0.65 (95% CI: 0.25–1.70) for retinopathy, 0.86 (95% CI: 0.51–1.46) for neuropathy, 0.88 (95% CI: 0.66–1.18) for CKD, and 1.57 (95% CI: 0.91–2.71) for PAD.

DISCUSSION

Our study suggests that LDL cholesterol has no causal effect on peripheral microvascular diseases, such as retinopathy and neuropathy; however, it may have a causal effect on peripheral arterial diseases involving larger arteries such as PAD and CKD. The findings were replicated in the UK Biobank cohort with similar results for retinopathy, neuropathy, and PAD, but with inconsistent results for CKD.[2] The inconsistent findings for CKD may be due to several reasons, including the low participation rate and shorter follow-up time in the UK Biobank may cause a healthy participant bias, which could explain the inconsistency.[3] Previous studies have found that fenofibrates reduce the risk of retinopathy progression.[4] Our findings suggest that this is through mechanisms other than the lowering of LDL cholesterol.

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Inhibition of Insulin Secretion by Cxcl14

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Keywords: Beta cells, Cxcl14, insulin secretion, islets, Type 2 diabetes mellitus (T2DM).

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G protein-coupled receptors are tractable targets for pharmacotherapies;[1] however, challenges arise when it is necessary to either deorphanise a known receptor by finding its ligand or identify the receptors responsible for mediating biological effects of particular ligands.[2] One of these orphan ligands is Cxcl14, a chemokine that has been linked with obesity and glucose intolerance,[3] although the molecular pathways underlying this association are poorly understood. Therefore, we investigated the role of Cxcl14 in islets by measuring its expression and quantifying its effects on beta cell function, and aimed to identify the signalling responsible for mediating these effects.

We identified that Cxcl14 mRNA was expressed in mouse islets, confirming our previous observation,[4] and demonstrated that the expression levels were approximately 20-fold lower than those in brown adipose tissue. Fluorescence immunohistochemistry analysis of a mouse pancreas demonstrated that Cxcl14 was absent from islet beta cells but was present in the majority of delta cells. To study the functional profile of this orphan ligand, insulin secretion from MIN6 beta cells and mouse islets was quantified in the presence of Cxcl14, which demonstrated that Cxcl14 induced a significant concentration-dependent decrease in glucose-stimulated insulin secretion. These results are in agreement with the expression of Cxcl14 by delta cells, suggesting that it may be co-released with somatostatin to have paracrine effects and inhibit beta cell secretory function. During discussion of this presentation, it was suggested that further exploration could focus on whether there are any changes in Cxcl14 expression by delta cells of islets isolated from organ donors with Type 2 diabetes mellitus (T2DM). This is part of our ongoing research and it is possible that Cxcl14 overexpression could contribute to insulin secretory dysfunction in T2DM.

Cxcl14 may signal via a chemokine receptor, similar to other chemokines, so we quantified mRNA expression profiles of all chemokine receptors in MIN6 beta cells and mouse islets by quantitative PCR; this indicated that Cxcr4 and Cxcr7 are the most likely candidates for transducing the effects of Cxcl14 in beta cells. However, beta-arrestin recruitment experiments indicated that Cxcl14 did not activate either of these receptors, ruling out their involvement in mediating its signalling.

Analysis of downstream signalling by Cxcl14 indicated that it had no effect on cAMP generation in beta cells. However, experiments using 2-deoxyglucose, which is phosphorylated by beta cell glucokinase to non-metabolisable 2-deoxyglucose-6-phosphate, indicated that Cxcl14 caused a concentration-dependent inhibition of 2-deoxyglucose-6-phosphate generation in MIN6 beta cells and mouse islets. This suggests that Cxcl14 can inhibit glucokinase activity, and the expected reduction in ATP production by Cxcl14 was confirmed in experiments using mouse islets. It was suggested during discussion of these results that identification of beta cell mitochondrial activity in response to Cxcl14 would provide additional understanding of how this chemokine disrupts glucose metabolism.

Table 1: Summary of the effects of Cxcl14 in islets and on Cxcr4/7 activities.

Cxcl14 effect	Cxcr4/7 response
Glucose-induced insulin secretion	Concentration-dependent inhibition
Islet cAMP levels	No effect
Islet 2-deoxyglucose-6-phosphate accumulation	Concentration-dependent inhibition
Islet ATP generation	Concentration-dependent inhibition
Cxcr4 and Cxcr7 activities	No effect

In summary, our data reveal that Cxcl14 exhibits direct inhibitory effects on islet beta cells to reduce glucose-induced insulin secretion, and this is most likely a consequence of impaired glucose metabolism (Table 1). Thus, these beta cell-directed effects of Cxcl14 will contribute to the glucose dysregulation that occurs as a consequence of its upregulation in obese individuals and its induction of insulin resistance.[3] These data highlight the utility of Cxcl14 inhibition as a possible therapeutic approach for T2DM.

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IRS1 Genetic Variants Associated with Glucose Control and Insulin Resistance in Type 2 Diabetes Mellitus Patients from Bosnia And Herzegovina

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Disclosure: Dr Semiz, Dr Bego, Dr Causevic, Dr Asimi, and Dr Prnjavorac were involved in the patient recruitment, sample collection, and data acquisition. Dr Sterner, Dr Gremsperger, and Dr Ahlqvist were involved in the genotyping analysis and data acquisition. Dr Mahmutovic and Dr Hamad were responsible for the statistical analysis and have made substantial contributions to the data interpretation. Dr Mahmutovic was involved in the writing of the initial draft of the manuscript. Dr Groop, Dr Ahlqvist, and Dr Causevic reviewed and revised the manuscript. Dr Semiz conceived and designed the study, co-ordinated and supervised the study, provided financial support, interpreted the data, and revised the manuscript. All authors read and approved the final manuscript. The authors have declared no conflicts of interest.

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Keywords: HbA1c, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), insulin resistance, *IRS1*, single nucleotide polymorphism, Type 2 diabetes mellitus (T2DM).

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INTRODUCTION

Previous studies have reported conflicting results regarding the association of *IRS1* gene

variation with Type 2 diabetes mellitus (T2DM) and insulin resistance in different ethnic groups.[1-4] Here, we examined the association of single nucleotide polymorphisms rs7578326, rs2943641, and rs4675095 in the *IRS1* gene with T2DM and related traits in a population from Bosnia and Herzegovina, which is among the European countries with the highest T2DM prevalence (12.3%).

MATERIALS AND METHODS

Our study involved 390 T2DM patients and 252 unrelated, nondiabetic control subjects. Biochemical parameters, including but not limited to, fasting glucose (FG), fasting insulin (FI), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), HbA1c, and lipid levels were measured in all participants. Genotyping analysis was performed by the Sequenom MassARRAY® iPLEX® platform (Agena Bioscience, Inc., San Diego, California, USA) in co-operation with Lund University Diabetes Centre, Lund University, Malmö, Sweden. In addition, we also performed a sensitivity analysis to identify the potential effects of *IRS1* genetic variation on T2DM development and T2DM-related traits in a subgroup of untreated T2DM patients.

RESULTS

Our results demonstrated that after adjustment for BMI, age, and sex, rs7578326 and rs4675095 variants were positively associated with FG levels. The risk A allele of rs7578326 was also associated with higher HbA1c (B=0.034; 95% confidence interval [CI]: 0.003–0.065; p_{dom}=0.035) and HOMA-IR levels (B=0.316; 95% CI: 0.026–0.607; p_{rec}=0.033) in non-treated T2DM patients. This is in line with a recent study showing that the rs7578326 risk A allele is associated with higher HOMA-IR and FI levels.[5] Importantly, rs2943641 T allele carriers had lower HbA1c levels in non-treated T2DM patients (B=0.034; 95% CI: 0.006–0.062; p_{rec}=0.017), confirming recent results of a study performed in >12,000 American Hispanic or Latino participants, which found that risk C allele was associated with HbA1c, FI, HOMA-IR, TG, and high-density lipoprotein levels.[6] Furthermore, risk C allele was associated with HOMA-IR (B=0.353; 95% CI: 0.095–0.611; p_{rec}=0.008), FI (B=0.350; 95% CI: 0.022–0.487; p_{rec}=0.033), and HbA1c levels (B=0.032; 95% CI: 0.002–0.065; p_{dom}=0.040) in non-treated T2DM patients. In addition, our results demonstrated an association of the risk rs7578326/rs2943641 haplotype with FG levels and HOMA-IR, thus confirming the observed effects of rs7578326 and rs2943641 risk alleles individually on FG levels and IR. Interestingly, the effects of the *IRS1* haplotype in the Bosnia and Herzegovina population on increased very low-density lipoprotein levels and waist circumference were also observed in control subjects. This is consistent with an adverse metabolic profile, including dyslipidaemia, which was recently reported to be associated with *IRS1* genetic variation.[5,6]

CONCLUSION

We reported that *IRS1* gene variants were significantly associated with insulin resistance markers, glucose, and HbA1c levels. Interestingly, rs7578326 and rs2943641 *IRS1* variants located near to each other on the *IRS1* gene showed relatively similar effects on HOMA-IR, glucose, and insulin levels, which was confirmed by haplotype analysis including these two single nucleotide polymorphisms. On the other hand, the rs4675095 variant was significantly associated with glucose levels in controls and lipid levels in diabetic patients. Thus, our findings confirmed that mutations in *IRS1* gene would interfere with the function of the IRS1 protein encoded by this gene.

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How Can We Develop More Effective Strategies for Type 2 Diabetes Mellitus Prevention? A Paradigm Shift from a Glucose-Centric to a Beta Cell-Centric Concept of Diabetes

EDITOR'S PICK

This thought-provoking paper by Saisho provides a very accessible discussion of the shift from a glucose-centric to a beta cell-centric understanding of diabetes. The need for this shift is supported by recent evidence on pathophysiological processes showing the damaging or killing of beta cells through increased beta cell workload. This, Saisho argues, will lead to earlier and better-focussed interventions, thus reducing the risks of hyperinsulinaemia and subsequent damage of beta cells. Identification of those at particular risk of moving from prediabetic states to Type 2 diabetes mellitus will be helped by this line of thinking. The need for early lifestyle interventions to manage weight in combination with the application of methods from precision medicine is now implied. This paper provides a very useful discussion of a topical and important shift in thinking about diabetes.

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Abstract

Diabetes is defined as chronic hyperglycaemia due to insufficient insulin action. Over the last few decades, various different types of antidiabetic medications have been developed and the management of patients with Type 2 diabetes mellitus (T2DM) has been substantially improved. While we can now successfully control hyperglycaemia in patients with T2DM, the number of patients with T2DM continues to rise. In addition, the financial cost of T2DM is a worldwide problem and cost-effective strategies for T2DM prevention are eagerly awaited. To develop and establish more effective prevention strategies for T2DM, this paper proposes a paradigm shift from a glucose-centric to a beta cell-centric concept of T2DM management. This concept makes it easier for medical staff and patients to understand the process of the development of T2DM and its complications in a pathophysiology-based, continuous, and integrated manner; the glucose-

centric concept has so far failed to emphasise the importance of intensive intervention before the onset of T2DM. It is hoped that this paradigm shift in the management of T2DM will foster the development of novel preventive strategies to effectively control this pandemic disease.

INTRODUCTION

Diabetes is defined as a chronic hyperglycaemic state due to insufficient insulin action. Although defective insulin secretion from pancreatic beta cells and reduced insulin action in the liver, skeletal muscle, and adipose tissue are well established mechanisms in the pathogenesis of Type 2 diabetes mellitus (T2DM), recent studies have suggested that other organs and tissues, such as the brain, gastrointestinal tract, pancreatic alpha cells, kidney, and vascular endothelial cells, are also involved in the pathogenesis of hyperglycaemia.[1]

Exploring the different mechanisms that cause hyperglycaemia has resulted in an increase in the number of therapeutic targets and the development of different types of novel glucose-lowering drugs. Two recently developed agents, sodium/glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists, have been shown to improve cardiovascular and renal outcomes in patients with T2DM,[27] beginning a new era in the treatment of T2DM.

Nonetheless, the number of patients with T2DM continues to rise across the world, resulting in a huge economic burden.[8] While we are succeeding in improving glycaemic control in patients with T2DM, it remains difficult to achieve cure or remission, suggesting the importance of T2DM prevention and that our understanding of the pathogenesis of this disease remains unsatisfactory. This paper proposes a paradigm shift in the concept of T2DM based on its pathogenesis, from glucose-centric to a novel, beta cell-centric concept, in order to establish more effective prevention strategies.

THE GLUCOSE-CENTRIC CONCEPT OF DIABETES

Currently, the diagnosis of diabetes is based on plasma glucose levels[9,10] and the diagnostic threshold of plasma glucose has been set based on the incidence of retinopathy, one of the microvascular complications of diabetes.[11,12]

People with impaired fasting glycaemia (IFG) and/or impaired glucose tolerance (IGT), known as prediabetes, are thereby defined as a population with a high risk of developing T2DM, but with a less severe glucose intolerance compared to T2DM patients.[9,10]

As a result, using this glucose-centric concept of T2DM, patients with IFG or IGT are recognised as having a less severe condition than those with T2DM, often resulting in a delay in intensive intervention for this population. However, while the diagnostic criteria of diabetes are based on the risk of developing microvascular complications, individuals with IFG or IGT have been shown to be at a high risk of developing atherosclerotic cardiovascular disease (ASCVD).[13,14] Recent studies have revealed that the effect of strict glycaemic control on cardiovascular outcomes is modest,[15-18] although such control does effectively reduce the risk of developing microvascular complications.[19,20] Thus, to improve cardiovascular outcomes and extend healthy longevity, more intensive intervention in individuals with IFG or IGT, who are at a high risk of ASCVD, is needed.

A Need for Multifactorial Intervention

Recent studies have shown that not only glycaemic control but also multifactorial interventions, including blood pressure and lipid control and smoking cessation, are important and effective for the improvement of cardiovascular outcomes and mortality,[21-23] even though some of the interventions, including smoking cessation and the use of statins, diuretics, and beta-blockers, may worsen glucose tolerance.[24-26] Given the current challenge of reducing ASCVD rates in patients with T2DM, a glucose-centric concept of diabetes may not appropriately capture its pathophysiology or lead to effective treatment strategies.

Patients with metabolic syndrome (MetS), which consists of visceral obesity, glucose intolerance, hypertension, and dyslipidaemia, have also been shown to have an increased risk of developing ASCVD, indicating that an overlap

of multiple risk factors has a major impact on the progression of atherosclerosis.[27] Therefore, intensive intervention to prevent the future development of ASCVD, as well as T2DM, is needed in patients with MetS who are also at a high risk of T2DM; however, since prediabetes is recognised as a milder form of T2DM in the glucose-centric concept, intensive treatment for these patients is often not considered.

What Are We Missing?

Although the importance of cardiovascular risk reduction beyond glycaemic control in patients with T2DM has been highlighted, it may be difficult to establish effective strategies to improve cardiovascular outcomes with a glucose-centric concept of T2DM. One significant difficulty is that classification of glucose intolerance based on the current threshold of plasma glucose level may become an obstacle in capturing the continuous pathophysiology underlying the development of T2DM and its complications. To facilitate a more effective approach for achieving healthy longevity, which is the goal of diabetes care, a more continuous, comprehensive, and integrated concept of T2DM is needed.

BETA CELLS: THE CORE PATHOLOGY OF DIABETES

A number of organs and tissues regulate glucose metabolism in the body;[1] however, it remains unclear as to what extent each mechanism is involved in physiological and pathological conditions. Recent genome-wide association studies have revealed a number of susceptible genes for T2DM, most of which are thought to associate with beta cell function or mass,[28,29] indicating the major impact of beta cells on the development of T2DM.

In a physiological condition, when insulin sensitivity is reduced due to various factors, such as overnutrition, an inactive lifestyle, or obesity, insulin secretion increases to compensate and maintain normal glucose tolerance, resulting in a hyperinsulinaemic state. Hyperinsulinaemia is also often observed in patients with T2DM; however, studies have shown that disposition index, the true beta cell function adjusted for insulin sensitivity, is always reduced in patients with IFG, IGT, or T2DM,[30,31] indicating that T2DM will not develop unless the compensatory mechanism of beta cells is impaired. In addition, histological studies have shown a reduction in beta cell mass in patients with IFG, IGT, or T2DM, irrespective of the presence of obesity.[32,33] These findings highlight that a deficit of beta cell mass and/or function is common and the most important pathological feature of diabetes. Thus, this paper proposes a shift to a novel beta cell-centric concept of diabetes.

A PARADIGM SHIFT TO A BETA CELL-CENTRIC CONCEPT

Although T2DM is a progressive disease,[34] this aspect makes the condition difficult to understand when using the categorical classification of diabetes based on plasma glucose level. Glycaemic control deteriorates with disease duration, which necessitates intensification of treatment; however, this nature of T2DM is related to progressive deterioration of beta cell function,[35-37] which is thought to occur before and after the onset of T2DM.

Various mechanisms that induce beta cell dysfunction have been postulated, including gluco(lipo)toxicity,[38] endoplasmic reticulum stress,[39,40] oxidative stress,[41] mitochondrial dysfunction,[42] autophagy dysfunction,[43] amyloid toxicity,[44,45] cytokine pathways,[46] and beta cell dedifferentiation and transdifferentiation.[47] Excess beta cell workload due to a compensatory increase in insulin secretion in response to reduced insulin sensitivity may induce beta cell dysfunction and/or death through any of the aforementioned mechanisms, even before the development of hyperglycaemia.

In humans, the increase in beta cell mass in obese individuals is only modest,[48,49] suggesting that the compensatory increase in insulin secretion in response to obesity is accomplished by an increase in insulin secretion from individual beta cells, which results in increased workload of these individual cells. Excess workload eventually induces beta cell dysfunction and/or death, leading to the development of hyperglycaemia.

Once beta cell mass is reduced, the workload on residual beta cells is further increased, resulting in a vicious cycle of beta cell

dysfunction that may explain the progressive nature of T2DM. Therefore, from the viewpoint of the beta cell-centric concept, treatment strategies for T2DM should be directed towards a reduction in workload and protection of residual beta cells. To reduce workload, intensive intervention for patients with obesity and insulin resistance is critical.

