EMJ EUROPEAN MEDICAL JOURNAL

DIABETES

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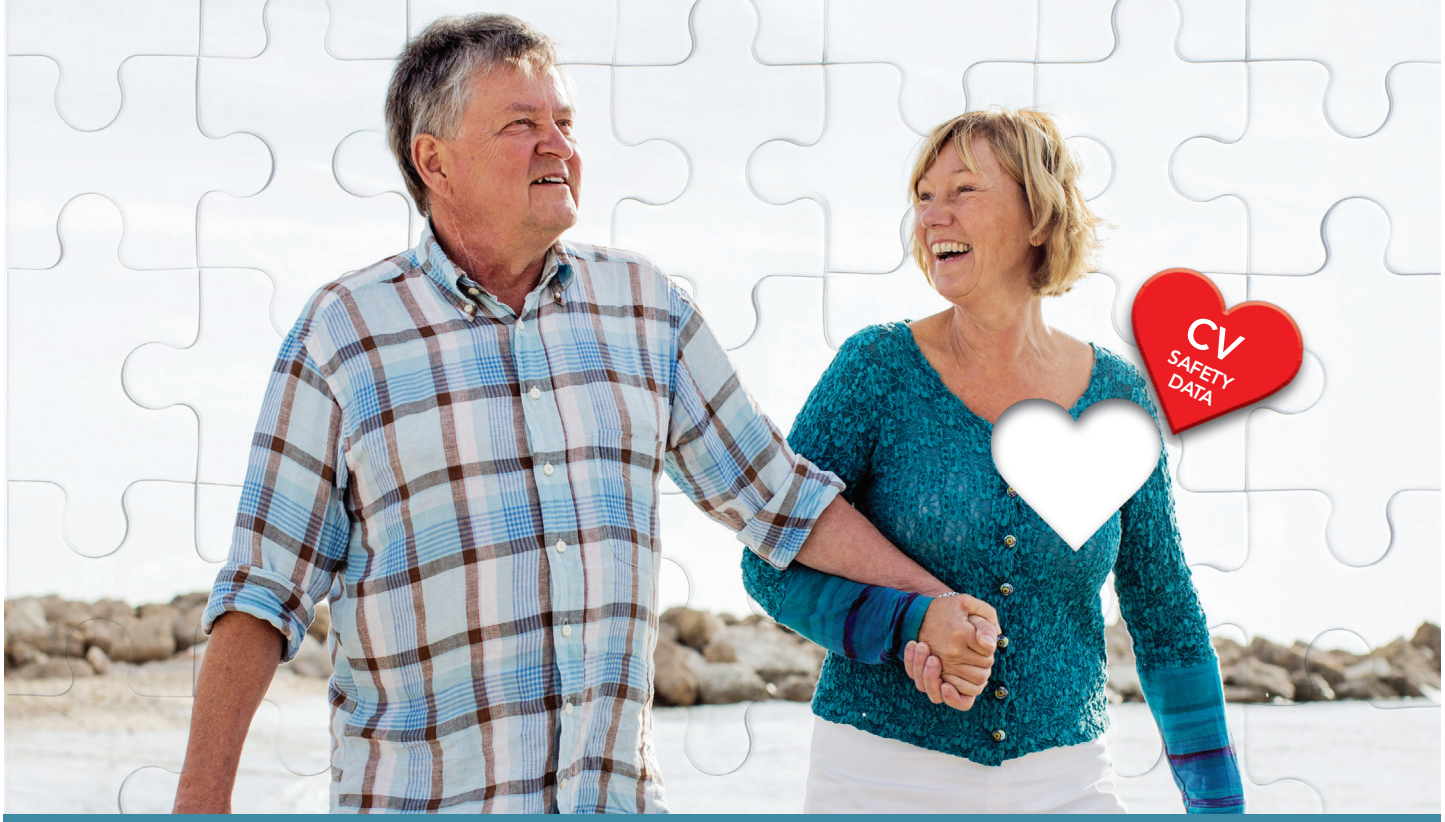
Diabetes

Editor-in-Chief: Dr Gill Hood

Research Delivery Manager, National Institute for Health Research (NIHR) Clinical Research Network: North Thames, Barts Health NHS Trust, London, UK.

Vipidia

In type 2 diabetes and CV risk
Every piece counts[1]



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*Major adverse cardiovascular events †Standard-of-care treatment for type 2 diabetes

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Presentation: Alogliptin 6.25 mg, 12.5 mg and 25 mg film-coated tablets. **Indication:** Adults aged 18 years and older with Type 2 diabetes mellitus to improve glycaemic control in combination with other glucose lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control. **Dosage & Administration:** Adults: the recommended dose of Vipidia is one tablet of 25 mg once daily (o.d.) with or without food. Elderly (≥65 y.o): no dose adjustment necessary. Renal impairment: Mild renal impairment (Ccl : [50-80]mL/mn), no dose adjustment necessary. Moderate renal impairment (Ccl : [30-50]mL/mn) 12.5 mg o.d. Severe renal impairment (Ccl : <30mL/mn) or end-stage renal disease requiring dialysis 6.25 mg o.d., experience limited. Hepatic impairment: mild to moderate hepatic impairment no dose adjustment necessary. Use in severe hepatic impairment not studied and therefore not recommended. Paediatric population: No data are available. **Contraindications:** Hypersensitivity to the active substance or to its excipients or history of a serious hypersensitivity reaction to any dipeptidyl-peptidase-4 (DPP-4) inhibitor. **Warnings & Precautions:** General: Do not use in patients with Type 1 diabetes mellitus or for treatment of diabetic ketoacidosis. Use with other antihyperglycaemic medicinal products and hypoglycaemia: When used in combination with a sulphonylurea, insulin or combination therapy with thiazolidinedione plus metformin, a lower dose of these medications may be considered to reduce the risk of hypoglycaemia. Combinations not studied: Has not been studied in combination with sodium glucose cotransporter 2 (SGLT-2) inhibitors or glucagon like peptide 1 (GLP-1) analogues or formally as triple therapy with metformin and sulphonylurea. Renal impairment: Renal function assessment is recommended prior to initiation of Vipidia therapy and periodically thereafter. Experience is limited in renal dialysis and has not been studied in peritoneal dialysis. Hepatic impairment: Has not been studied in patients with severe hepatic impairment (Child-Pugh score > 9) and therefore use is not recommended. Cardiac failure: As experience is limited caution is warranted in patients with congestive heart failure of New York Heart Association (NYHA) functional class III – IV. Hypersensitivity reactions: Anaphylactic reactions, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome have been observed for DPP-4 inhibitors and have been spontaneously reported for alogliptin in the post- marketing setting. Acute pancreatitis: Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Spontaneous reports of adverse reactions of acute pancreatitis in the postmarketing setting. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Vipidia should be discontinued; if acute pancreatitis is confirmed, Vipidia should not be restarted. Caution should be exercised in patients with a history of pancreatitis. Hepatic effects: Postmarketing reports of hepatic dysfunction, including failure, have been received. Patients should be observed closely for possible liver abnormalities and liver function should be obtained promptly in patients with any symptoms. Consider discontinuation of Vipidia if an abnormality is found and an alternative aetiology is not established. **Interactions:** Primarily excreted unchanged in the urine and metabolism by the cytochrome (CYP) P450 system is negligible. Studies show no clinically relevant pharmacokinetic interactions. **Fertility, Pregnancy & Lactation:** No data from use in pregnant women. Avoid use during pregnancy. Unknown whether Vipidia is excreted in human milk, a risk to the suckling child cannot be excluded. Consider the risk-benefit balance of use in breast-feeding mothers. The effect of Vipidia on fertility in humans has not been studied. **Undesirable Effects: Refer to the full local prescribing information before prescribing.** Common (≥1/100 to <1/10): Upper respiratory tract infections; nasopharyngitis; headache; abdominal pain; gastro-oesophageal reflux disease; pruritis; rash. Other serious undesirable effects (frequency unknown): Acute pancreatitis; hepatic dysfunction including hepatic failure; angioedema; hypersensitivity; exfoliative skin conditions, angioedema, urticaria. **Refer to the SmPC for details on full side effect profile and interactions. Legal Classification:** POM. **Marketing Authorisation:** Vipidia 25 mg EU/1/13/844/019-027; Vipidia 12.5 mg EU/1/13/844/010-018; Vipidia 6.25 mg EU/1/13/844/001-009 Marketing Authorisation Holder: Takeda Pharma A/S, Langebjerg 1, DK-4000 Roskilde, Denmark. For further information please consult the full Summary of Product Characteristics or contact your local Takeda representative. **Date of approval: 19/09/2013.**

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PI Approval Code: GLO/ALO/2014-00106.
Date of Preparation: September 2014.
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References:
1. Vipidia (alogliptin) Summary of Product Characteristics. 2014.
2. White WB, *et al. N Engl J Med* 2013; 369: 1327-1335.
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7. Trajenta (linagliptin) Summary of Product Characteristics. 2013.

GLO/ALO/2014-00082a
Date of preparation: September 2014

Takeda

Welcome

I would like to welcome you all to this eagerly awaited second edition of the *European Medical Journal Diabetes*. There are over 382 million people suffering from diabetes worldwide; it is through the sharing and advancement of knowledge, research, and education that this field will be driven forward and excellence in diabetes care promoted, all of which can be found in this journal.

Dr Michael Häupl, Mayor and Governor of Vienna, said: "Working with patients, science, and research are the pillars of our healthcare system because only new findings guarantee the quality of excellent and comprehensive healthcare in the future."

Research on new and existing treatments, such as insulin pens, is a necessity within this field to ensure that patients are provided with the best options. *'A practical review of insulin pen devices,'* written by Dr Pearson, highlights the benefits of the different insulin pens available. Dr Pearson suggests that in order to help patients make informed decisions about which insulin pen would benefit them, healthcare professionals need to be kept up-to-date about the new developments within this area.

The European Association for the Study of Diabetes (EASD), along with the American Diabetes Association, have issued a joint statement concerning insulin pumps as many of them have failed to pass safety and effectiveness trials. As these devices are of paramount importance to a diabetic patient, the malfunctions of the device could be fatal. We have reported the full story in our 'Congress Review' section which features the main highlights of the EASD Congress.

In our 'What's New' section - which informs diabetes specialists of recent updates within this field - we have reported on three companies who are aiming to help patients manage not only their condition but also their medication. As the number of people diagnosed with diabetes is expected to rise to 552 million people by the year 2030, producers of medical devices and drugs have been urged to provide solutions. MannKind, for example, are changing the way people receive their medication by allowing insulin to be given through an inhaler. Likewise, Novo Nordisk want to produce the drug in tablet form. Both of these approaches have received much positive attention from healthcare professionals and the public alike.

With the help of our highly esteemed Editorial Board, and our dedicated staff, we have created a journal which is both informative and enlightening, making it essential to every healthcare professional with an interest diabetes. I hope that this journal proves to be beneficial to you, and I wish you a most pleasant read.

Spencer Gore
Director, European Medical Journal

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EMJ GORELY NEW MEDIA

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Foreword

Dr Gill Hood

Research Delivery Manager,
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Dear Colleagues,

A very warm, autumnal welcome to this latest and stimulating issue of *EMJ Diabetes*! I am very proud to have been asked to present the journal this year as many of the articles within this publication reflect the diverse, multidisciplinary, and changing landscape of diabetes in 2014.

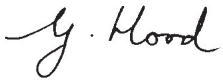
This changing landscape inevitably involves advancing the debate with regards to diabetes prevention: how do we prevent this global epidemic, and what is the evidence with regards to early interventions? At the other end of the spectrum, how can we promote exercise in an ageing Type 2 (T2) diabetes population? These important discussions are addressed in this edition, together with the very latest reviews on pharmacological treatments for cardiovascular risk, non-fatty alcoholic disease, and insulin resistance.

To advance the debate in diabetes we also need global collaboration in our research endeavours, in the manner with which we educate both patients and health professionals, and of course agreement on clinical pathways of care. These are all themes represented by this journal and also in the 50th EASD conference this year in September in Vienna. We have listened to reports on the new biology of diabetes, attended presentations on the outcome reports for SGLT2 inhibitors, and broadened our understanding on the evolving tools we can use for diabetes education.

But perhaps one of the most important sessions at this year's EASD was actually about reflection; allowing us all to value what we have so far achieved as scientists, clinicians, nurses, and other allied health professionals. Since the very first meeting of EASD in Montecatini, Italy, in 1965, we have been reminded of the enormous improvement in diabetes patient care. There are new understandings in the pathogenesis of both T1 and T2 diabetes, and an explosion in the variety of treatments we can offer our patients. We now advocate individual treatment for our patients, practise patient-centred care, and are willing to try new types of patient education such as internet-based learning and peer support.

This reflection of past achievements, keeping up-to-date with developments in journals such as *EMJ Diabetes* and attending EASD - the most important European conference for diabetes - helps us to be continually inspired to be even more effective in our work for diabetes in the future. I hope you enjoy!

Kind regards,



Gill Hood

Research Delivery Manager, National Institute for Health Research (NIHR) Clinical Research Network: North Thames, Barts Health NHS Trust, London, UK.

EASD ANNUAL CONGRESS 2014

MESSEZENTRUM VIENNA, VIENNA, AUSTRIA
15TH-19TH SEPTEMBER 2014

Welcome to the *European Medical Journal* review of the European Association for the Study of Diabetes Congress 2014

EMJ EUROPEAN MEDICAL JOURNAL

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MESSEZENTRUM VIENNA, VIENNA, AUSTRIA
15TH-19TH SEPTEMBER 2014

Welcome to the *European Medical Journal* review of the European Association for the Study of Diabetes Congress 2014

Hosted in one of Europe's glittering jewels, Vienna, the 50th EASD Annual Meeting summoned the beauty and prominence of the city in delivering groundbreaking and captivating developments on the crucial areas in diabetic medicine. As well as boasting world-famous landmarks, including Hofburg Palace and St Stephen's Cathedral, Vienna has produced a multitude of famous researchers, such as Sigmund Freud and Karl Landsteiner, as well as many diabetologists from the Vienna Medical School.

The dramatic architecture across this cultural and scientific centre sat suitably alongside the poignancy of the Congress, which presented 1,332 abstracts from a total of 2,264 submissions. Over 300 million people worldwide suffer from Type 2 diabetes (T2D); this number is expected to continue its exponential climb, with lifestyle and dietary changes proving insufficient for so many patients.

"We are trying to enforce the awareness, and give more background to the awareness, [of] diabetes for the whole population in Austria, and to support [the] understanding [of]... diabetes detection and treatment," said Prof Raimund Weitgasser, Chairman of the Local Organising Committee.

Indeed, if left untreated then the elevated glucose levels synonymous with diabetes can have a knock-on effect on almost every other organ in the body, akin to pushing over a row of dominos. Thus, drug targets need to be identified, along with the potential role of the *SLC30A8* gene in the onset of diabetes. This gene mutation reduces T2D incidence and indicates a step in the right direction for prevention and treatment of diabetes.

"We are trying to enforce the awareness, and give more background to the awareness, [of] diabetes for the whole population in Austria, and to support [the] understanding [of]...diabetes detection and treatment."

Prof Raimund Weitgasser, Chairman of the Local Organising Committee

Sadly, gestational diabetes, in tandem with stillbirth pregnancies, causes a near 50-fold increase in T2D incidence among pregnant women, compared with those who experience a normal pregnancy, and the association of diabetes with potentially fatal renal and cardiovascular risk makes dealing with the condition a matter of urgency.

The subject of insulin pumps dominated vast swathes of the Congress discussion. Such technology has come on leaps and bounds since the first attempts to perfect such a device in the 1970s; however, safety and efficacy of the pumps has come under fire from the EASD and American Diabetes Association, who have vowed collectively to enhance pumps on both fronts. In spite of this, insulin pumps trigger a dramatic decrease in all-cause mortality compared to multiple daily injections, underlining the prominent role they are set to play.

The debate over the merits of metformin as first-line therapy for T2D rages on, while an artificial pancreas – consisting of a closed-loop insulin delivery system - has been lauded as the next 'revolution' in diabetes care. IDegLira has emerged as a major catalyst of improved glycaemic control in adults with T2D, and its developer, Novo Nordisk, is among an elite group of companies, including Eli Lilly, that are leading the global assault on diabetes.

Next year's meeting in Stockholm has plenty to build on, and we hope that the same level of impact and enlightenment will materialise to ensure a quick curtail of a looming calamity.

Insulin pumps hit centre stage in global diabetes policy

IMPROVED insulin pump therapy has been called for in a joint statement by the EASD and American Diabetes Association (ADA), with many therapeutic devices currently falling short in safety and effectiveness trials.

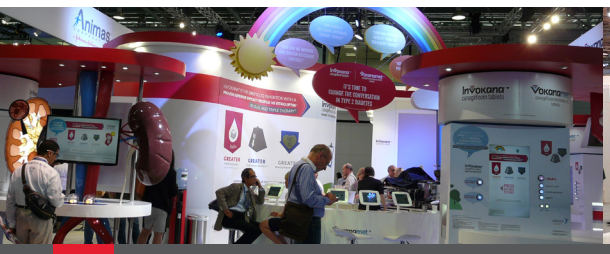
EASD/ADA have reacted to the flourishing emergency surrounding diabetes care by assigning Prof John R. Petrie, Professor of Diabetic Medicine, University of Glasgow, and Honorary Consultant in Medicine and Diabetes, Glasgow Royal Infirmary, Glasgow, UK, and his colleagues the task of surveying the current US and European systems that test the safety and effectiveness of insulin pumps. Quality control and regulation of insulin pumps, as well as the overall European medical device market, have so far proved insufficient in protecting patient safety.

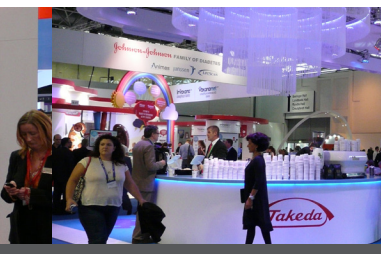
Optimising glucose control is vital in avoiding complications in diabetes; however, this is arduous in Type 1 diabetes (T1D) patients despite multiple daily insulin injections; insulin pumps have emerged as an alternative, more flexible treatment option, providing a continuous subcutaneous insulin infusion.

Armed with a multitude of adjustable settings and features in an increasingly diminutive, portable size, the pumps are becoming increasingly popular among patients of all ages with T1D. However, if the device malfunctions then diabetic ketoacidosis, hypoglycaemia, and possibly even death can occur.

Labelled by the FDA as a Class 2 device in the US, the insulin pumps need to be proven as equivalent to an already existing device in bench testing and non-clinical studies, in order to gain marketing approval. However, only a small amount of clinical data and human factor analyses are needed, and in the event of successful trials, there should be no need for systematic evaluations of sustained performance in long-term real-world use. The FDA reserves the right to terminate market use should adverse events or violations arise in plant inspections.

A Conformité Européenne mark from a notified body is required for the marketing of insulin pumps across European member states. Limited regulatory scrutiny of insulin infusion sets – with blockage, 'kinking', or formation of crystals responsible for a plethora of user problems – has proved to be a thorn in the side of the US and Europe. In the face of this, more robust systems need to be made available for evaluation, both pre-marketing and during marketed use, if the goal of enhanced safety and clinical efficacy in insulin pump therapy should be achieved.





Mutations can be good for diabetes prevention

MUTATIONS in a gene called *SLC30A8* have been identified that can potentially reduce the risk of developing Type 2 diabetes (T2D), even in those individuals who are at risk of developing the condition.

In a genetic analysis of 150,000 patients it was revealed that rare mutations in the *SLC30A8* gene can reduce the risk of T2D by 65%. These results extend throughout all multiple ethnic groups, suggesting that a potential drug, which mimics the effect of the mutations, could be utilised by patients across the globe.

Further laboratory experiments revealed that protective mutations disrupt the normal function of the protein ZnT8, which is encoded by *SLC30A8*. This protein transports zinc into insulin-producing beta cells where zinc plays a role in the insulin crystallisation. The exact function of ZnT8 reduction in the protective role is currently unknown.

"This work underscores that human genetics is not just a tool for understanding biology: it can also powerfully inform drug discovery by addressing one of the most challenging and important questions — knowing which targets to go after," said Prof David Altshuler, co-senior author, Deputy Director and Chief Academic Officer, Broad Institute, and Professor of Genetics and of Medicine, Harvard Medical School, Massachusetts General Hospital, Cambridge, Boston, Massachusetts, USA.

The prevalence of T2D is over 300 million people on a global scale and it is expected to significantly increase in years to come. The progression of the disease can be reduced with lifestyle changes and current therapeutic options, but for many individuals the latter option is considered inadequate. On the road to the development of a new therapy, the discovery and validation of a drug target - i.e. a human protein which, if activated or inhibited, results in the prevention and treatment of the disease - is the ultimate goal.

The identification of protective mutations through the utilisation of human genetic techniques continues to hold potential as a future source of therapeutic targets. Some significant examples include the discovery of mutations in the *CCR5* gene which protected against HIV, and drugs were developed to specifically block the encoded protein. Also, *PCSK9* gene mutations resulted in the lowering of cholesterol levels and heart disease risk.

These significant findings were the result of an international collaborative effort of researchers from the Broad Institute, Massachusetts General Hospital, Pfizer, Inc., Lund University, deCODE genetics, and the T2D-GENES Consortium.

Personalising diabetes medicine: all for one, not one for all

> "An important aspect is to better understand why patients respond so differently to drugs."
>
> *Dr Hiddo J. Lambers Heerspink, Clinical Pharmacologist, University Medical Center Groningen, Groningen, the Netherlands*

DRUGS that are optimised to groups of patients, rather than to the individual, may be the reason for the consistently high risks of renal and cardiovascular (CV) diseases, despite the availability of proven effective treatments.

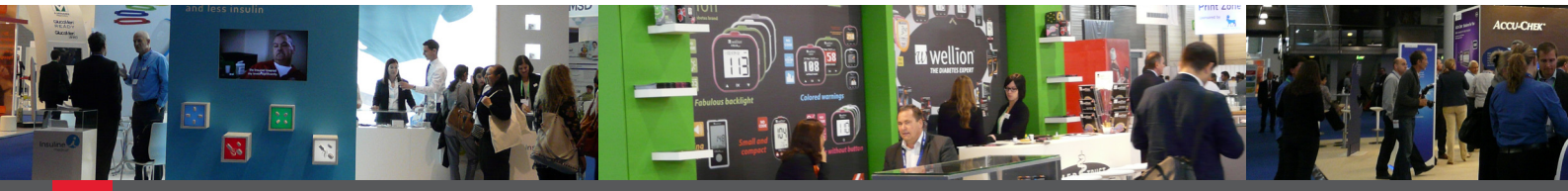
Type 2 diabetes is a vastly growing problem worldwide, and treatments for the CV and renal complications that come with the condition currently focus on targeting the risk factors of CV/renal disease and returning them to a normal range; drugs that are developed for this purpose are aimed towards a single risk factor.

Yet many drugs have multiple effects that can vary across patients. For instance, a drug-induced change in one parameter of a patient may benefit them in the long term, whilst a change in another can induce higher CV/renal risk. Such contrasting effects should be taken into consideration; however, they are often overlooked by healthcare professionals.

Thus, the responses in numerous parameters in individual patients should be monitored and optimised in order to enhance end-organ protection and provide the highest standard of care and treatment for diabetes patients.

Dr Hiddo J. Lambers Heerspink, Clinical Pharmacologist, University Medical Center Groningen, Groningen, the Netherlands, said of current practice: "An important aspect is to better understand why patients respond so differently to drugs. To this end, analyses of large scale clinical studies are conducted and genes, proteins, and metabolites are measured in blood and urine samples from these studies to investigate the underlying molecular mechanisms of response variability."

The key, it would seem, is to develop a more personal approach to the treatment of diabetes patients. What succeeds in one does not necessarily succeed in another; as Dr Heerspink concluded: "The conducted studies approach personalised medicine from a novel direction, namely, considering the effect of a single drug on multiple rather than a single parameter with the ultimate aim to enhance our understanding of how to improve CV/renal protection for the growing population with diabetes."



Renal failure reduced to rubble in Type 2 diabetes patients

SLASHES in renal failure rates, attained during intensive glucose control, are sustained for many years in Type 2 diabetes (T2D) patients.

5.5 years post-completion of a concentrated glucose lowering regimen based on gliclazide MR, T2D sufferers exhibit a significantly smaller risk of kidney failure requiring dialysis or transplantation, while risks of cardiovascular (CV) disease or death remain unchanged, according to the global ADVANCE-ON study.

These conclusions will provide a welcome boost for T2D sufferers, with end-stage renal disease having shown the smallest improvement among severe diabetes-induced complications, also including heart failure and limb amputation, over the last 20 years. Diabetes is the leading cause of kidney failure worldwide, with 90% of the estimated 382 million sufferers in the T2D category.

Prof Sophia Zoungas, study director and lead author, Associate Professor, George Institute for Global Health, University of Sydney, Sydney, Australia, said: "The findings highlight the importance of active and effective blood glucose management for renal protection in patients with T2D.

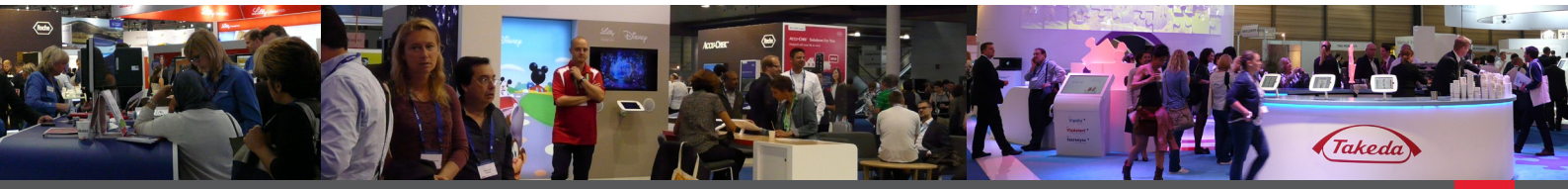
"By using this more intensive glucose-lowering regimen you obtain a substantial benefit in terms of renal protection without jeopardising cardiac safety. Intensive treatment is likely to have produced major long term benefits for the kidneys."

8,500 of 11,000 subjects who had taken part in the ADVANCE trial, which began in 2001, further enrolled in the 6-year ADVANCE-ON follow-up study, which spanned 20 countries. Upon a return to usual care in 2008, subjects were found to display diminished risk of renal failure following gliclazide MR-based treatment, which intensively reduced their glucose levels.

"This study adds meaningful information to other new findings from the ADVANCE-ON trial for patients with diabetes," said Prof John Chalmers, Senior Director, George Institute for Global Health.

A combined perindopril-indapamide regimen, administered in the blood pressure arm of the ADVANCE study, had catalysed a 14%, 18%, and 9% reduction in all-cause mortality, CV death, and vascular events in T2D patients, respectively. These benefits continued but were diminished upon the conclusion of the ADVANCE-ON study.

"The blood pressure study demonstrated persistent, but diminishing, benefits in death from all causes and from heart events, with a clear recommendation that active control of blood pressure, using perindopril and indapamide, should be maintained in both the short and the long term," said Prof Chalmers.



Treating two diseases: a modern necessity

> "Using animal models for FA and HD, we have found that it is primarily a disruption of the insulin-secreting β-cells that underlies the rise in blood glucose levels and ultimately development of diabetes."
>
> *Prof Hindrik Mulder, Lund University Diabetes Centre, Lund, Sweden*

SUFFERERS of neurodegenerative diseases experience greater risks of developing diabetes; diseases affecting the metabolism and the nervous system are becoming increasingly common, likely sharing disease-causing mechanisms and heightening risks of progressive conditions which afflict both brain and body metabolism.

Incidence of diabetes is significantly increased in subjects suffering from other diseases, in particular, the monogenic diseases Friedreich's Ataxia (FA) and Huntington's disease (HD). Though rare, information as to why diabetes is more frequent in subjects with these conditions can help us comprehend the coexistence of neurological and metabolic disorders in common diseases such as Alzheimer's and Parkinson's disease.

Evidence has also emerged that retinal neurodegeneration is an early event in the pathogenesis of diabetic retinopathy, a leading cause of preventable blindness. Therefore, studying mechanisms leading to neurodegeneration is essential for developing new therapeutic strategies.