In the beta cell-centric concept, pathophysiological changes prior to the onset of T2DM can be captured as a continuous process (Figure 1). Before the onset of T2DM, the reduction in beta cell mass is minimal, and improvement of obesity and insulin resistance at this stage could potentially normalise glucose metabolism.[30,50,51] On the other hand, during this phase, compensatory hyperinsulinaemia, together with hypertension, dyslipidaemia and dysregulated adipokines, and inflammation due to visceral obesity, promotes atherosclerosis.[52] Thus, timely intervention to improve obesity and insulin resistance through lifestyle modification is important because of two aspects: a) amelioration of hyperinsulinaemia will suppress progression of atherosclerosis, and b) reduction in beta cell workload will prevent beta cell loss and the development of T2DM. In this regard, assessment of insulin resistance in the non-diabetic population is important to identify individuals at a high risk of T2DM development, although obesity itself is already an established risk for ASCVD and most obese individuals also develop metabolic disorders in later life.[53,54]

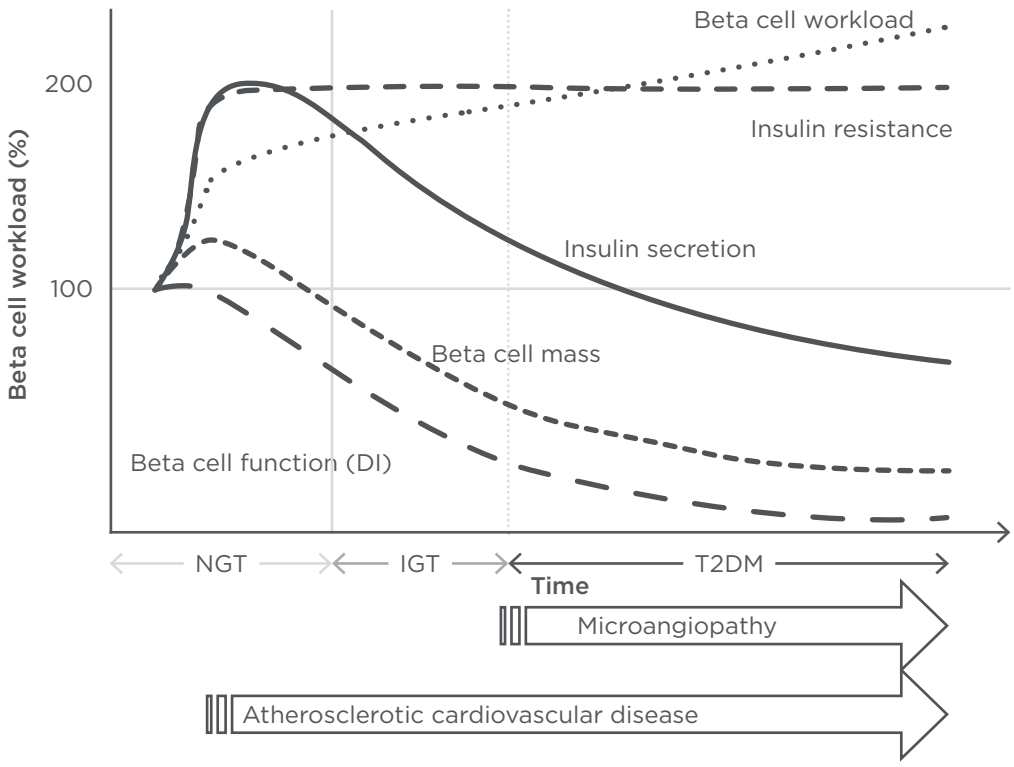

Figure 1: Changes in beta cell workload during the development of Type 2 diabetes mellitus.

Demand for increased insulin secretion upon insulin resistance due to excess caloric intake, physical inactivity, and obesity, but with a modest change in beta cell mass, results in an increase in individual beta cell workload. In this compensatory phase, the resulting hyperinsulinaemia, together with high blood pressure and dyslipidaemia, promotes atherosclerosis. Excess beta cell workload eventually leads to beta cell dysfunction and/or death, resulting in reduced beta cell functional mass. Once beta cell mass is reduced, workload on residual beta cells is further exaggerated, creating a vicious cycle. Finally, when beta cells fail to compensate, hyperglycaemia develops. After the development of diabetes, microvascular complications occur; therefore, to prevent both micro and macrovascular complications, reducing beta cell workload at an earlier stage prior to the onset of diabetes is needed.

DI: disposition index; IGT: impaired glucose tolerance; NGT: normal glucose tolerance; T2DM: Type 2 diabetes mellitus.

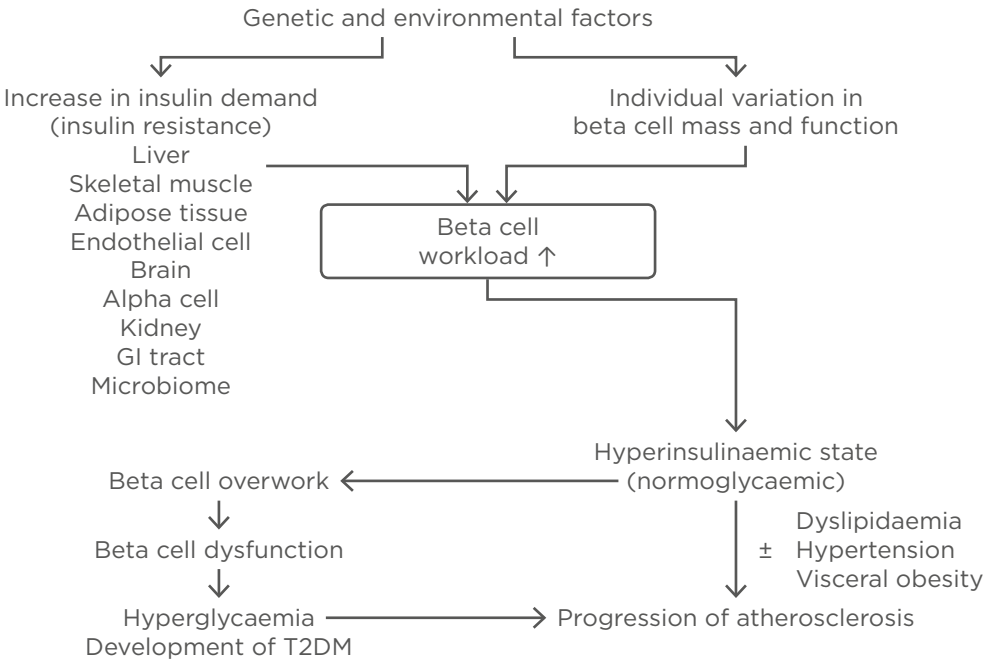

Figure 2: The beta cell-centric concept of Type 2 diabetes mellitus.

This concept emphasises the role of beta cells as the core pathoaetiological feature of T2DM and a therapeutic target to prevent the condition and its complications.

GI: gastrointestinal; T2DM: Type 2 diabetes mellitus.

Moreover, amelioration of hyperinsulinaemia may reduce the risk of developing cancer and dementia, which is increased in patients with T2DM.[55-57] The beta cell-centric concept is, therefore, a core therapeutic strategy to extend healthy longevity in people with and without diabetes (Figure 2).

CONCLUSION

A paradigm shift from a glucose-centric to a beta cell-centric concept of T2DM management will provide a continuous and integrated view of the pathophysiology involved in the development of T2DM. The beta cell-centric concept of diabetes has also recently been proposed and discussed in detail by other investigators.[58-60] Continuous and integrated understanding of the process during the development of obesity, IFG or IGT, and T2DM, as well as the progression of microvascular complications and ASCVD, will lead to more vigorous interventions in clinical practice and efforts to explore novel therapeutic strategies aimed at beta cell protection. Sharing this concept with patients will also improve the decision-making process and adherence to treatment, including lifestyle modifications. To achieve this goal, comprehensive patient education is necessary.[61]

Various indices have been proposed to identify subjects at risk of T2DM, such as family history of T2DM, homeostasis model assessment indices, obesity and being overweight, MetS, HbA1c, fasting plasma glucose level, plasma glucose level at 2 hours during oral glucose tolerance test, insulinogenic index, and disposition index. However, further innovations, such as determining individual genetic risks for T2DM and ASCVD, identifying novel markers predicting beta cell workload within the normal range of plasma glucose levels using new technologies, such as metabolomics and proteomics, and developing a beta cell imaging technique to evaluate individual beta cell mass *in vivo*, will enable fostering of precision medicine and identification of high-risk individuals who need early intensive intervention.

In conclusion, obesity is an established risk factor for T2DM and ASCVD and is currently one of the largest healthcare problems across the world. Therefore, reducing the incidence of obesity through a healthy lifestyle is urgent.

A paradigm shift from a glucose-centric to a beta cell-centric concept of T2DM will enable more comprehensive, integrative, and continuous intervention for individuals with obesity, IFG or IGT, and T2DM, and establish more effective prevention strategies for T2DM and its complications.

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Update on the Management of Diabetic Dyslipidaemia

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Abstract

Diabetic dyslipidaemia (DD) comprises a complex group of potentially atherogenic lipid and lipoprotein abnormalities, including both quantitative and qualitative changes. It is characterised by low high-density lipoprotein cholesterol, elevated low-density lipoprotein cholesterol (LDL-C), and a higher prevalence of small, dense LDL particles, as well as elevated fasting and postprandial triglycerides. Patients with Type 2 diabetes mellitus have an increased prevalence of lipid abnormalities and controlling dyslipidaemia in these patients has a big impact on morbidity and mortality. Lifestyle changes are still the pillar of treatment for DD and statins are the drugs of choice that decrease LDL-C and reduce cardiovascular events and cardiovascular death, either in primary or secondary prevention, in diabetic patients. Pitavastatin has a number of pleiotropic effects that reduce the metabolic changes associated with adiposity and improve glucose metabolism, which distinguishes it from other statins. New treatments, such as PCSK9 inhibitors, have proven to be powerful LDL-C-lowering agents; however, the need for long-term safety studies and the high associated costs are the main challenges. Future treatments, such as an intracellular PCSK9 inhibitor, a dual proliferator-activated receptor-alpha/gamma agonist, and bempedoic acid, are in development. The aim of this article is to review the pathophysiology of DD and discuss its role in cardiovascular event risk and treatment, as well as to study the effects of lipid-lowering therapy on glucose metabolism and the outcomes of antidiabetic treatment on dyslipidaemia.

INTRODUCTION

Diabetic dyslipidaemia (DD) is characterised by low levels of high-density lipoprotein cholesterol (HDL-C), elevated levels of low-density lipoprotein cholesterol (LDL-C), and a higher prevalence of small, dense LDL particles, as well as elevated fasting and postprandial triglycerides (TG). The major link between diabetes and the higher risk of cardiovascular disease in these patients is related to these common lipid abnormalities.[1] However, the underlying pathophysiology is only partially understood. Alterations in insulin-sensitive

pathways, increased concentrations of free fatty acids (FFA), and low-grade inflammation play a role and result in the overproduction and decreased catabolism of TG-rich lipoproteins (TRL) of intestinal and hepatic origin.[2] This article will review the pathophysiology of DD, discuss its role in cardiovascular event risk and treatment, and evaluate the effects of hypolipidaemic treatment on glucose metabolism and the outcomes of antidiabetic treatment in dyslipidaemia. The future directions and perspectives of non-statin therapies are also reviewed.

PATHOPHYSIOLOGY AND LIPID ABNORMALITIES IN TYPE 2 DIABETES MELLITUS PATIENTS

DD forms a complex group of potentially atherogenic lipid and lipoprotein abnormalities, including both quantitative and qualitative changes. The main alterations associated with DD (known as the triad of DD) are detailed below.

Increased Plasma Triglycerides

The metabolism of lipids in diabetes, particularly Type 2 diabetes mellitus (T2DM), is influenced by a series of factors, including the degree of glycaemic control and the presence of insulin resistance, which are the most prominent elements. Insulin resistance is the basis of the pathophysiological mechanisms of DD and is closely related to hypertriglyceridaemia and postprandial lipaemia.[3] Insulin reduces very LDL (VLDL) production by decreasing circulating levels of FFA, which are substrates of VLDL, and by exerting a direct inhibitory effect on VLDL production in hepatocytes. It has been shown that insulin inhibits the maturation phase of VLDL assembly through the phosphatidylinositol 3-kinase pathway, preventing the transfer of bulk lipids to VLDL precursors. This mechanism is involved in the inhibitory effect of insulin related to the secretion of VLDL. The binding of insulin to its receptor induces tyrosine phosphorylation of insulin receptor substrates, leading to the activation of phosphatidylinositol 3-kinase, which, once activated, induces the transformation of phosphatidylinositol 4,5-bisphosphate into phosphatidylinositol 3,4,5-triphosphate and leads to the activation of Akt, a serine/threonine kinase that is an effector of the metabolic actions of insulin.[1]

An important consequence of insulin resistance, with respect to lipid metabolism, is the loss of the suppressive effect of insulin on the mobilisation of adipose tissue fat.[4] As a result, there is an increase in FFA due to a reduction in the suppression of lipolysis. The lack of suppression of FFA in the postprandial period results as a consequence of the decrease in lipoprotein lipase activity, and the increase in plasma FFA is due to an increase in lipolysis in adipocytes. These form the key mechanisms that underlie the increase in hepatic TG secretion of VLDL.[5]

In healthy individuals, insulin inhibits the assembly and secretion of VLDL particles through an increase in the degradation of apolipoprotein B (ApoB) and a decrease in the expression of microsomal transfer protein in the hepatocytes. As a consequence, insulin inhibits hepatic secretion of TG-VLDL and ApoB-100.[6] In T2DM patients and those with other states of insulin resistance, an increase in microsomal transfer protein expression occurs in the liver, along with an increase in lipid bioavailability (i.e., the flow of FFA), and this leads to an overproduction of TG-VLDL and VLDL-ApoB. In this context, the overproduction of hepatic VLDL corresponds to large, floating VLDL particles, which are a predominant feature of DD. Most of the increase in TRL observed in DD is due to VLDL particles.[6]

Low Concentrations of High-Density Lipoprotein Cholesterol

The increase in plasma TG presents a central lipid exchange between TRL and HDL particles. There is an increase in the transfer of esterified cholesterol to the TRL, facilitated by the cholesterol ester transfer protein, and the transfer of TG to the HDL particles, which leads to an enrichment of TG in these particles. HDL TG are a suitable substrate for hepatic lipase and hydrolysis produces smaller HDL particles and free ApoA-I that are excreted by the kidneys. The catabolism of small HDL is faster than that of normal HDL, and this results in a reduction in the amount of circulating HDL particles.[7]

Predominance of Small, Dense Low-Density Lipoproteins and Excessive Postprandial Lipaemia

Small dense LDL particles (Phenotype B) are a prominent feature of DD and the number of these atherogenic particles is increased. It has been repeatedly confirmed that the concentration of plasma TG is the most important determinant of the size of LDL.[8] On the other hand, the size of LDL decrease progressively as glucose tolerance worsens, until overt diabetes is achieved. This decrease is greater in women than in men.[8]

TG of VLDL are the main predictors of LDL size in individuals with T2DM, and kinetic data indicate that VLDL are the precursors of small, dense LDL particles.[9] In fact, the long residence time of VLDL in the plasma, due to the reduction of lipolysis, is a prerequisite for the formation of small, dense LDL since it favours the excess lipid exchange of TG and cholesterol esters between TRL and LDL. When the LDL have depleted cholesterol esters and an enrichment of TG, an increase in the action of hepatic lipase results in the formation of the subclass of small, dense particles. Since each particle of LDL contains a molecule of ApoB-100, the number of small, dense LDL is increased and, similarly, the concentration of ApoB-100 increases in direct relation. Consequently, ApoB concentrations are a marker of the number of atherogenic particles and hypertriglyceridaemia with hyper-ApoB-100 is a well-known feature of DD and other conditions.[9]

CARDIOVASCULAR RISK AND DIABETIC DYSLIPIDAEMIA

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in patients with diabetes.[10] Diabetes itself is a major cardiovascular risk factor and the coexistence of other risk factors, such as hypertension and dyslipidaemia, is frequent. In particular, patients with T2DM have an increased prevalence of lipid abnormalities.[10] These lipid abnormalities are largely shared between two conditions when defined by HbA1c levels (HbA1c: >6.5% [48 mmol/mol] are classified as T2DM; HbA1c: 5.7–6.4% [39–46 mmol/mol] are classified as prediabetes). Prediabetes is characterised by lower ApoA-1 and HDL cholesterol levels and higher TG levels and ApoB/ApoA-1 ratio. Subjects with diabetes show lower ApoA-1, HDL cholesterol, and TG levels. When subjects treated with lipid-lowering drugs were excluded, no differences in LDL or non-HDL cholesterol were found between subjects with prediabetes and diabetic patients.[11]

It is very important to address multiple cardiovascular risk factors simultaneously. Thus, the maximum benefit is achieved when diabetes, hypertension, dyslipidaemia, smoking, and albuminuria are considered altogether. Controlling cardiovascular risk factors has a large impact on morbidity and mortality, which has been documented in many clinical trials.[10] Statin therapy reduces cardiovascular events and cardiovascular death, either in primary or secondary prevention, in diabetic patients.[10-15] Data from meta-analyses (>18,000 patients; mean follow-up: 4.3 years) show a 9% reduction in all-cause mortality and 13% reduction in vascular mortality for each 39 mg/dL reduction in LDL-C.[16]

Statins are the drug of choice for LDL-C treatment. Nowadays, the initiation of a statin in diabetic patients is mainly guided by focussing on the patient, particularly considering their age and history of previous cardiovascular events (primary or secondary prevention). As in non-diabetic people, absolute risk reduction will be greatest in subjects with a higher risk, but the benefits of statin therapy in people with diabetes at a moderate or low risk for ASCVD are also documented.[17]

Estimating cardiovascular risk in diabetic people can be challenging and diabetes itself confers an increased risk of ASCVD. Risk calculators are not useful in this population because they often do not include diabetes, its duration, or the presence of complications. Thus, the management of lipids in these patients relies on published evidence, guideline indications, and clinical judgement.

At diagnosis, or in those with a short duration of disease, diabetes is not a coronary artery disease (CAD)-risk equivalent state.[18,19] In general, risk levels approach CAD-risk equivalence after around a decade or in those with proteinuria or a low estimated glomerular

filtration rate.[20,21] Emerging data suggest that patients who develop T2DM at a younger age have a high complication burden.[22] People with diabetes and CAD have a vascular risk that exceeds that of CAD patients without diabetes, and have a substantially lower life expectancy.[23]

TREATMENT OF DIABETIC DYSLIPIDAEMIA

Treatment Targets

The American Diabetes Association (ADA) guidelines[10,24] recommend the following treatment for DD:

1. People <40 years:

- No ASCVD: no statin.
- With ASCVD: high-intensity statin (Table 1).

2. People ≥40 years:

- No ASCVD: moderate-intensity statin (Table 1).
- With ASCVD: high-intensity statin (Table 1) .

With ASCVD, if LDL-C is ≥70 mg/dL, despite a maximally tolerated statin dose, consider an additional LDL-lowering therapy (e.g., ezetimibe, PCSK9 inhibitor).

The Joint European Society of Cardiology (ESC) guidelines[18] also recommend lipid-lowering agents (principally statins) in patients with diabetes (Type 1 or Type 2) >40 years of age. They use LDL targets to guide therapy:

- In patients with diabetes at a very high risk (diabetes with target organ damage such as proteinuria or with a major risk factor, such as smoking or marked hypercholesterolaemia or marked hypertension), the LDL-C target is <1.8 mmol/L (<70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).
- In patients with diabetes at a high-risk (most other people with diabetes, with the exception of young people with Type 1 diabetes mellitus and without major risk factors that may be at low or moderate risk), the LDL-C target is <2.6 mmol/L (<100 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 2.6 and 5.1 mmol/L (100 and 200 mg/dL).

Table 1: High and moderate-intensity statin therapies.

High-intensity statin ↓LDL >50%	Moderate-intensity statin ↓LDL 30–50%
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin 80 mg
	Pitavastatin 2–4 mg

LDL: low-density lipoprotein.

Adapted from American Diabetes Association[24]

ESC guidelines also highlight that non-HDL-C is a reasonable and practical alternative target because it does not require fasting. Non-HDL-C secondary targets include:

- 2.6 mmol/L (100 mg/dL) for very high-risk subjects.
- 3.3 mmol/L (130 mg/dL) for high-risk subjects.