In light of this information, Prof Hindrik Mulder, Lund University Diabetes Centre, Lund, Sweden, commented: "While it has been known for quite some time that FA and HD patients exhibit a high prevalence of diabetes, the reason for this has remained unresolved."

Prof Mulder added: "Using animal models for FA and HD, we have found that it is primarily a disruption of the insulin-secreting β-cells that underlies the rise in blood glucose levels and ultimately development of diabetes. We believe that the intracellular environment in nerve cells and insulin-secreting β-cells is quite similar."

"This explains why both cell types are afflicted by the same disease-causing mechanisms: in one, system nerve function is damaged; in another, release of the hormone insulin is perturbed. We expect that when the disease-causing mechanisms in the common Alzheimer's and Parkinson's diseases have been better defined it will also be possible to understand why these patients are at greater risk to develop diabetes," Prof Mulder concluded.

Insulin pumps defy death in Type 1 diabetes patients

HIGH hopes are held for insulin pump treatment as the way forward in tackling heart-associated deaths in Type 1 diabetes (T1D) sufferers, rather than using multiple daily insulin injections.

Encouraging data were gathered by Dr Soffia Gudbjörnsdottir, University of Gothenburg, Gothenburg, Sweden and her colleagues, who conducted a study comparing the effects of the two insulin therapies on fatal cardiovascular disease (CVD) and all-cause mortality.

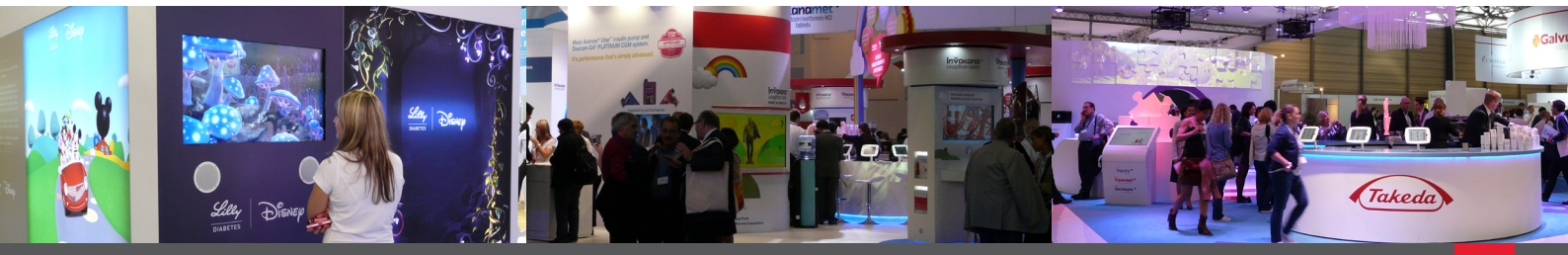
Blood sugar control and quality of life are the perceived primary beneficiaries of insulin pump treatment, a subcutaneous insulin infusion procedure (CSII) that has been applied for over 30 years. However, the effects of CSII on long-term CVD risk and mortality have, to date, been insufficiently investigated.

More than 18,000 T1D patients in the Swedish National Database enrolled in a nationwide study comparing CSII (n=2,441) and multiple daily insulin injections (n=15,727), which was followed up for a mean study period of nearly 7 years. All-cause mortality and fatal CVD were cut by 29% and 43%, respectively, while pump use catalysed an 18% risk reduction in the context of fatal or nonfatal coronary heart disease. However, pump treatment failed to provoke significant risk reductions for fatal/non-fatal CVD combined, and for non-CVD mortality.

Although the study's authors stressed that unmeasured confounders, including personality and type of care, may influence results, the results of a sensitivity analysis concluded that these factors were unlikely to affect proceedings. However, the authors warned that many T1D patients are unable and/or reluctant to deploy insulin pumps in self treatment.

"This study showed that pump treatment of T1D was beneficial with regard to long-term complications. However, it is important to note that the patients treated with pump therapy in this study were selected from the total patients with T1D because they were able and willing to manage use of a pump," said the authors.

All-cause mortality and fatal CVD were cut by 29% and 43%, respectively, while pump use catalysed an 18% risk reduction in the context of fatal or nonfatal coronary heart disease.



Reactive oxygen species:
the root of all diabetic complications?

> "Thus, the role of ROS in diabetic complications remains an active area of research, with potential new targets and drugs under ongoing preclinical and clinical investigation."
>
> *Prof Mark Cooper, Chief Scientific Officer, Baker IDI Heart & Diabetes Institute, Melbourne, Australia*

REACTIVE oxygen species (ROS) may have a significant role in multiple diabetic complications, and at the centre of attention for therapeutic development is a family of enzymes known as NADPH oxidase (Nox) - a major source of ROS.

Past investigations into ROS have focused on the mitochondrial sources of ROS generation in vascular injury. More recent research has revealed that there are, in fact, more sources of ROS, and also highlighted their role at other sites of injury in diabetes, including the kidney and retina.

"Additional research continues to explore the role of mitochondrial ROS generated from the electron transport chain as well as studies on antioxidant defence and ROS generated by other enzymes including xanthine oxidase and uncoupled NO synthase," said Prof Mark Cooper, Chief Scientific Officer, Baker IDI Heart and Diabetes Institute, and Director, Juvenile Diabetes Research Foundation Centre for Diabetes Complications, Melbourne, Australia.

Isoforms of Nox, particularly Nox 1 and Nox 4, have been implicated in diabetic complications. Nox 4 is the most abundant of all the Nox isoforms in the kidney and it is further upregulated in diabetic nephropathy. It is responsible for glomerular damage and kidney fibrosis, which can then progress onto albuminuria and end-stage renal disease, respectively; NOX 1 is responsible for angiogenesis, atherosclerosis, and other diabetic comorbidities.

The development of selective NOX inhibitors has shown to significantly hinder the progression of a range of diabetic complications in experimental models. Clinical safety studies of a Nox inhibitor, as well as a planned clinical trial in diabetic nephropathy, were the outcomes of this work.

"Thus, the role of ROS in diabetic complications remains an active area of research, with potential new targets and drugs under ongoing preclinical and clinical investigation," Prof Cooper concluded.

Improving glucose control via an artificial pancreas

IMPROVEMENT in glucose control overnight and a reduction in extreme glucose measurements could potentially be achieved by new closed-loop insulin delivery systems, which were successfully tested under realistic conditions.

Dubbed the 'artificial pancreas', the closed-loop delivery system has the potential to dramatically revolutionise diabetes care. It self-measures glucose levels in the interstitial fluid and administers the appropriate insulin dosage, without input from the patient using the system.

Free-living unsupervised randomised open-label crossover studies were used to compare overnight closed-loop therapy using the artificial pancreas with sensor augmented pump therapy, in which the patient uses information from the sensor to manually adjust the pump.

40 participants were recruited into the study which comprised 24 adults and 16 adolescents with Type 1 diabetes (T1D), with an average HbA1c of 8.0%. They were all trained to use the devices, followed by two periods of sensor augmented pump therapy in combination with or without an overnight closed-loop system. There was a random order of interventions and each period had a duration of 3 weeks in adolescents and 4 weeks in adults.

The closed-loop system was used for 866 nights, equating to 7,619 hours, without supervision or remote monitoring. Compared to the sensor augmented therapy, the closed-loop system maintained the glucose levels of individuals 18% longer within the target range of 3.9-8.0 mmol/l between midnight and 08:00. The mean overnight glucose was also reduced by 0.8 mmol/l under the loop system and there was no difference in glucose variability. Under this system, it was also noted that individuals spent less time in the hyperglycaemic or hypoglycaemic extremes.

Dr Hood Thabit, University of Cambridge Metabolic Research Laboratories and Wellcome Trust-MRC Institute of Metabolic Science, Cambridge, UK, and colleagues, concluded: "Unsupervised overnight closed-loop delivery at home in adults and adolescents with T1D is feasible, demonstrating improvements in glucose control and reducing the risk of nocturnal hypoglycaemia."

They added: "The next decade will see closed-loop systems progressively entering clinical practice and helping in the management of T1D. Our current priority is to demonstrate benefits of closed-loop systems when used over several months and in various sub-populations."


Is metformin an appropriate first-line diabetes therapy?

CONTROVERSY has arisen in the debate of whether metformin is the correct drug with which to treat Type 2 diabetes (T2D) patients; though one of only two oral antidiabetic drugs recorded by the World Health Organization in their List of Essential Medicines, evidence regarding the drug's safety and efficacy is lacking.

As part of management therapy for diabetes patients, metformin aims to improve quality of life, decrease both macro and microvascular complications, and reduce all-cause mortality; in a study of overweight T2D patients, metformin monotherapy reduced HbA1c from 8.4-7.1% in 29 weeks.

Results from the UK Prospective Diabetes Study (UKPDS) have focused on value of the drug for first-line therapy. UKPDS found that metformin treatment, when compared with conventional sulphonylurea or insulin treatment, significantly reduced any diabetes-related endpoint, diabetes-related deaths, and all-cause mortality.

Yet while there is no doubt that it works in lowering glucose, the drug's exact mechanism of action is unclear, as is the possibility that it can reduce one's risk of cardiovascular (CV) events; despite major reductions in the risks of myocardial infarction, as demonstrated by UKPDS, no other large-scale CV outcome trials have been performed.

Another reason for the popularity surrounding metformin is the suggestion that lack of hypoglycaemia, improvement of endothelial function, weight loss, and CV protection may be the mechanisms responsible for the unique vascular protection offered by the drug, and several studies have shown these to be characteristics of metformin effects.

In obese middle-aged subjects in particular, the use of metformin has been shown to prevent diabetes progression. However, many argue that solid evidence is still required before ruling out possibilities that the drug could harbour unforeseen and detrimental health effects, and it can become a first-line therapy.

"It is amazing that several decades after metformin's introduction we remain unclear about the true benefits and risks of the most widely-used antidiabetic drug on the planet," argued Prof Rury Holman, Director, Diabetes Trials Unit, University of Oxford, Oxford, UK. "GLINT, the first large-scale randomised controlled trial designed to examine the impact of metformin on the risks of CV disease and cancer in people at elevated risk of T2D and heart disease will commence shortly. Hopefully it will bring much-needed clarity by providing robust evidence for metformin effects."

Facultative pancreatic tissue stem cells: fact or fiction?

REPROGRAMMING of non-beta cells, endogenous to the pancreas, into beta-like cells may be a new prospective option in the quest to treat diabetes; signalling pathways capable of inducing therapeutic cellular plasticity have been discovered, which can potentially create new avenues in regenerative medicine.

"A major present challenge is to optimise the efficiency of beta cell differentiation, especially from cells of the human exocrine pancreas," said Prof Harry Heimberg, Coordinator and Principal Investigator, Beta Cell Neogenesis Unit, Diabetes Research Center, Vrije Universiteit Brussel, Brussels, Belgium.

The first pathway has been found to utilise partial duct ligation, where severe surgical injury can cause the non-endocrine cells to be activated in an adult mouse pancreas. These activated cells have progenitor-like abilities and, to a minor extent, the duct cells of the exocrine pancreas appear to contribute to this, though their origin is controversial.

> "A major present challenge is to optimise the efficiency of beta cell differentiation, especially from cells of the human exocrine pancreas."
>
> *Prof Harry Heimberg, Diabetes Research Center, Vrije Universiteit Brussel, Brussels, Belgium*

The second pathway involves the conversion of terminally differentiated acinar cells of the exocrine pancreas into beta-like cells; this process is brought about by the administration of two signalling peptides called ciliary neurotropic factor (CNTF) and epidermal growth factor (EGF). This pathway is based on toxin-induced chronic hyperglycaemia in adult mice.

Prof Heimberg explained: "As a proof of concept, we stimulated the pathways used by CNTF and EGF through ectopic expression of constitutively active intracellular mediators of signalling. The manipulated cells re-express the embryonic master switch Neurogenin 3 (Ngn3), show modest differentiation to beta cells in culture, but increased reprogramming efficiency following long term engraftment in diabetic mice."

Further research reveals that expanded pancreas progenitors from adult mice *in vitro* show bi-potent differentiation characteristics, which give rise to duct and endocrine cells. Although the expansion is possible from adult human pancreas tissue, the differentiation of expanded exocrine cells isolated from either mouse or human pancreas is inefficient and requires signals from a complex microenvironment.

Prof Heimberg concluded: "The present results support the potential of manipulation of signalling pathways as a therapy for diabetes."

On the road to reality – artificial beta cell

DREAMS of an artificial beta cell may finally be close to accomplishment, with crucial progress made in the development of glucose sensor control systems and insulin management.

For years patients have had particular difficulty in mastering their insulin treatment for diabetes. Administering daily injections or continuously sporting an insulin pump (the delivered doses of which require adjustment by the individual according to daily blood glucose measurements) are both impractical and disruptive of daily life. Furthermore, the need for near-normal blood glucose targets, to prevent long-term vascular and neurological complications, and avoid acute episodes of hypoglycaemia, add fresh patient pressures.

The first attempts to deliver continuously intravenous insulin from a pump were made in Europe and the US in the 1970s; the pump functioned according to continuous measurements of blood glucose via a specific sensor, due to computed patient needs by a control unit, in order to maintain normal glucose amounts. This 'artificial pancreas', though successful, was hardly transportable.

Both patients and clinicians have aspired to a miniaturisation of this system; however, the pump has allowed many thousands of patients to replace insulin injections for more secure glucose control; in 1999 wearable glucose monitors, implanted in the skin, became widely available.

Only in the last decade have we seen the development of glucose control systems, which constantly compute how much insulin is to be released, and maintain near-normal ranges of cellulose; bypassing animal studies, these systems have accelerated to clinical trials.

Combinations of wearable implantable pumps, glucose sensors, and computer/smartphone technologies have been tested in clinical and 'home-like' settings and proven their ability to dramatically reduce overnight hypoglycaemia.

Recent trials have highlighted the potential of these wearable systems even further, although glucose control during meal times and exercise remains to be improved upon as rapid glucose excursions require insulin preparations with faster and more efficient action.

Prof Eric Renard, Montpellier University Hospital and University of Montpellier I, Montpellier, France, said of the progress: "By now, the dream of an artificial beta cell can be considered as a reality, close to a move to the market for night time, and becomes continuously more achievable at all times at least in investigational conditions, but already in a home setting. New modes of patient education are currently being developed for this 'digital age' insulin therapy."

Do not put heart failure in the corner of diabetes trials

ASSESSMENT of cardiovascular diseases (CVDs), especially heart failure (HF), should be taken into consideration when diabetes therapies are tested in clinical trials. This is to prevent the cancelling-out effect of a therapy catering for one complication hindering or exacerbating another complication.

Diabetics tend to have a reduced life expectancy and are more prone to developing diseases that affect almost every organ in the body. In particular, these individuals are at high risk of developing CVDs, which include myocardial infarction, stroke, angina, and HF.

Development of CVDs in diabetics can possibly be attributed to the changes in the makeup of blood vessels, which can lead to a thickening of the lining of the blood vessels, and this, in turn, can impair blood flow. Also, poor circulation in diabetics can lead to vascular problems.

To evaluate the effect of therapies on health outcomes, a randomised controlled trial involving 120,000 diabetics is currently underway to analyse the effect of a variety of therapies on cardiovascular outcomes.

In the opinion of Prof Hertzel Gerstein, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada, there is not enough focus on HF included in the list of key outcomes currently assessed in clinical trials. He also stresses that this should not be overlooked since the probability of developing HF is very high, as high as the probability of heart attack or stroke.

> "The fact that at least one recent cardiovascular trial reported an increased risk of HF with the therapy being tested highlights the importance of assessing HF in all cardiovascular trials."
>
> *Prof Hertzel Gerstein, McMaster University and Hamilton Health Sciences, Hamilton, Canada*

"Moreover, people who develop HF are at high risk for recurrent episodes of HF that require hospitalisation or may be fatal. The fact that at least one recent cardiovascular trial reported an increased risk of HF with the therapy being tested highlights the importance of assessing HF in all cardiovascular trials. This defect is now beginning to be addressed and several large trials have explicitly included HF as a primary or secondary outcome," commented Prof Gerstein.

Prof Gerstein also noted that the effect of therapies on different outcomes is not confined to CVD but also affects a plethora of other conditions such as eye disease, kidney disease, cognitive decline, and cancers. On a positive note, he concluded that a large number of outcome trials are currently underway which will assess these implications, including CVDs and the effects of new drugs being tested.

The battle between therapies for lower limb disease in diabetes rages on

BATTLES between bypass and endovascular therapy as the prime weapon against lower limb disease continue to dominate a key area of diabetes.

Diabetic foot ulcers represent a powerful global obstacle; 20-40% of healthcare resources for diabetes are connected to diabetic feet, while foot ulcer complications are the main cause of hospitalisation and amputation in diabetic patients. Indeed, the statistics surrounding amputation are shocking, with diabetic foot complications accounting for one leg amputation every 20 seconds worldwide.

Recent research has unearthed the key role of ischaemia in occurrence of diabetic ulcer or gangrene. Emerging from lower limb arterial disease, ischaemia inhabits approximately 50% of diabetic ulcers, normally together with neuropathy. Ischaemia represents the most suitable therapy target, as without treatment, arterial flow cannot improve and ulcers cannot heal. Open vascular surgery can improve tissue perfusion of diabetic foot, with the patient's own veins acting as arterial conduits during surgery; endovascular techniques that open up occluded or dilate stenosed arteries constitute another option.

Unfortunately, available data comparing open surgery and endovascular therapy are inconclusive regarding which comprises the stronger method. Endovascular techniques are considered more easily tolerated by the patient and are thus preferred when the lesion is considered equally well treatable by either approach. However, over-use of endovascular therapy increases the risk of failure, complicates subsequent surgery, and deteriorates the overall result of the leg.

Prof Mauri Lepäntalo, Department of Vascular Surgery, Helsinki University Central Hospital, Helsinki, Finland, said: "The comparison of bypass surgery and endovascular therapy is further complicated by a new idea of angiosomes, i.e. 3D vascular territories of the foot. It may be more important to discuss whether to open up a pathway down to the ulcer area (angiosome) of the foot or just be satisfied with treating only occlusive lesions of the feeding arteries of thigh and calf. How far to go may be more important than what technique to use."

Traumas of stillbirth can worsen diabetes

STILLBIRTH trauma, combined with a diagnosis of gestational diabetes mellitus (GDM), make women almost 47-times more likely to develop Type 2 diabetes mellitus (T2DM).

GDM patients not only risk the onset of T2DM, but also cardiovascular (CV) disease in the years following pregnancy. In a population-based cohort study aiming to estimate the incidence of T2DM and CV events in women with previous GDM and normal glucose tolerance in pregnancy (and to evaluate the role of stillbirth in these risks), administrative data were taken from 12 local health authorities in Puglia, Italy, from 1st January 2002 – 31st December 2010.

Authors identified those with a diagnosis of GDM during the index period; these women were then matched with those who had no diabetes for age, local health authority code, and use of antihypertensive and antithrombotic agents. The main outcome measures were of T2DM development and hospitalisations for CV events occurring after a pregnancy complicated by GDM, and ended at term or in stillbirth.

Final analysis included 3,851 women with GDM, with a mean age of 37 years, and 11,553 matched controls without GDM. At median follow-up (5.4 years) incidences of T2DM were 2.1 per 1,000 women per year in those without GDM, 54.0 per 1,000 women per year among those with GDM and pregnancy at term, and 115.0 per 1,000 women among those with both GDM and stillbirth pregnancy.

GDM increased risks of T2DM 22-fold, and GDM complicated by stillbirth increased them by 47-fold, compared with women who experienced normal pregnancies; GDM and stillbirth during GDM were associated with a significantly higher risk of CV events.

Thus, a decisive factor is presented when GDM and stillbirth complicate pregnancy in women, determining the development of T2DM and future CV events.

The study's authors, Dr Basilio Pintaudi and colleagues, Mario Negri Sud Foundation, Chieti, Italy, said: "The most important action should be to act on modifiable risk factors such as diet and physical exercise, aiming to an intensive lifestyle change and cutting out unhealthy habits.

"A specific intensive and personalised CV and metabolic follow-up, including recommendations on lifestyle, should be planned for these high-risk women. Since most of the women who have had GDM do not comply with the recommendation to have a post-pregnancy glucose tolerance test, healthcare professionals should also increase their efforts to motivate these high-risk women to attend screening programmes."

Diverse ethnicity equals diverse insulin sensitivity

INSULIN sensitivity falls dramatically in South Asian people when compared to white people, prior to the diagnosis of diabetes.

Unlike white people, who are able to increase insulin secretion up to 7 years before diagnosis, South Asians, i.e. those of Indian, Pakistani, or Bangladeshi origin, show little sign of this compensatory mechanism, which causes an increased fasting plasma glucose (FPG) trajectory (pre-diabetes diagnosis); this is according to Dr Adam Tabak, University College London, London, UK, and Semmelweis University, Budapest, Hungary, and his colleagues.

Ethnic differences in trajectories of FPG and 2 hours post-meal plasma glucose (2hPG), insulin sensitivity (HOMA-S), and secretion (HOMA-B) pre-diabetes diagnosis were analysed in an effort to solve the uncertainty surrounding the role of insulin secretion in South Asians. 101 South Asian and 764 white subjects who developed Type 2 diabetes (T2D) during follow-up between 1992 and 2009 were enrolled in the Whitehall II study. This analysed blood sugar trajectories, pre-diabetes diagnosis, through modelling subject data which highlighted an elevated risk of diabetes onset during follow-up in 26.4% and 10.2% of South Asians and white people, respectively.

South Asians also exhibited a 0.34 mmol/l per decade faster increasing FPG trajectory pre-diagnosis and 0.36 mmol/l greater FPG levels at diagnosis than whites. A surprising observation was that 2hPG trajectories were equal between the two ethnicities, bucking the expectation of overall faster glucose generation pre-diagnosis in the more insulin-resistant South Asian group.

HOMA-B trajectories accelerated in both ethnicities until 7 years pre-diagnosis; this increase was minimal in South Asians and much quicker in whites. The trend served to expand the already vast gap in insulin sensitivity between the groups, with South Asians displaying significantly enhanced resistance, even 15 years pre-diagnosis. The team concluded that an impaired compensatory mechanism means that time is shorter for T2D prevention in South Asians.

"These findings extend our prior observation of inadequate pancreatic beta cell compensation with ageing in healthy South Asians," said the authors. "The more rapid increase of fasting glucose before the diagnosis of T2D in South Asians gives a shorter window of opportunity for prevention in this ethnic group. This observation, together with our previous finding, highlights the need for preventive efforts among healthy South Asians."

Seeking to build on these conclusions, the research team plans to compare trajectories of other biomarkers connected to insulin resistance and inflammation between South Asians and Whites.

Weight gain across the ages

> "Our findings propose that the mechanisms underlying the genetic susceptibility to obesity may have opposite consequences for weight gain before and after middle-age."
>
> *Prof Gull Rukh, Prof Marju Orho-Melander's research group, Lund University Diabetes Center, Malmö, Sweden*

INCREASING weight has long been considered a worldwide health threat; research has found that a genetic risk score (GRS), comprised of 31 body mass index (BMI) variants associated DNA regions, is associated with having a higher BMI at all stages of life.

Swedish authors, led by Prof Gull Rukh, Prof Marju Orho-Melander's research group, Lund University Diabetes Center, Malmö, Sweden, looked at the large prospective Malmö Diet and Cancer Study of 21,407 subjects with self-reported BMI at young-age (20 years) and measured BMI at both middle-age (58 years) and old-age (2,673 individuals, mean age 73 years).

Substantial weight gain (SWG) was characterised as gaining >10% of body weight from young-to-middle age, 20% or more from young-to-old-age, and 10% from middle-to-old-age; associated effect sizes per increasing quintile of GRS on BMI were analysed at all ages.

Researchers further analysed the risk, per GRS quintile, for belonging to a self-reported unstable weight group, and for SWG from young-to-middle-age and old-age, and from middle-to-old-age. Higher GRS was associated with elevated BMI at all ages, with higher risk for SWG and unstable weight from young adulthood-to-middle-age, as is consistent with previous findings. Yet after middle age, higher genetic risks for obesity became associated with a lower risk of SWG.

Investigators substantiated their results using another Swedish cohort with similar results. The results imply that genetic effects associated with higher BMI may not continually convert to increased weight gain throughout an individual's entire life, rather they appear to be age dependent; genetic risk for higher BMI before middle-age results in higher risk of weight gain, yet after this age, these risks result in reverse.

"Our findings propose that the mechanisms underlying the genetic susceptibility to obesity may have opposite consequences for weight gain before and after middle-age. The mechanisms behind this switched associated effect are unknown and could not be addressed in our study but they may be related to the more intensive weight gain before middle-age among individuals with a high number of BMI-associated genetic variants, which could ultimately lead to weight loss due to, for example, higher morbidity and accentuated loss of muscle mass in old-age. This needs to be verified in future studies," Prof Rukh commented.

Diabetes patients taking a tumble

FALLING down the stairs is more likely to occur in patients suffering diabetic peripheral neuropathy (DPN), a condition that affects the nerves in the limbs and causes the individual to sway during climbing.

In the study, both motion and force data were collected for 22 DPN sufferers, 40 diabetes patients without DPN, and 32 healthy non-diabetic controls. Using a 3D motion analysis system, movement data were retrieved from reflective markers, which were placed at anatomical locations on the body to calculate whole-body centre-of-mass (CoM); the centre-of-pressure (CoP) underfoot was recorded using four force platforms, mounted into the four middle steps of a seven-step staircase.

Participants ascended and descended the staircase at least three times. Balance was quantified by assessing the separation between the CoM and CoP (CoM-CoP separation) in the medial-lateral plane.

The DPN group showed significantly higher maximum CoM-CoP separation compared to both diabetes patients without DPN and controls, during stair ascent. Differences were also evident in stair descent, with DPN subjects showing significantly higher maximum separation and an increased variation of CoM-CoP separation; a wider stance width was also seen in the DPN group.

> "A larger and more variable medial-lateral sway means that patients with DPN are more likely to lose control of balance and experience a fall during what is known to be an activity – using stairs - where the risk of falls is already very high."
>
> *Dr Steven Brown, Manchester Metropolitan University, Manchester, UK*

Dr Steven Brown, Manchester Metropolitan University, Manchester, UK, and colleagues, concluded: "Diabetic patients with peripheral neuropathy display greater extremes in magnitude of medial-lateral sway during stair ascent and descent as well as displaying higher variability during stair ascent and descent.

"This indicates that patients with DPN have difficulty regulating control of balance during this challenging task. A larger and more variable medial-lateral sway means that patients with DPN are more likely to lose control of balance and experience a fall during what is known to be an activity – using stairs - where the risk of falls is already very high."

Those at higher risk should take measures to keep safe; avoiding steep stairs and using handrails helps to prevent falls. Further research is underway to better understand what contributes to unsteadiness and increased risks of falling.

Tresiba®: new hope for diabetic children and adolescents

> "These data show that Tresiba® has the potential to offer youngsters with diabetes a new treatment option, which may help them achieve better control of their diabetes."
>
> *Dr Nandu Thalange, Paediatric Endocrinologist, Norfolk and Norwich University Hospital, Norwich, UK*

IMPROVED long-term glycaemic control and safety profiles have been achieved with Tresiba® in combination with insulin, which can potentially bring hope to many children and adolescents with Type 1 diabetes (T1D).

Tresiba® (insulin degludec) is an ultra-long acting basal insulin which can be used by people with T1D or T2D to establish a routine for insulin treatment; this therapy can last for up to 42 hours, offering greater flexibility in day-to-day dosing times.

The BEGIN® YOUNG 1 trial was a randomised controlled, 26-week open-label, treat-to-target trial (with a 26-week extension) which evaluated once-daily Tresiba® against insulin detemir (given once or twice-daily), both in combination with bolus insulin aspart in children and adolescents aged from 1 year up until 18 years.

The primary endpoint of a mean change in HbA1c ($p<0.05$) at 26 weeks, a lower insulin dose, and a significantly greater reduction in fasting plasma glucose was achieved by Tresiba® in comparison to insulin detemir ($p<0.05$). There were similar rates of overall and nocturnal hypoglycaemia under both therapies, but the rate of severe hypoglycaemia was numerically higher with Tresiba® plus insulin aspart.