There is increasing evidence of a very high relative risk in younger individuals with T2DM so additional studies and guidance are needed in this group.[22]

Non-Pharmacological Therapy

Lifestyle Changes

Lifestyle changes remain the pillar of treatment, not only for DD but for diabetes in general, and are strongly advised for diabetic patients.[24] Nutritional therapy should be adapted to each patient and there is not enough evidence to recommend an ideal distribution of principal macronutrients. In terms of cardiovascular risk, the total amount of fat consumed is less important than the type of fat. In general, recommendations must focus on reducing cholesterol and saturated and trans-fat intake, and increasing fibre, n-3 fatty acids, and plant stanols/sterols intake. A Mediterranean-style diet (rich in monounsaturated and polyunsaturated fats) has been shown to be effective at improving lipid profile and glycaemic control.[24] In addition, the loss and maintenance of weight (of at least 5%), if indicated, is associated with

improvements in lipid levels.[10,25] Dietary fats and processed foods are rich in advanced glycation end-products, which are primarily elevated in diabetic patients, and an excessive consumption of these can increase the total pool in the body. Advanced glycation end-products can raise oxidative stress and increase arterial endothelial dysfunction.[26]

Physical activity, fundamentally aerobic exercise alone and in combination with resistance exercise, improves certain cardiovascular risk factors, including blood pressure, glucose metabolism, BMI, and waist circumference, but the effects on lipid parameters are inconsistent and sometimes contrasting. Combined exercise has shown better outcomes than each exercise separately.[27] The ADA recommends ≥150 minutes of moderate-to-vigorous aerobic activity weekly, divided between at least 3 days, combined with two or three sessions per week of resistance exercise on non-consecutive days. A combination of exercise and diet obtains better weight loss than diet alone and shows better improvements in lipid profile than exercise alone.[25,27] Smoking cessation is associated with elevation of HDL-C levels,[28] but there are no specific data in diabetic patients. Alcohol consumption must be moderate and should be avoided in hypertriglyceridaemia patients.[10]

Pharmacological Therapy

Classic Drugs

Diabetes is associated with a marked increased risk of premature ASCVD. Patients with diabetes have a high prevalence of lipid abnormalities and there is strong evidence that lowering cholesterol blood levels improves cardiovascular outcomes, even in patients with unremarkable lipid profiles.[29-31]

Statins are the first-choice drugs for lowering LDL-C in patients with diabetes and work by inhibiting HMG-CoA reductase, which is responsible for the production of cholesterol in human cells. The effectiveness of statins in diabetes relies on the upregulation of liver LDL receptors.[5] These drugs clear chylomicron remnants, intermediate-density lipoproteins, and LDL particles from the blood. The decreased LDL blood levels reduce the amount of the highly atherogenic oxidised-LDL and glycated-LDL as a consequence.[32]

The effectiveness of statins at reducing cardiovascular disease, all-cause mortality, and cardiovascular mortality has been observed in several clinical trials.[10] They are generally well tolerated; the most common adverse effects of statins are myalgias, which can, in rare cases, lead to rhabdomyolysis and increased levels of liver enzymes.

Moderate-intensity statin therapy (a 30–50% reduction target from pretreatment LDL-C level) is recommended in primary prevention for diabetic patients >40 years. Secondary prevention therapy with high-intensity statins (a >50% reduction target from pretreatment LDL-C level) should always be recommended (Table 1).[10,24]

Statin treatment raises glycaemia, with a subsequent increase in the incidence of T2DM, particularly in patients with a predisposition to the condition.[28,30] This effect correlates with statin potency dose[33] and with its hydrophilic (i.e., rosuvastatin) or lipophilic (i.e., atorvastatin) nature. Lipophilic statins are more diabetogenic because they can penetrate extrahepatic cell membranes, such as beta cells and adipocytes, while hydrophilic statins are more hepatocyte-specific. A high hepatoselectivity translates into minimal interference with cholesterol metabolism in tissues other than the liver and, consequently, in less diabetogenicity.[34] However, it must be highlighted that the benefits of lowering LDL-C levels outperform the risks of worse glycaemic control. Pitavastatin has a number of pleiotropic effects that reduce the metabolic changes associated with adiposity and improve glucose metabolism (suppressed GLUT4 expression, for example), which distinguishes it from other statins.[30,35]

Ezetimibe can be used in combination with statins in patients who do not achieve the therapeutic target. This drug limits dietary cholesterol absorption and the reabsorption of bile cholesterol by blocking the protein responsible for the transportation of cholesterol in the small bowel.[36] It can be used for patients with hepatic or renal dysfunction. The IMPROVE IT trial[37] demonstrated that the association of statins plus ezetimibe in diabetes patients resulted in a superior reduction of major adverse cardiovascular events over simvastatin therapy alone.

Fibrates reduce hepatic synthesis of VLDL by activating the peroxisome proliferator-activated receptor-alpha and increasing the activity of lipoprotein lipase that hydrolyses TG in lipoproteins. These drugs decrease TG levels, modestly increase HDL levels, and reduce total cholesterol but, in some patients, there is an increase in LDL levels because the treatment accelerates the degradation of VLDL to LDL.[38] The FIELD study[39] showed that fenofibrate slows progression of diabetic retinopathy and a 11% reduction of all CVD events has been reported.[40] Likewise, gemfibrozil led to a significant reduction in CVD events during a 5-year follow-up period in the VA-HIT trial;[41] however, the absolute benefits in primary prevention are modest and its use in monotherapy in this setting is not recommended.[42] Trials exploring the use of fibrates in combination with statins have failed to show positive results, except in those with elevated TG (>200 mg/dL) or low HDL-C (<40 mg/dL).[43] These drugs also increase the risk of gallstones; therefore, they are not recommended in patients with history of biliary colic. They have also been associated with an increased risk of rhabdomyolysis.[44] Monotherapy with fibrates should be discouraged because there is no evidence of a reduction in all-cause mortality.

Bile acid sequestrants (BAS) act in the gastrointestinal tract, exchanging chloride anions with anionic bile acids and binding them in a resin matrix. As a result of this loss of bile acids, more cholesterol (LDL) is converted to bile acid in the liver, lowering cholesterol levels.[5] There are four BAS available for the treatment of hypercholesterolaemia: colestipol, cholestyramine, colestilan/colestimide, and colesevelam.[45] These drugs are poorly tolerated due to frequent gastrointestinal side effects.[46] Apart from lipid-lowering effects, some older trials found an effect in lowering blood glucose and glycosylated haemoglobin levels (e.g., the GLOWS[47] trial). There is a paucity of evidence evaluating the impact of BAS on cardiovascular outcomes (i.e., the CPPT[48]), but the available data suggest positive results. Further studies are needed to evaluate the impact of BAS in combination with statin therapy on cardiovascular morbidity and mortality.[49]

Omega-3 fatty acids have little effect on HDL-C or LDL-C but they can lower TG levels and be used in combination with statins and fibrates.[38] However, no efficacy has been proven for the prevention of cardiovascular events in patients with glucose metabolism disorders.[29]

New Treatments

LDL particles are bound to LDL receptors and this complex is internalised into the cells to be dissociated by the endosome; LDL particles are eliminated by lysosomes and LDL receptors return to the surface to bind to another LDL particle. PCSK9 inhibitors block the dissociation of the LDL–LDL receptor complex and this is eliminated by lysosomes, reducing LDL receptor concentration and the clearance of LDL.[50,51]

Alirocumab and evolocumab are two fully human monoclonal antibodies that inhibit PCSK9 and decrease intrahepatic degradation of internalised LDL receptors, producing elevated hepatic expression of LDL receptors and a reduced level of circulating LDL-C. Both drugs have been evaluated in diverse populations, including diabetic patients, and have been proven to be safe and efficient for decreasing LDL-C concentrations in monotherapy or when given in combination with statins, with or without ezetimibe.[52,53] They have also been authorised as additional therapy for patients with ASCVD or familial hypercholesterolaemia who are taking the maximally tolerated dose of statins but who require a further reduction in their levels of LDL-C.[10]

FOURIER[54] and ODYSSEY OUTCOMES[55] showed a reduced number of cardiovascular events after treatment with evolocumab and alirocumab, respectively, related to the degree of further LDL-C lowering. While neither investigated a decrease in cardiovascular death, alirocumab, but not evolocumab, showed a decreased risk of all-cause death. In addition, more injection-site reactions than placebo have been reported for both drugs, as well as a higher rate of myalgia with alirocumab when compared with placebo.[56] No adverse neurocognitive events or side effects deriving from very low levels of LDL-C have been shown. In FOURIER, antidrug antibodies appeared in 0.3% of patients without neutralising antibodies.[54] In another trial with alirocumab,[56] 1.3% of patients developed neutralising antibodies.

Table 2: Effects of antidiabetics on lipid levels.

Drug	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglycerides
Metformin	↓ ↔	↓	↔ ↑	↓ ↔
Gliclazide	↓	↔	↔	↓
Glimepiride	↔	↔	↔ ↑	↔
Pioglitazone	↑	↔	↑	↓
Sitagliptin	↔	↔	↔ ↑	↔
Saxagliptin	↔	↔	↔	↔
Vildagliptin	↔	↔	↔ ↑	↔
Linagliptin	↔	↔	↔	↔
Dapagliflozin	↔ ↑	↔ ↑	↔ ↑	↓ ↔
Canagliflozin	↑	↑	↑	↑
Empagliflozin	↔ ↑	↔ ↑	↔ ↑	↔
Exenatide	↓ ↔	↔ ↑	↔ ↑	↓
Liraglutide	↔	↔ ↓ (small, dense LDL)	↔	↓

↓ Decrease ↓ ↔ Slight decrease ↔ No change ↔ ↑ Slight increase ↑ Increase

HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Adapted from Soran et al.[5]

Statins have shown a dose-dependent relationship with risk of new-onset diabetes and, moreover, mendelian randomisation studies with genetic variants in PCSK9 have shown an increased risk of diabetes;[53] however, the clinical trials with PCSK9 inhibitors have not shown a higher incidence of diabetes or metabolic worsening in diabetic patients.[53,56] PCSK9 inhibitors have proven to be powerful LDL-C-lowering agents; however, the need for long-term safety studies and the high associated costs are the main challenges.[10,53]

Possible Future Treatments

An intracellular PCSK9 inhibitor, inclisiran, is currently in development for diabetes; its main differences from other PCSK9 inhibitors are the intracellular inhibition of mRNA and administration only twice a year. In addition, an antisense oligonucleotide against ApoC-III has shown decreased plasma TG in Phase II–III trials.[57] 8-Hydroxy-2,2,14,14-tetramethylpentadecanedioic acid reduced total cholesterol, LDL-C, and non-HDL-C compared with placebo by modulating pathways of fatty acids and cholesterol. Saroglitazar is a dual proliferator-activated receptor-alpha/gamma agonist that reduces plasma TG, non-HDL-C, total cholesterol, VLDL, fasting plasma glucose, and HbA1c. Bempedoic acid is currently in Phase II trials and reduces LDL-C by up to 50% when combined with ezetimibe in diabetic patients.[53,57]

EFFECTS OF ANTIDIABETICS ON LIPID LEVELS

Table 2 provides a visual representation of the effects of antidiabetics on lipid levels. Metformin is often overlooked as a lipid-lowering agent and is generally considered only as a hypoglycaemic agent, but it has been associated with a significant decrease in plasma TG, total plasma cholesterol, LDL-C, and VLDL, as well as with a significant increase in plasma HDL-C.[58] This antihyperlipidaemic effect of metformin is due to the inhibition of fatty acid release from adipose tissues. Reductions in plasma

total cholesterol levels appear to be the result of decreased levels of LDL-C or VLDL. Additionally, liraglutide reduces the formation and progression of atherosclerosis; a recent study has reported for the first time that liraglutide decreases atherogenic, small, dense LDL particles known to be strongly associated with carotid atherosclerosis and CV risk.[59,60]

Other drugs used in the management of diabetes may also have unintended positive and negative effects on lipoproteins. For example, SGTL-2 receptor antagonists and pioglitazone may increase total cholesterol, LDL-C, and HDL-C, while TG levels are reduced by pioglitazone, gliclazide, exenatide, liraglutide, and dapagliflozin; however, TG levels are increased by canagliflozin.[61]

CONCLUSION

DD is characterised by qualitative and quantitative changes, such as increased TG, high LDL-C, and an alteration in the apolipoproteins of HDL. ASCVD is the leading cause of death in patients with diabetes and lifestyle changes remain the pillar of treatment for DD and diabetes as a whole. Statins continue to be the first-choice drugs for lowering LDL-C in patients with diabetes but new drugs, such as PCSK9 inhibitors, have been authorised as additional therapies for patients with ASCVD or familial hypercholesterolaemia who require a further reduction in their levels of LDL-C while taking their maximally tolerated dose of statins. New drugs used in the management of diabetes may also have unintended positive and negative effects on lipoproteins. Possible future treatments, including intracellular PCSK9 inhibitors, with administration twice per year, or dual proliferator-activated receptor-alpha/gamma agonists, are promising.

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Efficacy of Wearable Devices to Measure and Promote Physical Activity in the Management of Diabetes

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Abstract

Physical inactivity is a global health problem that contributes to the increasing risk of obesity and diabetes. Wearable devices are defined as technologies that can be comfortably worn on the body and that are designed to be effective at improving the health and overall fitness of the wearer. The aim of this narrative review is to summarise the current studies investigating the efficacy of wearable devices, especially mobile applications, for the management of diabetes. The use of pedometers or accelerometers has been shown to increase physical activity by approximately 1 hour per week; however, rates of obesity and diabetes were not affected. Although recent assessments of the effect of smartphone applications on physical activity and glycaemic control are sparse, they are useful for promoting physical activity and for treating diabetes. The interactions with patients using wearable devices for self-monitoring, education, and coaching are essential for the improvement of diabetes. However, there are currently no clinical trials investigating the efficacy of the 'perfect' wearable device, whereby patients with diabetes can accurately and comfortably monitor their physical activity, energy balance, blood pressure, heart rate, and blood glucose level. Analysis of big data from wearable device users will contribute to the development of effective wearable devices. Developments in wearable technology are anticipated and further studies will be required to assess the efficacy of wearable devices in measuring and promoting physical activity in the management of diabetes.

INTRODUCTION

In 2016, a smartphone game application, Pokémon GO, was released. The game encourages users to walk and explore their surroundings, using their mobile device's global positioning system, with the aim of catching Pokémon, which are typically located in public areas. Howe et al.[1] reported that playing Pokémon GO was associated with a moderate increase in daily physical activity; however, the increase in activity was no longer observed 6 weeks after installation of the game. Although the positive effect of Pokémon GO on physical activity tends to taper off, it is an important example of how to promote health, specifically increasing locomotive physical activity via a smartphone application.[2] Physical inactivity is a global health problem responsible for the increasing risk

of obesity and non-communicable diseases, such as diabetes, coronary heart disease, and breast and colon cancers. By increasing physical activity, the life expectancy of humans is expected to rise by 0.68 years.[3] Increasing physical activity is the cornerstone of obesity and diabetes management, two conditions that are now worldwide public health epidemics. Not only regular exercise, but also daily physical activity, is important for the prevention and management of obesity and diabetes;[4,5] therefore, it is essential for clinicians to measure and promote physical activity in individuals with these conditions.

There are many electronic technologies and computers that can comfortably be worn on the body and perform many tasks in conjunction with hand-held devices such as smartphones.[6] For example, commercially available wearable devices use applications to monitor vital signs and physical activity. However, there are challenges to the development of simple and powerful applications for medical use, and wearable health monitoring systems are becoming important for long-term health management, playing a pivotal role in the health of the elderly population.[7] Chen et al.[8] designed 'smart clothing' that incorporates mobile applications, cloud computing, and big data analytics in a wearable health monitoring system. The smart clothing includes a vital sign monitor, ECG, electroencephalogram, and blood oxygen monitor. It is clear to see that wearable devices, such as smart clothing, will have a large impact on healthcare.

While there is still no perfect wearable device for measuring physical activity, pedometers, accelerometers, and smartphone applications can be regarded as prototypic wearable devices. Although a systematic review and meta-analysis has shown that interventions using computer, mobile, and wearable technology tools reduce sitting time by approximately 40 minutes per day,[9] the feasibility, acceptability, and effectiveness of mobile-based technology to promote active lifestyles in individuals with Type 2 diabetes mellitus (T2DM) are inconclusive.[10] The focus of this review is to summarise the current studies investigating the efficacy of wearable devices (including pedometers, accelerometers, and mobile applications) for the management of diabetes and to discuss the future prospects for using wearable devices in clinical care.

PEDOMETERS AND ACCELEROMETERS

Pedometers are simple physical activity monitoring devices that display step count and are used by many people for health and fitness. Accelerometers were first developed in the 1980s and have been used extensively for measuring physical activity under free-living conditions. Recently developed accelerometers can characterise activity patterns (i.e., locomotive or non-locomotive movements) in addition to estimating physical activity and energy expenditure.[11] There have been a number of studies investigating the efficacy of pedometers and accelerometers for the management of diabetes, and randomised controlled trials (RCT) have also been conducted to investigate the usefulness of pedometers and accelerometers in patients with diabetes.[12-16] Baskerville et al.[17] assessed the impact of pedometers and accelerometers on physical activity and HbA1c levels in patients with T2DM. This systematic review and meta-analysis analysed nine pedometer studies and three accelerometer studies. The use of these devices increased free-living physical activity by approximately 1 hour per week; however, no significant effects were observed in BMI, HbA1c levels, blood pressure, or lipid profile in patients with T2DM. The heterogeneity between study duration and the types of pedometers and accelerometers used was a limitation of this meta-analysis, as well as the fact that all study subjects were physically active, with normal glycaemic control (average HbA1c: 7.6%) or progressed diabetic complications. However, these results indicate that physical activity monitoring (wearing pedometers and accelerometers) may be insufficient for improving diabetes. In addition, although there were strong correlations between accelerometer and pedometer-measured steps per day,[18] accelerometers can detect more steps than pedometers[19,20] and pedometers may not be suitable for monitoring daily physical activity in frail older individuals with slow gaits.[20] Some studies recommend the use of pedometers in normal-weight individuals, whereas accelerometers are more suitable for obese individuals.[21] On the other hand, accelerometer-

measured sedentary time was unfavourably associated with insulin sensitivity and triglycerides in cross-sectional data.[22] It is important to give individual feedback on physical activity data and instructions to patients for the management of diabetes, and the interaction with patients using smart devices will be required to achieve sufficient clinical effects.

SMARTPHONE APPLICATIONS AND WEARABLE ACTIVITY TRACKERS

In 2017, the percentage of people who used a smartphone was 77% in the UK, 78% in the USA, and 64% in Japan.[23] Considering the large number of smartphone users, interventions using electronic health (eHealth) and mobile health (mHealth) strategies are a promising way to promote physical activity. Several systematic reviews and meta-analyses have reported that internet-delivered intervention,[24] social media,[25] and smartphones[26] are useful for increasing daily physical activity. Moreover, eHealth and mHealth strategies may also be effective for improving obesity and diabetes outcomes: mobile phone application-based interventions were associated with a reduction in body weight (-1.04 kg) and BMI (-0.43 kg/m^2). Thomas et al.[27] also reported that a commercial programme for treating obesity, named Weight Watchers Online, could effectively reduce body weight in obese individuals, whereas participants with activity tracking devices did not achieve an additional increase in physical activity. However, the efficacy of eHealth and mHealth in increasing physical activity in patients with diabetes has not been fully investigated.

The author searched English literature using PubMed/MEDLINE and EMBASE. To identify potential studies the following search terms were used: "diabetes," "smartphone" or "wearable device," "physical activity" or "exercise," and "randomized controlled trial." Studies were included if they met the following criteria: study subjects were ≥18 years of age and were diagnosed as having diabetes or prediabetes, the study was a randomised controlled trials, and the study duration was ≥12 weeks. Four studies were eligible (Table 1).[28-31]

Table 1: Randomised controlled trials investigating the efficacy of a smartphone application and wearable activity tracker for the management of diabetes.