There were significantly lower rates of hyperglycaemia with ketosis ($p<0.05$) in patients under Tresiba® therapy. Weight increase was experienced by those on Tresiba® and remained unchanged with insulin detemir. There were similar adverse event profiles in both drug therapies.

"When treating children and adolescents with T1D, it is critical that the right balance between glycaemic control and side-effect management is maintained to ensure the best possible long-term outcomes. These data show that Tresiba® has the potential to offer youngsters with diabetes a new treatment option, which may help them achieve better control of their diabetes," said Dr Nandu Thalange, Paediatric Endocrinologist, Norfolk and Norwich University Hospital, Norwich, UK.

Tresiba® has been approved and launched in the EU, Japan, and other markets; however, in the USA more information about this drug is required by the FDA, which will be resubmitted for drug approval.

Diabetics gain protection from high-fat dairy products

GLUTTONY may pay off when it comes to dairy consumption, with the food group being heavily linked to reduced Type 2 diabetes (T2D) incidence.

Unlike general animal fats, dairy product-specific fats could be a key preventer of T2D. People who consume the most high-fat dairy products (eight or more portions per day) are 23% less likely to develop T2D than those who consume the least (one or less per day), according to Dr Ulrika Ericson, Lund University Diabetes Centre, Malmö, Sweden, and colleagues.

Dietary fats may influence glucose metabolism and insulin sensitivity, thus indicating a potentially major contribution in T2D onset. Plant sources of fat have been hinted as being superior to animal sources when seeking to displace saturated fat with monounsaturated and polyunsaturated fats, which may prove superior in T2D prevention; this is supported by proof of increased T2D incidence, through a diet consisting of red meat and meat products.

Recent research has indicated that the protective effects can be found in a diet which is high in dairy products. 26,930 subjects (60% women), aged 45-74 years, enrolled in a comparison study; this sought to build on previous findings by analysing the association of main dietary fat sources, graded by fat content, with T2D onset. 2,860 T2D cases were recorded during 14 years follow-up, with the 20% biggest consumers of high-fat dairy products showing 23% reduced risk of T2D incidence, compared with the 20% smallest consumers.

Examining the effects of specific high-fat dairy foods, cream posted a 15% risk reduction of T2D onset in the highest consumers, compared to the lowest consumers, with amounts measuring at least 30 ml a day and, at most, 0.3 ml a day, respectively. T2D incidence was also slashed through high-fat fermented milk consumption, with a 20% decrease found in the top 10% highest consumers (180 ml/day) next to non-consumers (60%). However, no relationship was found between low-fat dairy product intake and T2D onset risk.

"Our observations may contribute to clarifying previous findings regarding dietary fats and their food sources in relation to T2D. The decreased risk at high intakes of high-fat dairy products, but not of low-fat dairy products, indicate that dairy fat, at least partly, explains observed protective associations between dairy intake and T2D. Meat intake was associated with increased risk of developing diabetes regardless of fat content," said Dr Ericson.



IDegLira boosts glycaemic control in Type 2 diabetes patients

WHIRLWIND improvements in glycaemic control are experienced by Type 2 diabetes (T2D) patients within a month of starting IDegLira treatment.

According to Phase IIIa DUAL™ clinical data, a once-daily single injection combination of Tresiba® (insulin degludec 50 units), a once-daily basal insulin analogue with an ultra-long period of action, and Victoza® (liraglutide 1.8 mg), the once-daily human glucagon-like peptide 1 analogue, IDegLira, improved glycaemic control in adults with T2D as soon as 4 weeks post-initiation in both insulin-naïve patients and those uncontrolled on basal insulin compared to its individual ingredients. Pre-prandial (before meal) and post-prandial (after meal) blood glucose targets were also more easily attainable in IDegLira-treated patients, hinting at an enhanced predictability with treatment.

Approximately 2,000 subjects with T2D enrolled in the DUAL clinical programme, consisting of two Phase IIIa trials - DUAL I (n=1,663) and DUAL II (n=398). DUAL I compared IDegLira versus Tresiba and Victoza alone in insulin-naïve adults with T2D, uncontrolled, with metformin with or without pioglitazone. DUAL II compared IDegLira and Tresiba once-daily, both added onto metformin in T2D adults, uncontrolled, on basal insulin in combination with metformin with or without sulfonylureas/glinides.

Breakfast, lunch, and dinner post-prandial blood glucose values within the target <9 mmol/l were achieved far more easily in IDegLira subjects (DUAL I: 51%; DUAL II: 37%) than in Tresiba (DUAL I: 38%; DUAL II: 25%) or Victoza subjects (DUAL I: 36%). Furthermore, the chances of hitting all four pre-prandial target ranges in the recommended range of ≥3.9 to ≤7.2 mmol/l were greatly enhanced by IDegLira therapy (DUAL I: 48%; DUAL II: 44%) compared to Tresiba (DUAL I: 41%; DUAL II: 27%) or Victoza therapy (DUAL I: 32%).

> "Getting to glycaemic target faster and with more predictable control motivates patients to adhere to therapy and proactively manage their disease."
>
> *Prof Tina Vilsbøll, Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark*

Prof Tina Vilsbøll, Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark, indicated that these conclusions may strongly affect how T2D patients observe their treatment progress, potentially boosting clinical outcomes. "Getting to glycaemic target faster and with more predictable control motivates patients to adhere to therapy and proactively manage their disease," Prof Vilsbøll said.

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15TH-19TH SEPTEMBER 2014

EASD 2014 AWARDS

Delegates have been recognised for their contributions to the progress of knowledge within the field of diabetes; such honours were originally created in memory of the individuals who helped to shape mankind's understanding of diabetes through history. The candidates selected to receive these prestigious awards have left their mark on a rapidly evolving field, and helped to light the way to further understand this significant clinical area for years to come. The Rising Star Symposium highlighted the exceptional work of four promising and innovative young researchers across Europe.

THE CLAUDE BERNARD AWARD

Dr Domenico Assili,
USA

THE EASD CAMILLO GOLGI PRIZE

Prof Soloman Tesfaye,
UK

THE ALBERT REYNOLD PRIZE

Prof Steven E. Kahn,
South Africa

THE MINKOWSKI PRIZE

Prof Anna L. Gloyn,
UK

RISING STAR SYMPOSIUM

Dr G. H. Goossens,
the Netherlands

Targeting adipose tissue oxygen tension to improve insulin sensitivity in humans.

Dr Hiddo J. Lambers Heerspink,
the Netherlands

A new approach for personalised medicine in type 2 diabetes: integrating multiple effects of a single drug.

Dr Lorenzo Pasquali,
Spain

Identification of type 2 diabetes target genes.

Dr Rinke Stienstra,
the Netherlands

A shift in macrophage metabolism drives obesity-induced inflammation and the development of insulin resistance.

INVESTIGATING THE DIFFERENT DIMENSIONS OF DPP-4 INHIBITORS

Summary of Presentations from the Takeda Pharmaceuticals International-Sponsored Symposium, held at the 50th Annual Meeting of the EASD, Vienna, Austria, on 15th September 2014

Chairperson

Heinz Drexel[1]

Speakers

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MEETING SUMMARY

This Takeda-sponsored European Association for the Study of Diabetes (EASD) symposium addressed the pharmacology, clinical use, and future therapeutic application of dipeptidyl-peptidase-4 (DPP-4) inhibitors. The scientific programme covered the clinical efficacy of DPP-4 inhibitors, their durability in clinical practice, and their use in combination therapy with other antidiabetic drugs. The important issue of the effect of this class of drugs on cardiovascular (CV) outcomes was also explored. The symposium was chaired by Prof Heinz Drexel and included insightful talks from an expert faculty comprising of Profs Jørgen Rungby, Jochen Seufert, and Kausik Ray.

Welcome to Different Dimensions of DPP-4 Inhibitors

Professor Heinz Drexel

Prof Heinz Drexel introduced the session by outlining the agenda of the symposium and introducing the faculty members and main themes. These included the pathophysiology and epidemiology of diabetes, and the exploration of pharmacology of DPP-4 inhibitors and their durability and application in clinical practice. This was followed by a discussion of the data linking

insulin resistance and CV disease, which formed the basis for an introduction to recent data from CV outcomes trials for the currently available DPP-4 inhibitors.

The Structural Dimension: Exploring the Pharmacology of DPP-4 Inhibitors in More Detail

Professor Jørgen Rungby

Impaired regulation of insulin is a known contributor to hyperglycaemia[1] and the pathophysiology of Type 2 diabetes (T2D). Defects in the secretion and action of the two main incretin hormones, gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), contribute to this. GIP facilitates fat deposition, promotes bone formation, increases glucagon production, and decreases gastric acid secretion;[2] while GLP-1 is involved in gastric emptying, increasing insulin production, and decreasing glucagon production. It also plays a role in increasing cardiac output and has a cardioprotective effect, particularly during ischaemia.[2] Both GIP and GLP-1 are involved in increasing beta cell mass and insulin production.[2] These incretin hormones work in conjunction to lower glucose levels and therefore prevent hyperglycaemia, one of the hallmarks of T2D.

Following ingestion of a meal, levels of GLP-1 increase in the portal vein and in the peripheral circulation, increasing meal-stimulated insulin secretion, and thereby reducing liver glucose production and increasing peripheral glucose uptake.[3,4] Endogenous GLP-1 stimulates insulin secretion directly but also via afferent neurones located in the intestines, portal vein, and/or liver.[5] The ability of incretin hormones to stimulate insulin secretion after meals has been dubbed 'the incretin effect'. The impaired incretin response observed in T2D has been associated with decreased levels of GLP-1.[6] GLP-1 and GIP have a half-life of 2 and 5–7 minutes, respectively, due to their rapid inactivation by DPP-4 and clearance via the kidneys.[7,8] Therefore, inhibition of DPP-4 results in increased plasma levels of GLP-1 following meal stimulation, a reduction in glucagon secretion, an increase in insulin release, and subsequent lowering of blood glucose levels.[9] DPP-4 inhibitors have several clinical benefits, including their ability to reduce glycated haemoglobin (HbA1c) by, on average, 0.5–0.8%, a reduction which is enhanced when they are used in conjunction with insulin, thiazolidinediones (TZDs), metformin, or sulphonylureas (SUs).[10] Generally, DPP-4 inhibitors are well tolerated as mono and combination therapies, even in patients with renal insufficiency. They are associated with only a minimal risk of hypoglycaemia and weight-neutral effects, characteristics that may increase patient adherence to this therapy.[10]

Alogliptin is the most recent addition to the DPP-4 inhibitor class, which has been shown to be selective for DPP-4 over other DPP enzymes, including DPP-8 and DPP-9, and to have a long half-life and favourable safety profile. These properties, in addition to the pathways utilised for their metabolism and excretion, and their suitability for use in special populations, their glycaemic efficacy, and potential for interactions with other drugs, should be considered when choosing between the currently available DPP-4 inhibitors.[11]

One important factor that differentiates the individual DDP-4 inhibitors is the number of sites they are able to bind to on the DPP-4 enzyme. The higher the number of points of interaction, and the closer these are to the active site of the enzyme, the higher the selectivity and efficacy of the inhibitor.[12,13] Due to the distribution of DPP enzymes throughout the body, selective inhibition is extremely important; the DPP-4 inhibitors alogliptin and linagliptin have been shown to be highly selective for DPP-4 over DPP-8 and 9 *in vitro*, in comparison with saxagliptin, sitagliptin, and vildagliptin.[12] In addition, DPP-4 inhibitors, including alogliptin, have been shown to be suitable for use in special populations, including in the elderly and in individuals with mild-to-moderate hepatic and renal insufficiency.[14,15] Key differentiating characteristics of DPP-4 inhibitors include their chemical structure, metabolism, *in vitro* selectivity, dosing frequency, and their use in special patient populations.

The Clinical Dimension: Efficacy and Durability of DPP-4 Inhibitors in Practice

Professor Jochen Seufert

The incidence and prevalence of T2D is increasing across the world, with the biggest increase in prevalence observed in the Far East, the Western Pacific, Africa, and South America.[16] T2D is a

progressive disease associated with a decline in endogenous insulin secretion, and with progression, eventual treatment intensification in order to maintain control of blood glucose levels in patients is required. Due to the need for treatment intensification, antidiabetic drugs must also allow for the possibility of broad combination therapy and have a favourable CV safety profile.[17] Over the past 20 years the rate of introducing new classes of antidiabetic agents has increased, with DPP-4 inhibitors being amongst the newest and most effective class of drug now available.[18]

Despite the availability of newer agents, up to two-thirds of patients fail to achieve glycaemic targets.[19-21] As a consequence, treatment guidelines have been devised with the aim of optimising glucose control strategies. The American Diabetes Association/EASD guidelines recommend the use of biguanides (metformin) as a first-line therapy - a recommendation that is consistent with many other available guidelines.[22] However, recommendations for subsequent therapy intensification after first-line therapy differ between the various guidelines and include treatment with TZDs, GLP-1 receptor agonists, Sus, and insulin.[22] The decision to make the transition from first-line therapy to a more intensive treatment regimen is an issue frequently faced by physicians in the clinic. The action profile of anti-hyperglycaemic drugs should be favourable in terms of HbA1c reduction, blood pressure, and body weight, and be associated with a low risk of hypoglycaemia.[22] When compared against these criteria, DPP-4 inhibitors reduce HbA1c by up to 1.1%, with little effect on systolic blood pressure, neutral effects on body weight, and a low risk of hypoglycaemia.[22-24] The most common treatment strategy followed in 2014 was the addition of an oral agent to metformin, such as an SU, a DPP-4 inhibitor, or pioglitazone.[22] However, injectable therapies, including insulin, a GLP-1 agonist, or a combination of both, are alternative treatment strategies. More importantly, in order to achieve optimum glycaemic targets, the treatment regimen must be tailored to the patient and their individual treatment needs.[22]

A retrospective cohort study from the UK General Practice Research Database has shown that SUs remain the most popular second-line therapy.[25] This is despite evidence that patients initiating SU or metformin have an increased long-term risk of mortality and CV events compared to patients on metformin alone,[26] and that the durability of SU treatment for glycaemic control is reduced over time.[27] In contrast, DPP-4 inhibitors have demonstrated superior durable glycaemic control. A study comparing alogliptin and glipizide over 2 years has shown that alogliptin (12.5 and 25 mg) produced rapid HbA1c and fasting plasma glucose (FPG) reductions that were sustained over 104 weeks, and that were statistically superior to glipizide treatment for alogliptin 25 mg.[28] Additionally, there were significantly greater reductions in postprandial glucose with both doses of alogliptin versus glipizide, and a significant reduction in body weight and lower risk of hypoglycaemia with alogliptin treatment.[28]

The characteristics of DPP-4 inhibitors include their consistent HbA1c lowering effect, their long-term durability in maintaining glycaemic control, and their association with a low risk of hypoglycaemia. As a class they are well-tolerated, offer the possibility of broad combination therapy, and may have a favourable CV safety record.[17]

A New Dimension: What about Insulin Resistance? Exploring the Pioglitazone and Alogliptin Combination

Professor Heinz Drexel

Insulin resistance is caused by an interplay between genetic factors: abnormal insulin receptor function, abnormal signalling proteins, or abnormal insulin levels; and environmental factors such as obesity, a sedentary lifestyle, and ageing. It is often a combination of these that contribute to the characteristic hyperglycaemia, increased free fatty acids, and atherogenic lipid profile seen in individuals with T2D (Figure 1).[29] Patients with these clinical characteristics, who also display elevated FPG levels, a high body mass index, and increased urinary albumin excretion, are likely to have metabolic syndrome (MetS).[30,31]

The San Antonio Heart Study has demonstrated that as insulin resistance increases there is a proportional increase in the risk of cardiovascular disease (CVD).[32] Similar results have been found in a cohort of 750 patients undergoing coronary angiography, where a lower rate of glycaemic control was associated with a decrease in high-density lipoprotein cholesterol (HDL-C) and high levels of low-density lipoprotein cholesterol (LDL-C).[33] Over half of patients referred to a cardiologist displayed insulin resistance, indicating a link between insulin

resistance and increased risk of vascular events.[34] Therefore, pharmacological treatments that target insulin resistance may offer therapeutic benefit in the prevention of CV event risk. The UK Prospective Diabetes Study (UKPDS) has demonstrated that the rate of myocardial infarction (MI) was significantly lower in patients treated with metformin, than those treated with conventional therapy. These patients also had a lower rate of microvascular (MV) disease and a lower rate of death from any cause.[35]

Pioglitazone - an insulin sensitiser - decreases insulin resistance, enhances insulin action, and reduces blood glucose levels. In addition, it regulates the transcription of genes involved in carbohydrate, lipid, and protein metabolism;[36] these are favourable characteristics in treating patients with MetS. Pioglitazone monotherapy has been shown to provide durable glycaemic control and increase HDL-C, whilst lowering LDL-C levels, over 2 years in comparison to gliclazide, in patients with T2D.[37,38-40] In addition, macrovascular benefits on pioglitazone monotherapy have been demonstrated in several clinical trials. Monotherapy has been shown to reduce the risk of secondary stroke by 47% in patients with T2D[41] and in high-risk patients with T2D and previous MI; pioglitazone reduced the risk of secondary MI by 28%, and acute coronary syndrome by 37%.[42] Furthermore, in patients with chronic kidney disease, pioglitazone reduced the composite endpoint of all-cause death, MI, and stroke, independent of the severity of renal impairment.[43] However, pioglitazone is also associated with several risks, including increases in body weight due to fluid retention in the weeks following initiation of therapy.[44] Furthermore, a meta-analysis comparing both pioglitazone and another insulin sensitiser, rosiglitazone, with placebo or active comparator found an increased risk of bone fracture (p=0.001).[45]

The combination of a TZD and metformin has previously been associated with a 48% relative risk reduction in mortality in diabetic patients within 1 year of an acute MI.[46] Alogliptin/pioglitazone is the only fixed dose combination of a DPP-4 inhibitor and an insulin sensitiser. It may offer significantly greater glycaemic control than the two therapies separately. In a 26-week, double-blind, parallel group study, HbA1c was significantly reduced by 1.6% and 1.7% in patients treated with the combination of alogliptin/pioglitazone 12.5/30 mg or alogliptin/pioglitazone 25/30 mg, respectively, versus monotherapy with alogliptin or pioglitazone ($p<0.05$).[47] Furthermore, combining the two therapies and adding them to metformin resulted in a significantly greater and more durable reduction in HbA1c versus metformin plus pioglitazone over 52 weeks.[48] This combination has also been associated with a low incidence of hypoglycaemia and a neutral effect on weight gain over 26 and 52 weeks of treatment, respectively.[48,49] The positive benefit–risk profile of pioglitazone, which includes potent HbA1c reduction, durable glycaemic control, and low risk of hypoglycaemia, outweighs the treatment-associated bone fracture risk.

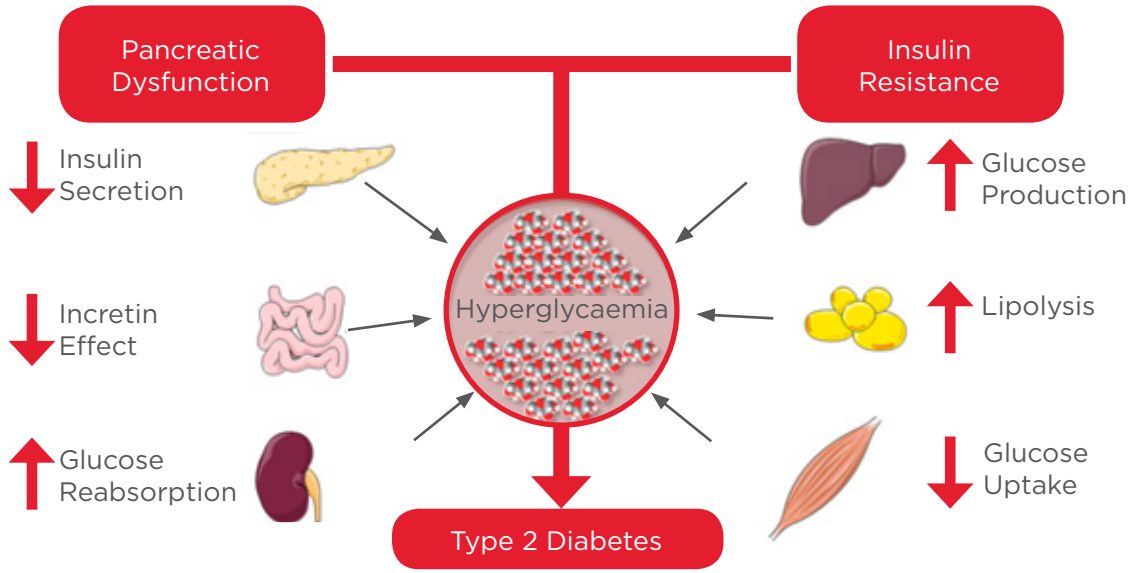

Figure 1: Pathogenesis of Type 2 diabetes - insulin resistance in muscle and liver and impaired insulin secretion represent the core defects in Type 2 diabetes.[1]

The fixed combination of a DPP-4 inhibitor plus pioglitazone may have a complementary mode of action and offer favourable CV outcomes.

The Future Dimension: What do the CV Outcome Studies for DPP-4 Inhibitors tell us?

Professor Kausik Ray

Epidemiological data show that diabetes doubles the risk of coronary artery events and ischaemic and haemorrhagic stroke.[50] Meta-analysis data have demonstrated that more intensive glycaemic control therapy is associated with a 17% relative risk reduction in non-fatal MI and a 15% risk reduction in coronary heart disease, versus less intensive glycaemic control therapy, but it makes no difference to stroke or all-cause mortality.[51] Overall, CV risk reduction requires multiple interventions including blood pressure control and lipid lowering, and although lowering HbA1c may not have as high an impact on CV risk reduction as targeting blood pressure and lipid lowering, it may be an additional beneficial intervention in a high-risk patient population.[51] In support of this, results from UKPDS have demonstrated that reducing HbA1c by 1% results in a 37% reduction in MV endpoints.[52]

Existing anti-hyperglycaemic therapies have several limitations, including the risk of hypoglycaemia, gastrointestinal side-effects, and weight gain. In particular, weight gain associated with these therapies is likely due to increased adiposity, consequent increase in blood pressure, and more atherogenic lipid profiles.[53] In particular, meta-analysis data have shown that SUs are associated with an increased risk of mortality and stroke[54] leading to guidelines from the US FDA requiring CV outcome studies for new antidiabetic agents.[55]

CV outcome studies have been conducted for the DPP-4 inhibitors, alogliptin (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care [EXAMINE]),[56] and saxagliptin (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction [SAVOR-TIMI]).[57] Results have shown that alogliptin significantly reduced HbA1c, but did not increase CV-related mortality, versus placebo in T2D patients with very high CV risk (previous acute coronary syndrome 15–90 days prior to randomisation).[56]

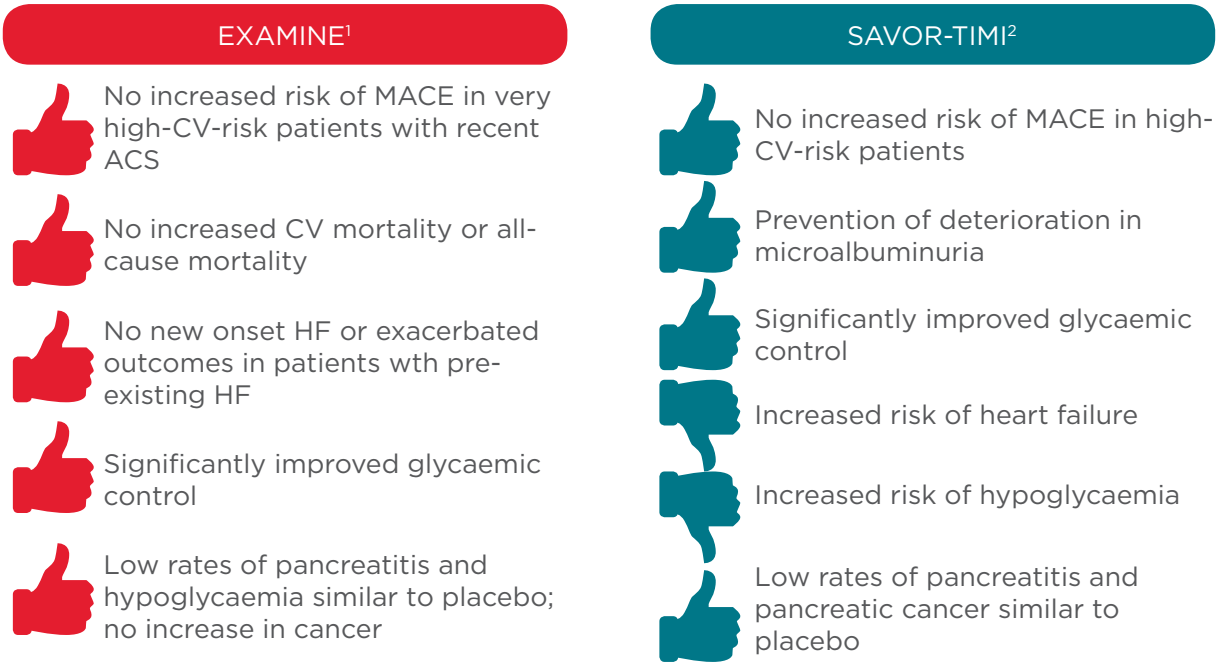

Figure 2: Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) and Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR-TIMI) trials: conclusions.

MACE: major adverse cardiac event; ACS: acute coronary syndrome; CV: cardiovascular; HF: heart failure. *White W et al.,[56] Scirica B et al.[57]*

Saxagliptin was associated with superior glycaemic control compared to placebo in a T2D population with a history of CVD or with multiple associated risk factors, and demonstrated non-inferiority to placebo for the primary composite outcome of non-fatal MI, non-fatal stroke, or CV death. Alogliptin had no effect on the *post hoc* composite endpoint of CV death and hospitalisation for heart failure (HF) in patients with or without a prior history of HF. Measurement of N-terminal pro-brain natriuretic peptide, a predictor of HF, after 6 months of alogliptin treatment, revealed a reduction in levels when compared to baseline, although a mechanism for this is yet to be elucidated.[58] In contrast, more patients receiving saxagliptin were hospitalised for HF in comparison to placebo (Figure 2).[57] Although both alogliptin and saxagliptin were able to meet their primary endpoints in these outcome studies, it should be noted that these outcome studies were not designed to demonstrate superiority in CV-protective benefit.

Currently available data from CV outcome studies provide valuable evidence on the CV safety of DPP-4 inhibitors; however, concerns remain about the possibility of increased HF risk. Future DPP-4 inhibitor studies will provide further data on the treatment-associated CV event risk, and consequently aid clinical decisions about treatment intensification.

Symposium Summary

The meeting explored the pharmacology of DPP-4 inhibitors in detail and provided an insight into the structural differences that influence the selectivity and efficacy of the currently available DPP-4 inhibitors. Clinically, DPP-4 inhibitors consistently achieve a reduction in HbA1c, have long-term durability in maintaining glycaemic control, and are associated with a low risk of hypoglycaemia. Furthermore, they are well-tolerated and can be administered as combination therapy. Recent data also indicate that DPP-4 inhibitors do not alter the risk of CV events. The relationship between increased insulin resistance and CV risk was explored. Pioglitazone targets insulin resistance, and therefore – alongside potent HbA1c reduction, durable glycaemic control, and low risk of hypoglycaemia – may offer favourable CV outcomes when provided in combination with DPP-4 inhibitors.

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DIFFUSION TENSOR IMAGING OF THE BRAIN IN TYPE 1 DIABETES

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ABSTRACT

Individuals with Type 1 diabetes mellitus (T1DM) are required to carefully manage their insulin dosing, dietary intake, and activity levels in order to maintain optimal blood sugar levels. Over time, exposure to hyperglycaemia is known to cause significant damage to the peripheral nervous system, but its impact on the central nervous system has been less well studied. Researchers have begun to explore the cumulative impact of commonly experienced blood glucose fluctuations on brain structure and function in patient populations. To date, these studies have typically used magnetic resonance imaging to measure regional grey and white matter volumes across the brain. However, newer methods, such as diffusion tensor imaging (DTI) can measure the microstructural properties of white matter, which can be more sensitive to neurological effects than standard volumetric measures. Studies are beginning to use DTI to understand the impact of T1DM on white matter structure in the human brain. This work, its implications, future directions, and important caveats, are the focus of this review.