Study	Subjects (versus control group)	Intervention	Results
Plotnikoff et al.,[28] 2017	84 patients with T2DM and/or a high risk of T2DM. Age: 44.2±13.5 years versus 45.1±14.7 years. Sex: (male/female) 30/12 versus 29/13. BMI: 35.0±5.9 kg/m^2 versus 31.7±5.1 kg/m^2. HbA1c: NA.	eCoFit (smartphone application) Study duration: 20 weeks.	Aerobic fitness↑, upper and lower body muscular fitness↑, functional mobility↑, systolic blood pressure↓ physical activity↑, and waist circumference↓ at the 10-week follow-up.
Block et al.,[29] 2015	339 subjects with prediabetes. Age: 55.0±8.8 years versus 54.9±9.1 years. Sex: (male/female) 111/52 versus 122/54. BMI: 31.1±4.5 kg/m^2 versus 31.2±4.3 kg/m^2. HbA1c: 5.6±0.3% versus 5.6±0.3%.	Alive-PD (internet, smartphone application, and automated phone calls) Study duration: 6 months.	HbA1c↓, fasting blood glucose↓, weight↓, BMI↓, waist circumference↓, the ratio of T G/HDL-C↓, and self-reported physical activity↑.
Frias et al.,[30] 2017	109 patients with T2DM and hypertension. Age: 57.8±1.1 years versus 61.6±1.7 years. Sex: (male/female) 35/45 versus 19/10. BMI: 31.8±0.9 kg/m^2 versus 31.3±1.0 kg/m^2. HbA1c: 8.7±0.2% versus 8.3±0.4%.	Digital medicine offering (Proteus Digital Health) Study duration: 4 or 12 weeks.	Systolic blood pressure↓ and LDL-C↓; no statistically significant change in HbA1c levels.
Wang et al.,[31] 2018	26 patients with T2DM (mobile group: 11; paper group: 9; control group: 6). Age: 58.8±5.9 years versus 49.2±10.2 years. Sex: (male/female) 2/9 versus 1/5. BMI: 38.9±9.0 kg/m^2 versus 33.7±2.7 kg/m^2 . HbA1c: 8.4±2.3% versus 8.9±1.6%.	LoseIt! (smartphone application) Study duration: 6 months.	Weight↓ and adherence to self-monitoring for diet and physical activity↑; no statistically significant change in HbA1c levels.

↑: increased; ↓: decreased; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NA: data not available; T2DM: Type 2 diabetes mellitus; TG: triglyceride.

Plotnikoff et al.[28] assessed the efficacy of an innovative lifestyle programme named eCoFit to improve health and fitness in patients with T2DM. The eCoFit application consists of workout circuits (eCoFit Challenge), self-monitoring functions (Fit Mind Challenges), and a link to social media (Facebook). This application instructs users where and how to increase physical activity in the city of Newcastle upon Tyne, UK, and integrates aerobic exercise and resistance training using the outdoor environment in the city. Aerobic fitness (evaluated using the single stage submaximal treadmill walking test), lower body muscular fitness (evaluated using the chair stand test), upper body muscular fitness, and functional mobility were all improved after 10 weeks of intervention. Physical activity also increased by an average of 1,330 steps per day, while waist circumference (-2.8 cm) and systolic blood pressure (-10.4 mmHg) were reduced. Moreover, aerobic fitness, lower and upper body muscular fitness, functional mobility, waist circumference (-2.14 cm), and systolic blood pressure (-11.3 mmHg) improved in the study subjects compared with the controls at the 20-week follow-up. However, no significant differences in physical activity, diastolic blood pressure, or BMI were observed between the groups. The retention rate was 71% at the 20-week follow-up. This RCT suggests that intervention using a smartphone application and social media has the potential to increase physical activity in patients with T2DM. The eCoFit is also unique in its practicality in locating places to exercise in the public space. However, the study participants were relatively young and might have been more motivated to engage in physical activity than typical patients with T2DM. The generalisability of the results remains to be tested.

A fully automated, tailored, online behavioural change programme using a mobile phone application can effectively improve glycaemic control and obesity, although it does not monitor physical activity continuously.[29] The Alive-PD provides a 1-year programme for the prevention of diabetes and includes individually tailored goal setting and other activities that are supported by the internet, email, and a mobile phone application. Participants set goals of 150–300 minutes of aerobic exercise per week based on their self-reported physical activity level at baseline, and the programme recommends personally achievable small-step goals of dietary and physical activity habits. In addition, Alive-PD provides tools for tracking diet, physical activity, and weight; health information on diabetes; virtual social support; feedback on diet and physical activity; and weekly reminders. Furthermore, Alive-PD has a point system with monetary rewards and team competition, promoting engagement and retention. The retention rate was 86.1% at the 6-month follow-up assessment. The mean reduction in fasting glucose level was greater in the Alive-PD group (-7.36 mg/dL) compared with the control group (-2.19 mg/dL), as was the mean reduction in HbA1c level (-0.26% and -0.18%, respectively). Body weight, BMI, and the ratio of triglycerides to high-density lipoprotein cholesterol were all also significantly reduced in those taking part in the programme. Furthermore, after a 6-month intervention, the Framingham 8-year diabetes risk was reduced from 16% to 11%. Self-reported physical activity, dietary habits, sleep, fatigue, and self-confidence were improved. Therefore, this internet and mobile-based programme was clinically effective at preventing the incidence of diabetes and these results show that eHealth and mHealth strategies can be a valuable tool for diabetes prevention and management.

A recent RCT conducted in the USA by Frias et al.[30] investigated the effect of a digital medicine offering that measures physical activity using medication taken with an ingestible sensor, wearable sensor patches, and a mobile application. Patients with uncontrolled hypertension and T2DM were enrolled in a 12-week RCT. The ingestible sensor is activated when the patients take a pill, which sends a specific signal that is detected by the wearable sensor patch. Patient information is recorded and transmitted to a mobile application, secure cloud storage, and a web portal. All clinical data are used by the healthcare team, and the investigators review reports on the web portal, adjust medications, and provide patient education and counselling at any time. The mean adherence was 84% for 12 weeks. The digital medication offering group had a significant reduction in systolic blood pressure compared to the usual care group at Week 4 (-21.8 mmHg versus -12.7 mmHg, respectively); this reduction

was maintained at Week 12 (-24.6 mmHg versus -15.2 mmHg, respectively). On the other hand, no significant difference in HbA1c reduction was observed between the digital medication offering group and controls. However, in patients with a baseline HbA1c of ≥8%, the digital medication offering group showed a significant decrease in HbA1c compared to an increase of HbA1c in the usual care group (-0.31% versus 0.26%, respectively). The change in physical activity was not measured; thus, the effect of a digital medicine offering on physical activity promotion was unknown. Nonetheless, digital medicines may improve self-care in patients with T2DM.

Wang et al.[31] assessed the feasibility of the mHealth intervention and compared its efficacy with the paper-based behavioural intervention and standard care in individuals with T2DM. The participants in the mHealth group used the LoseIt! smartphone application for self-monitoring diet, physical activity, and weight loss, as well as Diabetes Connect connected with a Bluetooth®-enabled glucometer (MyGlucoHealth). This pilot study was a small-scale RCT that enrolled 26 subjects, approximately 70% of whom were African-American. The retention rates at 3 and 6 months were 96% and 92%, respectively. The median percentage of days with self-monitoring entries for diet, physical activity, weight, and glucose level were 96.6%, 37.3%, 49.7%, and 72.7%, respectively, in the mHealth intervention group; these numbers were significantly higher than those in the paper-based intervention group. The 6-month mHealth intervention decreased participants' HbA1c levels from 8.4% to 6.9%, whereas those using the paper-based intervention had an average HbA1c level of ≥9% for 6 months; the control group exhibited no change in glycaemic control. In addition, the participants in the mHealth intervention group achieved an average weight loss of 1.8%, whereas the paper-based intervention group and controls showed weight gain. Patient adherence to self-monitoring of physical activity was low compared to their dietary monitoring. However, the adherence rate for physical activity in the paper-based intervention group was only 1.2%, which suggests that a mobile application was useful for self-monitoring of physical activity. Using mHealth tools has the potential to increase patient adherence to behavioural self-monitoring and to improve diabetes and obesity.

These studies showed that using smartphone applications could promote physical activity and help control weight, blood pressure, and lipid levels in the management of diabetes. However, no study duration was >6 months; thus, the long-term efficacy of smartphone applications for the management of diabetes is not clear.

Smartphones are useful as activity tracking devices.[32,33] However, steps measured by iPhone step counts seem to be underestimated by approximately 1,340 steps per day in the free-living condition.[34] Smartphone applications also underestimate changes in the time spent undertaking light-intensity and moderate-to-vigorous-intensity physical activity and overestimate changes in sedentary time with reference to an accelerometer.[35] Wearable devices, including smartphone applications, can reliably measure heart rate, distance, and sleep duration; however, the measurement of energy consumption is still inaccurate.[36] It is indisputable that the manufacturers of wearable devices that measure physical activity should improve their algorithms and devices for medical use.

FUTURE STUDIES

Although current evidence regarding the impact of wearable devices on the management of diabetes is limited, a number of well-designed studies are ongoing. Alonso-Domínguez et al.[37] are investigating the effect of a multifactorial intervention that includes the use of a smartphone application, EVIDENT II, on changes to physical activity in primary care. In addition, Valentiner et al.[38] are investigating whether 8–12 weeks of interval walking training supported by the smartphone-based InterWalk application is effective for increasing moderate and vigorous-intensity physical activity in patients with T2DM. Recently, a RCT investigating whether an mHealth intervention using a smartphone application (Pregnant+) improves glycaemic control in women with gestational diabetes has been completed.[39] The primary outcome of this study focussed on the 2-hour blood glucose level during an oral glucose

tolerance test; however, the secondary outcome included change in physical activity.

The DiaCert-study evaluated the effect of a 12-week smartphone application intervention aimed at increasing physical activity in Swedish patients with T2DM.[40] It is noteworthy that physical activity and sedentary behaviour were measured by the wGT3x-BT triaxial accelerometer (Actigraph, Pensacola, Florida, USA) in addition to counting daily steps by a smartphone application. Muralidharan et al.[41] are investigating the feasibility, cost-effectiveness, and sustainability of an mHealth intervention programme (mDiab) in individuals at high risk of T2DM in India. The mDiab programme involves 12 weeks of video lessons for diabetes prevention, tracking of lifestyle behaviours, and weekly communication with health coaches. The outcomes include weight loss, changes in physical activity, diet, quality of life, and cardiometabolic risk factors. This RCT focusses on the prevention of T2DM in individuals with prediabetes and/or obesity.

Exergaming is a novel approach to increase physical activity (e.g., Pokémon GO). Höchsmann et al.[42] developed a smartphone-based, game-like software application and platform (MOBIGAME) specifically designed for middle-aged patients with T2DM. The players' physical activity is responsible for their achievements in the game, and they are motivated to increase physical activity in reality. The results should indicate whether exergaming is useful for increasing physical activity in middle-aged individuals as well as adolescents. Osborn et al.[43] reported that using the One Drop mobile application on iPhone and Apple Watch was associated with a reduction in HbA1c levels of 1.36%. There are many commercial smartwatches that show promise in healthcare[44] and the smartwatch is the most familiar wearable device to consumers; collection and analysis of big data from real-world users will contribute to the development of a perfect wearable device.

Furthermore, artificial intelligence will play a crucial role in the development of wearable devices for the management of diabetes. Artificial intelligence methods have become increasingly important for diabetes management: blood glucose control, blood glucose prediction, detection of adverse glycaemic events, detection of meals and exercise, insulin bolus calculators, and lifestyle support in diabetes management.[45] Therefore, artificial intelligence methods in combination with wearable devices will enable the creation of personalised diabetes management.

CONCLUSION

In conclusion, using smartphone applications and accelerometers or pedometers in the management of diabetes is effective for promoting physical activity, and the future of wearable device looks promising for the healthcare field. Ideally, everybody should be able to wear high-tech devices without feeling uncomfortable. For individuals with diabetes, physical activity, blood glucose level, blood pressure, heart rate, and energy intake and consumption should be objectively and accurately measured using wearable devices, such as glasses, watches, belts, and shoes, under a free-living condition. Wearable, non-invasive epidermal glucose sensors are currently under development and will improve glycaemic control and reduce the risk of complications.[46] However, such wearable devices are still not routinely used and there are currently no clinical trials investigating the efficacy of the perfect wearable device for promoting physical activity and treating diabetes. On the other hand, a smartphone could be a substitute for a wearable device if users always carry it with them. In addition, in recent years, big data have become increasingly important in scientific research. Big data analysis integrates a large amount of heterogeneous data, such as demographic, physiological, biomedical, and omics (e.g., genomics, epigenomics, and metabolomics) data in medicine.[47] The ehealth data recorded by wearable devices will be useful for big data analyses in the future. The results of the studies included in this review demonstrate that wearable devices have a beneficial potential for the management of diabetes. However, ideally, systematic searches and statistical evaluation should be performed to assess all the relevant studies. Therefore, it remains inconclusive whether using wearable device is truly effective for the management of diabetes and the improvement in wearable technology and further studies are required.

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Low-Carbohydrate Diets and Glycaemic Control in Type 1 Diabetes Mellitus

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Abstract

In recent years the successful treatment of Type 2 diabetes mellitus through total calorific and/or dietary carbohydrate restriction has been well established. The use of low-carbohydrate diets for the adjunctive management of Type 1 diabetes mellitus has been studied but to a lesser extent. Over the past 20 years, a growing body of evidence has examined the effects of daily carbohydrate restriction on the key markers of glycaemic control, including blood glucose variability, average daily blood glucose readings, and HbA1c. The majority of publications to date have demonstrated a beneficial impact of carbohydrate reduction on glycaemic control. Indeed, similar findings have also been replicated using diets restricted to foods with a low glycaemic index. Interestingly, following a low-carbohydrate diet can also uncover the hyperglycaemic effects of fat and protein consumption, and the clinical implications of this will be discussed within this review. There is evidence, however, to suggest that these diets can be difficult to adhere to and that they may even pose health risks to the patient. Acutely, they can cause hypo or hyperglycaemic events, potentiate the risks of ketosis, and deplete systemic glycogen stores. The long-term effects of a low-carbohydrate diet are not well documented; however, possible complications can include alterations in lipid profiles, micronutrient deficiencies, cardiac complications, and nephrolithiasis. This review presents an overview of the major studies to date that have looked at carbohydrate dietary manipulation and the subsequent impact on glycaemic control in populations with Type 1 diabetes mellitus.

INTRODUCTION

In recent years much research has demonstrated the beneficial effects of low-carbohydrate and/or low-calorie diets on the clinical outcomes of patients with Type 2 diabetes mellitus (T2DM). Some of these regimes have shown a significant improvement, and occasionally pre-diabetic states approaching normoglycaemia have been achieved in certain individuals.[1,2] The volume of studies examining carbohydrate intake manipulations in patients with Type 1 diabetes mellitus (T1DM) over the past 40 years have been more limited, but the results are promising.

The therapeutic use of low-carbohydrate diets in patients with T1DM has been used historically. Prior to the advent of medicinal insulin in the 1920s, management of this condition was via adherence to a strict low-carbohydrate intake or an intense fasting regime.

The latter was hazardous, and patients often succumbed to emaciation or infection due to an undernourished immune system. However, just before the advent of parenteral insulin, promising results promoting careful adherence to a low-carbohydrate, high-fat diet emerged. These were even quoted as 'staving off the emergence of severe acidosis.'[3]

This article reviews the studies to date that have investigated the use of carbohydrate manipulation to ameliorate glycaemic control in patients with T1DM. Additionally, the authors explore the challenges and the possible complications of following such a diet.

CARBOHYDRATES AND CIRCULATING GLUCOSE

Carbohydrates are one of the three macronutrients that are consumed in the human diet, with the other two being fat and protein. Carbohydrates can exist in several forms, including simple monosaccharides (e.g., glucose and fructose), disaccharides (e.g., sucrose and lactose), or in a polymeric form, sometimes known as complex carbohydrates (e.g., starch).[4] Simple carbohydrates are very typically cheap and readily available, and it is unsurprising that they form an increasingly dominant proportion of processed food consumed in the developed world.[5]

The glycaemic load (GL) refers to the total amount of carbohydrate in any foodstuff, and by how much this will raise blood glucose (BG) levels. Additionally, the type of carbohydrate also affects postprandial glycaemic rise. The glycaemic index (GI) is a method of relatively ranking this change. Mono or disaccharides tend to have a higher GI, with complex carbohydrates having a lower GI.[6] Consumption with protein or fat can lower the GI, leading to a more gradual postprandial rise in BG.[7]

METHODOLOGY

The authors of this article searched the databases of MEDLINE, Google Scholar, The Cochrane Library, and Web of Science for articles published between 1st January 1980 and 5th July 2018. Studies included were control trials, cohort studies, case-controls, cross-sectional studies, and case reports. Relevant review articles and meta-analyses were individually checked to ensure referenced studies were included. Participants were limited to T1DM patients following low-carbohydrate or low-GI diets. Outcomes were limited to the measures of glycaemic control (HbA1c, average daily BG, and BG variability).

LOW-CARBOHYDRATE AND LOW-GLYCAEMIC INDEX FOODS IMPACT ON GLYCAEMIC CONTROL

Dietary manipulation, specifically the adjustment of the GL of meals, has a significant influence on circulating BG levels thereafter.[6] In the past 40 years, several studies have looked at how low-carbohydrate diets and/or low-GI diets affect glycaemic control in patients with T1DM. This review presents and discusses the clinical impact of these findings, with particular reference to low-carbohydrate diets (Table 1).[8-16]

In 2018, Eiswirth et al.[8] reported on the impact of a very low-carbohydrate diet (30–50 g) on average BG values, daily variability, and HbA1c in a patient over a 6-month period. They found a near normalisation of glycaemic indices (HbA1c: 34 mmol/mol; average daily BG: 6.1 mmol/L) with no significant hypoglycaemic episodes and minimal impact on circulating lipids. Although this was a case report limited to a single patient, the findings were further corroborated by a larger study, which examined 11 patients with T1DM over a 2–3-year period.[9] Sustained consumption of <55 g carbohydrate daily demonstrated similar alterations in HbA1c levels (average HbA1c: 35 mmol/mol; average daily BG: 6.1 mmol/L) as well as reduced daily BG variability. However, the study showed an overall increased risk of hypoglycaemic episodes as well as an increase in non-high-density lipoprotein circulating lipids. The study was well designed and patients were followed-up for an average of 2.6 years. However, due to the low participant numbers the authors concluded that caution must be observed with the diet and larger scale studies were merited.

Ranjan et al.[10] presented the short-term impact of either a high (>250 g) or low (<50 g) carbohydrate diet on glycaemic indices in a

2-week crossover trial. Their findings revealed similar average daily BG measurements between the two groups. In the low-carbohydrate diet group, significantly reduced BG variability was noted and, furthermore, a significantly higher proportion of the BG readings fell in the 3.9–10.0 mmol/L range compared to the high carbohydrate diet. It was a well conducted study, limited only by participant numbers (n=10). Another small trial in 2016,[11] demonstrated significant HbA1c reductions (63–55 mmol/mol) in five patients following a carbohydrate restricted diet (average of 100 g) over 12 weeks. There were no adverse changes observed in BP, renal function, or lipid profiles. The study found that carbohydrate restriction required larger than predicted insulin doses to adequately control BG, which is discussed in a subsequent section of this review.

Nielsen et al.[12] published an interventional study of 24 patients with T1DM, who followed a low-carbohydrate diet (70–90 g) for 1 year.

Table 1: Impact of altered dietary carbohydrate load on glucose homeostasis in patients with Type 1 diabetes mellitus.

Study	Type of study	N	CHO intake	Duration	HbA1c (mmol/mol)	Insulin dose	Daily BG (mmol/L)	Variability	Other notable findings
Eiswirth et al.,[8] 2018	Case report	1	30–50 g daily	6 months	Reduction from 58.0 to 35.0	Reduced from 50.0 to 30.0 units	Reduced from 10.4 to 6.1	Reduced by 27.0%	No change in lipid profile, no significant hypoglycaemic events
Leow et al.,[9] 2018	Observational study	11	<55 g daily	2.6 years	Maintenance at 35.0	18.4 units daily	Average 5.8	Low, SD 1.5 mmol/L	Raised lipids, higher hypoglycaemic rates
Ranjan et al.,[10] 2017	Crossover study	10	<50 g daily	1 week	N/A	21.6 units daily	No significant change from control 7.4	Reduced by 27.0% to 1.9 mmol/L	Increase in circulating ketones, no change in lipid profile
Krebs et al.,[11] 2016	Randomised control trial	10	<75 g daily	12 weeks	Reduction from 63.0 to 55.0	Reduced from 64.0 to 44.0 units	Reduced from 10.2 to 8.9	N/A	No change in lipid profile
Nielsen et al.,[12] 2005	Cohort study	15	70–90 g daily	1 year	Reduction from 59.0 to 46.0	Reduced from 21.1 to 12.4 units	Reduced from 12.9 to 5.9 in a representative patient	Reduced	Static cholesterol, TG decreased, low number of hypoglycaemic events
Nielsen et al.,[13] 2012	Cohort study	48	<75 g daily	4 years	Reduction from 61.7 to 42.1	Reduced from 23.0 to 13.0 units	Reduced from 14.0 to 6.4 in a representative patient	Reduced	Increase in HDL, no change in LDL
Baechle et al.,[14] 2018	Cross-sectional study	712	Increased total daily	N/A	Increased HbA1c	N/A	N/A	N/A	N/A
Lennerz et al.,[15] 2018	Observational online survey	31	36±15 g daily	2.2 years	Reduction from 54.0 to 38.5	0.4 units/kg/day	Averaged 5.9	N/A	Low rates of severe hypoglycaemia, raised HDL and LDL, low TG
McKewen,[16] 1999	Crossover study	7	59% of total calorific intake	3 weeks	N/A	15.0% increase with high CHO intake	Average increase of 10.0%	N/A	Decreased muscle glycogen and reduced exercise performance

BG: blood glucose; CHO: carbohydrate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; N/A: not applicable; SD: standard deviation; TG: triglycerides.

They found significant reductions in HbA1c (58.5–46.4 mmol/mol), reduced BG variability, a nearly 6-fold reduction in hypoglycaemic events, a 16% reduction in serum triglycerides, and unchanged serum cholesterol levels. It was well conducted with significant findings, limited only by the small numbers, with data from 15 subjects used in the final analysis. These discoveries were replicated several years later by the same group who examined the impact of low carbohydrate intake on glycaemic control over 4 years on a group of 48 patients.[13] Restriction to a daily carbohydrate intake of <75 g resulted in a sustained decrease of average HbA1c from 61.7 to 42.1 mmol/mol. Moreover, daily variability in BG readings was reduced as well. Interestingly, even patients only partly adherent to this diet over time sustained a reduction in HbA1c from an average of 59.6 to 51.9 mmol/mol. Conversely, patients who returned to a normal diet trended back to their average baseline HbA1c of 57.4 mmol/mol. The study gave a valuable observation into the impact of a low-carbohydrate diet on glycaemic variables, as well as providing extended follow-up that demonstrated the favourable longer-term dietary effects.

Beyond direct interventions, observational data have also demonstrated the beneficial impact of a low carbohydrate intake on glycaemic control in patients with T1DM. A nationwide survey of 712 11–19 year-olds with T1DM in Germany revealed a direct relationship between increased HbA1c and carbohydrate intake at breakfast and total daily carbohydrate intake.[14] Additionally, an online survey of 316 patients following a low-carbohydrate diet (both adults and children) was published in 2018.[15] Lennerz et al.[15] found a normalisation of HbA1c (38.5 mmol/mol), with a low incidence of hospitalisation for ketoacidosis (1%) or hypoglycaemia (1%). The latter study did have several limitations, including an inability to confirm all medical data. Moreover, the study was pursued through an online social media group, which also increased the risk of selection bias.

Evidence further supporting that moderation of carbohydrate intake is beneficial for improved glycaemic control was further validated by a study over two 3-week periods that included seven males with T1DM.[16] The subjects were grouped into a high carbohydrate diet group or a normal mixed diet group. Overall, a marked negative effect was noted with excessive carbohydrate intake. This caused a deterioration in glycaemic control (raised mean BG measurements), reduced exercise performance, and decreased glycogen storage.

Independent of the GL, low-GI diets can also improve the glycaemic control of patients, as demonstrated by an observational study by Queiroz et al.[17] One hundred and forty-six patients (7–19 years old) were reviewed, and those who consumed either a lower carbohydrate (GL: <100) or lower GI (<55) diet had better glycaemic control than those who had a higher consumption of either high-carbohydrate or high-GI diets.

A publication by Giacco et al.[18] investigated the long-term effects of a high-fibre, low-GI diet (average GI: 70%) versus a diet with an average GI of 90%. This was a large multicentre study that included 63 patients with T1DM. After 24 weeks, average daily BG, HbA1c measurements, and hypoglycaemic events were significantly lower in the low-GI diet group. Notably, the low-GI diet GI diet contained significantly more fibre (50 g versus 15 g), which may have had an influence on the improved glucose homeostasis. Reinforcing these findings, a small trial over 6 weeks found that a low-GI diet resulted in a more blunted postprandial BG rise following a carbohydrate challenge and also improved lipid parameters in a study of seven children.[19]

Even acute alterations in GI intake can have a marked influence on BG values. This was highlighted in a study of 23 paediatric patients, which examined the impact, in terms of glycaemic control, of alternating between a low-GI (<55) and a normal diet on 2 different days. The results were promising and revealed a 32% drop in average BG values on low GI days, as well as a reduction in the number of hyperglycaemic events.[20] Another crossover paediatric trial of 20 patients in 2008 also found that low-GI diets can acutely reduce average daily BG readings from 10.2 mmol/L to 7.6 mmol/L, and reduce excursion out with the normal range. However, the study did demonstrate an increase in the frequency of minor hypoglycaemic events.[21] Extrapolating this, a long-term trial with 104 children over 12 months found significantly lower HbA1c values

in low-GI diets compared with carbohydrate exchange diets (64.5 versus 70.6 mmol/mol). Moreover, the low-GI diets resulted in fewer episodes of hyperglycaemia, better quality of life, and similar levels of hypoglycaemia.[22]

Further evidence in adults supporting low GI intake was presented by Lafrance et al.[23] in 1998, who demonstrated that short-term intake of lower GI foods (GI of 66 versus 77) over 12 days was associated with lower daily average BG measurements in a crossover study of nine patients. Conversely, it is already known that consumption of high GI foods, such as cornflakes, cause a rapid rise in postprandial glucose,[24] which can be more difficult to correct. However, low GI foods not only cause a gentler postprandial rise, but the BG area under the curve has been found to be up to 20% lower with lower GI food in macronutrient-matched meals.[25] Such data highlight not only the importance of careful meal planning in terms of carbohydrate counting and load but also demonstrate that all carbohydrate sources are not equal in their net glycaemic effect.

Convincing large-scale observational data exist supporting the beneficial impact of low GI intake. A publication from the EURODIAB study of >2,800 patients with T1DM has shown that lower GI foodstuff consumption is linked to significantly lower HbA1c levels.[26] Another publication analysed the same dataset and found higher carbohydrate intake to be associated with significantly increased HbA1c levels.[27] Evidence further supporting these findings was published in a study of both patients with T1DM and T2DM in 2006.[28] This study found that lower GI diets (25% lower mean GI) improved HbA1c levels by an average of 19%. There were similar findings in a meta-analysis of 14 randomised control trials examining the impact of low GI diet on T1DM and T2DM.[29] The authors found an overall 7.4% reduction in HbA1c measurements with this dietary intervention.

Collectively, much evidence has shown the beneficial impact of low-GI or low-carbohydrate diets on key markers of stable glucose homeostasis. However, not all studies have supported the use of a low-carbohydrate or low-GI diet to improve glycaemic control, and indeed some have produced some conflicting evidence. The Diabetes Control and Complications Trial (DCCT) examined associations of nutritional intake, physiological parameters, and impact of daily activities on average HbA1c.[30] The authors found that lower carbohydrate and higher fat intake were associated with higher HbA1c measurements. Furthermore, a paper published in 2015 studied 33 patients with T1DM, using linear regression models to compare nutritional intake and glycaemic indices.[31] The authors demonstrated that increased carbohydrate intake was associated with greater periods of time spent in a euglycaemic state and less in a hyperglycaemic state. They postulated that the reason for this was that the patients were only correcting for glucose intake and were possibly not correcting the fat and protein content of their diet, thus creating a mismatch with the insulin dosing. This provides a credible explanation as to why, on occasion, low-carbohydrate diets can result in raised glycaemic indices.

In summary, a significant body of research from diverse study types has demonstrated that low-carbohydrate diets have the potential to reduce average HbA1c and BG variability in patients with T1DM. Low-GI diets have also shown clinical benefit; however, if an individual consumes large volumes of low GI food and increases their total GL then they risk negating the improvements in glycaemic control. In a similar manner, intake of high carbohydrate foodstuffs tends to cause a deterioration of glycaemic control. When consuming a low-carbohydrate meal, it would appear to be essential to also consider the impact of other macronutrients and correct insulin accordingly. Failure to do so may result in hyperglycaemia. The findings presented here must be taken with caution as larger, longer-term research is needed to explore the acute and chronic impacts of these diets. However, in order to pursue this several challenges and cautions should be addressed.

DIETARY CHALLENGES AND GLUCOSE HOMEOSTASIS

Modern diets are predominantly carbohydrate-rich. Worldwide guidelines differ regarding optimal target carbohydrate levels, but generally advise that carbohydrates should

constitute from 45–65% of the total daily caloric intake.[32] This equates to approximately 225–325 g carbohydrate per day, whereas a low-carbohydrate diet aims to restrict carbohydrates to <130 g per day and a very low-carbohydrate diet to usually <30–50 g per day.[33] Such a dramatic reduction can be difficult, as it requires a good knowledge of food excipients, as well as careful meal planning on a daily basis. It may be restrictive in social situations, such as eating in restaurants or when consuming convenience food. Furthermore, there may be added financial costs, as many protein-rich foods (e.g., meat, fish, fowl, dairy) are more expensive than carbohydrate-rich alternatives (e.g., potato, rice, cereal, bread).[34]

Supporting patients through significant dietary change requires close input from dietitians, as well as the endocrinology and the primary care teams. This should be undertaken in a guided and transitory manner, facilitating incremental adjustments to lifestyle, cooking, and eating patterns over several weeks to months. Ideally, ketone levels should be monitored closely, as well as a personalised titration of insulin to nutritional intake to prevent hypo or hyperglycaemic events. Following a diagnosis of T1DM, patients are routinely taught by their clinical team how to match carbohydrate intake with insulin dosing for each meal;[35,36] however, low-carbohydrate diets have a higher proportion of fat and protein content, which can also influence the pattern of postprandial glycaemic homeostasis.[7]

The evidence examining the effect of protein and fat on postprandial BG has been conflicting, but several recent studies have shown these macronutrients can independently and significantly impact BG. A study of 33 children by Smart et al.[37] revealed an additive effect of both protein and fat to BG values 180–300 minutes post meal. Indeed, Paterson et al.[38] demonstrated that an intake of 75–100 g of protein had a similar impact on BG measurements to 20 g carbohydrate after 240–300 minutes in control participants with T1DM. It was noteworthy that the postprandial increase in BG due to protein was more gradual compared to the rapid rise following carbohydrate intake. Although smaller doses of protein (21.5 g) have been found to have no appreciable effect on BG,[39] severely restricting protein in the diet has been shown to cause a decrease in average daily BG by up to 30%, which was found to be mediated partly by reduced hepatic gluconeogenesis.[40]

In a recent case study, a patient with a daily carbohydrate intake <30 g regularly had to correct for fat and protein in her diet with larger boluses of insulin.[8] This phenomenon showing that protein or fat can lead to postprandial glycaemic rises was also replicated by Krebs et al.[11] and Uthoff et al.[41] The latter paper studied 16 T1DM volunteers, and consistently found a rise in BG of an average of 2.2 mmol 4 hours after consumption of a fat and protein dominant meal. In line with this, dietary fat has also been shown to increase postprandial BG, independently of either carbohydrate or protein.[42] The biochemistry underpinning these findings is complex; however, we know that glucose can be actively generated from protein catabolism through gluconeogenesis. It is not unreasonable to suggest that this process may be driven forward during a ketogenic diet and may partially explain the observed findings.

To address this phenomenon, two algorithms have emerged which help correct for consumption of these other macronutrients. These include the Warsaw Pump Therapy School formula,[43] also known as the 'Warsaw formula,' and the Food Insulin Index method.[44] They have both been found to decrease postprandial hyperglycaemic events; however, there is a potential increased risk of hypoglycaemia in the postprandial period with the Warsaw formula.[43]

CAUTIONS AND COMPLICATIONS

If a low-carbohydrate diet is adopted by an individual with T1DM, then several precautions should be acknowledged because clinical risks may exist. Acutely, alterations in biochemistry include risks of ketosis, hypo or hyperglycaemia, and glycogen depletion.[9,30,31,45] With minimal carbohydrate intake, the body will increasingly catabolise protein and fat and become more dependent on circulating ketone bodies. In a normal individual these are unlikely to pose an acute health risk; however, in patients with T1DM they may contribute to an increased risk of ketoacidosis.[46,47] On a more practical matter, as BG is generally lower due to decreased carbohydrate intake, there is the possibility of

overcorrection when titrating insulin resulting in hypoglycaemia.

Another significant biochemical alteration can become more apparent, specifically the potential to deplete glycogen stores. This can blunt the physiological response to glucagon and contribute to hypoglycaemic mechanisms.[48] It is essential, therefore, that when glucagon is required, supplementary carbohydrate should be administered as well, especially in patients following a reduced carbohydrate diet.

There are longer term risks to patients that low-carbohydrate diets may exacerbate. A review article published in 2016 explored these in detail, with specific attention to long-term complications, including growth alterations, hyperlipidaemia, nephrolithiasis, micronutrient deficiencies, and cardiac complications.[47] Additionally, a series of six detailed case reports by de Bock et al.[49] reinforced the risks associated with low-carbohydrate diets in children, including reduced growth velocity, increased risks of hypoglycaemia, micronutrient deficiencies, and dyslipidaemia. Collectively, these findings suggest caution is required in the use of such a diet in paediatric patients and may in theory be extrapolated to the adult population as well.

CONCLUSION

The emerging evidence supporting carbohydrate-based dietary modification for supplementary management of T1DM is indeed both controversial and compelling. In the short to medium-term it can lower daily BG variability and in certain cases even return HbA1c values to normal levels.[8,9] Importantly, it is known that the amelioration of both of these parameters is associated with improved microvascular and macrovascular outcomes in patients with T1DM.[50] However, this diet may be too restrictive or too difficult to adhere to for certain patients, and it is not without any adverse risks.[47,49] These findings highlight the importance of a multidisciplinary approach in supporting patients wishing to pursue a low-carbohydrate diet, particularly providing guidance on how to follow such a diet in a safe and structured manner. The authors acknowledge that there are quantitative gaps in the literature that need to be addressed. Additionally, as insulin pumps can independently improve glycaemic control,[51] low-carbohydrate dietary studies within this subgroup of patients also merits more detailed review. In conclusion, further research with larger scale studies conducted over an extended period are warranted to establish the long-term impact of low carbohydrate dietary manipulation on the overall health outcomes of patients with T1DM.

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Growth Hormone and Metabolic Homeostasis

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Abstract

Pituitary growth hormone (GH) is a peptide hormone predominantly secreted by somatotrophs in the anterior pituitary under the tight control of the hypothalamic–pituitary axis and GH secretagogues. GH elicits its effects directly on target organs and cells interacting with GH receptors and through stimulation of insulin-like growth factor 1 production. GH plays critical roles in regulating somatic growth and the metabolism of carbohydrates, lipids, and protein. GH increases insulin secretion and glucose uptake. Conversely, a GH deficient state is characterised by enhanced insulin sensitivity. Diabetogenic actions of GH are evident in conditions of GH excess, such as acromegaly or poorly controlled Type 1 diabetes mellitus. In patients with GH deficiency, administration of GH resulted in impaired glucose tolerance and insulin sensitivity. Owing to its multiple and complex effects, the regulation of GH secretion and its function in normal health and metabolic diseases is a major research interest in the field of molecular endocrinology. This review provides an overview of the effects of GH on glucose, lipid, and protein metabolism, insulin resistance, and metabolic homeostasis.

INTRODUCTION

Hormones control several steps of intermediary metabolism, including glucose oxidation, glycogen metabolism, gluconeogenesis, and fatty acid oxidation. The importance of hormones from the anterior pituitary, the islets of Langerhans, adrenal glands, and the thyroid in intermediary metabolism is well recognised. Over recent years there has been a significant increase in the understanding of how these hormones regulate metabolic homeostasis. An array of hormones, including insulin, glucagon, adrenaline, cortisol, thyroxin, amylin, glucagon-like peptide-1, glucose-dependent insulinotropic peptide, and pituitary growth hormone (GH), play prominent roles in the maintenance of glucose metabolism and homeostasis. Impaired glucose homeostasis is evident in several clinical conditions

characterised by altered hormone levels, such as diabetes mellitus (Type 1 [T1DM] and Type 2), obesity, metabolic syndrome, hypothyroidism, Cushing's disease, and acromegaly. Among the endocrine factors, pituitary GH deserves special attention owing to the myriad direct and indirect roles GH has on somatic growth, musculoskeletal anabolism,[1] and regulation of carbohydrate, protein, lipid metabolism, and body fat distribution.[2] The pituitary gland was first linked to carbohydrate metabolism when increased sensitivity to insulin was identified in hypophysectomised dogs, in a classic study by the Argentinian physiologist, Bernardo Alberto Houssay.[3] Increased sensitivity to insulin was reversed when hypophysectomised animals were injected with pituitary extracts. A direct effect of GH was identified by demonstrating that injection of GH reduced glucose uptake in both adipose tissue and skeletal muscle.[4] GH counteracts the overall effects of insulin on glucose and lipid metabolism;[5] glucose uptake by skeletal muscle and adipocytes was blocked when both insulin and GH were co-administered.[4]

Acromegaly is a condition caused by elevated levels of circulating GH, usually secondary to a pituitary adenoma.[6] In addition to inappropriate tissue and skeletal growth, acromegaly is characterised by perturbations of intermediary metabolism and diabetes.[7] Ever since the Houssay studies showed reduced insulin requirement and improvement of hyperglycaemia in hypophysectomised animals,[3] the influence of GH on glucose homeostasis has been explored by several studies.[8-10] GH decreases glucose tolerance and glucose use that, in turn, results in compensatory hyperinsulinaemia. Prolonged administration of GH can induce diabetes in adult animals.[11] A moderate elevation in the circulating levels of GH results in a spectrum of abnormal metabolic fuel concentrations associated with poor diabetes control. Patients with poorly controlled T1DM exhibit a 2–3-fold increase in GH levels that result in significant metabolic abnormalities.[12] Thus, the hypersecretion of GH in T1DM may serve as a major contributor of poor glycaemic status associated with the disease.[13] Humans with GH deficiency exhibit a higher BMI with obesity, hypertension, and elevated C-reactive protein levels. GH deficiency is associated with increased visceral adipose tissue.[14] Treatment with either recombinant human GH (rhGH) or enhanced endogenous GH secretion affects glucose metabolism, reduces visceral fat, and ameliorates dyslipidaemia.[15] This review discusses the metabolic perturbations such as hyperglycaemia, hyperinsulinaemia, and insulin resistance that arise due to alterations in GH levels, including the conditions of GH excess (acromegaly and T1DM) and GH deficiency.