Keywords: Type 1 diabetes mellitus, diffusion tensor imaging, white matter, hyperglycaemia.

INTRODUCTION

Individuals with Type 1 diabetes mellitus (T1DM) are required to carefully manage their insulin dosing, dietary intake, and activity levels in order to maintain optimal blood sugar levels. Despite these goals, on average, patients are hyperglycaemic (plasma glucose >180 mg/dL) up to 50% of the day and hypoglycaemic (plasma glucose ≤70 mg/dL) for an hour or more each day.[1] Over time, exposure to hyperglycaemia is known to cause significant damage to the peripheral nervous system in the form of neuropathy, neuropathic pain, and retinopathy.[2] The impact of hyperglycaemia on the central nervous system (CNS) has not been studied so well, despite the fact that the brain uses more glucose by weight than any other organ in the body.[3] Profoundly low or high blood glucose levels clearly affect brain function and structure in the short-term and, in some documented cases, the long-term.[2,4] These findings have motivated researchers to explore the cumulative impact of the less profound and more commonly experienced blood glucose fluctuations on brain structure and function in patient populations. To date, these studies have typically used magnetic resonance imaging to measure regional grey and white matter volumes across the brain, and these limited but intriguing results have been reviewed in detail recently.[5-7]

However, animal (and some human) studies have shown that glycaemic extremes can impact the brain in more subtle ways than can be detected with gross regional volume measurements. For example, pathological examination of animal models of diabetes exhibit demyelination,[8] axonal atrophy and degeneration, and failure to re-innervate.[9] Similarly, diabetic patients also exhibit demyelination and decreased axonal diameter in peripheral nerves.[10] If such changes occur in the human brain, *in vivo* neuroimaging using diffusion tensor imaging (DTI) could be used to detect their imaging correlates. DTI is a newer imaging methodology that measures the microstructural properties of white matter.

Studies are beginning to use DTI to understand the impact of T1DM on white matter structure in the human brain. This work, its implications, future directions, and important caveats, are the focus of this review.

BACKGROUND ON DTI

DTI relies on the properties of water molecule diffusion to characterise brain microstructure.[11] It is easiest to interpret DTI parameters in well-defined white matter tracts but these measures can also be acquired in grey matter. Traditional DTI parameters include fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD). FA reflects the degree of directionality of water molecule diffusion. Well-defined white matter tracts have strong directionality, as water molecules tend to move parallel to the fibres that compose the tracts. Histological studies in animal models have shown that increases in fibre diameter and density, myelination, and intravoxel fibre-tract coherence are reflected as higher FA.[12] AD is a measure of the degree of water diffusivity along the primary axis of diffusion. Increased fibre coherence and structure of axonal membranes, as well as decreased axonal branching, can result in higher AD.[13] Axonal damage can lead to a decrease in AD. RD is the mean of the diffusivities perpendicular to the predominant direction of water diffusion, and is thought to represent myelin and membrane integrity. Increased level of myelination leads to decreased RD while decreased myelin sheath and/or membrane integrity leads to higher RD.[14] MD is the average of diffusion in all three directions. General loss of neuronal tissue can lead to an increase in MD.

By examining all of the parameters of water molecule diffusion in a white matter tract, certain interpretations can be made about the underlying nature of the tissue based on animal model histology findings. For example, in animal models of multiple sclerosis,[15] lower FA, higher RD, and lower AD has been correlated to acute axonal degeneration when compared to controls, while similar FA, higher RD, and lower AD, compared to controls, has been correlated with demyelination of white matter tracts.[15] However, higher FA is not always beneficial, as it has been associated with decreased dendritic branching, when seen in the context of lower RD and AD.[16] DTI findings are also difficult to interpret in regions with a large amount of crossing fibres, due to partial volume effects. Thus, one must be cautious in interpreting DTI parameters in isolation. Our understanding of how altered DTI parameters relate to grey matter microstructure is much less advanced. This is due to the difficulty in measuring DTI values in the thin cortical grey matter which is volume-averaged with the nearby cerebral spinal fluid of the subarachnoid space. Importantly, definitive conclusions about the meaning of DTI measures can only be made through direct histological examination of biological tissue.

APPLICATION OF DTI TO T1DM

The application of DTI to human T1DM populations has a relatively short history and, to date, is represented by only five unique samples with published papers split between adult and child cohorts. The first study appeared in 2008 and reported that middle-aged adults with T1DM had decreased FA in specific regions (posterior corona radiata and optic radiation) compared to controls.[17] Diffusivity (MD, RD, or AD) was not examined. Within the T1DM group, regional FA was negatively correlated with age, duration of diabetes, and recent hyperglycaemia, but not with a history of severe hypoglycaemia.[18] Lifetime history of hyperglycaemia was not assessed. A secondary analysis of the same subjects and scans found reduced cortical thickness in the regions with high connectivity to the optic radiations and posterior corona radiate tracts.[19] In a much larger cohort of adults with T1DM,[19] patients had lower FA and AD in multiple white matter tracts, including inferior fronto-occipital and corticospinal tracts and higher RD, primarily in the corpus callosum, compared to controls. Patients with microangiopathy had lower FA and higher RD compared to those without microangiopathy. Severe hypoglycaemia was not related to any DTI parameters, and lifetime or recent hyperglycaemia was not examined.

Although studies in adults with long-standing T1DM are an important contribution to the field, it can be difficult to determine in such complicated patients which facet of T1DM (i.e. hyperglycaemia, hypoglycaemia, diabetic ketoacidosis [DK], age of onset, duration) is most closely associated with alterations in white matter microstructure. By studying children and adolescents with T1DM, with a more limited diabetes history and few comorbid conditions (e.g. hypertension), these factors can often be more clearly investigated. However, it is important to take into account that DTI measures change during normal brain development. In general, FA in white matter tracts increases from

birth to adulthood and is quite heterogeneous in the adult brain, having the highest values in the corpus callosum and the lowest values in subcortical white matter.[20,21] MD tends to decrease from birth to adulthood in white matter, primarily driven by decreasing RD,[21,22] and becomes increasingly homogenous across the brain over time. This pattern of normal development proceeds in a posterior-to-anterior and central-to-peripheral direction of maturation.[23] Most changes in DTI values occur within the first 4 years of life,[21] but surprisingly, more brain regions exhibit increases in FA and decreases in MD during the teenage years than during the 8-12-year-old time period, suggesting two epochs of rapid white matter development.[21] Furthermore, developmental changes in diffusion properties within grey matter structures, especially in the basal ganglia, show maturational decreases in the diffusion of water along the three different axes, resulting in decreased MD, AD, and RD.

Several DTI studies (Table 1) have examined T1DM within this diverse and rapidly changing context. Our group examined T1DM youth (mean age 16 years old), and found that they had lower AD in multiple white matter tracts, similar to the van Duinkerken study[18] in adults.

Table 1: DTI studies in T1DM, listed by age of the study samples [table is organised by the age of the study population].

First Author	Year	Study Groups	n	Mean Age	DTI Findings
Barnea-Goraly[26]	2013	T1DM Controls	127 67	7.1 7.0	T1DM had lower AD; no differences seen in FA and RD. Earlier age of onset correlated with increased RD. Longer duration of disease correlated with decreased AD and RD and increased FA. Hyperglycaemia negatively correlated with FA and positively correlated with RD.
Aye[25]	2012	T1DM Controls	26 16	7.8 7.2	T1DM had lower AD in multiple regions. No differences were seen in FA and RD. Hyperglycaemia correlated with RD in widespread regions.
Antenor-Dorsey[24]	2013	T1DM Controls	73 30	16.8 15.9	T1DM had lower FA and higher RD in the superior parietal lobule, lower RD in thalamus, and lower AD in the cerebellum compared to controls. Severe hyperglycaemic episodes were associated with lower FA and higher RD in the superior parietal lobule and higher RD in the hippocampus. Severe hypoglycaemia was associated with higher FA in the superior parietal lobule.
van Duinkerken[18]	2012	T1DM Controls	100 49	~41.3 36.7	T1DM had lower FA and AD in widespread regions and higher RD in corpus callosum primarily. Lower FA and higher RD were associated with the presence of microangiopathy.
Kodl[17] and Franc[19]	2008 and 2011	T1DM Controls	25 25	45.1 45.6	T1DM had lower FA in posterior corona radiata and optic radiation, which correlated with age, duration of disease, and greater hyperglycaemia as well as reduced cortical thickness in regions with high connectivity to affected white matter tracts.

DTI: diffusion tensor imaging; T1DM: Type 1 diabetes mellitus; FA: fractional anisotropy; AD: axial diffusivity; RD: radial diffusivity.

In addition, a history of severe hyperglycaemic events was associated with lower FA and higher RD in the superior parietal lobule. Interestingly, a history of severe hypoglycaemic events was associated with higher FA in the superior parietal lobule.[24] A small study on much younger subjects (mean age 7 years old) also found that the T1DM group had lower AD in primarily temporal and parietal cortical regions compared to controls.[25] No differences were found between groups in FA or RD measures. Greater hyperglycaemia exposure in the past was correlated with higher RD in several white matter tracts, although RD was not different overall between groups. A larger multicentre study on similarly young T1DM patients replicated the findings for AD.[26] In addition, an earlier age of disease onset was correlated with increased RD in multiple areas throughout the brain, while longer disease duration correlated with decreased AD, decreased RD, and increased FA. Greater hyperglycaemia (as measured by haemoglobin A1c test measures since diagnosis, and recent continuous glucose monitoring), but not hypoglycaemia (as measured by a history of severe episodes, and recent continuous glucose monitoring), correlated with all three DTI parameters.

DTI abnormalities in T1DM have been inconsistently related to cognitive performance variables within T1DM. However, the specificity of these findings to T1DM, and to particular white matter tracts and cognitive variables, is still unclear. These relationships may also differ depending on the age of the sample as DTI parameters and cognitive function normally undergo dramatic changes across development and ageing. Of the five DTI papers reviewed here, only four performed correlations between cognitive function and DTI parameters, and cognitive batteries and correlational methods differed substantially across these papers. Nevertheless, these studies each found unique associations within their T1DM group between DTI parameters and cognitive variables, such that lower cognitive performance was related to presumed, more abnormal DTI values (e.g. lower FA, higher RD). For example, in a small sample of younger children with T1DM, lower FA in numerous regions was related to lower performance on a speed of processing task and a short-term memory task.[25] Higher RD was related to lower IQ and auditory attention. In a larger and similarly aged sample, lower FA was associated with lower IQ, particularly within the right superior temporal gyrus and bilateral parietal regions. This pattern was not seen in the control group in this study, but has been seen in normal development in other studies.[27] In adults with T1DM, lower FA in the posterior corona radiata was associated with lower visuo-motor performance and lower FA in the optic radiation; posterior corona radiata and splenium of the corpus callosum was associated with slower fine motor performance. However, control subjects also demonstrated correlations between FA and performance on these tasks in overlapping - but not identical - regions.[17] Finally, within a different sample of adults with T1DM, but not controls, higher FA of the left corticospinal tract was related to better general cognitive ability and attention. Higher RD in left inferior fronto-occipital and corticospinal tracts were related to lower attention and executive performance.[19] These findings are clearly diverse and hard to compare across studies. Prospective studies using clearly defined cognitive variables are needed to confirm or expand these relationships.

Across this fairly limited range of studies, there are few patterns that appear to be emerging. AD is consistently decreased in both adults and children with T1DM, but FA may be more consistently decreased in adults with T1DM and more consistently related to cognitive outcome. This discrepancy may be due to the longer disease duration and/or greater degree of exposure to hyperglycaemia in T1DM adults, underscoring the necessity of conducting separate neuroimaging studies during development. In support of this idea - within both adult and child T1DM samples - hyperglycaemia exposure was consistently associated with lower FA and higher RD. Perhaps with more prolonged exposure over time, group differences in FA and RD would ultimately be detected in these younger samples. Animal studies suggest that decreases in AD reflect axonal degeneration if accompanied by decreases in FA, or demyelination if no difference in FA is observed.[12] Both findings have been reported in T1DM patients. Thus, similar to the T1DM rodent models, T1DM-related DTI changes may be manifestations of demyelination, axonal degeneration, or both, depending on the region examined and the degree of exposure to hyperglycaemia.

There are several issues that may interfere with our ability to detect consistent findings across these studies. The characteristics of the patient samples in these papers differ in many ways, including degree of diabetic complications, the degree

and manner in which their exposure to glycaemic extremes was characterised, the cognitive batteries used, and the type of imaging analyses that were performed (voxel-wise versus region of interest). In addition, all of the studies discussed in this section are cross-sectional, making it difficult to address causality of any relationships between glycaemic control and DTI parameters. Prospective longitudinal studies would best address these issues, but are currently lacking in the literature, although several are underway.

As previously mentioned, white matter structural changes can only be confirmed by direct histological examination of biological tissue. Thus, animal model work is critical for a deeper understanding of results from human DTI studies. For example, DTI analyses of animal models of T1DM found reduced FA, decreased AD, and slightly increased RD in the striatum, and reduced FA with unchanged AD and slightly increased RD in the cortex.[28] These regions were then examined histologically in the same animals. Striatal fibre bundles had signs of demyelination (rarefaction of the myelin sheath, myelin loss) and axonal degeneration, and cortical regions had axonal degeneration and/or neuronal loss. Due to the limited number of animals examined histologically in this study, no correlations were performed between diffusion indices and degree of histopathological alteration. However, these results suggest that diabetes-related DTI changes in the brain can reflect demyelination and axonal degeneration.

Multiple mechanisms have been suggested to mediate white matter nerve damage due to hyperglycaemia. Hyperglycaemia causes intracellular activation of the polyol pathway (sorbitol metabolism) resulting in the accumulation of advanced glycation end products (AGE).[29] AGE accumulation can also cause non-enzymatic glycation of myelin,[30] making myelin more susceptible to macrophages, which, in turn, release proteases that further contribute to demyelination.[31,32] On the other hand, intracellular AGE interacts with matrix proteins,[33] leading to structural and functional nerve and neuroglia defects. Increased levels of intracellular AGE also cause glycation of cytoskeletal proteins, such as tubulin, neurofilament, and actin,[30,34,35] resulting in axonal atrophy. Finally, hyperglycaemia has been shown to cause alterations in mitochondrial dynamics and function,[36] leading to accumulation of reactive oxygen species, oxidative stress,[37] and impaired axonal transport in CNS axons, which can result in axonal degeneration.[38] These mechanisms could be the basis for DTI alterations related to hyperglycaemia, although clearly, more direct investigation is necessary in animal and human tissue to explore these issues.

CONCLUSIONS

Several studies have detected white matter structural differences in T1DM compared to controls, and many of these effects appear to be linked to hyperglycaemia. However, the data on which these conclusions are based are quite limited to date, both in terms of sample size and patient characterisation. The next logical step is to determine how different types of events in the course of diabetes management, such as chronic hyperglycaemia and DK, affect white matter structure during development. The best way to address these complex questions is to conduct prospective longitudinal studies on both paediatric and adult populations, starting with newly-diagnosed diabetics. These types of studies would help tease out normal brain development from diabetes-related changes and provide the basis for more causal interpretations.

One of the main reasons for the interest in examining white matter structural integrity in diabetes is due to subtle, but consistently observed, cognitive deficits in diabetic subjects.[39-45] Given that alterations in white matter structure have been associated with some cognitive function in the existing T1DM studies, this issue requires more investigation to confirm or refute these preliminary findings. It remains to be seen if glycaemic exposure induces these white matter changes in T1DM and whether these changes can predict cognitive outcome. Future longitudinal studies, in both animal models and human populations, across both development and adulthood, will be necessary to support such a causal model. Ultimately, it is hoped that this information will be helpful in guiding treatment choices and preventing future negative cognitive outcomes in individuals with T1DM.

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DETECTION AND EARLY LIFESTYLE INTERVENTION IN THOSE AT RISK OF TYPE 2 DIABETES

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ABSTRACT

The prevalence of Type 2 diabetes mellitus (T2DM) has reached epidemic proportions in recent years. It is now widely recognised that T2DM is a highly preventable disease. This article highlights the evidence to date for the prevention of T2DM. In order to prevent or delay the onset of T2DM, people at high risk of developing the condition need to be identified and treated using evidenced-based and cost-effective approaches. Risk scores offer a quick, simple way of identifying those at high risk for invitation to screening programmes without the need for initial invasive tests. Best practice guidance, including those from National Institute for Health and Clinical Excellence (NICE) in the UK and the European wide IMAGE project, recommend that a two-stepped approach whereby the identification of a high-risk status through risk score technology is confirmed by a blood test. Once identified, those at high risk can be offered a lifestyle intervention programme. Landmark diabetes prevention studies show that lifestyle intervention, focusing on increases in physical activity, improvements in diet, and reductions in weight, reduces the risk of progression to T2DM by 30-60% and can have lasting benefits after the active intervention ceases. Recent pragmatic prevention programmes also demonstrate encouraging results. However, research targeted to the prevention of T2DM must continue to be expanded to find the most effective methods of T2DM prevention in various societies and cultural settings. There is also a need for research focusing on young people at high risk and novel approaches, such as targeting a reduction in sitting and use of technology, to support behaviour change.

Keywords: Type 2 diabetes, prevention, high risk, lifestyle, risk score.

INTRODUCTION

An estimated 366 million people worldwide have diabetes, which is expected to rise to 522 million by 2030,[1,2] with death rates attributable to diabetes doubling between 2005 and 2030.[3] Prevention of Type 2 diabetes mellitus (T2DM) is therefore a public health priority. In order to prevent or delay the onset of T2DM, people at high risk of developing the condition need to be identified and treated using evidenced-based and cost-effective approaches. This article will highlight the latest evidence for the prevention of T2DM.

Identification

Glucose is a continuum and there is a (clinically important and much researched) high-risk state where glucose levels are elevated but not over the threshold for the diagnosis of T2DM. There are a number of invasive tests, for example HbA1c or fasting blood glucose, that can be used to identify those at high risk of T2DM. Impaired Glucose Regulation (IGR) is a high-risk state where impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) have been identified using an oral glucose tolerance test.[4] Individuals with IGR are significantly more likely to develop T2DM than

those with normal blood glucose levels; estimates of progression to T2DM within a year suggest those with isolated IGT have >5-times the risk, those with isolated IFG have 7-times the risk, and those with both IGT and IFG have >12-times the risk compared to normoglycaemic individuals.[5] There are now also recommendations that HbA1c levels raised above normal levels, but not in the range for a diagnosis of T2DM, should be classified as at high risk of diabetes.[6,7] However, there is no agreed consensus on the HbA1c range that should be classified as at high risk of diabetes, with the International Expert Committee and the UK-based National Institute for Health and Clinical Excellence (NICE) recommending it should be 6.0-6.4% (42-46 mmol/mol), whereas the American Diabetes Association suggests 5.7-6.4% (39-46 mmol/mol).[8-10] Follow-up studies have shown similar rates of progression to diabetes from the HbA1c defined as the high-risk state as seen for IFG.[11]

RISK SCORES

Risk scores offer a quick, simple way of identifying those at high risk. The EU-wide IMAGE project recommended the use of risk scores for identifying those at risk of T2DM.[12] Risk scores generally follow one of two approaches: either being applied as questionnaires to the individual being assessed – 'self-assessment' - or as a query to a general practice database where all those 'at risk' are identified using routinely stored data. The Finnish Diabetes Risk Score (FINDRISC) is an example of a self-assessment for predicting the risk of future diabetes; it includes eight questions: age, body mass index (BMI), waist circumference, blood pressure, history of high blood glucose, family history of diabetes, physical activity, and consumption of vegetables, fruits, or berries.[13] An example of a risk score which uses routinely stored data is the UK Leicester Practice Risk Score (LPRS). This score, with accompanying software applications, ranks all individuals within a given primary care dataset for their diabetes risk status based on age, sex, ethnicity, family history of diabetes, BMI, and antihypertensive use.[14] Scores can also be categorised based on the outcome they predict. Scores which have been developed using cross-sectional data can predict prevalent disease; the LPRS detects current undiagnosed IGR and T2DM, in contrast with scores which have been developed using longitudinal data, where incidence can be predicted, such as FINDRISC. The scores developed to date tend to be for a specific population as studies have found that scores which have been developed elsewhere and used on a different population tend to have low validity.[15,16]

The PREDICT-2 group have summarised the currently available risk scores worldwide, and this is hosted on the International Diabetes Federation website (http://www.idf.org/risk-prediction-tools-predict-2).[17] A number of risk scores have been developed for use in Europe and these are summarised in Table 1. Additionally, the FINDRISC has been validated for use in Greece, Bulgaria, Italy, Spain, and Sweden. Although many risk scores exist,[18-21] relatively few are currently used in practice.[22] One review stated that this could be because the way in which the risk score will be used is not considered in the development stage.[20] A systematic review of the implementation of risk scores reported a number of barriers to the uptake of risk scores by healthcare professionals which included: attitudes toward the tools; impracticality of using the tools; and lack of reimbursement and regulatory support. As previously introduced, the LPRS was derived for population level screening within primary care.[14]

The developers of this tool have tried to overcome these barriers by developing a piece of software which runs alongside the practices' electronic medical records to make the score easy to use, in practice. This software was used across 54 general practices in two large prevention studies[23,24] where it was used to identify and invite the top 10% at highest risk within each practice for screening.[25] Of the 21,741 invited, 4,282 attended (20%). Of these, 25.7% were found to have IGR, with 4.2% having undiagnosed T2DM. These rates were significantly higher than when a population screening approach was taken in the same vicinity.[26] This risk score also has regulatory support and is recommended by NICE.[27] Risk scores incorporating invasive measures also exist, i.e. biomarkers or genetic factors.[28] These generally do not out-perform their non-invasive counterparts and are not routinely used. Using non-invasive risk scores allows people to assess their own risk, and therefore might engage people who do not routinely visit their GP.

Stepped Approach

Best practice guidance, including those from the IMAGE project, recommend that a two-stepped approach - whereby the identification of a high-risk status through risk score technology - is confirmed by blood test.[9,29] This type of stepped approach

has been shown to be the most cost-effective method of identifying risk status.[30] A recent study estimated that using a one-step screening strategy where everyone receives an HbA1c, costs around €1,084 per case of T2DM detected. This is reduced to around €658 per case, if a two-stage strategy, employing a risk score, is used.[31] Risk scores avoid the need for universal screening and the subsequent blood tests, ensuring that metabolically healthy individuals are not subject to intervention, and that those with undiagnosed T2DM are picked up earlier.

LIFESTYLE INTERVENTIONS FOR THOSE AT RISK OF T2DM

Observational research has consistently shown that 80-90% of all cases of T2DM result from an unhealthy lifestyle.[32,33] Over the past two decades there have been several landmark diabetes prevention randomised controlled trials (RCTs) that have been conducted across diverse countries and populations,[34-38] which have consistently shown that lifestyle intervention can reduce the risk of progression to T2DM by 30-60% in those with IGT. The Finnish Diabetes Prevention Study (DPS)[34] and the American Diabetes Prevention Program (DPP)[35] found that the risk of T2DM was reduced by 58% in people with IGT or IFG, given lifestyle counselling over a 3-year period. Similar findings were also seen in India,[37] Japan,[36] and China.[38] Table 2 summarises the design and main findings from the major lifestyle intervention trials.

Lifestyle intervention in the prevention of T2DM has typically been focused on achieving a weight reduction, usually prescribed as a percentage of initial body weight (e.g. at least 5%) until a desirable BMI was achieved, increasing moderate intensity aerobic physical activity to at least ≥150 minutes per week (one study also offered supervised resistance training), and diet modifications such as a reduction in total calories, total and saturated fat and sugar intake, and an increase in fibre, vegetables, and wholegrain products. These recommendations were delivered during one-to-one counselling sessions, and behaviour modification techniques such as motivational interviewing, self-monitoring, and individualised short and long-term goals were employed.

Table 1: Risk scores developed for use in Europe.

Score	Country	Outcome	Use
Inter99[73]	Denmark	Undiagnosed T2DM	Self-assessment
DESIR[74]	France	Incident T2DM	Primary care*
PROCAM[75]	Germany	Incident T2DM in males only	Primary care
German diabetes risk score[76]	Germany	Incident and undiagnosed T2DM	Self-assessment
FINDRISC[13]	Finland	Incident T2DM	Self-assessment
Hoorn[77]	Netherlands	Undiagnosed T2DM	Self-assessment
Rotterdam scores[78]	Netherlands	Undiagnosed T2DM	(1) Primary care; (2) Self-assessment
SUNSET study[79]	Netherlands	Known and undiagnosed T2DM	Self-assessment
PORMETS[80]	Portugal	Undiagnosed IFG and T2DM	Self-assessment
Canary islands[81]	Spain	Known and undiagnosed T2DM	Primary care
PREDIMED[82]	Spain	Incident T2DM	Self-assessment
Cambridge[83]	UK	Known and undiagnosed T2DM	Primary care
QD Score[84]	UK	Incident T2DM	Primary care
Leicester risk scores[14,85]	UK	Undiagnosed IGR and T2DM	(1) Primary care; (2) Self-assessment

*Those marked primary care are for population screening on medical records or require the results from invasive tests.
T2DM: Type 2 diabetes mellitus; IGR: impaired glucose regulation; IFG: impaired fasting glucose.

Table 2: Characteristics of the primary lifestyle interventions that have been tested in the prevention of Type 2 diabetes.

Country Study name	Sample size (men/women)	Inclusion criteria	Interventions	Lifestyle intervention targets	Study duration (weeks)	Risk reduction at end of intervention period*
China The Da Qing IGT and Diabetes Study[38]	530 (283/247)	IGT, Age ≥25 years	1. Control 2. Diet 3. Exercise 4. Diet and Exercise	**Diet group:** Weight maintenance for normal weight. Weight reduction for those with a BMI ≥25 kg/m^2 through reduced energy intake **Exercise group:** Participants were encouraged to increase their physical activity by at least one prescribed unit per day (such as slow walking for 30 minutes, or fast walking for 20 minutes) and by two units per day where possible **Diet-plus-exercise group:** Combination of above	6	Diet: 31 Exercise: 46 Exercise and Diet: 42
USA Diabetes Prevention Research Group[35]	3,234 (1,043/2,191)	IGT, Age ≥25 years, BMI ≥24 kg/m^2 (≥22 kg/m^2 if Asian), fasting plasma glucose ≥5.3 mmol/l	1. Control 2. Lifestyle 3. Metformin	150 minutes per week of MVPA and weight reduction (7% of initial body mass) through a healthy, high fibre, low-energy, fat controlled diet	2.8	58
Finland Finish Diabetes Prevention Study[34]	522 (172/350)	IGT, age 40 to 64 years old, BMI ≥25	1. Control 2. Lifestyle	30 minutes per day of MVPA and weight reduction (5% of initial body mass) through a healthy diet based on reduced saturated fat (10% of energy intake), reduced fat (30% of total energy intake), and high fibre	3	58
India Indian Diabetes Prevention Programme[37]	531 (420/111)	IGT	1. Control 2. Lifestyle 3. Metformin 4. Lifestyle plus Metformin	30 minutes per day of MVPA and healthy diet based on reduced energy intake with fibre rich foods low in refined carbohydrates and fats	3	Lifestyle: 29 Lifestyle and Metformin: 28
Japan[36]	458/0	IGT	1. Control 2. Lifestyle	30 minutes per day of MVPA and weight reduction through a healthy diet	4	67

***% reduction compared to controls.**

IGT: impaired glucose tolerance; BMI: body mass index; MVPA: moderate-to-vigorous physical activity.

Overall, tested lifestyle interventions based on these targets have been shown to be equally or more effective than most pharmaceutical interventions in the prevention of T2DM.[39] Importantly, successful lifestyle interventions have also been shown to have lasting benefits, even after the active intervention ceases. For example, in the DPS study, the intervention effect was sustained at 7 years[40] and in the DPP, a relative reduction of 34% in diabetes incidence was maintained 10 years

after randomisation (7 years after the intervention ended).[41] Furthermore, the China Da Qing Diabetes Prevention trial[42] showed that a relative risk reduction of 43% was maintained at 20 years (14 years after the intervention ended).