GROWTH HORMONE SECRETION

GH secretion occurs episodically and is primarily under the control of two hypothalamic neuroendocrine hormones: GH-releasing hormone (GHRH), which stimulates GH secretion, and somatostatin, which inhibits GH secretion (Figure 1). Several other endocrine mediators also regulate GH gene transcription, including insulin-like growth factor 1 (IGF-1). IGF-1 is a major suppressor of GH transcription, whereas thyroxine, glucocorticoids, and ghrelin stimulate GH secretion. GH secretion also exhibits sexual dimorphism due to differential effects of oestrogen versus the androgens on GH. Pulsatile GH secretion occurs with a major surge at the onset of slow-wave sleep with less noticeable secretory episodes a few hours after meals. In healthy individuals, GH pulses discharge every 1–3 hours at an average of 45 µg per pulse, which equates to approximately 400–500 µg released every 24 hours, which occur as pulses within pulses. Autocrine secretion of GH by non-pituitary sources, such as mammary epithelial cells, have also been reported.[16]

In circulation, the preponderance of GH binds to the GH binding protein (GHBP), which regulates GH bioavailability. GHBP corresponds to the extracellular domain of the GH receptor (GHR) and is generated by proteolytic cleavage of the extracellular domain of the GHR in humans. In contrast, in rodents, alternative splicing of the GHR transcript generates GHBP. Hepatic IGF-1 secretion is one of the best-characterised effects of GH action. IGF-1 is also produced locally by tissues and elicits its effect via a paracrine and/or an autocrine manner. IGF-1 plays a critical role in inhibiting the secretion of the GH via negative feedback by stimulating somatostatin and inhibiting GHRH release (Figure 1). IGF-1 also has a direct effect on GH secretion,

which is independent of GHRH and somatostatin. It is noteworthy that GH and IGF-1 secretion are regulated by each other, where the former induces the latter and the latter induces the former in a feedback loop. In healthy individuals, GH secretion is inhibited by hyperglycaemia and stimulated by sleep, stress, exercise, hypoglycaemia, and amino acids.

GROWTH HORMONE SIGNALLING

GH exerts its pleiotropic effects by binding to GHR. The prevailing model is that GHR exists as an inactive dimer and a single molecule of GH binds to two GHR molecules. The binding of the GH molecule to the extracellular domain of the GHR facilitates rotation of the two GHR molecules that results in the intracellular domain of each GHR molecules binding to a JAK2 molecule.[17] JAK2 constitutively associates with the cytoplasmic domain of GHR and in the unliganded states the pseudokinase domain of JAK2 masks its catalytic domain. Binding of GH to the GHR re-orientates and rotates the receptor subunits, which results in the transition from parallel transmembrane domains to one where the transmembrane domains separate at the point of entry into the cytoplasm.[18] This arrangement facilitates the movement of the pseudokinase inhibitory domain of one JAK2 away from the kinase domain of the other JAK2 within the receptor dimer–JAK2 complex. This results in the transactivation of JAK2. Activated JAK2 then phosphorylates the cytoplasmic domain of the GHR, which then recruits several downstream proteins as depicted in Figure 2.

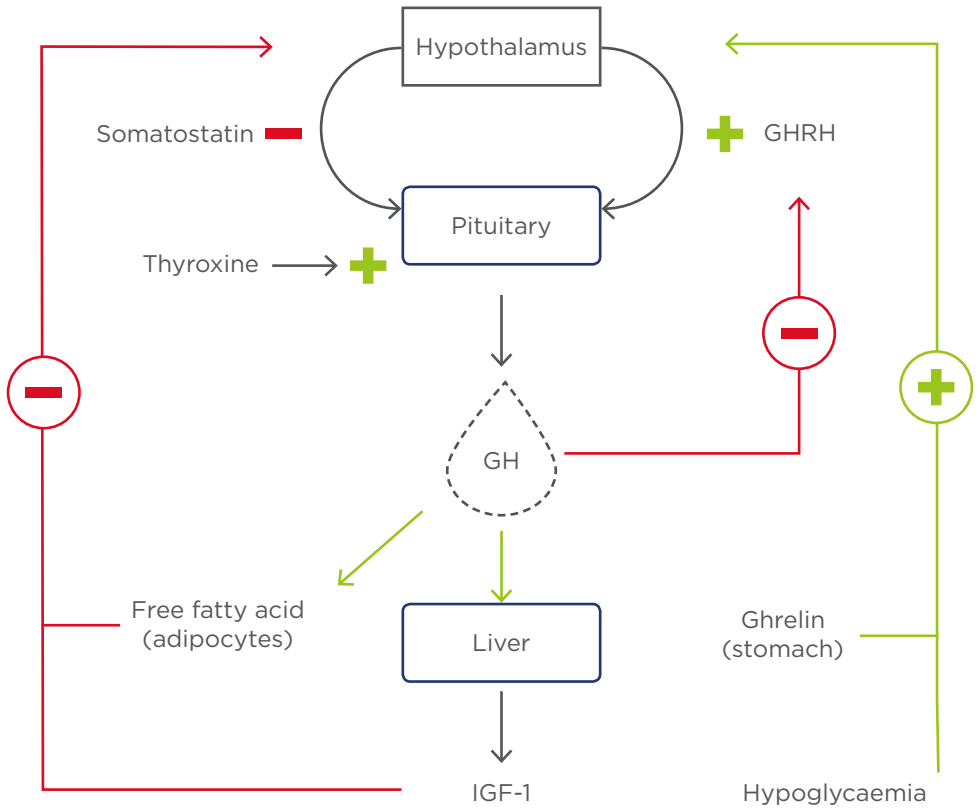

Figure 1: Factors regulating growth hormone secretion.

GH secretion by the pituitary gland is regulated by two hypothalamic hormones: GHRH, which has a stimulatory action at the level of gene transcription, and somatostatin, which has an inhibitory effect on GH secretion. IGF-1 plays a crucial role in regulating GH. IGF-1 is secreted by the liver under the influence of GH; however, IGF-1 also regulates GH release via a negative feedback loop. Elevated levels of circulatory IGF-1 stimulates somatostatin, thus resulting in decreased secretion of GH. High levels of GH inhibit GHRH. Ghrelin is a gastric hormone that positively regulates GH release, whereas plasma free fatty acids and low glucose levels also stimulate GH under physiological conditions.

GH: growth hormone; GHRH: growth hormone-releasing hormone; IGF-1: insulin-like growth factor.

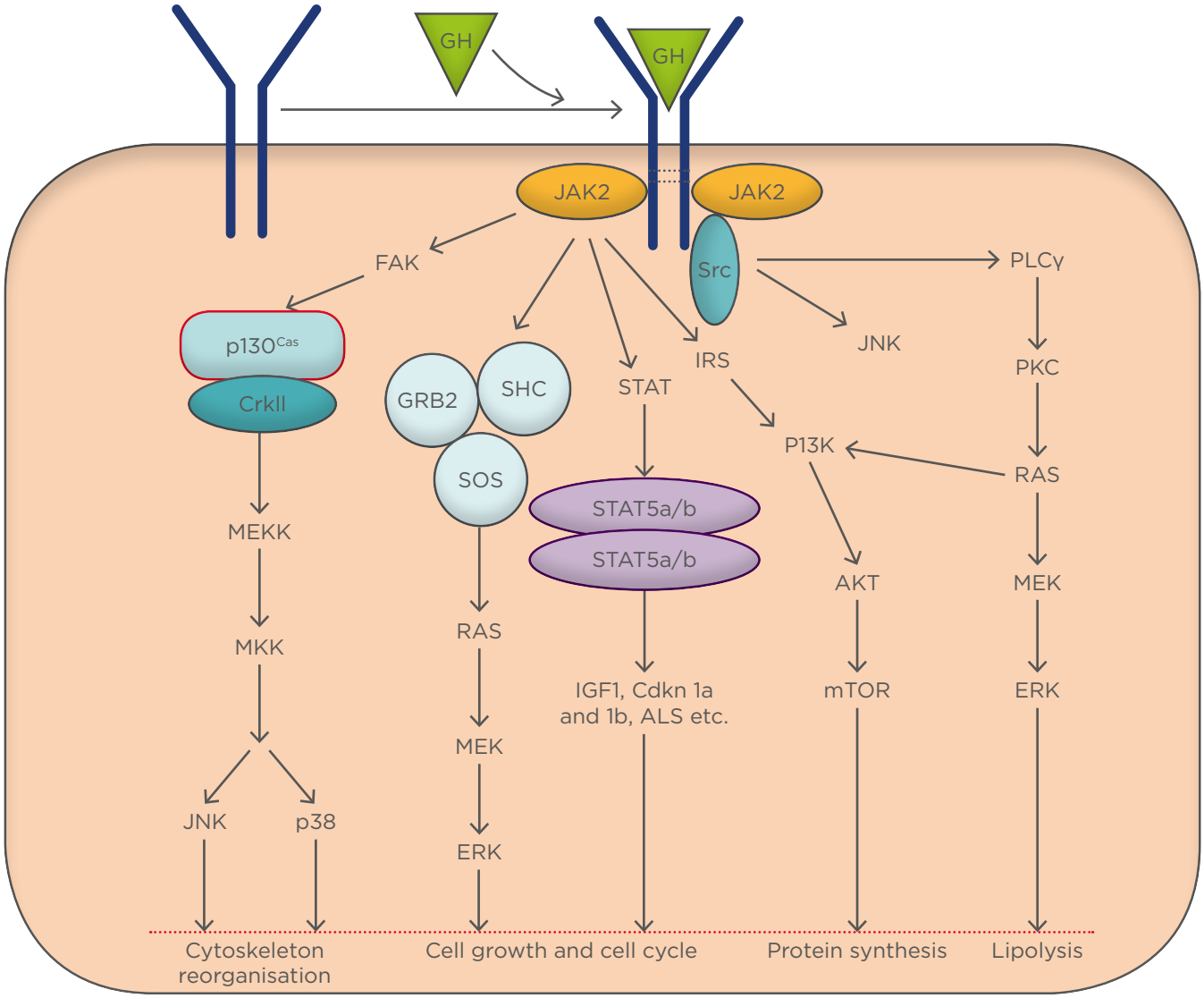

Figure 2: Cellular and molecular events triggered by growth hormone signalling.

GH acts via a variety of signal transduction pathways. Multiple GH signalling pathways can contribute to specific GH responses. GH binds to GHR and activates JAK2, which in turn triggers an array of signalling cascades. These interconnected signal transduction pathways regulate various metabolic and cellular events.

FAK: focal adhesion kinase; GH: growth hormone; GHR: growth hormone receptor; GRB2-SOS: growth factor receptor-bound 2-son of sevenless complex; IRS: insulin receptor substrate; PI3K: phosphatidylinositol 3-kinase; SH2-Bβ: src-homology 2 domain Bβ; STAT: signal transducer and activator of transcription.

Activation of JAK2 is a critical step for triggering GHR signalling. The STAT family of transcription factors is recruited to the activated GHR–JAK2 complex. STAT proteins are phosphorylated at a single tyrosine residue by JAK2. Phospho-STAT then undergo either homo or hetero-dimerisation and migrate to the nucleus where they act as transcription factors. Among various STAT proteins, STAT5b exerts the majority of the biological effects of GH. GHR can also activate MAPK, downstream of both JAK2 and Src kinase. GHR localisation to the lipid raft preferentially activates MAPK while cytosolic GHR localisation activates STAT5. Insulin receptor substrate-1 (IRS-1) plays a critical role in GHR-induced MAPK activation.[19] Furthermore, GHR signalling is also associated with the activation of the phosphatidylinositol-3 kinase (PI3K)/Akt pathway in a JAK2/IRS-1-dependent manner. Attenuation of GHR activation is arbitrated by the proteins of suppressor of cytokine signalling (SOCS)

family, which includes SOCS-1–7, and cytokine-inducible SH2-domain containing protein. It is noteworthy that SOCS family proteins are also induced by the JAK/STAT signalling cascade. GH itself has been shown to induce SOCS-2 and SOCS-3. SOCS proteins suppress GH signalling by inhibiting JAK2 activity and compete with STAT for binding with GHR or by inducing the proteasomal degradation of the GHR complex. Additionally, protein tyrosine phosphatases have also been implicated in terminating the GHR signal cascade.[20] JAK2 binding stabilises and prevents GHR from degrading;[21] on the other hand, GH induces desensitisation of the GHR via JAK2 kinase activity.[22]

GROWTH HORMONE AND CARBOHYDRATE METABOLISM

The pioneering work of Houssay established the role of anterior pituitary in the carbohydrate metabolism.[3] The two classical findings of Houssay include hypophysectomy ameliorated the pancreatectomy-induced diabetes in dogs, and administration of the anterior pituitary extract induced hyperglycaemia, glycosuria, and ketonuria in normal dogs.[3] Permanent diabetes was produced in dogs by injecting anterior pituitary extract.[23] Histological studies in the dogs that received pituitary extract revealed degeneration of the islets of Langerhans.[24] The diabetogenic effect of GH is further evidenced by studies that used purified GH. Several researchers, including Young[25] and Campbell et al.,[26] were able to induce diabetes in dogs and cats by administering purified GH.[11] Furthermore, it was demonstrated that GH can induce diabetes in pancreatectomised animals.[27] Hypophysectomy results in increased insulin sensitivity and prolonged GH administration abrogate the increase in insulin sensitivity.[28] In hypophysectomised animals, administration of GH elicits glucose intolerance and insulin resistance. Diaphragms from hypophysectomised rats display decreased glucose uptake when treated with GH, compared with diaphragms from hypophysectomised rats naïve to GH treatment.[29] GH inhibits the peripheral utilisation of sugars, thereby antagonising the action of insulin and serving to raise the blood glucose levels. Injection of GH into the brachial artery reduced forearm glucose uptake in both skeletal muscle and adipose tissue and blocked the action of insulin when both hormones were co-administered.[4]

The major steps in glucose metabolism include glucose uptake by tissues, such as the liver, muscles, and adipose tissue; glucose oxidation; glycogenesis; glycogenolysis; and gluconeogenesis. The precise role of GH on glucose uptake by tissues that play key roles in fuel homeostasis is unclear. Increased hepatic glucose uptake and glycogenesis were noticed in transgenic rats overexpressing the *hGH* gene, while insulin-dependent glucose uptake by adipocytes and muscle was impaired.[30] In *hGH* transgenic mice, glucose infusion rate increased to 4.4 mg/kg/min, compared to 3.1 mg/kg/min in wild-type mice, and endogenous glucose production was suppressed with pegvisomant (an GHR antagonist) treatment in acromegalic patients assessed by the euglycemic clamp technique.[31] Therefore, it was argued that the role of GH was to increase endogenous glucose production while its role in glucose utilisation is limited. Short-term exposure to GH inhibited insulin-stimulated glucose disposal by 27% and also blunted glycogen synthase activity in skeletal muscle.[32]

It has been established that GH stimulates glucose production in the liver, but it is unclear whether GH preferentially stimulates glycogenolysis or gluconeogenesis. Administration of rhGH to HIV patients for 6 months increased gluconeogenesis but not glycogenolysis.[33] In healthy volunteers, GH administration (40 ng/kg/minute for 4 hours) increased glycogenolysis without altering the rate of gluconeogenesis.[34] In a cohort of patients with acromegaly studied pre and post-pituitary microsurgery, glycogenolysis decreased by 29%, whereas gluconeogenesis remained unchanged, suggesting that GH preferentially increases glycogenolysis.[35] It is noteworthy that the expression of gluconeogenic genes was not altered in GHR-/- mice compared with wild-type mice.[36] These observations present a case for the fact that GH has a preferential effect on glycogenolysis compared to gluconeogenesis.

Contrary to the aforementioned studies, short-term administration of rhGH in lactating women increased gluconeogenesis, but not

glycogenolysis.[37] GH induces gluconeogenesis and glucose cycling in several organs, including splanchnic tissues, the liver, and adipose tissue. In healthy men, overnight administration of GH stimulates gluconeogenesis. Dogs treated with high doses (1 mg/kg/day) of GH for several days had increased liver glycogen content.[38] Although baseline uptake of glucose by muscle tissue is low, a further suppression of glucose uptake is typically seen immediately following GH administration. Concomitant with decreased glucose oxidation, suppressed muscle glucose uptake in the presence of unchanged glucose turnover strongly suggests that GH promotes non-oxidative glucose disposal in a non-muscle compartment of the body.[39] It is well established that intact GH secretion is crucial to combat prolonged hypoglycaemia, and GH is implicated as being a major mediator of the nocturnal increase in insulin requirements (also known as the dawn phenomenon) in patients with insulin-dependent diabetes.

GROWTH HORMONE AND INSULIN SENSITIVITY

In general, GH is thought to increase insulin resistance. Insulin resistance during puberty and pregnancy is, in part, attributed to increased concentrations of circulating GH.

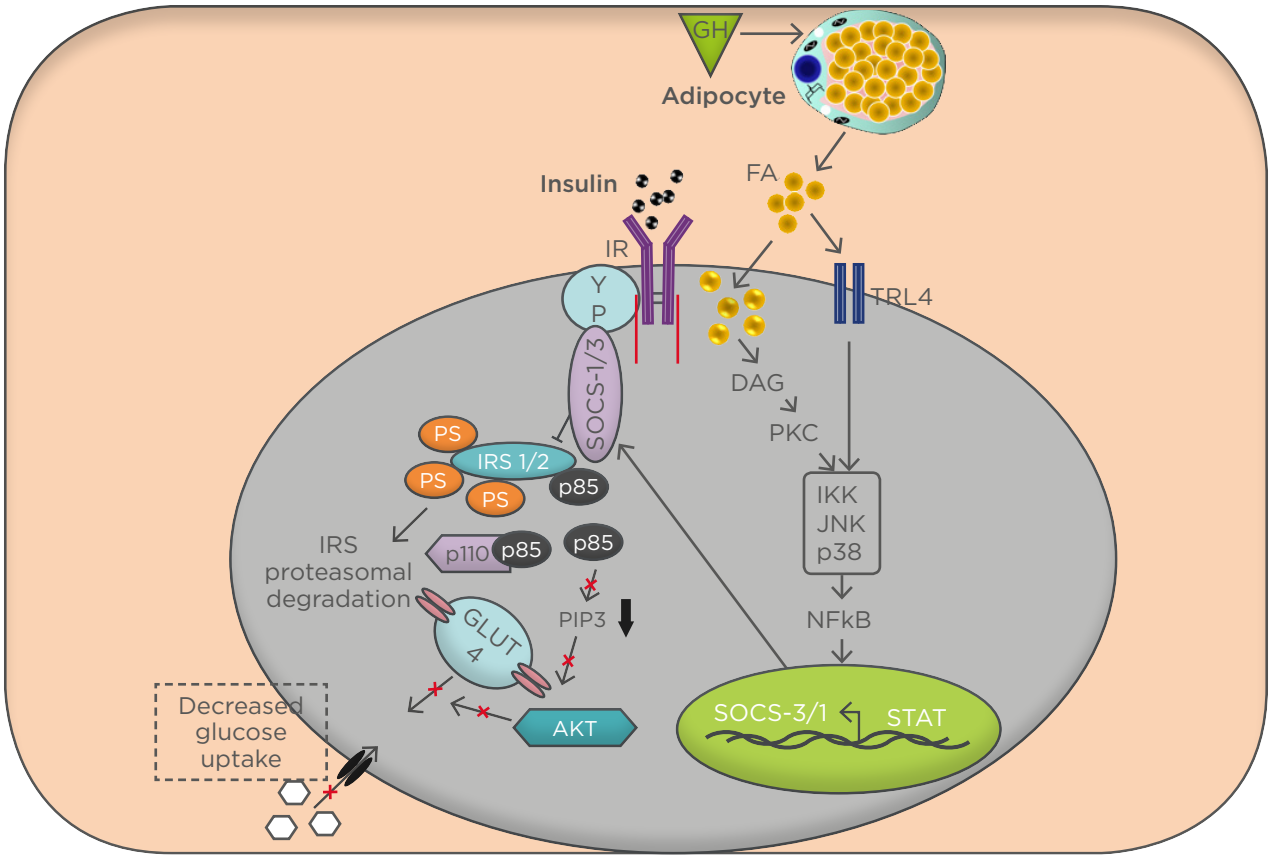

Figure 3: Mechanism of insulin resistance by excess growth hormone conditions.

The pathway for insulin stimulation of glucose transport in muscle involves activation of the insulin receptor protein, which docks IRS-1 and IRS-2 and phosphorylates these proteins on tyrosine residues (pY). IRS-1 recruits the p85α regulatory subunit of PI3K (p85-p110), resulting in phosphorylation of membrane-bound PIP3. Production of PIP3 is required for activation of Akt and signalling for GLUT4 translocation. Excess p85α acts as a dominant-negative signalling molecule by blocking the association of PI3K (p85-p110) with IRS-1 and thereby attenuating PI3K activation. Loss of PI3K activation from increased p85 and increased serine phosphorylation of IRS-1 both lead to reduced translocation of GLUT4 to the plasma membrane and result in decreased insulin-stimulated glucose uptake to skeletal muscle.

FA: fatty acid; GH: growth hormone; IR: insulin receptor; IRS: insulin receptor substrate; PIP3: phospholipids at the 3′ position; TLR: toll-like receptor.

Insulin resistance is one of the clinical manifestations of GH treatment in humans. Administration of GH either within physiological range or supraphysiological doses leads to both hepatic and peripheral insulin resistance in healthy volunteers.[40,41] The tissue that contributed most to the decreased insulin sensitivity was the muscle. Evidence for the direct effect of GH on insulin sensitivity has also come from studies in acromegaly subjects. Blocking GHR activation by pegvisomant for 4 weeks improved peripheral and hepatic insulin sensitivity in acromegalics.[31] Although a GH-induced increase in free fatty acids (FFA) flux from the adipose tissue is associated with impaired insulin action at target tissues,[42] studies in liver-specific IGF-1 deficient mice revealed a 3–4-fold increase in circulating GH levels and insulin resistance, without a significant increase in circulating FFA.[43] Therefore, in addition to the increase in FFA, other factors also contribute to insulin resistance in GH elevated conditions. The possible mechanisms of GH-induced insulin resistance are presented in Figure 3, including SOCS-1 and 3-mediated insulin resistance and deregulation of insulin signalling.[44] Interestingly, SOCS-2 serves as a negative regulator of GH signalling.[45]

GH elicits insulin resistance by increasing the expression of the p85α regulatory subunit of the PI3K.[42] PI3K exists as a dimer of two subunits: p85 and p110; p85 is the regulatory subunit whereas p110 is the catalytic subunit. The p85 subunit binds to the insulin signalling molecule IRS-1 and inhibits insulin signalling. Heterozygous knockout of p85α improved insulin sensitivity in mice and complete absence of the p85 isoform resulted in hypoglycaemia.[46,47] Hence, GH-induced expression of p85 would result in p85α homodimers competitively binding IRS-1 and blocking insulin signalling. Conversely, in GH deficient states, the p110 subunit binds to other p85 isoforms, such as p85β, and enhances insulin signalling. Transgenic mice expressing bovine GH have increased adipose tissue expression of a p85α subunit, concomitant with insulin resistance.[42] Increased p85α in skeletal muscle induces insulin resistance in conditions of GH excess.[48] Expression of p85 monomers is increased in transgenic mice overexpressing placental GH,[49] and mice with a heterozygous deletion for p85α were protected from GH-induced insulin resistance.[48] These multiple studies suggest that increased expression of p85α plays a critical role in GH-induced insulin resistance.

An alternative mechanism for GH-induced insulin resistance is via GH-dependent increase in plasma FFA. The inhibition of glucose oxidation by fatty acids is also termed the Randle cycle effect. Formation of TG from fatty acids results in accumulation of diacylglycerol and ceramides. These re-esterification intermediates activate protein kinase C isoforms, which downregulates insulin signalling by multiple mechanisms. GH replacement therapy is associated with inhibition of glucose metabolism as a result of the lipolytic effect of GH.[50]

A recent study conducted by the authors broadened their understanding of the biological roles of GH on insulin resistance in diet-induced obesity in mice. Under high-fat diet conditions, a lack of GHR in macrophages resulted in increased inflammation and decreased insulin sensitivity in adipose tissue.[51] One of the physiological roles of GH in the macrophages is to attenuate NFκB activation and, in turn, suppress osteopontin expression. In the absence of functional GHR in macrophages, increased expression of osteopontin was associated with migration of inflammatory macrophages into adipose tissue and decreased insulin sensitivity in adipose tissue.[51]

GROWTH HORMONE AND LIPID METABOLISM

Acromegaly is characterised by profound disturbances of not only carbohydrate metabolism but also lipid metabolism. The principal effect of GH on lipid metabolism is to stimulate lipolysis and lipid oxidation, thereby sparing carbohydrates and proteins from immediate oxidative demands and constitutes a homeostatic mechanism.[9] In addition to hyperinsulinaemia, patients with acromegaly have increased levels of circulating lipid intermediates, increased rates of lipid oxidation, and decreased rates of glucose oxidation.[52] These lipid intermediates are absorbed by the muscle and interfere with glucose uptake and suppress glucose oxidation. To evaluate the importance of the raised GH levels in

patients with poorly controlled diabetes, Press et al.[13] injected GH at a rate of 100 µg pulses per hour for 45 hours into diabetic subjects. Plasma glucose concentrations doubled (86±11 to 204±17 mg/dL) within 8–10 hours and remained elevated until GH was discontinued. The hyperglycaemia was due to stimulation of hepatic glucose production in the absence of a significant change in levels of either insulin or glucagon. With GH administration, levels of circulating FFA, ketones, and branched-chain amino acids were also increased.[13] This study suggested that in addition to hepatic glucose production, GH excess triggers ketosis and resulting acidosis. In another study, it was shown that administration of GH (210 µg) to diabetic subjects caused a significant increase in FFA (70%) levels and 3-hydroxybutyrate (400%) compared with subjects naïve to GH administration.[52] Furthermore, increased non-oxidative glucose utilisation was observed and was evidenced by an increase in plasma lactate concentrations. GH-injected diabetic subjects also responded with increased lipid oxidation. These results suggest that GH is an important regulator of fuel fluxes in T1DM subjects, the key outcome being a transient stimulation of lipolysis.[52] A steep increase in plasma FFA levels following a single GH pulse reflects the stimulation of lipolysis. Both pulsatile and continuous administration of moderate amounts of GH to healthy human volunteers lead to a dose-dependent stimulation of lipolysis as revealed by increased circulating FFA levels, glycerol, and increased lipid oxidation rates. The association of GH pulses with decreased rates of peripheral glucose uptake and increase in endogenous glucose production were entirely reversed by acipimox, an antilypolytic drug.[53] A study in healthy adults showed that the nocturnal mean peak of GH precedes the increase in FFA by 2 hours,[54] a time lag that mirrors the one observed after GH bolus administration,[55] suggesting that GH is a regulator of diurnal fluctuations in oxidation rates of lipids and other fuel substrates.

Adiponectin, acting via the adiponectin receptor, increases fatty acid oxidation. GH increases expression of adiponectin receptor 2 in the liver.[56] Exogenous GH administration to obese rats prevented hepatic steatosis and was associated with increased adiponectin receptor 2 expression.[57] In addition to increased adiponectin receptor expression, decreased expression of peroxisome proliferator-activated receptors (PPAR)-α/β/γ isoforms in states of GH excess may facilitate enhanced triglycerides secretion. In PPAR-α knockout mice, a higher triglycerides secretion was observed with GH treatment than control mice. Furthermore, GHR knockout mice show decreased hepatic PPAR isoforms.[58] GH stimulates lipolysis in visceral and subcutaneous adipose tissue by increasing the hormone-sensitive lipase activity, possibly by activating the β-adrenergic receptor. Similarly, there is evidence that suggests GH induces hormone-sensitive lipase in skeletal muscle.

GROWTH HORMONES AND PROTEIN METABOLISM

GH is an anabolic hormone that promotes protein synthesis both by decreasing the oxidation of amino acids and increasing the uptake of branched-chain amino acids by skeletal muscle.[59,60] Under physiological states, the effect of GH on protein metabolism is limited to the augmentation of protein synthesis with a decreased breakdown at the whole-body level. GH mediated nitrogen retention is evidenced by reduced urinary excretion of urea, ammonium, and creatinine. GH induces protein synthesis by stimulating the mTOR/S6 kinase signalling pathway. Fasting is a state of GH resistance due to downregulation of GHR in the liver and other relevant tissues. In a fasting state, the decrease in GH action results in an increase in both protein catabolism by 25% and excretion of urea-nitrogen by 50%.[61] Administration of GH to hypophysectomised rats restored the growth defects and decreased hepatic urea formation.[62] GH administration contributed to muscle protein mass with no significant change in protein catabolism in malnourished haemodialysis patients.[63] Age-related loss of muscle mass, also known as sarcopenia, correlates with diminished production of GH from the pituitary gland. Administration of GH induced accumulation of muscle mass during the aging process. Older rats who were administered GH exhibited improved sarcopenia associated with increased mitochondrial biogenesis and protection against oxidative damage in skeletal muscle by the induction of antioxidant enzymes.[64]

SUMMARY

To summarise, GH plays a complex role in the regulation of carbohydrate, lipid, and protein metabolism; increases circulating levels of glucose via increased endogenous glucose production; stimulates lipolysis to increase FFA, which in turn inhibits glucose oxidation; and impairs both hepatic and peripheral insulin sensitivity, particularly in the muscle where glucose oxidation is reduced. Therefore, GH reduces both insulin-dependent and glucose-dependent glucose disposal. The anabolic effect of GH on proteins is a consequence of the activation of lipolysis and the protein sparing actions of lipid fuels. To generalise, GH effects metabolism, it suppresses glucose uptake and glucose oxidation, and stimulates gluconeogenesis, glycogenesis, and lipolysis. GH antagonises the action of insulin on peripheral tissues and thereby decreases glucose uptake and increases glucose production. Insulin levels increase to counterbalance the elevated glucose following GH administration. GH-induced lipolysis in the visceral tissues and subsequent increased FFA interferes with insulin signalling pathways.

Although GH therapy in GH deficient adults reduces visceral adiposity, improves dyslipidaemia, and metabolic disturbances, GH treatment elicits impaired fasting glucose and increased insulin resistance, particularly in obese patients.[65] Because insulin resistance and glucose intolerance are linked to the risk of diabetes, there is due concern that patients with metabolic disorders may develop diabetes following GH treatment. While short-term treatment with GH elicits insulin resistance in children and adolescents, the long-term consequences of GH replacement therapy on glucose metabolism is a matter of debate. Therefore, longitudinal studies with increased sample size are warranted to delineate the effect of GH administration on metabolic disorder and cardiovascular outcomes.

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Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors: Efficacy and Safety in the Treatment of Hypercholesterolaemia

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Abstract

Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9I) are a new class of medication that has recently arisen to combat hypercholesterolaemia. They are targeted towards patients who are unable to achieve low levels of low-density lipoprotein cholesterol despite maximum statin therapy, as well as those who are unable to tolerate maximum statin therapy due to side effects. Two of these medications were released in the summer of 2015: alirocumab and evolocumab. This article provides an overview of this medication class and analyses the clinical data from the numerous studies and trials conducted on both of these medications for their efficacy and safety outcomes. Data indicate that PCSK9I are both a safe and effective means of lowering low-density lipoprotein cholesterol levels of resistant or otherwise currently unmanaged hypercholesterolaemia patients.

INTRODUCTION

Atherosclerosis can be considered a metabolic disease and the clinician needs to realise this and consider cardiovascular disease prevention. Low-density lipoprotein cholesterol (LDL-C) is a causal risk factor for atherosclerotic cardiovascular disease (ASCVD) and statins represent the most commonly prescribed class of LDL-C-lowering medications. However, despite attempts at adequate pharmacologic treatment, acceptable LDL-C levels cannot be achieved in certain patients due to statin intolerance or ineffectiveness. These gaps in patient coverage have led to the development of additional therapies to improve treatment. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (PCSK9I) are quickly rising to the occasion, providing benefit to those neglected patients in clinical trials.

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9

PCSK9 is an important serine protease involved in the regulation of LDL-C metabolism. Hepatocytes are the predominant site for PCSK9 production.[1] Expression of PCSK9 and LDL receptors (LDLR) are closely regulated by sterol regulatory element-binding protein-2 and intracellular cholesterol.[2] PCSK9 circulates in three forms: a PCSK9 monomer, LDL-C-bound PCSK9, and a 55 kDa furin-cleaved inactive fragment.[3] PCSK9 acts both intracellularly

(as a chaperone rather than a catalytic enzyme) as well as a secreted factor.[3,4] Extracellular PCSK9 binds to epidermal growth factor-like repeat-A located at the extracellular domain of the LDLR and interferes with the LDLR, recycling back after internalisation with LDL-C and directing the LDLR to the lysosomes for its destruction.[5]

Gain-of-function mutations alter the natural function, leading to hyperactivity of the *PCSK9* gene, which degrades LDLR in excess, thus increasing LDL-C levels.[6-8] These rare mutations, recognised as a third cause of autosomal-dominant familial hypercholesterolaemia (FH), are not only associated with high cholesterol levels but also with a greater atherosclerotic burden.[6-9] Conversely, loss-of-function mutations result in lower LDL-C levels throughout the course of life and a lower rate of cardiovascular events.[10,11] Therefore, these findings definitively established PCSK9 synthesis, activity, and/or the PCSK9–LDLR binding mechanism as a therapeutic target for reducing LDL-C and the risk of ASCVD.

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 INHIBITORS

Various modalities to inhibit PCSK9 have been studied, including inhibition of production by gene silencing through antisense oligonucleotides or small interfering RNA; prevention of PCSK9 binding to LDLR using monoclonal antibodies (mAb), epidermal growth factor-like repeat-A, mimetic peptides, or adnectins; and inhibition of PCSK9 autocatalytic sites.[12-15]

Inclisiran is a long-acting RNA-interference agent targeting PCSK9 synthesis. A Phase I trial[16] demonstrated reductions of 75% and 51% in PCSK9 and LDL-C concentrations, respectively, with doses ≥300 mg. In a Phase II randomised clinical trial (RCT),[17] including adults unable to reach LDL-C goals with maximum-tolerated statin doses, the mean reductions in LDL-C levels were 27.9–41.9% after a single dose of inclisiran and 35.5–52.6% after two doses ($p<0.001$ for all comparisons versus placebo) at Day 180. At Day 240, the reductions in PCSK9 and LDL-C remained significantly lower than baseline with all the studied doses. Two 300 mg injections produced the greatest reduction in LDL-C, with 48% of patients achieving an LDL-C level <50 mg/dL. Serious adverse events (AE), tracked until Day 210, occurred in 11% of inclisiran recipients and 8% of placebo recipients. Injection-site reactions, the most common AE, occurred in 5% of inclisiran recipients but in no placebo recipients. Injections were given every 3 or 6 months. The results of this study will inform the dose and dosing regimen for a Phase III cardiovascular outcomes study with inclisiran.

Use of mAb has been the most efficacious approach thus far in inhibiting PCSK9. Systemic absorption of PCSK9-specific mAb occurs via lymphatic circulation and via diffusion to blood vessels in proximity of the injection site.[18,19] The time required to reach the peak of maximal concentration varies between 2 and 8 days, with absolute bioavailability that ranges from 50–100%.[20] Indeed, LDL-C levels decrease rapidly, reaching their lowest concentrations by approximately 15 days. With time, levels of plasma mAb decrease, reaching undetectable levels by around 60 days.[21] Unlike small molecule drugs, which are commonly eliminated via renal or hepatic routes, mAb are cleared by different mechanisms, including fluid-phase pinocytosis and receptor-mediated endocytosis in phagocytes.[18,22] However, no additional information has been provided to fully understand the mechanisms of Ab internalisation and clearance.

Currently, at least six mAb have been or are being developed and tested. Alirocumab and evolocumab are the front-runners of the PCSK9I that are approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) to be used in adult patients with heterozygous FH and non-FH or clinically significant ASCVD requiring additional LDL-C lowering or mixed dyslipidaemia, as adjunct treatment to diet. These include the following cases:

- In combination with a statin or a statin with other lipid-lowering therapies (LLT) in patients unable to reach LDL-C goals with maximum-tolerated statin doses.
- Alone or in combination with other LLT in patients who are statin-intolerant or for whom a statin is contraindicated.

Evolocumab reduced LDL-C by approximately 30% in a patient subgroup that had at least one mutant *LDLR* allele with residual functionality, whereas individuals with two null or completely non-functional alleles did not respond.[23,24] Therefore, evolocumab has received an additional indication in homozygous FH adults and adolescents >12 years old with residual LDLR function in combination with other LLT.

The starting dose of subcutaneously injected alirocumab is 75 mg biweekly; it can be increased up to 150 mg biweekly. In comparison, the dose of evolocumab is 140 mg biweekly or 420 mg monthly. The global clinical development programme for bococizumab, a humanised, rather than fully human, mAb with approximately 3% murine sequence remaining in the antigen-binding complementarity-determining regions, was discontinued due to an unanticipated attenuation of LDL-C lowering over time, a higher level of immunogenicity, and a higher number of injection-site reactions.

Table 1: Efficacy of anti-proprotein convertase subtilisin/kexin type 9 antibodies in patients with hypercholesterolaemia: summary of Phase III and long-term trials selected for inclusion of review of data.

Study	Number of participants	Follow-up, weeks	Population	Treatment	Percentage reduction in LDL-C
ALI					
ODYSSEY LONG TERM[25]	2,341	24–78	HeFH with CHD or CHD equivalent with LDL-C ≥70 mg/dL on maximum tolerated statin therapy	ALI 150 mg Q2W or PBO	At 24 weeks: ALI: 61.0%; PBO: 0.8%; (p<0.0001) At 78 weeks: ALI: 52.0%; PBO: 3.6%; (p<0.0001) Pooled analysis at 78 weeks: ALI: 63.0%
Ray et al.,[26] 2016	4,974	24–104	Established ASCVD or high CV risk such as HeFH with LDL-C inadequately controlled on existing treatment (statin/other LLT/diet)	ALI 75–150 mg Q2W or control	PBO-controlled trials: ALI: 55.4%; PBO: 2.7% EZE-controlled trials: ALI: 48.1%; EZE: 18.0%; An average LDL-C <50 mg/dL: 33.1%
EVO					
Combined OSLER-1 and OSLER-2[27]	4,465; EVO: 2,976; HeFH: 247; statin intolerance: 254; PBO: 1,489	52	Subjects who completed Phase II or III EVO studies	ST plus EVO (420 mg Q4W or 140 mg Q2W) or ST alone	EVO: 61.0%
Koren et al.,[28] 2017	543	>4 years	Patients who completed double-blind Phase II studies and entered into a multiyear, open-label extension	EVO 420 mg Q4W plus SoC	57.0% (median)
DESCARTES[29]	901	52	Hypercholesterolaemia; LDL-C ≥75 mg/dL on background of atorvastatin 10–80 mg/day with or without EZE	EVO 420 mg Q4W; PBO	EVO: 50.1%; PBO: 6.8% LDL-C goal of <70 mg/dL: EVO: 82.3% PBO: 6.4%
GLAGOV[30]	968	76	Angiographic coronary disease	EVO 420 mg Q4W; PBO	EVO: 56.3 mg/dL decrease (61.1%); PBO: 0.2 mg/dL increase (p<0.0001)
FOURIER[31]	27,564	48	High-risk, stable patients with established CVD with LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL	EVO or PBO Q2W or Q4W with atorvastatin with or without EZE	59.0%

ALI: alirocumab; ASCVD: atherosclerotic cardiovascular disease; CHD: coronary heart disease; CV: cardiovascular; CVD: cardiovascular disease; EVO: evolocumab; EZE: ezetimibe; HeFH: heterozygous familial hypercholesterolaemia; LDL-C: low-density lipoprotein cholesterol; LLT: lipid-lowering therapy; PBO: placebo; Q2W: one dose every 2 weeks; Q4W: one dose every 4 weeks; ST: standard therapy; SoC: standard of care.

OVERVIEW OF CLINICAL TRIALS OF PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9: SPECIFIC MONOCLONAL ANTIBODIES

To date, almost 30 Phase II and III RCT have been reported, mainly using evolocumab or alirocumab versus various comparators. Patient groups studied included those with FH, hypercholesterolaemia with high cardiovascular risk on usual or maximal LLT, and statin intolerance.