Although highly successful and shown to be potentially cost-effective in the longer term for 'high risk' individuals,[43] these landmark intervention studies used intensive behaviour change strategies relying on multiple and lengthy one-to-one patient contacts which would be incompatible and unsustainable in a routine healthcare setting. For example, the DPS had a median of 20 one-to-one counselling sessions over a 4-year period. Several countries including the UK, US, Finland, Germany, and Australia responded to this limitation by developing, evaluating, and implementing diabetes prevention programmes that have been tailored to the needs of their specific healthcare settings.[44] Although these pragmatic programmes have varied in context and scope, they have tended to centre on utilising group-based health educational programmes as the primary vehicle for promoting behaviour change. Evidence suggests that group-based programmes can be delivered successfully by a range of staff including nurses, dieticians, exercise specialists, and lay people.[45]

In the UK it has been shown that a 3-hour group-based, theory-driven, structured education programme - combined with personalised pedometer use - can be highly successfully when delivered in a healthcare setting, with significant changes to health behaviour and improved metabolic health over a 12 and 24 month period in those with a high risk of T2DM.[46,47] This brief group-based programme was refined into the Walking Away from T2DM programme, which includes a fully operational commissioning pathway for healthcare providers,[23] including a standardised and accredited educator training and quality assurance programme. In Finland, population approaches to diabetes and cardiovascular disease prevention, that incorporate all elements of the healthcare profession, local government, and community partners, including offering individuals group-based lifestyle educational programmes, have been found to be effective.[48] Similar approaches have also been introduced within other regions of Europe, including in Germany and countries involved in DEPLAN (diabetes in Europe-prevention using lifestyle, physical activity and nutritional intervention).[49] Beyond Europe, the Centres for Disease Control in the United States have led the way in developing and evaluating components of a multi-faceted stepped approach to prevention that includes working with health insurance companies and referring high-risk individuals to community-led group-based diabetes prevention programmes run through YMCA facilities.[49,50]

Evidence from several recent systematic reviews[51-53] on the effectiveness of translational diabetes prevention programmes, suggests that a mean waist measurement reduction of around 4.5 cm[52] and a mean weight reduction of around 2 kg is achievable over 12 months.[52] This is lower than the amounts achieved by the intervention arms, the Finnish DPS (~4.2 kg) and the US DPP (~6.7 kg), at the same time point.[34,35] However, a 2 kg weight loss is still clinically meaningful, with findings from the US DPP study suggesting that future diabetes incidence may be reduced by as much as 16% for each kilogram of weight lost.[54] Whilst these results are encouraging, more research is needed to assess the longer-term (>12 months) effectiveness and cost-effectiveness of diabetes prevention programmes that have been implemented into routine care.

Guidelines for Diabetes Prevention

Recent evidence-based guidelines for diabetes prevention, compiled by NICE[9] and the IMAGE project (Development and Implementation of a European Guideline and Training Standards for Diabetes prevention),[12] make clearly defined recommendations for the essential components to include in any lifestyle programmes in order to maximise their effectiveness. Table 3 summarises the recommendations for design and content of lifestyle change programmes for preventing T2DM. These recommendations were informed by robust reviews of the relevant literature, and supplemented by expert opinion. It has recently been demonstrated that adherence to guideline recommendations on intervention content and delivery are associated with greater weight loss in a dose-dependent manner, with greater adherence leading to greater effect.[52]

The Future of Diabetes Prevention Lifestyle Research

Recently, there has been increasing political recognition that diabetes prevention should be a major worldwide priority. For example, in 2011, the United Nations adopted a political declaration on

the prevention and control of non-communicable diseases (NCDs) that acknowledged the global burden and threat of NCDs including diabetes, and recognised that prevention must be the cornerstone of the global response to NCDs (http://www.un.org/ga/search/view_doc.asp?symbol=A/66/L.1).

Table 3: Recommendations for design and content of lifestyle-change programmes for preventing T2DM.

Essential components of lifestyle programmes		Details
Content	Establish motivation for behaviour change	Exploration of perceptions of risk for developing T2DM, exploration and reinforcement of reasons for wanting to change, confidence about making changes and expectations
	Information provision	Raise awareness of the benefits of lifestyle changes (and changes needed)
	Lifestyle changes - aim to promote changes in both diet and physical activity	• ≥150 minutes/week of MVPA • Weight loss to reach and maintain a 'healthy' BMI • Consume wholegrain food products, at least five portions of fruit and vegetables, limit sugar and salt intake, increase consumption of dietary fibre, consume fish regularly, alcohol in moderation, reduce total amount of fat, and eat less saturated fat
	Behaviour change and self-regulatory techniques – utilise established, well defined techniques	• Self-monitoring of physical activity and eating (e.g. with use of diet or pedometer) • Action plan of short and long-term goals (SMART goals) • Providing feedback on performance • Problem solving • Reflection • Relapse prevention • Overcoming barriers • Motivational interviewing • Prompting self-talk • Prompting practice • Individual tailoring • Time management
	Social support	Facilitate/encourage social support (family, friends, and colleagues) for the planned behaviour change
Design	Contact time	• Maximise the frequency or number of contacts (within the resources available) • Provide at least 16 hours of contact time over the first 9-18 months
	Group versus individual	To balance cost and effectiveness - use group-based interventions with around 10-15 people where feasible
	Person-centred approach	• Ensure programmes adopt an empathy-building approach. Supports person to become the expert and puts them in control
	Time between sessions	• Ensure sessions are spread over a period of time - to allow people to make gradual changes to their lifestyle and reflect and learn from experiences • Allow time during group sessions for people to share this learning with others
	Training and quality assurance	• Ensure lifestyle programmes have a systematic and accredited method of training educators and regularly assessing compliance and competency; this is crucial for the professional development of health care professionals and standardisation of delivery when implemented over multiple sites

T2DM: Type 2 diabetes mellitus; MVPA: moderate-to-vigorous physical activity; BMI: body mass index.
Summarised from IMAGE[12] and NICE[9] guidance.

Research targeted to the prevention of T2DM must continue to be expanded to find the most effective methods of T2DM prevention in various settings.[55] It is promising that major funding bodies have responded to this need. For example, the EU in general, especially through the Horizon 20/20 study,[56] has put the prevention of chronic diseases at the heart of their agenda, with a range of calls from societal interventions to healthcare reorganisation and technological innovation. Ongoing EU funded work is also set to significantly advance knowledge. The PREVIEW study will include a multicentre RCT comparing two diet and two exercise strategies for 2,500 individuals with IGT and other risk factors. This study targets participants across the age spectrum, from children to the elderly (http://preview.ning.com/). This is timely since the sharp rise in the levels of obesity and sedentary lifestyles witnessed in younger age groups has resulted in up to a 10-fold increase in the prevalence of T2DM in younger adults and youth.[57] If left unconsidered, T2DM in the young will become one of the primary clinical priorities within the next couple of decades.[58] This need also prompted the European Commission to set up tenders for pilot projects aimed at the development and implementation of successful prevention strategies for T2DM among children. Furthermore, diabetes prevention studies focusing on children are also ongoing in the US.[59-61]

Individual countries have also recognised the need for effective diabetes prevention strategies and have funded research and policy change accordingly. For example, in England the National Institute for Health Research has committed substantial resources to funding research aimed at the prevention of T2DM and related chronic conditions across the translational spectrum, from experimental studies to implementation within primary care (http://www.nihr.ac.uk/Pages/default.aspx). However, at a national level, policy and research innovation tends to be very country-specific, reflecting the cultural and healthcare norms of the country in question. In order for diabetes prevention to be truly effective, it is likely that shared learning across countries will need to be actively promoted and supported. For example, the high-risk strategies currently promoted in the UK will only be effective if they are also combined with the societal, population-wide approaches that have been effective in Finland. Grassroots learning platforms have been set up to help disseminate international best practice, such as the network of diabetes prevention (http://nebel.tumainiserver.de/dp/); such initiatives should be commended and actively supported.

It is also clear that along with these broader issues, diabetes prevention will also be influenced by other areas of importance, such as technology and targeted health behaviours. In recent years, it has been acknowledged that modern technology is likely to be of fundamental importance in providing a pragmatic and cost-effective avenue for self-management and behaviour change in the prevention and management of highly prevalent chronic diseases; the most ubiquitous of such approaches are based on mobile or smart phones. A recently published systematic review revealed that text messaging or smartphone applications are well accepted by participants, and may provide beneficial effects on reducing weight, decreasing waist circumference, decreasing BMI, decreasing fat mass, increasing physical activity, decreasing sugar-sweetened beverage intake, decreasing screen time, and encouraging healthier eating patterns.[62] Furthermore, mobile phones have been used successfully in the prevention and management of T2DM. Results from recently published meta-analyses provide strong evidence that mobile phone interventions led to statistically significant improvements in glycaemic control and self-management in patients with T2DM.[63,64] Researchers in India also demonstrated that in comparison to standard care, a mobile phone text messaging intervention reduced the incidence of T2DM in a high-risk population.[65] Similar studies are also ongoing in Canada and the UK.[66,67]

Lifestyle interventions used in the prevention of T2DM are also likely to receive innovation through the targeting of new behaviours. Over the past decade, sedentary behaviour (defined as non-exercise sitting) has emerged as an independent risk factor for chronic disease, including for T2DM.[68] Indeed, recent studies in high-risk populations have shown that sedentary time actually has stronger associations with various markers of cardiometabolic health when compared with moderate-to-vigorous physical activity (MVPA).[69,70] Furthermore, emerging experimental research demonstrates that reducing sitting time by regularly (e.g. every 20 or 30 minutes) performing short bouts (e.g. 2 minutes) of light ambulation throughout the day, significantly decreases postprandial glycaemia and insulinaemia compared to prolonged sitting.[71,72] These studies

suggest that focusing on sedentary time and total movement throughout the day may be a more effective behavioural approach than solely promoting increased MVPA. The emerging evidence around sedentary behaviour has been picked up by several high profile international groups who are investigating the effectiveness of integrating interventions aimed at reducing daily sitting time into prevention initiatives. If successful, it is likely that diabetes prevention programmes in the future will include a strong focus on reducing daily sitting time in addition to the traditional behavioural targets.

CONCLUSION

In conclusion, those at high risk of T2DM can be readily identified as part of routine care, and the development of T2DM in such populations can be slowed or prevented through lifestyle intervention. However, further work is needed to effectively translate and embed this knowledge into routine clinical care throughout Europe and worldwide. Healthcare policy and law, research, technological innovation, and shared international learning are all central to ensuring the epidemic of T2DM is effectively addressed for future generations.

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A PRACTICAL REVIEW OF INSULIN PEN DEVICES

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ABSTRACT

Since the advent of insulin pens in 1985, there have been ongoing improvements providing several advantages over the traditional vial and syringe method of insulin delivery. In recent years, pens have become increasingly user-friendly, and some models are highly intuitive to use, requiring little or no instruction. Despite this progress, there remains to be disparity in access to insulin pens to people with diabetes in various countries. There is a need for improved awareness of the benefits of insulin pens among healthcare professionals. Continual advances have been made to address patient needs such as improved technology to make them easier to use; less painful; more discreet and convenient; and more accuracy for small doses of insulin, as well as the incorporation of a memory function, all contribute to an insulin delivery device that allows the patient to better manage their diabetes anytime and anyplace, without the bulk and challenge of carrying a vial and syringe. These advances have resulted in increased patient satisfaction with insulin pens and most importantly, all of these benefits improve adherence and result in improved clinical outcomes. This review highlights these benefits of insulin pen use and presents the issues to be considered when helping patients decide on the insulin pen that will best suit their needs.

Keywords: Type 2 diabetes, insulin, insulin pen, practical use.

INTRODUCTION

For over 50 years, vial and syringe was the only method of delivering insulin. While life-saving, it was crude at best, and ever since its discovery much effort has gone into improving the insulin. Initially, insulin was used primarily for people with Type 1 diabetes mellitus (T1DM), but research has shown that most people with Type 2 diabetes mellitus (T2DM) will also require insulin to maintain HbA1c at levels recommended by the American Diabetes Association/European Association for the Study of Diabetes.[1,2] While insulins have improved, they still require an injection. Additional effort has gone into finding an adequate delivery method; in the 1970s insulin pumps became available, and in 1985, the first insulin pen was introduced.[3] This review will focus on insulin pens.

Insulin pens have been shown to have several advantages over the traditional vial and syringe method of insulin delivery, including improved patient satisfaction and adherence, greater ease of use, and superior dosing accuracy.[4-10] About two-thirds of insulin prescriptions in Europe and about three-quarters in Japan are for pen devices[9] while only 15% of patients are thought to use insulin pens in the US.[11] According to the recent report, *Access to Quality Medicines and Medical Devices for Diabetes Care in Europe*,[12] there remains a great disparity in access to insulin pens across Europe. While insulin seems to be a covered benefit in most countries, use of insulin pens varies more widely and may, in some cases, be restricted to people with T1DM and/or to children under the age of 18 years.

In spite of the convenience and greater ease of use, cost may be an issue. The greater cost of insulin cartridges and prefilled insulin pens, compared with insulin vials, can impact the acceptance of insulin pens as a viable option for people with T2DM. For some patients, the cost may be the same depending on coverage, and in fact, if they have

one co-payment per box of pens, the cost to the patient may actually be less per unit of insulin. If this seems to be an issue it is important to consider that despite the higher unit cost of insulin in pen devices versus vials, several studies have found that overall diabetes-related treatment costs are lower with pen devices than with vial and syringe.[3,4,11] Increased adherence with the use of insulin pens has been demonstrated and further emphasises the need to consider them as an option when initiating insulin.[5,11,13] Therefore, in theory, costs should not prevent the use of these devices.

PERSPECTIVES

Healthcare Providers

Despite the many advantages of insulin pens, there is a lack of awareness among healthcare providers of those advantages which have been cited as a possible reason for low adoption rates in some countries.[14,15] It has been shown that the physician plays a significant role in the patient's acceptance of the insulin pen as an option.[16] In fact, the most powerful predictor of pen use was found to be physician recommendation. This emphasises the importance of the role of the physician in this self-care practice. It also emphasises the need to ensure that physicians are aware of insulin pens and how they can benefit patient adherence resulting in better outcomes. Nurses and diabetes educators should also become familiar with the various insulin pens available so they can discuss the potential benefits with their patients and offer advice on which device best meets their patients' needs. Nurses, diabetes educators, and pharmacists have particularly important roles in educating patients on how to use insulin pens. Incorrect use can affect pen performance, and thus, the accuracy of the administered dose.[17] Healthcare professionals have been found to be strongly supportive of the use of insulin pens and they find them to be easier to handle, preferable to use, and more accurate in delivering insulin doses as compared to vial and syringe.[18,19]

Patients

Patient perception has also been found to be an important predictor of pen use. A vial and syringe is clumsy to say the least but, over time, most people adapt to it quite well. The insulin pen, on the other hand, can easily fit into a pocket or purse, is durable, and much more discreet to use. In an open-label, randomised, multicentre study, patient preference for insulin pens versus vial and syringe was statistically significant[18] citing convenience, ease of use - including assembly - injection, and confidence in the dosage. The visual and auditory cues from the pen contribute to the increased level of confidence. Two open-label, randomised, crossover studies found that patients have greater dose confidence with a prefilled insulin pen over a vial and syringe.[6,20] In the first of these studies, 73% of patients felt more confident in the accuracy of the insulin dose delivered with the pen, compared with 19% for the vial/syringe.[6] In the other study, 88% of patients had greater confidence that they were taking the right dose with the pen than with the vial and syringe.[20] The vial and syringe do not offer this level of confidence and, as eyesight and dexterity decrease with age, the vial and syringe become much more challenging to handle.

The vial and syringe has many disadvantages including fear of injections, poor dose accuracy, lack of social acceptance, lengthy training time, and difficulty of transportation.[21] These are potential barriers to insulin therapy, impacting flexibility, and affecting adherence to treatment, thus negatively impacting the achievement of euglycaemia.[22,23] Insulin pens were designed to help address these issues, with resulting improvements in portability, dosing accuracy, mealtime flexibility, and convenience of delivery.[7-9,24] Increased patient preference, treatment satisfaction, and quality of life have been reported for pen devices compared with the vial and syringe.[6,10,25,26] Other studies have shown that pen devices are associated with improved costs of care, less reported injection pain, and improved patient self-management behaviours, including adherence to treatment, compared with the vial and syringe.[4,27-29] Many of these benefits make insulin pens especially beneficial to people with visual impairment or reduced dexterity.

USING AN INSULIN PEN

Once in use, most insulin analogue vials, cartridges, and prefilled pens must be discarded after 28 days. The exceptions to the 28-day discard date is insulin detemir (Levemir®), which can be kept for up to 42 days once in use. Two types of insulin pens are available: prefilled disposable pens and refillable pens.[30-46] Most insulin pens are proprietary devices, and are designed to work with specific insulins from the same manufacturer.

Insulin cartridges or prefilled disposable pens are available for all insulin analogues (rapid-acting, long-acting, ultra-long-acting, and premixed) and for most human insulins. Most currently-available pens are either prefilled with 3 ml of insulin or are refillable pens that are designed for use with 3 ml insulin cartridges. U100 insulin is used in most devices providing 300 units of insulin per cartridge or prefilled device. However, insulin degludec (Tresiba®) is also available in U200 strength, providing 600 units of insulin per device. The dose counter window for degludec will show the number of units, irrespective of the strength, so no dose conversion is required.[47]

For all insulin pen devices, pen needles are purchased separately and may require a separate prescription. Pen needles are available from various manufacturers and come in gauges ranging from 29 G to 32 G, and in lengths from 4 to 12.7 mm.[46] More recent developments have resulted in the introduction of safety needles with protective shields that not only reduce needle-stick injuries but may also allay patient anxieties about needle use.[48] Health professionals are also being advised to use these safety needles in accordance with the safety recommendations of the EU Council Directive 2010/32/EU.[49] As shorter needles have become available, the question of how to select the appropriate needle length has come up. For the average adult, 4, 5, and 6 mm needles are appropriate and can be injected at a 90-degree angle. For the overweight or obese patient, research shows that needle length should not be a concern.[50-52] According to the First Injection Technique (FIT) Guidelines,[52] there really is no reason, even for very obese patients, to use a needle longer than 8 mm.

For very lean patients, it is recommended to raise a fold of skin and inject at an angle to prevent a possible intramuscular (IM) injection, especially if using an 8 mm needle or greater.[50,52,53] For children, 6 mm or shorter needles are recommended. A 4 mm needle may be injected at a 90-degree angle while a 5 or 6 mm needle will require a lifted skin-fold to avoid possible IM injection. If an 8 mm needle is all that is available for a child it is essential to do a lifted skin-fold. Therefore, needle length should not be a concern but proper injection technique should be a part of the training for both insulin pens and vial and syringe use.[50,54] The use of the FIT Guidelines is an excellent resource if any questions remain.

ASSISTING YOUR PATIENTS

Healthcare practitioners should work with the patient to select the insulin pen that is most suited to their insulin regimen, lifestyle, and personal preferences. A regimen that causes the least disruption to the patient's lifestyle is much more likely to be used. Pens are more than just a matter of convenience, though; their ease of use allows patients to take better care of their own condition.[16] Patients across all age groups often have concerns regarding insulin therapy, and many of these concerns can be effectively addressed through choosing an insulin pen.[55] In particular, adolescents and children may find insulin pens more socially acceptable because of the pens' greater portability and discreetness. The NovoPen® Junior, the HumaPen® Luxura™ HD, and the NovoPenEcho®, have been developed specifically for use in children and others requiring the ability to adjust their insulin in half-unit increments.[36]

For people with visual impairment there are some advantages to using an insulin pen over a vial and syringe. For example, the numbers on insulin pens are larger than those on syringes, making it easier to select the correct dose. The audible clicks notify the user of the number of units injected, as well as when the insulin has been fully injected. And patients with impaired manual dexterity may find insulin pens easier to use because it eliminates the process of drawing up the insulin from the vial with the syringe. There have also been advances to improve needle safety and potentially reduce any anxiety about needles. The use of safety needles has been shown to reduce the incidence of needle-stick injuries among nurses, a common occupational hazard.[48,49] While the safety needles are not readily available outside the hospital setting, they may be a consideration for secondary caregivers to avoid needle-stick injuries. The safety pen needles conceal the needle, so could potentially be used to reduce needle anxiety. There are injection aids for insulin pens that also conceal the needle: NeedleAid™ and NovoPen® 3 PenMate®. Concealing the needle using the NovoPen 3 PenMate has been shown to reduce pain perception.[53] The NeedleAid is an attachment designed to help visually impaired patients self-administer insulin.

Limitations of Insulin Pens

Insulin pens are not without their limitations and it is important that patients and healthcare workers

are aware of these to ensure the best outcomes. The maximum dose with most insulin pens is 60-80 units, but with a syringe it is 100 units. Patients cannot mix their own insulin formulations for use in a single injection given by insulin pen. Despite their ease of use, there have been some cases of malfunction reported in the literature.[57] Therefore, patients using an insulin pen should have a backup pen with them at all times.

Choosing Between Insulin Pens

The choice of insulin pen will be, to a large extent, determined by the choice of insulin, as particular insulins are specific to certain makes of insulin pen. Anecdotally, many patients prefer prefilled disposable pens to refillable pens, because disposable pens are typically lighter and smaller, and are also simpler to use, as there is no requirement to load new insulin cartridges. However, some refillable pens have features, such as a memory function or the ability to dial in half-unit increments that are not available with prefilled pens. This may be important in children or in those sensitive to insulin. Some insulin pens have a larger maximum dose (80 units) than the other insulin pens, and therefore, may be preferable in patients who take large doses of insulin.[58]

Newer technologies have improved the push-button mechanisms to reduce injection force while maintaining dose accuracy[59,60] and still retaining the ability to dial back. This may be particularly suitable for patients with impaired manual dexterity or conditions such as arthritis. Colour coding has also been incorporated into several of the pens to distinguish between insulin types. Some pens now supply auditory feedback to assist patients with T2DM who may suffer from visual impairments and/or manual dexterity.[61] Several insulin pens provide a confirmatory click when the correct dose has been delivered. Memory is an added feature that is now available. In a study comparing an insulin pen with memory function to a pen without memory function it was found that significantly more patients preferred the memory function, indicating that it gave them more confidence about when they last injected, how much insulin they injected, and in improving their diabetes management.[62]

How to Use an Insulin Pen

In a study assessing the patient and physician acceptability of a prefilled insulin pen device, 88% of the 33 physicians who completed questionnaires at the end of the study said it took less time to teach patients to use a pen, and 73% thought that it took less time to initiate insulin therapy with the pen, compared with a vial and syringe.[63] The basic steps in teaching patients how to use an insulin pen are shown in Figure 1.

1. Ensure insulin is at room temperature.
2. If using a pre-mixed insulin, first gently roll the insulin pen ten times and then gently invert ten times (not shaken) to resuspend the insulin. The solution should be a milky white.
3. Attach the needle to the pen.
4. Prime the insulin pen (also referred to as 'doing a safety test' or 'doing an air shot'[a]).
5. Select the dose by dialling.
6. Hold the pen gently against the skin.
7. Inject the dose by depressing the button, holding it in position in the skin for at least 10 seconds.[b]
8. After the injection, remove the needle from the pen and replace the cover on the pen.

Figure 1: The eight steps of insulin pen use.

[a] This is performed by instructing the patient to dial up 2 units and to inject these units into the air.

[b] The button needs to be pressed and the needle held in the skin for 5–10 seconds to ensure complete delivery of insulin dose. The easiest way to ensure this is to instruct the patient to count to five (or ten if using the SoloSTAR®) before removing the needle.

Because it is possible for insulin to still be flowing out of the pen for several seconds after the button has been fully depressed,[15] to prevent any leakage of insulin, it is important to instruct patients to hold the pen in place with the button pressed in for 5–10 seconds (the exact time varies between the various insulin pens and is described in their respective package inserts).[38,39,41,43] The easiest way to ensure this is to instruct the patient to count to five (or ten, if using the SoloSTAR®) before removing the needle. If the patient is using >50 units of insulin per dose, a good rule of thumb might be to instruct them to count to ten regardless of the pen they are using to ensure complete absorption of the insulin.

If patients are using a pen that contains neutral protamine Hagedorn insulin, or an insulin premix, it is important that they gently mix the insulin by carefully rolling or tipping the pen for the recommended number of times according to the package insert to ensure even mixing of the insulin suspension before attaching the needle. Emphasise this even for patients who have used the vial and syringe method, as vials have a greater diameter than cartridges and so need to be tipped less often.[64] Pens must be primed before each injection, and the needle removed immediately after each use.[15] This is performed by instructing the patient to dial up 2 units and inject these units into the air (also called an 'airshot'). This will displace any air in the needle and ensure an accurate injection.

Insulin pens should never be used by more than one individual, even if the pen needle is changed, because sharing of insulin pens can result in transmission of hepatitis viruses, HIV, or other blood-borne pathogens. Prior to first use, the insulin cartridge or pen should be stored in the refrigerator. The pen should be warmed to room temperature (30 °C) for most insulin analogues before use. After the first use, the pen should remain at room temperature (<30 °C) in order to avoid producing air bubbles, which can form when the pen mechanism and the insulin expand/contract during a temperature change. As with all types of insulin, pens in use should be kept from extremes in temperature; keep them as close as possible to room temperature (<30 °C) at all times. Insulin glulisine (Apidra®) has a narrower temperature range for storage than the other insulin analogues; once in use, insulin glulisine must be stored <25 °C. In some buildings, for example schools, air conditioning is turned off at night, which may result in the room temperature rising above 25 °C or 30 °C. If a change in temperature is anticipated, insulated storage packs are recommended. If a patient is switching from one type of insulin pen to another, it is important to check whether the procedure used for the previous pen also applies to the new pen.

Clinical Studies Comparing Insulin Pens

Several studies have investigated dosing accuracy between pens. Generally, dosing accuracy is good.[56,65-70] Insulin pens also differ in the force required to inject an insulin dose, and this feature has been investigated in several studies.[56,68,71-73] In general, differences in the injection force between insulin pens are relatively small.[59,72] Data on ease of use and patient preference for different types of pen have been assessed in a number of clinical studies and in clinical practice. Many open-label studies have obtained information on patient preference, and the results show that newer designs of pens are increasingly user-friendly, and are intuitive to use, requiring little or no instruction.[57,74-80]

CONCLUSIONS

In conclusion, insulin pens offer many benefits to people with diabetes who use insulin. They provide an opportunity to select a delivery device that will meet the specific needs of the patient. Insulin pens are increasingly more user-friendly requiring little or no instruction. For the healthcare professional, this means that teaching a patient how to use an insulin pen, along with the importance of accurate dosing, can be done quickly and efficiently in a busy clinical setting. In spite of the ease of use with insulin pens, educating patients about the practical aspects and purpose of insulin in general remains important. It is important that healthcare providers are aware of the benefits of insulin pens and the role they play in increasing adherence. It is important for healthcare professionals to keep up-to-date on the latest developments in pen devices and teaching approaches in order to assist their patients in making informed, individualised decisions.

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MEMBRANE FLEXIBILITY AND CELLULAR ENERGY MANAGEMENT IN TYPE 2 DIABETES, GESTATIONAL DIABETES, AND OBESITY

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ABSTRACT

In the search to understand the onset of life's biochemistry, scientists attached a great deal of importance to unravelling the replication mechanism of a cell, and the cell membrane was accepted as an indispensable entity. In this review, we give an account of the recent progress of the understanding that the cell membrane has also continuously evolved over the long-term, leading to the important insight that the membrane unsaturation index (USI) - a measure of unsaturation - plays a pivotal role in the basal metabolic rate of a cell and in the aetiology of Type 2 diabetes mellitus (T2DM). It is now clear that increasing the USI with long-term interventions - in the form of aerobic exercise and caloric restriction - can contribute to the prevention or postponement of the onset of T2DM, gestational diabetes, and prediabetic obesity.

Keywords: Membrane flexibility, exercise, gestational diabetes, glucose transporter, obesity, phospholipids, Type 2 diabetes, unsaturated fatty acid.

INTRODUCTION

About 20 years ago, Shulman et al.[1,2] reported that *in vivo* carbon-13 nuclear magnetic resonance spectroscopy had measured human muscle glycogen synthesis rates in patients with Type 2 diabetes mellitus (T2DM) and matched controls. They showed that the muscle glycogen synthesis rates in the patients were approximately 50% of the rate observed in controls. The same group[3] investigated, under hyperglycaemic-hyperinsulinaemic conditions, the pathway: transmembrane glucose transport into the muscle cell, conversion of intracellular glucose into glucose-6-phosphate, and then, after two more intermediates, the addition of the latter through glycogen synthase to the glycogen polymer. They concluded that the transmembrane glucose transport into the muscle cell is the rate-controlling step; this is newsworthy biochemistry because it indicated that there must be an essential difference in plasma membrane function between patients with T2DM and the matched healthy controls. Two important questions arise: first, is it an isolated event that transmembrane glucose transport is the rate-controlling step or does this reflect the inherent nature of an evolutionary process? Second, what is the relationship between the chemical structure and physical properties of the various phospholipid molecules, and can this relationship elucidate how membrane function might be altered? To shed more light on the molecular processes underlying these phenomena, we summarise current knowledge about cell membranes.

CELL MEMBRANES

Phospholipid bilayers form rapidly and spontaneously when phospholipids are added to water. The two acyl chains yield a roughly cylindrical molecule that can easily pack in parallel arrays to form extended sheets of membranes composed of a mosaic of proteins and phospholipids in a fluid phospholipid matrix.[4] The driving force of this aggregation phenomenon is the weak, noncovalent bond (van der Waals force) between a

pair of carbon atoms, which can be calculated with the Lennard-Jones (L-J) potential: $U=(11.5 \times 10^{-6})/r^{12} - (5.96 \times 10^{-3})/r^{6}$. The interaction energy (U) is related to the distance (r) between two carbon atoms, as shown graphically in Figure 1.[5] Recently, Sun et al.[6] provided experimental data indicating the correctness of the L-J potential. What we can conclude from this graph is, firstly, that the minimum energy principle favours a carbon-carbon distance of ~4 Å, which is the most stable distance between the centres of two carbon atoms, with a minimum interaction energy of –0.77 kJ/mol. Secondly, when the carbon atoms in two acyl chains of a phospholipid diverge, their interaction energy decreases, and when they approach each other, their interaction energy increases. Thus, the sum of weak noncovalent forces of many carbon-carbon interactions creates flexibility in a lipid bilayer.

Membrane Flexibility

An exciting result recently achieved by the discipline of physical chemistry was the notion that (poly)unsaturated acyl chains of phospholipid membranes have an intrinsic propensity toward cell membrane flexibility. Saturated fatty acids possess essentially linear alkyl chains, with no double bonds. Conversely, double bonds in unsaturated fatty acids are nearly in the *cis* configuration, which produces a bend in the fatty acid chain.[7,8] This bend makes it more difficult for phospholipids with unsaturated acyl chains to pack close together, thus promoting bilayer flexibility. The most basic structural result obtained from X-ray scattering analyses of oriented bilayers in model phospholipid membrane systems is the area (A) per lipid molecule, which denotes the cross-section of the cylindrical space occupied by a phospholipid. Various studies of fully hydrated, fluid phase, model phosphatidylcholine bilayers (Table 1) have demonstrated that introducing one or more carbon-carbon *cis* double bonds into the saturated acyl chains will increase the cross-sectional area A by approximately 18%.[9-12] Thus, an 8.5% increased interchain distance results in a 33% decreased attraction energy per pair of fatty acyl carbon atoms. Consequently, due to reduced van der Waals interactions, an increased interchain distance of a phospholipid results in greater membrane flexibility.

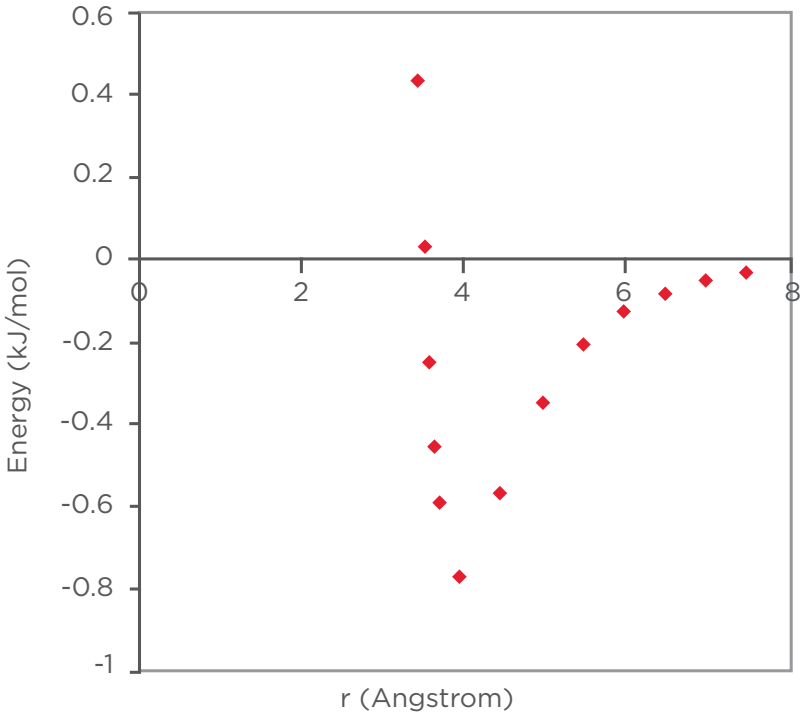

Figure 1: The van der Waals interaction energy profile as a function of the distance (*r*) between the centres of two carbon atoms.

The energy was calculated using the empirical equation $U= B/r^{12} - A/r^{6}$. Values for the parameters B= 11.5 $\times 10^{-6}$ kJnm^{12}/mol and A= 5.96 $\times 10^{-3}$ kJnm^{6}/mol for the interaction between two carbon atoms.

Adapted from Levitt.[5]

Table 1: Experimental data of fully hydrated fluid phase phosphatidylcholine lipid bilayers.

	DLPC	DMPC	DPPC	DOPC	PDPC
Reference	9	9	10,11	10	12
Fatty acid structure	$[C12:0]_2$	$[C14:0]_2$	$[C16:0]_2$	$[C18:1]_2$	C16:0,C22:6
Temperature (˚C)	30	30	50	30	30
Area A per lipid molecule $(Å)^2$	63.2	60.6	64.0	72.5	74.8
Mean Area A per lipid molecule $(Å)^2$		62.6		73.6	
Carbon interchain distance (Å)		4.46		4.84	
Interchain distance increase (%)				8.5	
Attraction energy U (kJ/mol)		–0.59		–0.39	
Attraction energy decrease (%)				32.9	

DLPC: dilauroylphosphatidylcholine; DMPC: dimyristoylphosphatidylcholine; DPPC: dipalmitoylphosphatidylcholine; DOPC: dioleoylphosphatidylcholine; PDPC: palmitoyl-docosahexaenoic-phosphatidylcholine.

A number of papers have reported examples of reduced membrane flexibility; a review by Cho et al.[13] indicated that patients with T2DM exhibited reduced erythrocyte deformability compared to healthy controls. Also, Gupta et al.[14] showed that reduced microvascular endothelial flexibility was characteristic of asymptomatic obesity combined with prediabetes. The erythrocyte membrane is compositionally very similar to the vascular endothelium. This has crucial implications because, in capillaries, the size of red blood cells is of the same order of magnitude as the capillary lumen (~8 μm); thus, deformability is an important determinant of blood flow. Increased stiffness of both the microvascular endothelium and the erythrocyte membrane decreases the microcirculatory flow, which leads to reduced oxygen supply, and consequently, to chronic tissue hypoxia, reduced adenosine triphosphate (ATP) production, and ultimately, increased endothelial dysfunction. Also, reduced oxygen uptake may be the cause of the failure of the endoplasmic reticulum to generate sufficient oxidative potential for disulphide bonds to be formed, as mentioned by Watson[15] in a recent paper. It is noteworthy that a decrease in microcirculatory flow leading to reduced oxygen uptake was demonstrated in the 6-year Malmö feasibility study; i.e. at baseline, subjects with newly-detected T2DM and those with impaired glucose tolerance showed a significantly reduced maximal oxygen uptake compared to strictly healthy individuals.[16]

Allometry

With the technique of biological scaling (allometry), the discipline of biology achieved an innovative result. Allometry, in its broadest sense, describes how the characteristics of living creatures change with size. For example, the observation that mammalian basal metabolic rate (BMR) changes with increases in species size, has been the subject of routine investigations for over a century. White et al.[17] compiled relevant data from the literature for 619 species with masses that ranged from 3-300,000 g. From that data, they derived the relationship between mammalian body mass (M, g) and BMR (ml of O_2 per h) in an allometric equation of the form: $BMR = 4.12\ M^{0.69}$. The result is endlessly fascinating because this relationship, with an allometric coefficient of 0.69, means that the BMR grows at a slower rate than the body mass (the slow-down principle). To understand the rationale behind the slow-down principle, let us suppose the existence of an extinct cubic species that consists of one unit cell with a length of 1 cm. The outer surfaces of this species are used for, among other things, exchange of metabolic heat with the environment. Then, the cubic species evolved over time to a larger cubic species with a total volume of 8 cm^3. Each of the 8 unit cells of this larger cubic species exposes only 3 outer surfaces for heat exchange with the environment, which means a 50% decrease in outer surface per unit cell, compared to the original cubic cell. To prevent

overheating of the larger cubic cell, evolution developed the slow-down principle.

A consequence of the allometric equation is that a doubling of body mass involves a 19.3% decrease in the mass-specific basal metabolic rate. For the reader's mind-set, our common ancestor - the species *Homo habilis* - had a body mass of approximately 32 kg. Thus, after a period of about 2 million years, the species *Homo sapiens* arrived with a body mass of about 70 kg and a 19.3% decreased mass-specific BMR compared to that of *Homo habilis*; i.e. a 1 per mille decrease in the BMR per 13,350 years. This is a fine example of regulated cellular basic metabolic rate sensing, but even more importantly, it is an indication of the existence of a genetically-regulated species-dependent set point of basic metabolic rate. The answer to the question: 'What is the principal cause of the slow-down mechanism for BMR?' starts with the observation that, heart, skeletal muscle, liver, and kidney tissue phospholipids, which have been shown to have significant influence on many aspects of membrane function, have also exhibited allometric trends. Phospholipid acyl chains have shown a significant decrease in the unsaturation index (USI) (i.e. the mean number of *cis* double bonds per fatty acid residue, multiplied by 100) with increases in species body size from 7-370,000 g.[18] Also, although membrane bilayers showed essentially no change in the percentage of saturated acyl chains with changes in species size, the membrane bilayers of small mammals were generally high in docosahexaenoic acid (DHA) (C22:6) and low in oleic acid (C18:1), and the opposite was observed in large mammals.[18]

This observation gave rise to the membrane pacemaker theory of metabolism, which suggests that the relative balance between monounsaturated and polyunsaturated acyl chains, particularly DHA, in cell membranes is a fundamental determinant of the metabolic rate of a species. In other words, the BMR of a cell, an important characteristic of a cell's energy management, depends on its cell membrane flexibility. Because the thermoregulation of a species may be the driving force behind the pacemaker theory, it is attractive to hypothesise that the primary cause of T2DM is a hypothalamic dysfunction, critically involved in thermoregulation, which in turn, results in a decrease in the USI, in keeping with the slow-down principle.

Transmembrane Glucose Transport

Focusing on membrane flexibility, we will discuss some aspects of membrane insertion of both the non-insulin-mediated glucose transporter Type 1, GLUT1, and the insulin-mediated glucose transporter, GLUT4. GLUT1 is a monomeric protein with 12 transmembrane helical segments.[19] A fundamental aspect of the transmembrane insertion machinery, located in the endoplasmic reticulum, is that the transporter protein must traverse the plasma cell membrane 12 times in a zigzag fashion, before initiating the folding necessary to form the three-dimensional structure. Moreover, hydrodynamic size analysis and electron microscopy of GLUT1 proteoliposomes support the hypothesis that GLUT1 is a multimeric (probably tetrameric) complex of GLUT1 proteins.[20] Thus, the process of inserting this glucose transporter into a bilayer membrane requires high membrane flexibility.

GLUT4 insertion into the plasma membrane follows a somewhat more complicated route that consists of two important phases (Figure 2). In the first phase, GLUT4 is inserted into the membrane of intracellular vesicles. As discussed in the aforementioned paragraph, this process demands flexibility of the vesicular membrane. In the second phase, the vesicles that contain GLUT4 take part in a fusion process with the cell membrane. This process of membrane fusion is described by the 'stalk-pore' hypothesis, and involves three decisive steps.[21,22] In the first step, opposing membranes of the vesicle and the cell membrane are separated by at least a 10-20 nm gap. Their contact involves specialised tethering molecules. Next, fusion proteins induce bending of the plasma membrane bilayer, which establishes a very close contact between the two membranes; and finally, activated fusion proteins drive fusion pore formation by assembling into an interconnected protein coat surrounding the fusion gate. Clearly, high flexibility of the cell membrane plays a central role in this fusion process. Thus, high flexibility of the cell membrane represents a key determinant in glucose transport due to its influence on all Class 1 GLUT proteins.

Replies to the Questions

Now we have summarised the current knowledge about cell membranes, we can answer the two questions raised in the Introduction. First, the presented data show that the BMR of a cell

depends on its plasma membrane flexibility, and this flexibility, in turn, determines the number of GLUTs present at the cell surface. These findings are consistent with the observation that transmembrane glucose flux (TGF) is the rate-controlling step in muscle glycogen production, as demonstrated in the experimental work of Shulman's group.[2] Those results have provided an impressive indication of the correctness of the pacemaker hypothesis. Second, this mechanism did not arise from an isolated event. Far from it, they shed light on the inherent nature of an evolutionary process, which is based on maintaining the relative balance between monounsaturated and long-chain polyunsaturated acyl chains in membrane bilayers. With elegant simplicity, this is a fine example of energy management over the long-term.

Now, we can quite simply answer the open question of how an elevation in plasma-free fatty acids (FFAs) causes inhibition of transmembrane glucose transport, as reported by Shulman's group.[23] In that study, an increase in plasma-FFA levels in healthy subjects was created with intravenous infusions of a triglyceride emulsion, Liposyn II. Lyposyn II comprises a 50/50 safflower/soybean oil mixture, where the major component fatty acids are approximately 65.8% linoleic (C18:2), 17.7% oleic (C18:1), 8.8% palmitic (C16:0), 3.4% stearic (C18:0), and 4.2% α-linolenic (C18:3) acid. Due to the absence of long-chain polyunsaturated fatty acids in Liposyn II, its intravenous infusion caused a decreased USI, decreased membrane flexibility, and finally, a decrease in all functional Class 1 GLUTs.

A NEW ROUTE TO THE DEVELOPMENT OF T2DM

In the aetiology of T2DM, a new working hypothesis that attempts to accommodate findings from numerous laboratories is presented in Figure 3. Shulman's group demonstrated that a reduced ATP production in the skeletal muscle of young, lean insulin-resistant offspring of parents with T2DM probably occurs due to decreased mitochondrial activity,[24,25] which is a characteristic for T2DM individuals.[26] To acquire extra ATP, this leads to gradual elevation of plasma-FFAs, which in turn, causes a shift from unsaturated to saturated fatty acyl chains in membrane phospholipids, and a decreased USI. Consequently, there is harmful increased membrane stiffness with a concomitant reduction in all functional Class I GLUTs. The net effect would be a decrease in glucose flux into cells, which would further stimulate hepatic lipolysis.

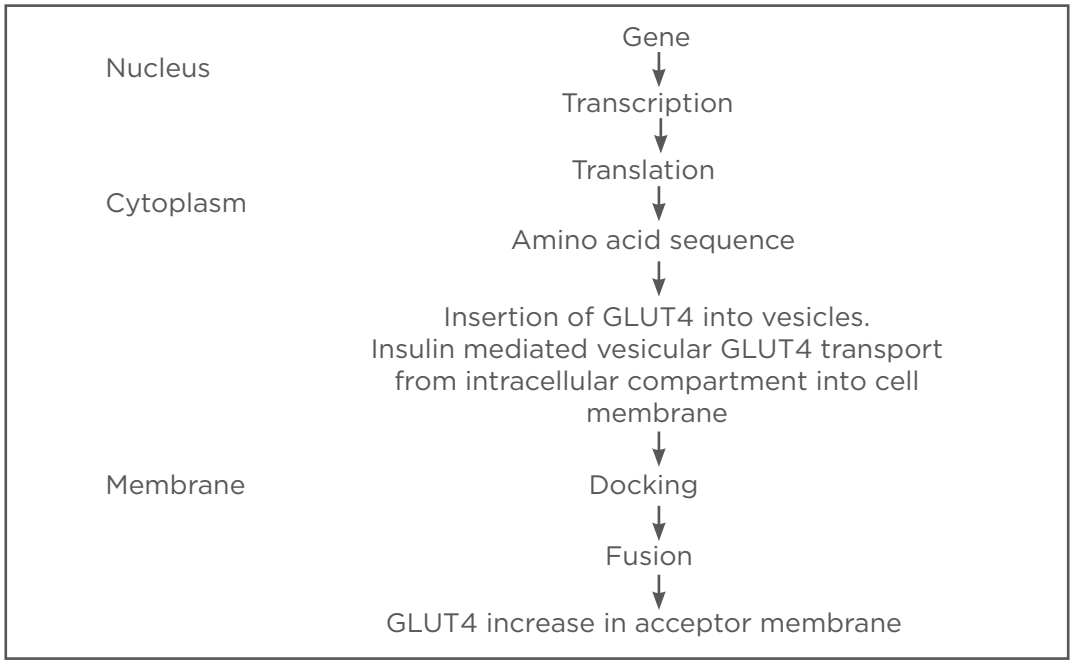

Figure 2: Glucose transporter type 4 (GLUT4) protein biogenesis.
The membrane protein is modified by engineering of the structural gene, where the critical steps in the biosynthetic pathway, leading to the folded GLUT4 in the membrane, are its insertion into the vesicle and the vesicle fusion with the acceptor membrane where events are under control of membrane flexibility.

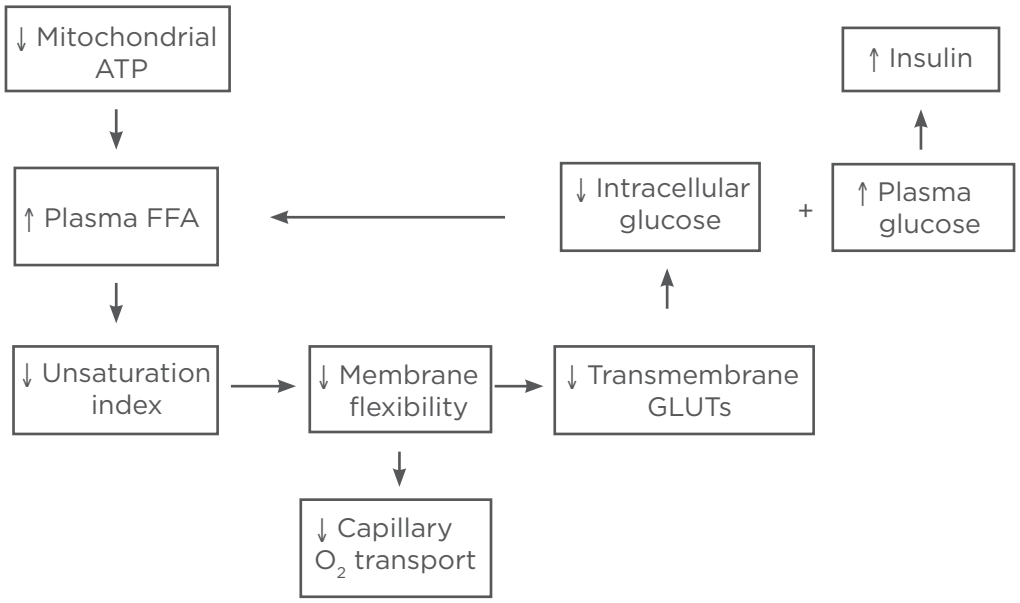

Figure 3: Hypothetical pathway of the development of Type 2 diabetes.
ATP: adenosine triphosphate; FFA: free fatty acid; GLUT: glucose transporter.

The progress of these events sets up a vicious cycle. The reduced glucose uptake causes increases in plasma glucose and insulin concentrations, which are positively related up to a plasma glucose concentration of about 10 mmol/L. Thereafter, ß-cell failure occurs, and due to insufficient insulin, the condition of glucose intolerance gives way to frank T2DM. From the Liposyn II experiments, we may conclude that the increasing level of plasma-FFAs is the initiating cause of the vicious cycle.[23] Moreover, this logical sequence of events explains the time-dependent increase in both glucose and insulin concentrations during the prediabetic phase.[27] Additional experimental data in favour of the new working hypothesis has been summarised in a recent study.[28]

Obesity is characterised by an elevation in plasma-FFAs because enlarged, stressed adipose tissue releases more FFAs, and FFA clearance may be reduced compared to the non-obese condition.[29] According to our proposed scheme (Figure 3), this elevation of FFAs would reduce the USI, which would finally result in a reduction in all functional Class I GLUTs and the development of T2DM. In the case of obese, but otherwise healthy individuals, an over-secretion in insulin compensates for an increased plasma glucose concentration. However, in prediabetic individuals, this compensation fails and the consequence is overt T2DM. Gestational diabetes mellitus (GDM) arises from two underlying phenomena; first, a temporary increased plasma concentration of FFAs, which induces a reduced glucose flux into maternal cells, along with a concomitant increased insulin level during pregnancy,[30] and ensures an adequate glucose supply for foetal growth and development; second, a chronic increase in plasma-FFAs due to the presence of a prediabetic state. Together, these independent increases in FFAs result in serious decreased membrane flexibility that causes metabolic abnormalities to culminate in the characteristics of GDM.[31] After delivery, the temporary increased FFAs ceases, which results in apparently normal glucose homeostasis.

Another argument for our proposed scheme (Figure 3) is the observation that individuals with T2DM have higher basal metabolic rates than nondiabetic control subjects.[32] After all, in individuals with T2DM, the reduction in all Class 1 GLUTs, followed by an increase in plasma-FFAs induces a shift from glucose oxidation towards fatty acid oxidation. In eukaryotes, complete glucose oxidation involves the breakdown of the glucose carbon-carbon bonds, which require (per carbon-carbon bond) 6/6 = 1.00 molecule of O_2; in contrast, the complete oxidation of palmitoyl-coenzyme A involves the breakdown of the palmitoyl carbon-carbon bonds, which require (per carbon-carbon bond) 23/16 = 1.43 molecules of O_2.[33] Consequently, oxygen consumption, which is a measure of basal

metabolic rate, should be higher in individuals with T2DM than in non-diabetic control subjects. This hypothesis had to be demonstrated.

Aerobic Exercise

We speculate that aerobic exercise is essential for restoring flexibility to stiff membranes, a common characteristic of T2DM, GDM, and prediabetic obesity. Exercise training showed direct effects on the 'browning' of white fat through irisin.[34] The function of brown adipose tissue is to transfer energy from fatty acids into heat. Because brown adipose tissue is more saturated than white adipose tissue,[35] and because exercise burns mostly brown fat, exercise acts to reduce the body's saturated fatty acid content, and consequently, promotes an increase in membrane flexibility and TGF. A number of studies that focused on lifestyle changes, such as diet and physical exercise, have supported the hypothesis that T2DM can be prevented or delayed with exercise in individuals at high risk of the disease,[16,36-38] and that exercise can be beneficial as an adjuvant therapy in GDM.[39] Although the study designs differed from each other to some extent, the results may be summarised as follows: a 5-year protocol which aimed to achieve and maintain at least 5% weight reduction through a healthy low-caloric, low fat diet, and to engage in physical activity of moderate intensity, had reduced the risk of diabetes by approximately 50% in adults at high risk of developing T2DM. To obtain continued optimisation of a lifestyle-modification programme, the author regards the assessment of membrane flexibility as an essential factor. In fact, erythrocyte deformability was found to be significantly reduced in patients with T2DM compared to healthy controls[13] due to a decreased USI, and not by an increased percent of glycated membrane proteins.[13]

CONCLUSION

Notwithstanding the fact that diabetes is a disease with a genetic component of unknown origin, the good news is that an individual with high risk of T2DM, or with T2DM, is the conductor of his/her own USI, with all its benefits. This control provides an individual with a unique position because normalisation of both glycaemia and the USI are cornerstones of effective T2DM management. Knowledge and understanding of the presented concept are essential to informing public health programmes and policy, based on the expectation that these concepts will affect governmental decision-making regarding public health issues.

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TARGETING ADIPOSE TISSUE LIPID METABOLISM TO IMPROVE GLUCOSE METABOLISM IN CARDIOMETABOLIC DISEASE

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ABSTRACT

With Type 2 diabetes mellitus and cardiovascular disease prevalence on the rise, there is a growing need for improved strategies to prevent or treat obesity and insulin resistance, both of which are major risk factors for these chronic diseases. Impairments in adipose tissue lipid metabolism seem to play a critical role in these disorders. In the classical picture of intracellular lipid breakdown, cytosolic lipolysis was proposed as the sole mechanism for triacylglycerol hydrolysis in adipocytes. Recent evidence suggests involvement of several hormones, membrane receptors, and intracellular signalling cascades, which has added complexity to the regulation of cytosolic lipolysis. Interestingly, a specific form of autophagy, called lipophagy, has been implicated as alternative lipolytic pathway. Defective regulation of cytosolic lipolysis and lipophagy might have substantial effects on lipid metabolism, thereby contributing to adipose tissue dysfunction, insulin resistance, and related cardiometabolic (cMet) diseases. This review will discuss recent advances in our understanding of classical lipolysis and lipophagy in adipocyte lipid metabolism under normal and pathological conditions. Furthermore, the question of whether modulation of adipocyte lipolysis and lipophagy might be a potential therapeutic target to combat cMet disorders will be addressed.

Keywords: Lipolysis, lipophagy, cardiometabolic disease, obesity, adipose tissue, insulin resistance, Type 2 diabetes, lipid metabolism.

INTRODUCTION

Obesity and related insulin resistance are major risk factors for cardiometabolic (cMet) disorders including Type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). Increased fat mass is associated with increased mortality rates, mainly due to vascular diseases.[1] Adipose tissue is the most important organ for lipid storage in the human body, in which lipids are stored mainly in the form of triacylglycerol (TAG) in intracellular lipid droplets (LD). Subcutaneous adipose tissue (SAT) serves as a buffer to store lipids in times of excess energy intake (e.g. after meal ingestion) and to release non-esterified free fatty acids (FFA) for use by oxidative tissues (e.g. skeletal muscle, heart, and liver) in times of energy demand (e.g. fasting, exercise). In obesity, the adipose tissue depot is enlarged to a size that exceeds its storage capacity; lipid overflow results in increased fat deposition outside the SAT (i.e. visceral adipose tissue, skeletal muscle, heart, and liver).

Substantial evidence indicates that this is associated with the development of obesity-associated insulin resistance and cMet diseases.[2] Indeed, metabolically healthy (insulin sensitive) obese subjects have significantly lower visceral fat mass, a decreased liver fat content, less macrophage infiltration, and a smaller adipocyte size, both in visceral and subcutaneous fat depots, compared to insulin resistant obese subjects.[3] It is

interesting to note that surgical removal of either visceral[4-6] or subcutaneous fat[7] does not affect cardiovascular (CV) and metabolic risk factors, suggesting that adipose tissue function, rather than fat mass per se, determines cMet risk.[8]

Classical lipolysis and the recently discovered alternative pathway for lipid breakdown, lipophagy, largely determine intracellular lipid turnover. Therefore, understanding depot-specific regulation of both pathways under normal and pathological conditions is crucial to develop novel therapeutic strategies to prevent or treat obesity-associated cMet disorders. In this review, we will discuss the current knowledge about the potential involvement of classical lipolysis and lipophagy in adipocyte lipid metabolism under normal and pathological states, and highlight potential therapeutic targets.