Efficacy of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors Long-Term Trials (Table 1[25-31])

ODYSSEY LONG TERM[25] was a Phase III RCT comparing the efficacy of alirocumab with placebo for 78 weeks in patients at high ASCVD risk. At Week 24, there was a 61.0% reduction from baseline in LDL-C levels in the alirocumab group compared to a 0.8% increase in the placebo group (62.0% reduction in alirocumab group compared to placebo) (p<0.0001). The difference between alirocumab and placebo in LDL-C reduction at Week 24 was similar in patients with heterozygous FH and non-FH. The LDL-C at Week 48 in alirocumab versus placebo groups was 57.9 mg/dL versus 122.6 mg/dL, respectively. Alirocumab therapy sustained a 58.0% reduction in LDL-C at 78 weeks. Eighty-one percent of alirocumab patients achieved their prespecified LDL-C goal compared to 9% for placebo (p<0.0001).

Data from the open label OSLER-1 and OSLER-2 RCT assessing the efficacy of evolocumab were combined into a single analysis set.[27] After a median follow-up of 11.1 months, evolocumab reduced LDL-C from a mean of 120 mg/dL to 48 mg/dL and patients achieved a 61.0% reduction in LDL-C compared to standard therapy alone (p<0.001). Significant reductions in lipoprotein (Lp)a and triglyceride levels with a mild increase in high-density lipoprotein cholesterol (HDL-C) with treatment of either evolocumab or alirocumab were also noted.[25,27] Evolocumab reduced non-HDL-C levels by 52.0% and apolipoprotein B (apoB) by 47.3% (p<0.001).[27] Results from an open-label extension (OLE) study showed sustained reductions in LDL-C levels. At approximately 2, 3, and 4 years of follow-up, the median LDL-C concentration was reduced by 59.0%, 59.0%, and 57.0%, respectively, from parent study baseline.[28]

Pooled Analyses and Meta-Analyses

Data were pooled from 10 Phase III ODYSSEY trials, including patients randomised to alirocumab 75/150 mg every 2 weeks or control for 24–104 weeks and added to background statin therapy in 8 trials.[26] Six of the studies, representing ~80% of the population, had a minimum study duration of 52 weeks. The average percentage change in LDL-C from baseline was -55.4% for alirocumab and 2.7% for placebo, and -48.1% with alirocumab and -18.0% with ezetimibe. Overall, 33.1% of patients achieved an average LDL-C <50 mg/dL during treatment (44.7–52.6% allocated to alirocumab, 6.5% allocated to ezetimibe). The overall distribution of each lipid parameter during treatment largely reflected the greater proportion of patients achieving very low levels of LDL-C, non-HDL-C, and apoB in the alirocumab group.

Three meta-analyses confirmed the efficacy of PCSK9I (Table 2).[32-34] Zhang et al.[32] demonstrated that for equipotent dosages and dosing intervals, evolocumab and alirocumab had essentially identical LDL-C-lowering efficacy at 52 weeks follow-up. The LDL-C reduction following evolocumab treatment was 54.6%, and the absolute mean reduction was -78.9 mg/dL versus placebo and -36.3% versus ezetimibe. HDL-C increased by 7.6% versus placebo and 6.4% versus ezetimibe. The efficacy outcome for alirocumab was similar. LDL-C reduced by >50% versus placebo. A less marked reduction in LDL-C was found when compared with ezetimibe (-29.9%). HDL-C level increased by a mean of 8%. Besides a significant reduction in non-HDL-C, there was a reduction in very-LDL-C with evolocumab and in apoB with alirocumab.[32] Lipinski et al.[33] reported that PCSK9 inhibition alone led to 57.0% lower LDL-C, 46.0% lower apoB, and 24.3% lower Lpa. Compared with placebo, PCSK9I resulted in a LDL-C reduction of 69.0%. A maximum reduction of LDL-C of 57.8% was seen in patients with high baseline statin therapy. Many trials found at least one LDL-C value as low as 25 mg/dL.

Navarese et al.[34] conducted a meta-analysis of 24 RCT with a mean follow-up of 44.6 weeks.

Table 2: Comparison of four meta-analyses on proprotein convertase subtilisin/kexin type 9 inhibitors.

Study	Number of trials analysed	Total number of patients	Reduction in LDL-C	Clinical outcome			Adverse effects of PCSK9 inhibitors (severe, leading to discontinuation of drug)
				All-cause mortality	CV mortality	CV events	
Zhang et al.,[32] 2015	25	12,200	EVO: 54.6% ALI: 52.6%	Reduced	Reduced	Reduced	N/A
Lipinski et al.,[33] 2016	17	13,083	57.0%	Reduced	N/A	N/A	1.6–1.9%
Navarese et al.,[34] 2015	24	10,159	47.5%	Reduced	Reduced	Reduced	N/A
Li et al.,[35] 2015	20	9,880	65.29 mg/dL (95% CI: -72.08–[-58.49])	N/A	N/A	N/A	No significant difference between the groups

ALI: alirocumab; CI: confidence interval; CV: cardiovascular; N/A: data not available; LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9.

Most trials involved patients treated with statins who had not met target LDL-C goals, although some focussed only on statin-intolerant patients. Data showed that PCSK9I led to a 25.0% average reduction in Lpa and a 47.5% reduction in LDL-C ($p<0.001$), with a larger reduction when compared with placebo (-58.8%) than when compared with ezetimibe (-36.2%). The relative reduction in LDL-C levels with PCSK9I was similar to, or even slightly greater, in statin-treated patients. Although statins might induce PCSK9 upregulation, partially attenuating the LDL-C-lowering effect of PCSK9I, a combination of statins and mAb results in an additional reduction of LDL-C by 50–60% compared to statin monotherapy; this finding highlights the potential value of PCSK9 inhibition as an adjunct to standard therapy.[36,37] In addition, the effect was measured independent of the applied statin doses.[29] Zhang et al.[38] found that PCSK9-specific mAb reduced LDL-C in combination with a statin and suppressed hepatocyte sterol regulatory element-binding protein-regulated genes. Li et al.[35] reported similar efficacy of evolocumab and alirocumab in absolute terms (Table 2). Since other meta-analyses evaluated efficacy in relative terms, this meta-analysis could not be compared directly; however, the overall results were consistent with studies reporting percent changes.

Recently, a pooled analysis focussing on elderly patients demonstrated that evolocumab-treated patients ≥65 years achieved an LDL–C reduction of 58.4–62.9% at the mean of Weeks 10 and 12.[39] The LDL–C concentration in patients ≥75 years was reduced by 59.9–68.6%.

Safety and Adverse Events of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors (Table 3)

In the ODYSSEY LONG TERM trial,[25] overall AE rates were similar among the groups. Myalgia was more frequent with alirocumab than with placebo (5.4% versus 2.9%; p=0.006). Injection-site reactions and neurocognitive and ophthalmologic events were also more frequent in the alirocumab group, but differences did not reach statistical significance. Discontinuation due to AE was comparable among groups. Of interest, AE in the subgroup of patients with a LDL-C level <25 mg/dL were similar to the overall alirocumab group.

In the OSLER trials, most AE occurred with almost similar frequency in all groups.[27] Injection-site reactions led to 0.2% of patients stopping therapy. Arthralgia, headache, limb pain, and fatigue were more frequent in the evolocumab group, but liver function and creatine kinase remained unchanged. Rates of overall AE, serious AE, and elevations in aminotransferase or creatine kinase levels were similar among evolocumab-treated patients with LDL-C levels <40 mg/dL or <25 mg/dL as in those with higher levels. A total of 79% of patients persisted with evolocumab treatment, with a mean exposure duration of 44 months.[28]

Table 3: Safety of anti-proprotein convertase subtilisin/kexin type 9 monoclonal antibodies in patients with hypercholesterolaemia.

Study	Any TEAE	Serious TEAE	Major CV events	AE leading to discontinuation	ADA testing results	Mortality
ALI						
ODYSSEY LONG TERM[25]	ALI: 81.0%; PBO: 82.5%	ALI: 18.7%; PBO: 19.5%	CV AE confirmed by adjudication: ALI: 4.6%; PBO: 5.1% Major CV AE in post hoc analysis confirmed by adjudication: ALI: 1.7%; PBO: 3.3%, (p=0.02); 48% relative risk reduction in CVD events	ALI: 7.2%; PBO: 5.8%	NR	AE leading to death: ALI: 0.5%; PBO: 1.3%
Ray et al.,[26] 2016	PBO-controlled trials: ALI: 79.9%; PBO: 81.3% EZE-controlled trials: ALI: 76.0%; EZE: 73.9%	PBO-controlled trials: ALI: 16.6%; PBO: 17.2% EZE-controlled trials: ALI: 17.0%; EZE: 13.9%	NR LDL-C percent reduction was inversely correlated with MACE rates (HR: 0.71 [95% CI: 0.57–0.89)] per additional 50% reduction in LDL-C; p=0.003	PBO-controlled trials: ALI: 6.2%; PBO: 5.7% EZE-controlled trials: ALI: 9.7%; EZE: 10.7%	NR	PBO-controlled trials: ALI: 0.7%; PBO: 1.1% EZE-controlled trials: ALI: 0.7%; EZE: 1.5%
EVO						
Combined OSLER-1 and OSLER-2[27]	EVO: 69.2%; ST: 64.8%	EVO: 7.5%; ST: 7.5%	EVO: 0.95%; ST: 2.18%; 53% reduction in CV events in post hoc analysis at 1 year	EVO: 2.4%; ST: N/A	Binding Ab: 0.3%; non-neutralising Ab	EVO: 0.14%; ST: 0.41%
Koren et al.,[28] 2017 (>4-year data)	37.6%	3.5%	0.9%	0.2%	Binding Ab: 0.0% Neutralising Ab: 0.0%	21% (during an average of 44 months of drug exposure)
DESCARTES[29]	EVO: 74.8%; PBO: 74.2%	EVO: 5.5%; PBO: 4.3%	Atherosclerotic events confirmed by adjudication: EVO: 1.0%; PBO: 0.7%	EVO: 2.2%; PBO: 1.0%	Binding Ab: 0.5%; no anti-evolocumab-neutralising Ab	EVO: 0.3%; PBO: 0.0%
GLAGOV[30]	NR	NR	EVO: 12.2% PBO: 15.3% PAV: EVO: decreased by 0.95%; PBO: increased by 0.05%	NR	Binding Ab: 0.2%; non-neutralising Ab	CV death: EVO: 0.6%; PBO: 0.8%
FOURIER[31]	EVO: 77.4%; PBO: 77.4%	EVO: 24.8%; PBO: 24.7%	EVO: 9.8%; PBO: 11.3% (p<0.001)	EVO: 1.6%; PBO: 1.5%	Binding Ab: 0.3%; no non-neutralising Ab	EVO: 3.2%; PBO: 3.1%
Toth et al.,[42] 2017 A pooled safety analysis from Phase II or III randomised trials	Integrated parent studies EVO: 51.1%; control*: 49.6% Integrated interim extension studies Year 1 SoC-controlled period EVO: 70.0%; SoC: 66.0%	Integrated parent studies EVO: 2.8%; control*: 21.% Integrated interim extension studies Year 1 SoC-controlled period EVO: 7.8%; SoC: 7.8%	NR	Integrated parent studies EVO: 1.9%; control*: 2.3% Integrated interim extension studies Year 1 SoC-controlled period EVO: 2.5%; SoC: N/A	Integrated parent studies Binding Ab: 0.2%; no neutralising antibodies Integrated interim extension studies Year 1 SoC-controlled period Binding Ab: 0.4%; no neutralising Ab	Integrated parent studies EVO: 0.08%; control*: 0.05% Integrated interim extension studies Year 1 SoC-controlled period EVO: 0.13%; SoC: 0.4%

*Control includes placebo and ezetimibe treatment groups.

Ab: antibody; ADA: antidrug antibody; AE: adverse event; ALI: alirocumab; CI: confidence interval; CV: cardiovascular; CVD: cardiovascular disease; EVO: evolocumab; EZE: ezetimibe; HR: hazard ratio; LDL-C: low-density lipoprotein cholesterol; MACE: major adverse coronary events; N/A: not applicable; NR: not reported; PAV: percent atheroma volume; PBO: placebo; SoC: standard of care; ST: standard therapy; TEAE: treatment-emergent adverse event.

Four meta-analyses confirmed the safety of PCSK9I, without differences regarding serious AE among patients treated with both mAb and placebo or standard therapy.[32-35] Zhang et al.[32] showed that for equipotent dosages and dosing intervals, evolocumab and alirocumab

had essentially identical side effect profiles. Overall, no significant difference between PCSK9I and placebo (or ezetimibe) was noted, except that alirocumab was associated with an increased rate of injection-site reactions (p=0.02) and evolocumab reduced the rate of abnormal liver function (p=0.03), both compared with placebo. No significant difference in safety outcomes was detected between monthly 420 mg and fortnightly 140 mg evolocumab treatments.

In a pooled analysis of alirocumab trials up to 78 weeks in duration, overall rates of treatment-emergent AE (TEAE), serious AE, discontinuations because of TEAE, and deaths were comparable with controls.[40] Alirocumab was associated with a higher incidence of local injection-site reactions, pruritus, and upper respiratory tract infection signs and symptoms. As patients with persistently positive antidrug antibody (Ab) have been shown to experience a greater incidence of injection-site reactions, an immune-based response is possible; however, the precise mechanism is unknown.[41] Similarly, the precise mechanism for the increased rate of pruritus with alirocumab is unknown. Jones et al.[40] considered the higher incidence of upper respiratory tract infection signs and symptoms to be a chance finding. It was not related to low LDL-C concentrations and there was no mechanistic basis for an increase in this AE category with alirocumab. The incidence of musculoskeletal, neurologic, ophthalmologic, and hepatic events was similar between alirocumab and control groups.

Similarly, a pooled safety analysis of evolocumab in >6,000 patients from double-blind and OLE studies demonstrated comparable overall AE rates between evolocumab and control in parent trials and in Year 1 of OLE trials, as were those for serious AE.[42] Nasopharyngitis was the most common AE documented. Injection-site reactions were reported by 3.3% of patients receiving evolocumab and 3.0% of controls in the parent studies and by 4.1% in the extension studies. Infrequent elevations of serum transaminases, bilirubin, and creatine kinase, as well as muscle-related AE, occurred, with similar rates between groups. Neurocognitive AE were infrequent and balanced during the parent studies. In the OLE trials, 0.9% of evolocumab-treated patients and 0.3% of controls reported neurocognitive AE.

No new safety concerns were identified in the GLAGOV trial.[30] The study was not large enough to make any definitive statements about safety, but AE looked reassuring, with no significant excess in rate of injection-site reactions, myalgia, and neurocognitive events. The rates of laboratory abnormalities were low in both groups. The FOURIER study[31] found no significant difference between the groups with regard to AE, with the exception of injection-site reactions, which were more common with evolocumab (2.1% versus 1.6%).

Muscle-related AE occurred in 12% of evolocumab-treated patients and 23% of ezetimibe-treated patients in the 12-week, Phase III GAUSS-2 trial evaluating statin-intolerant patients.[43] The percentage of patients who discontinued participation in the study was similar among patients receiving evolocumab and ezetimibe.[44] The Phase III ODYSSEY ALTERNATIVE trial[44] included patients with a history of muscle symptoms related to at least two previous statins. This was the only study design to include a placebo run-in period and a statin-rechallenge to confirm statin intolerance. The run-in period was completed by 87.0% of patients, with 15.9% of alirocumab-treated patients discontinuing due to muscle-related symptoms. The rate of skeletal muscle-related TEAE was significantly lower for alirocumab-treated patients than for atorvastatin-treated patients.[45]

A potential problem of long-term Ab treatment is the occurrence of antidrug Ab. Humanised mAb are immunogenic and can trigger production of neutralising antibodies. Approximately 16% of patients taking bococizumab develop high titres of neutralising Ab that interfere with the capacity of the Ab to bind to PCSK9, resulting in marked attenuation of its LDL-C-lowering effect. Evolocumab and alirocumab are fully human mAb and, therefore, are theoretically less likely to induce auto-Ab compared to humanised (95% human sequence) therapeutic Ab. Very few cases of antidrug Ab have been published to date. Only 0.2–0.3% of patients developed transient anti-evolocumab Ab.[28,37] No PCSK9-neutralising Ab were observed.[27,28,30,42] No reduction of LDL-C-lowering or an off-target effect has been reported, but this topic requires long-term observation.[42]

PCSK9 inhibition has been suggested to have a deleterious impact on adrenal function as a result of impaired delivery of Lp cholesterol to the adrenal glands to support adrenal steroidogenesis, particularly when LDL-C is reduced to extremely low levels. Evaluation of a male patient with a heterozygous PCSK9 loss-of-function mutation provided the opportunity to determine the effect of PCSK9 deficiency on adrenal function.[46] The patient had no detectable plasma PCSK9 and an LDL-C level of 24 mg/dL. Baseline adrenal function tests and cortisol response to adrenocorticotropic hormone stimulation were normal, suggesting that genetic PCSK9 deficiencies were not associated with abnormal adrenal function. Moreover, the safety of PCSK9 inhibition was evident in a family, including the proband with an LDL-C of 49 mg/dL and a daughter with an LDL-C of 14 mg/dL. The daughter had a premature stop codon in the protein transcript inherited from her mother and a second mutation from her father that deleted an arginine residue at codon 97. She was reported to have total deficiency of PCSK9 but normal intelligence, motor skills, kidney and liver function, and blood pressure.[47]

An analysis including Phase II and III trials showed that alirocumab was associated with a favourable safety profile when LDL-C was reduced to very low levels.[48] Of alirocumab-treated patients, 23.8% achieved LDL-C <25 mg/dL and 8.6% achieved LDL-C <15 mg/dL. No safety signals were observed and TEAE were generally similar among all alirocumab-treated patients, those achieving very-LDL-C levels, and those in the control group.

Since cholesterol is an important component of neurons and PCSK9 is involved in cortical neuron regeneration, impairments of neurocognitive function have been a major concern of the drastic LDL-C reduction following PCSK9I administration.[49] However, PCSK9 loss-of-function variants have not been associated with impaired cognitive performance.[50] In addition, Lp and mAb do not cross the blood–brain barrier and there is even some evidence of a possible decrease in dementia risk.[51] In the ODYSSEY LONG TERM and OSLER studies, neurocognitive changes were more common with PCSK9I (although not statistically significant) but were infrequent (<1%) and not related to the degree of LDL-C reduction.[25,27,28] However, these studies have several limitations: the occurrence of AE may have been confounded by the open-label design of the OSLER studies; the number of patients is relatively small and the duration of follow-up is too short to be considered definitive; and there is no information about the patients' baseline cognition. Neurocognitive events were self-reported by patients and no formal neurocognitive testing was used.

Navarese et al.[34] did not provide any neurocognitive AE data. A network meta-analysis found a significant 2.3-fold increased risk of neurocognitive AE with PCSK9I, primarily because of the inclusion of the aforementioned two trials.[25,27,33] The most common events were memory loss and amnesia (both ≤0.5%).[40] Serious neurologic events were single occurrences, without evidence of a common pathogenic mechanism. In contrast, a pooled analysis did not find any neurocognitive event differences between alirocumab and placebo or ezetimibe.[40] A more objective assessment of evolocumab's neurocognitive effects was recently completed in the EBBINGHAUS study, showing no differences between groups with regard to executive function as well as working memory, memory function, and psychomotor speed after 20 months.[52] It should also be noted that LDLR can act as the entry point for some viruses, including hepatitis C virus,[53] and it is unknown whether PCSK9I can increase the risk of hepatitis C virus infection.

CONCLUSION

PCSK9I have satisfactory lipid-modifying effects with acceptable safety profiles in patients with FH or non-FH. Some issues, however, should be taken into consideration. First, the mAb is injected subcutaneously, making it less possible for a long-term treatment. Additionally, caution needs to be taken for possible hypocholesterolaemia-associated AE and antidrug Ab. More clinical data are needed to ascertain whether these are potential problems or are of no concern.

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