REGULATION OF ADIPOCYTE LIPID METABOLISM BY INTRACELLULAR LIPOLYSIS AND LIPOPHAGY

Intracellular Lipolysis: the Classical Way of Fat Breakdown

Intracellular or cytosolic lipolysis is the process via which stored TAG is hydrolysed in order to provide sufficient energy in times of increased energy demand (e.g. fasting or exercise). The complexity of its regulation has been investigated extensively and is illustrated in Figure 1A. Up to a decade ago, when natriuretic peptides (NPs) entered the lipolytic picture, catecholamines, secreted by the adrenal medulla and sympathetic nervous system, were considered to be the sole physiological lipolytic agents (Figure 1A). In general, visceral adipocytes are more sensitive to catecholamine-induced lipolysis compared with subcutaneous adipocytes due to differences in the expression of adrenoceptor subtypes and key lipolytic proteins.[9-12]

Sengenes et al.[13] has shown that atrial (ANP), brain-type, and C-type NPs, produced in the myocardium and central nervous system, are potent activators of human lipolysis. Physical exercise increases plasma ANP levels, which is accompanied by an increased lipid mobilisation to serve as subsequent substrate in oxidative tissues (e.g. skeletal muscle).[14,15] Although data on depot-specific differences in NP-sensitivity are limited, two studies have suggested that NP-sensitivity is comparable between the visceral and SAT.[12,16]

In the postprandial state, lipolysis is suppressed due to a rise in insulin, which is the major anti-lipolytic hormone in human adipocytes (Figure 1A). In contrast to catecholamine-mediated lipolysis, insulin does not seem to have a direct anti-lipolytic effect on NP-mediated lipolysis.[17,18] Adipocytes from visceral adipose tissue (VAT) are more insulin resistant than subcutaneous adipocytes, and smaller adipocytes tend to be more insulin sensitive, while large (hypertrophic) adipocytes become more insulin resistant.[19-21] Besides insulin, gut-derived short chain fatty acids (SCFA), formed after fermentation of dietary fibres, have a potent anti-lipolytic effect, suggesting metabolic cross-talk between the gut and peripheral lipid metabolism (Figure 1A).[22,23] Recent data have shown that metabolites produced by the adipocyte, such as lactate and β-hydroxybutyrate, exert anti-lipolytic effects via inhibitory G-coupled receptors, suggesting the importance of autocrine regulation of adipocyte lipolysis.[24,25] Finally, preliminary evidence suggests that adipose tissue oxygen tension may be involved in the regulation of adipose tissue lipolysis.[26]

In summary, two major lipolytic hormones (e.g. catecholamines and NPs) and several anti-lipolytic hormones, of which insulin is the most potent, regulate human fat cell lipolysis. In the last decade, tremendous progress has been made by the discovery of several regulatory proteins, adding remarkable complexity to the regulation of classical intracellular lipolysis.

Lipophagy: an Alternative Pathway for Lipid Breakdown Enters the Picture

Autophagy is a homeostatic mechanism functioning as a 'self-digestion' system that degrades unnecessary or dysfunctional cellular components to generate essential nutrients in times of energy deprivation to ensure cellular survival. Although autophagy is largely viewed as a non-selective process, three recent studies[27-29] have clearly implicated autophagy in selective degradation of LD in adipocytes and subsequent lipid hydrolysis, both under basal and β-adrenergically stimulated conditions, a process termed lipophagy. As illustrated in Figure 1B, the three major steps in this alternative pathway for lipid breakdown - including autophagosome formation, lysosomal degradation, and mitochondrial oxidation of the lysosomal lipid products - are tightly regulated by phosphorylation and nuclear translocation of transcription factor EB (TFEB).[30]

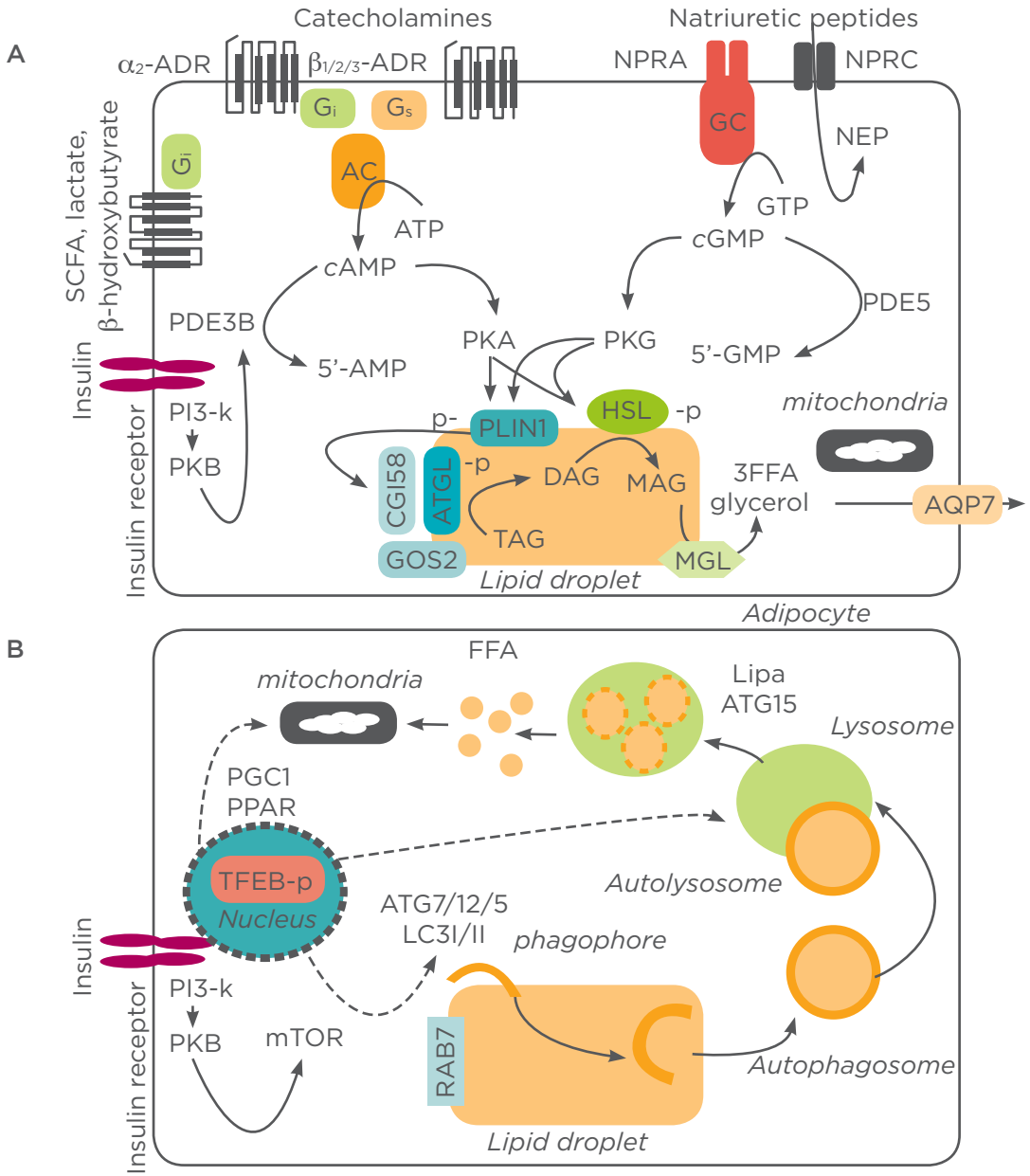

Figure 1: Schematic illustration of: A) the regulation of classical lipolysis in adipocytes; B) Lipophagy. Catecholamines signal via α and β-adrenoceptors, and NPs exert their effect via NPRA and the scavenging receptor NPRC. Subsequent phosphorylation of lipid droplet associated proteins including PLIN1, HSL, and ATGL ensures complete hydrolysis of stored triacylglycerol (TAG) in one glycerol and three free fatty acid (FFA) molecules. Insulin increases PDE3B activity, which converts cAMP in 5'-AMP, decreasing PKA activity and subsequent HSL phosphorylation. Lipophagy, is tightly regulated by phosphorylation and nuclear translocation of transcription factor EB (TFEB).

AC: adenylate cyclase; ADR: adrenoreceptor; ATG: autophagy-related gene proteins; ATGL: adipose triglyceride lipase; ATP: adenosine triphosphate; AQP7: aquaporin 7; cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; DAG: Diacylglycerol; FABP4: fatty acid binding protein 4; GC: guanylyl cyclase; Gi: inhibitory G protein; Gs: stimulatory G protein; GTP: guanosine triphosphate; HSL: hormone-sensitive lipase; LC3I/II: microtubule-associated protein light chain 3 (mammalian homologue of ATG8); Lipa: lysosomal lipase; MAG: monoacylglycerol; MGL: monoglyceride lipase; mTOR: mammalian target of rapamycin; NPs: natriuretic peptides; NEP: neutral endopeptidases; NPRA/C: natriuretic peptide type A and C receptor; PDE3B/5: Phosphodiesterase 3B and 5; PGC1: PPAR co-activator type 1; PI3-k/PKB: phosphoinositide/protein kinase B; PLIN1: perilipin 1; PPAR: peroxisome proliferator-activated receptor; RAB7: ras-related protein 7; SCFA: short-chain fatty acid.

ADIPOSE TISSUE LIPID METABOLISM IN OBESITY AND CVDS

Elevated Basal but Blunted Catecholamine-Stimulated Lipolysis

Obesity is the most often studied clinical condition regarding pathophysiological aspects of lipolysis. As far as *in vivo* whole-body lipolysis under fasting conditions (basal lipolysis) is concerned, this rate may be increased in obesity because of the increased total adipose tissue mass. However, if obese adipose tissue would release FFA at the same rate as lean adipose tissue then circulating FFA would be much higher than the observed 20-30%, suggesting that FFA concentrations are not elevated in proportion to the increase in fat mass.[31] Indeed, others[32] and ourselves,[33] have demonstrated that fasting lipolysis expressed per unit of fat mass is rather reduced in obesity. This was accompanied by downregulation of the expression of several key lipolytic enzymes.[33,34] *In vitro*, basal spontaneous lipolysis expressed per number of adipocytes is higher in obese compared to lean adipose tissue[35] and subcutaneous versus visceral adipocytes.[36]

Adipocyte enlargement (hypertrophy), as observed in human obesity, is associated with increased macrophage infiltration, chronic low-grade inflammation, and release of pro-lipolytic cytokines (e.g. tumour necrosis factor alpha), which may contribute to the enhanced basal lipolysis.[37,38] Since humans are in the post-prandial state most of the day, insulin-mediated inhibition of adipose tissue lipolysis (ATL) is a major regulator of basal lipolytic rate. Insulin-mediated suppression of ATL per unit of fat mass is normal[39] or slightly attenuated in obese individuals,[40-43] suggesting that chronic hyperinsulinaemia cannot overcome the increase in whole-body lipolysis.

Others,[35,44] and ourselves,[33] have clearly shown that *in vitro* and *in vivo* catecholamine-induced lipolysis is blunted in SAT of obese subjects, which persists after significant weight loss.[45] This was also shown in normal weight subjects with obesity among first-degree relatives.[46] The blunted catecholamine-mediated lipolytic response supports the observation that adipocyte lipid turnover is decreased in human obesity,[47,48] which might be an important primary factor in the development of increased fat stores in obese subjects.[49] On the other hand, visceral adipocyte lipolysis, induced by catecholamines, is increased and strongly correlates with CV and metabolic risk factors in obesity.[50] These data support the 'portal hypothesis',[51] postulating that the liver in obese subjects is directly exposed to an increased release of FFA derived from visceral lipolysis (≈10-50%) into the portal vein.[52-54]

With respect to NP-induced lipolysis, data are scarce. However, reduced circulating NP levels[55] and a defective *in vivo* ANP-mediated lipolytic response in SAT from young overweight/obese subjects has been observed.[56] This may partly be explained by upregulation of the scavenging receptor, NP receptor C, in SAT of obese subjects.[57] In contrast, patients with chronic heart failure, with elevated circulating NP levels, show a preserved,[58] or even increased, catecholamine and ANP-mediated lipolytic response in subcutaneous adipocytes,[59] possibly contributing to the development of cardiac cachexia.[60]

In summary, obesity is characterised by an increased basal and a blunted catecholamine and NP-stimulated lipolysis in subcutaneous adipocytes, while catecholamine sensitivity in the visceral depot is increased. This altered lipid turnover may be an early factor in the development of increased fat stores in obesity and associated cMet complications.

Defective Regulation of Autophagy

Under normal physiological conditions, adipocytes rely mainly on cytosolic lipolysis, while lipophagy may become more important in pathophysiological conditions to maintain lipid homeostasis (Figure 2A). Indeed, autophagy markers and fluxes appear to be elevated in the cardiometabolically unhealthy VAT depot of obese insulin-resistant and T2DM subjects, and these markers are reduced following weight loss.[61-65] Furthermore, autophagy markers and fluxes are increased in adipose tissue of lean mice upon caloric restriction (CR), whereas they decrease in obese mice,[65] suggesting defective nutritional and hormonal regulation of adipose tissue autophagy in obesity. Interestingly, adipose tissue of adipose triglyceride lipase (ATGL) deficient mice showed increased lipophagy,[66] suggesting lipophagy might be upregulated in order to compensate for the reduced expression and activity of cytosolic lipases in obesity. On the other hand, autophagy is involved in adipocyte differentiation.[29] Therefore, it could be primarily elevated in order to accommodate expansion and growth of adipocytes to deal with the increased lipid availability in obesity.

As illustrated in Figure 2B, induction of autophagosome formation will increase delivery of lipids to lysosomes, which may accumulate to a toxic level in this organelle if subsequent lysosomal hydrolysis and mitochondrial oxidation are not adapted accordingly to accommodate the increased lipid cargo. This hypothesis is supported by the observation that upregulation of autophagy, in ATGL deficient mice, is accompanied by increased lysosomal lipid accumulation and severe metabolic complications.[67] Furthermore, upregulation of Lipa - an enzyme involved in lysosomal lipid hydrolysis - in adipose tissue of severely obese individuals has recently been shown, suggesting increased processing of the excess lysosomal lipid cargo.[68] Finally, excessive lipid delivery and accumulation in lysosomes evoked lysosomal destabilisation, cell apoptosis, and a subsequent inflammatory response in 3T3-L1 adipocytes,[69] supporting the view that increased autophagy and inadequate handling of the lipid cargo may contribute to adipose tissue inflammation, which has been linked to obesity-associated insulin resistance (Figure 2B).

In summary, lipophagy might be increased in adipose tissue of obese subjects as a compensatory mechanism to deal with increased lipid availability. A disbalance between autophagosome formation, lysosomal degradation, and mitochondrial oxidation is proposed to be one of the putative mechanisms that may contribute to an inflammatory response, which may lead to obesity-related insulin resistance in humans (Figure 2).

ADIPOCYTE LIPID METABOLISM: A TARGET TO PREVENT CMET DISORDERS

Modulation of Classical Lipolysis

Lifestyle interventions are the most effective way to improve lipid metabolism and to prevent the development of T2DM and subsequent CV events.[70-73] However, long-term outcomes of a dietary and physical activity programme for older adults and for those with significant comorbidities (e.g. heart failure) remain to be improved. Therefore, research is increasingly aimed at identifying natural and/or pharmacological CR and exercise mimetics.[74]

Inhibition of ATL might be a therapeutic strategy to limit excess FFA release, thereby alleviating the development of insulin resistance and cMet abnormalities.[75] On the other hand, a diminished ATL could favour the development of obesity through retention of lipids within adipocytes. The interest in anti-lipolytic drugs has been illustrated, for instance, by nicotinic acid (NA), which has been used for decades as a lipid-lowering drug.[76,77] However, NA shows receptor-independent effects, and the use of the drug has been restricted due to upper-body skin flushing.[78-81] Therefore, the search for alternative drugs with anti-lipolytic effects has led to the synthesis of selective hormone-sensitive lipase (HSL) inhibitors.[82] Although data are scarce, reduced plasma FFA and glucose levels have been demonstrated in diabetic rats treated with a selective HSL inhibitor.[83] Recently, Girousse et al.[84] showed that systemic glucose tolerance was improved in mice treated for 7 days with a HSL inhibitor and haploinsufficient HSL +/- mice, possibly through induction of adipocyte *de novo* lipogenesis (DNL).[84] Evidence is accumulating that adipose tissue DNL might significantly contribute to whole-body insulin sensitivity,[85,86] possibly via secretion of beneficial lipids (lipokines), by adipose tissue upon activation of lipogenesis.[87] In addition to selective inhibition of HSL, recent data report on the development of a selective inhibitor of ATGL, atglistatin, highlighting the development of selective lipase inhibitors to correct defects in lipid metabolism for the treatment and prevention of cMet diseases.[88]

It has been shown that intravenous acetate administration decreases plasma FFA concentrations and improves insulin sensitivity in humans.[89] These data suggest that modulation of systemic SCFA levels by colonic fermentation of certain types of dietary fibres might affect systemic lipolysis, and therefore, improve insulin sensitivity and cMet health, by reducing adipose tissue FFA efflux.[90,91] Nevertheless, to optimise the effectiveness of this type of nutritional intervention, further studies are required since the effects may depend on the type and amount of SCFA produced.

In contrast to the anti-lipolytic approach with selective lipase inhibitors and SCFAs, several sympathomimetic agents have been used to treat obesity because of lipolytic, thermogenic, and anorectic effects.[92] However, the earlier use of non-selective β-adrenergic compounds was associated with adverse reactions such as tachycardia and tremor. The discovery of a β_3-adrenoceptor expressed in white and brown adipose tissue gave new impetus to the field.[93,94] However, activation of lipolysis and browning by β_3-agonists in human

white adipose tissue have, so far, not provided promising results due to the low abundance of β_3-adrenoceptors in human adipose tissue compared to rodents, difficulties of extrapolating *in vitro* data, CV side-effects, and receptor desensitisation.[95-97] Recent data have shown that, next to catecholamines, NPs are able to enhance human skeletal muscle mitochondrial function and induce browning in human adipocytes.[98,99] Furthermore, inhibition of NP degradation and increasing the cyclic adenosine monophosphate/cyclic guanosine monophosphate content, via inhibition of neutral endopeptidases (NEP, neprilysin) and phosphodiesterases (PDE), has demonstrated only limited beneficial cMet effects.[100] Therefore, research is currently focused on dual angiotensin converting enzyme (ACE)/NEP inhibitors (LCZ696),[101] having both CV and metabolic effects. So far, the limited available data of PDE and ACE/NEP inhibition on adipose tissue lipid metabolism are not conclusive and warrant further investigation.[102-104]

In summary, modulation of classical lipolysis recently regained interest in the treatment of obesity-related insulin resistance by the development of selective ATGL, HSL, NEP, and PDE inhibitors. However, to prevent excessive gain or loss in body weight, tissue FFA turnover (uptake, esterification, and oxidation) should be adapted accordingly.

Modulation of Lipophagy

The potential involvement of the lipophagy pathway in adipocyte lipid metabolism makes it an attractive target for the prevention and treatment of cMet disorders. However, before considering manipulation of the adipose tissue lipophagy pathway for therapeutic purposes, a better insight into its role in pathophysiology is warranted.

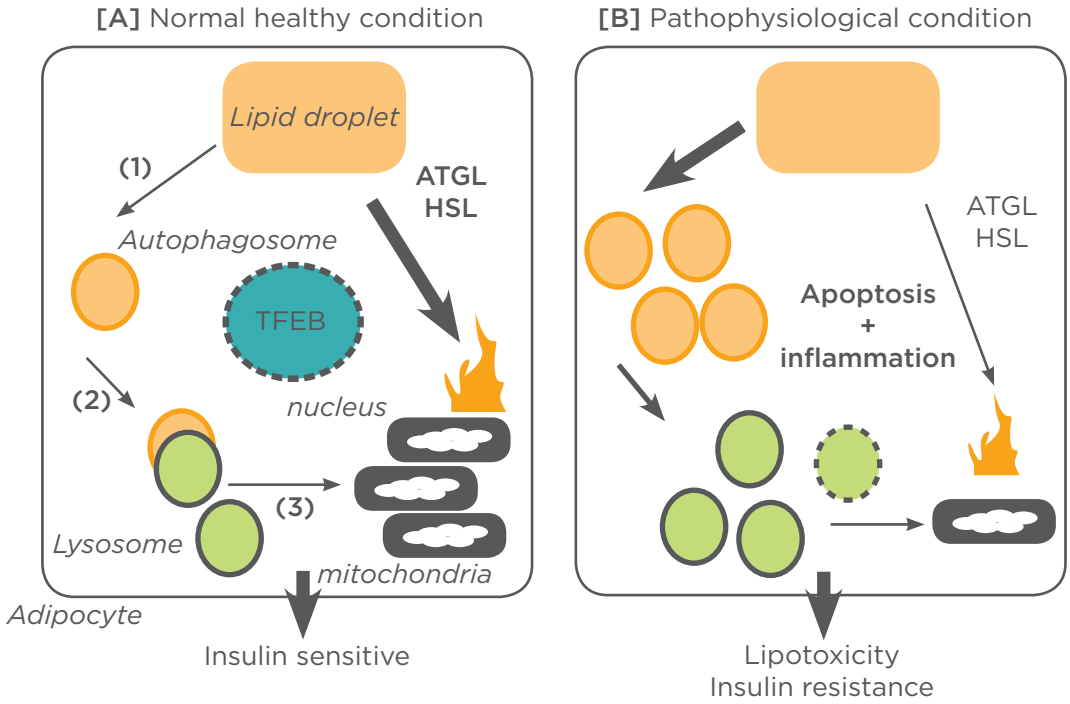

Figure 2: Putative mechanism for impaired adipocyte lipid metabolism in obesity. Under normal physiological conditions (panel A), adipocytes rely mainly on cytosolic lipolysis for hydrolysis of stored TAG. Under pathological conditions (e.g. obesity), autophagy is increased to compensate for the lack in cytosolic lipolysis (panel B). Phosphorylation and nuclear translocation of TFEB regulates all three major steps in this alternative pathway: 1) autophagosome formation; 2) lysosomal lipid hydrolysis; and 3) mitochondrial oxidation. Impaired fine-tuning of all three steps prevents flawless progression of lipids through this pathway, resulting in toxic accumulation of lipids in lysosomes. This might elicit lysosomal destabilisation and cell apoptosis and a subsequent inflammatory response, playing a crucial role in the development of obesity-associated insulin resistance.

ATGL: adipose triglyceride lipase; HSL: hormone-sensitive lipase; TFEB: transcription factor EB.

Recently, we have shown that dietary polyphenols, including resveratrol and epigallocatechin-3-gallate, found naturally in red wine and green tea, have CR-like effects in overweight humans.[105,106] Interestingly, our microarray data showed that resveratrol supplementation affected the expression of the master of lipophagy TFEB and improved adipose tissue function in humans.[105,107] However, it needs to be determined whether lipophagy-mediated lipid catabolism in adipose tissue is directly involved in the potential beneficial metabolic effects of polyphenols. Finally, it has been shown that autophagy might regulate lipid accumulation by controlling the balance between white and brown adipose tissue mass, which favours lipid oxidation and increases systemic insulin sensitivity by limiting FFA efflux.[27,29,108] Overall, we propose that the success of modulating lipophagy, as a potential strategy in the management of obesity, is largely dependent on the fine tuning of all three steps in this pathway, namely autophagosome formation, lysososmal breakdown, and final mitochondrial oxidation of the lipid cargo (Figure 2).

CONCLUSION AND PERSPECTIVE

Research over the last decade has substantially increased our understanding, but also added complexity to the regulation of adipose tissue lipid metabolism in cMet diseases. Increased basal and desensitisation of catecholamine and NP-stimulated adipose tissue lipolysis, due to downregulation of the expression of the key lipolytic enzymes, is a hallmark of human obesity (Figure 2). However, there is no straightforward relationship between fat mass, systemic FFA flux, and the development of insulin resistance and cMet diseases. Nevertheless, the interest in anti-lipolytic drugs, which have been used for decades as a lipid-lowering agent, recently regained interest by the development of selective HSL and ATGL inhibitors. Partial inhibition of HSL shows promising effects, preventing extra weight gain by reshaping FFA fluxes and improving systemic glucose metabolism via stimulation of adipose tissue DNL.[84] However, long-term human clinical trials using selective ATGL and HSL inhibitors are lacking.

In contrast to this anti-lipolytic approach, the effect of increasing NP and catecholamine sensitivity/signalling, using NEP or PDE inhibitors, on lipid metabolism needs to be investigated in more detail. Importantly, exaggerated inhibition or activation of ATL may result in excessive weight gain or the development of cachexia when tissue FFA uptake, esterification, and oxidation are not adapted accordingly. In addition, the alternative pathway for adipocyte lipid breakdown, lipophagy might be an interesting target for treatment. Increased autophagy, as observed in obese adipose tissue, might be a compensatory mechanism for an impaired classical lipolysis, and contribute to the development of systemic insulin resistance when all steps in this pathway are not aligned with each other (Figure 2). Thus, fine-tuning all three steps in the autophagy-lysosomal-mitochondrial pathway in human adipose tissue may be critical regarding treatment outcome. For this reason, components with dual/multiple action on lipid metabolism might hold promise for future treatment of cMet disorders.

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RESIDUAL CARDIOVASCULAR RISK IN DIABETIC PATIENTS: THE ROLE OF FIBRATE/STATIN COMBINATION

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ABSTRACT

Patients with Type 2 diabetes mellitus (T2DM) have increased cardiovascular disease (CVD) risk. The use of statins significantly reduces the rate of CVD events but many T2DM patients, especially those with mixed dyslipidaemia (MD), have residual CVD risk. The use of fibrates, which improve triglyceride and high-density lipoprotein cholesterol levels, is beneficial for the treatment of patients with MD. Evidence from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid study showed a possible beneficial effect on CVD events of the addition of fenofibrate (FF) to statin treatment in patients with T2DM and atherogenic MD. Furthermore, FF has been associated with slowing of the progression of early diabetic retinopathy. The combination of statin with a fibrate may improve the residual CVD risk and microvascular complications of patients with T2DM. However, trials specifically designed to assess the effects of fibrate-statin combination on cardiovascular outcomes in patients with T2DM are missing.

Keywords: Fibrate, fenofibrate, fenofibric acid, statin, diabetes, cardiovascular risk, retinopathy.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is associated with a significantly increased risk of cardiovascular disease (CVD).[1,2] The increased CVD risk is, in part, attributed to an adverse lipid profile observed in T2DM patients, which includes increased levels of low-density lipoprotein cholesterol (LDL-C), increased concentration of triglycerides (TG), and reduced levels of high-density lipoprotein cholesterol (HDL-C).[3,4] The primary target of lipid lowering therapy in T2DM patients is the reduction of LDL-C levels. The use of statins is the cornerstone of therapy in patients with T2DM, since these drugs significantly reduce the concentration of LDL-C and have been proven efficacious for the reduction of CVD risk.[5,6] In the Collaborative Atorvastatin Diabetes Study,[7] which included 2,838 patients with T2DM, atorvastatin reduced the rate of major vascular events by 37% in a period of 4 years ($p<0.001$).

Many patients with T2DM, despite receiving a statin and having a satisfactory LDL-C concentration, are characterised by the presence of atherogenic mixed dyslipidaemia (MD) (elevated TG concentration and low levels of HDL-C).[3,4,8] This adverse lipid profile is considered a main factor for the increased CVD risk of diabetic patients on statin treatment. Indeed, in the Treating to New Targets study[9] and in the Pravastatin or Atorvastatin Evaluation and Infection Therapy study,[10] it was shown that patients with LDL-C <70 mg/dl, low HDL-C levels, and/or increased TG levels had higher CVD risk compared with patients without MD. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid study,[11] patients with T2DM and atherogenic dyslipidaemia (AD) had 70% greater rate of major CVD events compared with the group of T2DM patients without AD.

The 'residual' CVD risk in T2DM patients on statin treatment has also been attributed to many other variables that affect the atherosclerotic

progression in patients with T2DM, including the presence of the atherogenic small-dense LDL particles, alterations in the distribution of HDL-C subclasses, and increased levels of inflammatory markers, such as high-sensitivity C-reactive protein (hs-CRP) and lipoprotein-associated phospholipase A_2.[12-27] The residual CVD risk in diabetic patients could be targeted with the combination of statins with other hypolipidaemic drugs that improve MD, such as fibrates.

FIBRATES

Fibrates are a class of drugs that activate peroxisome proliferator-activated receptor α. Bezafibrate (BF), gemfibrozil (GF), and the newer agents, fenofibrate (FF) and fenofibric acid (FA), are members of this family. These drugs reduce TG levels by 30-50% and increase HDL-C concentration by 2-20%. Furthermore, fibrates have been associated with improvement of the distribution of LDL and HDL subclasses and other markers of the atherosclerotic process.[28-35]

The administration of BF and GF as monotherapy in patients with T2DM has been proven beneficial in terms of CVD risk reduction.[36,37] In a more recent study, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial,[38] FF 200 mg/day or placebo was given for 5 years in 9,795 patients with T2DM. FF administration did not significantly reduce major coronary heart disease (CHD) events (primary trial outcome; -11%, p=NS). However, FF administration was associated with a significant reduction of total CVD events (-11%, p=0.035) compared with placebo, which was attributed mainly to the reduction of non-fatal myocardial infarctions (NFMI) (-24%, p=0.01) and coronary revascularisations (-21%, p=0.003).[38] It should be noted that significantly more patients in the placebo group were receiving statins during the trial compared with the FF group (17% versus 8%, p<0.0001), a fact that may have obscured the possible beneficial CVD effect of FF.[38]

A meta-analysis of 18 trials with 45,058 participants showed that fibrates resulted in a 10% relative risk reduction for major CVD events (p=0.048) and a 13% risk reduction for coronary events (p<0.0001).[39] Another meta-analysis of six trials examined the effects of fibrates in patients with AD.[40] The administration of fibrates reduced the risk of vascular events by 25% (p<0.001) in 7,389 subjects with high TG levels, by 29% in 5,068 subjects with high TG and low HDL-C levels (p<0.001), and by 16% in 15,303 subjects with low HDL-C (p<0.001). Of note, fibrate therapy did not reduce the risk of vascular events in 9,872 subjects without high TG and low HDL-C (p=0.53).[40] The beneficial effects of fibrates in reducing TG levels and increasing HDL-C concentration seem promising targets for the reduction of CVD risk in patients with MD. These beneficial effects, as well the effects of fibrates on inflammatory markers and the distribution of LDL subclasses, make these drugs candidates for use in combination with a statin aiming to reduce the residual CVD risk in patients with T2DM.

STATIN-FIBRATE COMBINATION THERAPY IN PATIENTS WITH T2DM

Effects on Metabolic Variables

Several clinical trials have shown beneficial effects on the lipid profile in patients with T2DM when these individuals are treated with a statin/fibrate combination.[41-44] The larger trial examining the statin-fibrate combination is the ACCORD Lipid study,[11] which randomised 5,518 patients with T2DM in FF or placebo on top of simvastatin (SV). The combination of FF with SV led to significantly greater improvements of total cholesterol (-13.5%), TG (-22.2%), and HDL-C (+8.4%) levels compared with placebo/SV (-12.5%, -8.7%, and +6%, respectively, all p<0.05). However, the improvement in LDL-C levels did not differ between combination (-18.9%) and placebo groups (-20.9%, p=0.16).[11] The effects of SV/FF combination on postprandial lipid profile was investigated in a subgroup of 139 subjects from the ACCORD Lipid trial[45] who received an oral fat load. The combination treatment significantly reduced the TG incremental area under the curve compared with the placebo + SV group (p=0.008). Furthermore, in patients with increased fasting TG levels, a significant reduction of the atherogenic apolipoprotein B-48 (ApoB48) was observed (p=0.008).[45] Another double-blind study of 196 patients with newly onset, untreated T2DM, and MD (treatment groups: SV 40 mg/day, FF 200 mg/day, SV/FF combination, or placebo) showed that the combined therapy produced greater improvements in the levels of TG and ApoA-I compared with SV monotherapy, and in the concentration of total cholesterol, LDL-C and ApoB levels compared with FF monotherapy (all p<0.05).[46] Furthermore, the combination therapy

significantly improved inflammatory markers, such as hs-CRP, interferon-gamma, tumour necrosis factor alpha, and lymphocyte release of interleukin-2, compared with monotherapy groups.[46]

The newer FA has also shown beneficial effects in terms of lipid profile when combined with a statin.[47] A pooled subgroup analysis of three randomised, controlled, double-blind trials that included 586 patients with MD and T2DM showed that the combination of FA and moderate-dose statin significantly improved the concentration of TG (-43.4%) and HDL-C (+16.3%) compared with moderate-dose statin monotherapy (-24.2% and +8.7%, respectively), as well as LDL-C (-32.6%) compared with FA monotherapy (-5.3%, p<0.05 for all comparisons).[48] The combination of FA and low-dose statin produced similar results compared with monotherapy with low-dose statin or FA. Of note, the combination of FA with low or moderate-dose statin led to a 5-fold higher percentage of patients with simultaneously optimal levels of LDL-C, TG, non-HDL-C, and HDL-C.[48] It should be mentioned that GF should not be given combined with a statin due to the increased risk of rhabdomyolysis. The other fibrates appear safe when combined with a statin.

Effects on T2DM-Related Complications

The addition of fibrates to statin treatment results in the improvement of lipid profile and reduction of estimated cardiovascular risk.[41] The effect of statin/fibrate combination on hard CVD endpoints was investigated in the ACCORD Lipid trial.[45] As mentioned above, the addition of FF to SV resulted in significant reductions of total cholesterol, TG, and HDL-C levels (all p<0.05) compared with the placebo/SV group. However, the observed reduction in LDL-C levels was similar between groups (p=0.16).[11] The annual rate of the primary outcome (first occurrence of a major CVD event, i.e. NFMI, nonfatal stroke, or death from CVD causes) was 2.2% in the FF group and 2.4% in the placebo group (HR for the FF group 0.92, 95% CI 0.79-1.08; p=0.32). Similarly, no significant differences were seen in secondary outcomes (HRs ranged from 0.82-1.17, p≥0.10 for all comparisons).[11] Furthermore, the annual rate of death from all causes was 1.5% with the combination of FF/SV, and 1.6% with the placebo/SV (HR 0.91, 95% CI 0.75-1.10, p=0.33).[11]

These results do not support the administration of FF/SV combination therapy in patients with T2DM. However, the study has received some criticism based on the open-label administration of SV and the fact that the enrolment of patients did not achieve the predetermined power. Furthermore, in a pre-specified analysis in the subgroup of patients with high baseline TG (≥204 mg/dl) and low baseline HDL-C (≤34 mg/dl) levels, a significant reduction in CVD events was observed in the FF + SV group compared with the placebo group (-28%, p<0.05).[11] This result implies that the addition of a fibrate to statin treatment is beneficial in patients with AD. Notably, a similar analysis of patients with marked dyslipidaemia in the FIELD trial showed a significant reduction of CVD events with FF compared with placebo (-27% relative risk reduction, p=0.005).[49]

Microvascular complications are another major factor for the increased morbidity of T2DM patients. Diabetic retinopathy is one of the most devastating disabilities. The addition of FF to SV in the ACCORD Eye Study[50] (n=2,856) reduced the rate of progression of diabetic retinopathy compared with the administration of placebo/SV (-6.5% versus -10.2%, OR 0.60, p=0.006). The magnitude of this effect was greater than the benefit observed with the intensive glycaemic treatment when compared with the standard glycaemic treatment in the ACCORD study (OR 0.67). Additionally, FF in the FIELD trial[51] significantly reduced the rate of first laser treatment for retinopathy compared with the placebo group (3.4% versus 4.9%, HR 0.69, p=0.0002). These effects support the use of FF in patients with T2DM and early retinopathy. Indeed, the FF manufacturer has recently announced that it secured an indication by the Australian Therapeutic Goods Administration for the use of the drug to slow the progression of diabetic retinopathy.[52]

Patients treated with FF usually experience an increase in serum creatinine levels, which has been attributed to several mechanisms.[53-56] Generally, the increase in serum creatinine levels during FF treatment is reversible. In the ACCORD Lipid study,[11] serum creatinine levels increased from 0.93 to 1.10 mg/dl in the FF group during the first year, and from 0.93 to 1.04 mg/dl in the placebo group. Despite these increases, no significant difference in the occurrence of end-stage renal disease and the need for dialysis was observed between treatment groups. Moreover, the incidence of microalbuminuria (38.2% versus 41.6%, p=0.01) and macroalbuminuria (10.5% versus 12.3%, p=0.04) was lower in patients treated with FF/SV compared with placebo/

SV, an effect that seems promising for the prevention of diabetic nephropathy.[11] Furthermore, there is evidence that long-term FF treatment is protective against pathological changes in diabetic nephropathy, and slows the progression of renal function impairment.[57, 58]

CONCLUSION

Patients with T2DM have a high risk for CVD. The administration of statins aiming to decrease LDL-C levels is the cornerstone of therapy in patients with T2DM. However, many patients with T2DM have residual CVD risk despite treatment with statins, which is mainly attributed to the presence of MD. The addition of a fibrate to statin treatment in T2DM patients with MD seems promising in terms of lipid profile improvement and CVD risk reduction. However, aside from the prespecified analysis from the ACCORD study, there are no clinical trials yet to show that fibrate/statin combination therapy has better results on CVD risk than statin alone in patients with the atherogenic phenotype.

In conclusion, clinicians could use a fibrate combined with a statin in T2DM patients at high CVD risk and MD, since this combination leads to an overall improvement of the lipidaemic profile. However, we live in the era of evidence-based medicine and clinicians should discuss with their patients that the effects of this combination on CVD events has not been studied in specifically designed studies. Medical associations should increase pressure on drug companies to design one or more future trials focusing on the role of fibrate-statin combination in T2DM patients with MD.

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PATHOPHYSIOLOGY AND IMAGING TECHNIQUES OF DIABETIC HEART DISEASE

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ABSTRACT

Diabetic patients are at an increased risk of developing heart failure. The aetiology of diabetic heart disease is likely to be multifactorial, ranging from altered myocardial metabolism, increased interstitial fibrosis, endothelial dysfunction, microvascular disease, and coronary atherosclerosis. These factors act synergistically with resultant myocardial systolic and diastolic dysfunction. The aim of the present review is to illustrate the role of multimodality cardiac imaging such as echocardiography, nuclear imaging, computed tomography, and magnetic resonance imaging in providing insights into these pathological processes, and to quantify the extent of myocardial diastolic and systolic dysfunction.

Keywords: Diabetes mellitus, heart disease, echocardiography, magnetic resonance imaging, computed tomography.

INTRODUCTION

Diabetes mellitus is an increasingly common disease worldwide. Recent estimates suggest its incidence has more than doubled over the last three decades and that there are currently 347 million people living with the condition.[1] The risk of cardiovascular disease (CVD) has increased 2 to 3-fold in this population[2,3] and half of all diabetic patients will die from CVD.[4] In particular, heart failure is twice as common in diabetic men and 5-times in diabetic women as age-matched controls.[2] Even after correction for the presence of other risk factors including obesity, hyperlipidaemia, hypertension, and coronary artery disease (CAD), diabetic patients remain at an increased risk of developing heart failure.[2,5,6] Diabetic heart disease (DHD) is defined as myocardial dysfunction (MD) that occurs independently of CAD and hypertension. This dysfunction may be subclinical but patients are at high risk of developing clinical heart failure.[5] Furthermore, patients have a higher risk of developing heart failure secondary to traditional myocardial insults such as hypertension and CAD.[7] MD in diabetics is a consequence of multiple pathological processes, including altered metabolism, interstitial fibrosis, endothelial dysfunction (ED), autonomic dysfunction (AD), microvascular disease (MVD), and coronary atherosclerosis (AS). This review will outline how multimodality imaging can demonstrate each of these pathological processes, and their effects on myocardial diastolic and systolic function.

AETIOLOGY OF DHD

The metabolic disturbances that cause MD in DHD are not completely understood, but abnormal glucose supply, utilisation, and abnormalities of free fatty acid (FFA) metabolism contribute significantly.[8] Glucose metabolism is disrupted via multiple pathways in diabetes, resulting in reduced myocardial contractile function.[9] Hyperglycaemia and insulin resistance also increase myocardial oxidative stress.[10] Circulating FFA levels are elevated in diabetes and obesity, due to increased nutritional fatty acid intake and lipolysis.[11] This leads to increased uptake and β-oxidation in the heart.[11-13]

In a process called myocardial steatosis (MS), excess fatty acids are stored as triglycerides (TGs) within myocytes. However, toxic intermediates, generated when FFA uptake by the cardiomyocytes exceeds its oxidative capacity, disrupt normal cellular signalling, and alter myocyte structure and function.[11-14] The increased FFA oxidation also produces reactive oxygen species (ROS), impairing mitochondrial coupling and decreasing adenosine triphosphate (ATP) production. As such, diabetic patients develop impaired cardiac energetics, as reflected by reduced phosphocreatine/ATP ratio, independent of the duration of diabetes and coronary microvascular function.[15,16] This process, known as lipotoxicity, eventually leads to cellular apoptosis and replacement fibrosis.

Extracellular structural changes, such as interstitial fibrosis, also occur in the diabetic heart.[17,18] These fibrotic changes are due to increased deposition of collagen and advanced glycation end-products, as well as cell necrosis.[8,19,20] The increased interstitial fibrosis leads to extracellular matrix expansion and is associated with myocardial contractile and vasomotor dysfunctions, arrhythmias, and increased mortality.[21] Angiotensin has emerged as a likely driver of myocardial cellular necrosis.[22-24] Negative regulators of the renin-angiotensin system have been shown to reduce cardiac hypertrophy, lipotoxicity, and inflammation in rat models of DHD, resulting in the reversal of diastolic dysfunction (DD).[25] The metabolic abnormalities that characterise diabetes also lead to increased mitochondrial superoxide generation, reduced endothelial nitric oxide production, increased endothelin synthesis, and the production of prothrombotic factors.[26,27] This disruption of vascular homeostasis causes endothelial dysfunction and MVD Additionally, these processes are the precursor for coronary AS,[26] and together they impair myocardial function.

Altered Metabolism

In a process synonymous with 'fatty liver disease', current evidence suggests altered FFA metabolism in the pathogenesis of DHD. It is generally accepted that intracellular TGs are probably inert but are reflective of increased intracellular concentrations of toxic fatty acid intermediates. Intramyocardial TGs can be quantified by hydrogen-1 magnetic resonance spectroscopy (^{1}H-MRS) (Figure 1).[28] A volume of interest triggered to both cardiac and respiratory motions is placed in the interventricular septum. A typical cardiac ^{1}H-MRS spectrum displays signals arising from water, creatine, choline, and TG. Using dedicated curve fitting software, signal amplitudes from intracellular TGs and water can be quantified and expressed as TG/water ratio.

Studies have correlated intramyocardial TG levels with left ventricular (LV) function.[28-33] van der Meer and co-workers[32] demonstrated that intramyocardial TG content increases with ageing and is inversely correlated with the age-related decline in myocardial function. Similarly, diabetic and obese patients have significantly higher intramyocardial TG levels when compared to controls, and this is associated with MD.[30,31,34] Animal models showing direct toxic effects of fatty acid intermediates on the myocardium provide further evidence for lipotoxicity.[35,36] Importantly, studies have demonstrated that weight loss is associated with a concomitant reduction in intramyocardial TG levels and improvement in LV function.[29,37] However, the effectiveness of pharmacological therapy for MS remains unclear, with studies showing conflicting results.[33,38] Diabetic patients can also develop impaired cardiac energetics due to increased ROS production from increased FFA production.[15,16] This results in reduced phosphocreatine/ATP ratio compared to normal controls as quantified by phosphorus-31 MRS (^{31}P-MRS).[16] Similar to ^{1}H-MRS, pharmacological intervention studies to date failed to demonstrate changes in cardiac energetics by ^{31}P -MRS despite improvements in cardiac function.[33]

Interstitial Fibrosis

Histological studies of diabetic hearts without significant CAD demonstrated increased collagen deposition in the perivascular and interstitial regions.[18,39,40] These structural changes lead to increased LV stiffness, impaired systolic and diastolic functions, and the development of clinical heart failure. Currently, both echocardiography and magnetic resonance imaging (MRI) can non-invasively quantify the burden of interstitial fibrosis. Echocardiographic integrated backscatter analysis was the first imaging modality to non-invasively quantify the burden of myocardial fibrosis (Figure 2, left panel). From the parasternal long-axis view, volumes of interest are placed in the anteroseptal and inferolateral walls at end-diastole, and the value of myocardial integrated backscatter is corrected for the pericardial integrated backscatter, thereby providing a calibrated backscatter value. Picano and co-workers[41] demonstrated that there was

a linear correlation between calibrated integrated backscatter and the burden of fibrosis on histology. Other studies have demonstrated increased calibrated integrated backscatter in diabetic patients compared to controls.[42,43]

MRI can quantify the burden of interstitial fibrosis using T1 mapping sequences and gadolinium-based contrast agents. Normally, gadolinium-based contrasts accumulate within myocardial fibrous tissues due to the absence of viable myocytes.[44] Iles and co-workers[45] histologically validated and demonstrated an inverse linear relationship between global contrast-enhanced myocardial T1 time and the burden of interstitial fibrosis (Figure 2, right panel). Ng and co-workers[46] were first to demonstrate that diabetic patients had significantly shorter global contrast-enhanced myocardial T1 time compared to normal controls ($p<0.001$), suggesting an increased burden of interstitial fibrosis. Furthermore, there was an independent correlation between global contrast-enhanced myocardial T1 time and myocardial function.[46]

CARDIAC AD

Diabetic AD is a well-known complication of diabetes. Its pathophysiology is likely to be multifactorial, involving metabolic alterations, neurohormonal growth factor deficiency, microvascular dysfunction, and autoimmune nerve damage.[47]

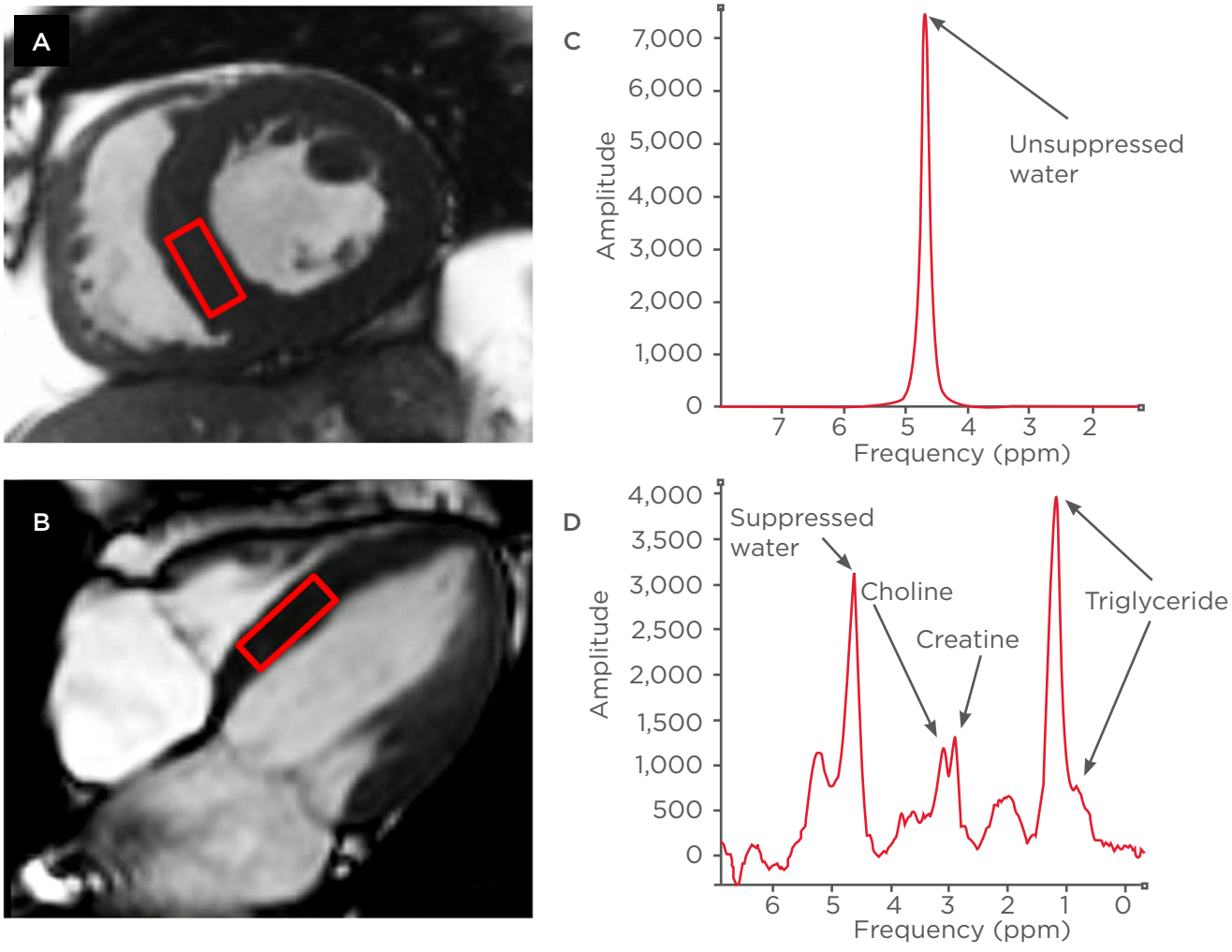

Figure 1: Example of hydrogen-1 magnetic resonance spectroscopy acquisition from a patient.
Panel A and B: short axis and 4-chamber view with the volume of interest placed in the interventricular septum; Panel C: unsuppressed spectrum showing the water peak; Panel D: water-suppressed spectrum showing peaks from choline, creatine, and triglyceride. Intramyocardial triglyceride (IMT) is quantified by summing the amplitudes of lipid resonances at 0.9 and 1.3 ppm, whilst water peaks at 4.7 ppm. IMT content relative to water is then calculated and expressed as a percentage based on: (signal amplitude of triglyceride)/(signal amplitude of water) x100.

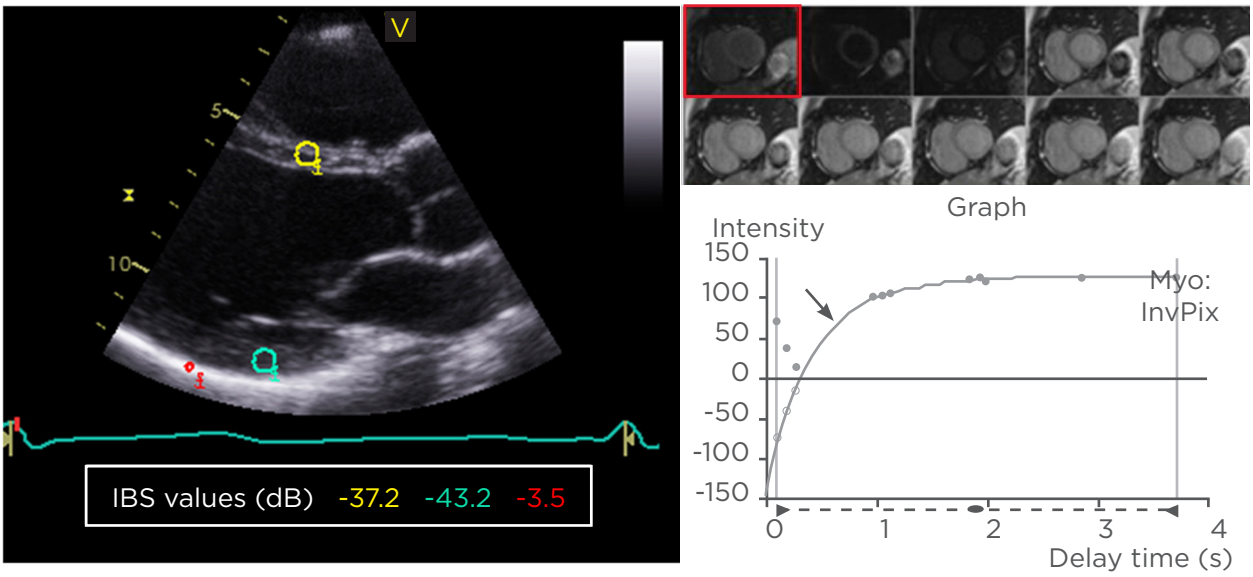

Figure 2: Echocardiographic quantification of myocardial fibrosis.
Left panel: using calibrated integrated backscatter (IBS). From the parasternal long-axis view, the IBS of the myocardium is measured at the anteroseptal and inferolateral walls and corrected for the pericardial IBS value. Therefore, calibrated IBS is calculated as the average IBS of the anteroseptal and inferolateral myocardium minus the pericardium. A less negative value calibrated IBS value indicates more interstitial fibrosis. Right panel: magnetic resonance imaging example of myocardial fibrosis quantification by T1 mapping. Left ventricular endocardial and epicardial borders were outlined for all images (top right panel). The myocardial signal intensities (y-axis) were plotted against the inversion time (x-axis) (bottom right panel). Finally, the global contrast-enhanced myocardial T1 time is calculated by the software which performed curve-fitting of the data points to an exponential recovery curve (arrow) representing the recovery of myocardial longitudinal magnetisation. Therefore, a short global contrast-enhanced myocardial T1 time indicates a higher burden of interstitial fibrosis due to a greater concentration of gadolinium within the fibrous tissues, and vice versa.

Cardiac autonomic neuropathy (CAN) is associated with increased risk of silent myocardial infarction (MI) and sudden cardiac death.[48] Clinical manifestations of CAN include resting tachycardia, postural hypotension without an appropriate reflex increase in heart rate, and exercise intolerance due to blunting of cardiac output in response to exercise.[49,50] Single photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging are available for the assessment of cardiac sympathetic adrenergic innervation and activation.[51-53]

Currently, sympathetic innervation is most commonly assessed using 123-iodine metaiodobenzylguanidine (^{123}I-MIBG), a norepinephrine analogue which is taken up and accumulated in the presynaptic nerve terminals.[54-56] Planar and SPECT images are acquired 10-20 minutes (early) or 3-4 hours (late) after ^{123}I-MIBG administration. From the planar images, semi-quantitative measurements such as heart-to-mediastinum (H/M) ratio and cardiac washout rate are used to evaluate global sympathetic innervation. SPECT images are used to assess regional abnormalities in sympathetic innervation. Previous studies demonstrated reduced ^{123}I-MIBG uptake in diabetic patients,[57] and the presence of CAN and reduced H/M ratio on delayed ^{123}I-MIBG imaging were independently associated with increased all-cause mortality.[58] Unlike SPECT, PET allows absolute quantification of the myocardial sympathetic innervation. Previous study demonstrated that carbon-11 meta-hydroxyephedrine PET imaging can detect regional differences in sympathetic innervations in diabetic patients compared to healthy controls.[52] In addition, patients with more severe autonomic neuropathy had significantly more extensive regional sympathetic denervation.[52] Importantly, defects in sympathetic innervation can regress or progress in diabetic subjects with good and poor glycaemic control respectively.[59]

MVD AND ED

ED and MVD can be evaluated directly using various imaging techniques including flow-mediated dilatation (FMD), myocardial contrast echocardiography, nuclear SPECT perfusion imaging, PET imaging, and MRI perfusion imaging. Endothelial function can be assessed non-invasively by FMD of the brachial artery (Figure 3, top panel). The brachial artery diameter is measured with ultrasound at baseline and at maximal vasodilation achieved during reactive hyperaemia. A blood pressure cuff is used to occlude the distal brachial artery and, when it is deflated, the increased flow causes endothelium-dependent dilatation. FMD is expressed as the percentage change relative to the baseline diameter. The related technique of low-flow-mediated constriction can be used to assess vascular tone at rest.[60] Impaired FMD in the brachial artery has been shown to correlate with coronary artery ED[61] but clinical applications for FMD testing are still emerging.[60,62] The technique has been used to demonstrate ED in patients at risk of AS before there is anatomical evidence of plaque formation.[63] In diabetic patients without obstructive CAD, Djaberi and co-workers[64] demonstrated that impaired FMD is associated with abnormal myocardial perfusion (MP).

Myocardial contrast echocardiography can be used to detect microangiopathy by evaluating MP and blood flow.[65,66] Microbubble contrast agents have similar rheology to red blood cells, so they stay within the intravascular compartment. These microbubbles resonate and appear bright on echocardiography when imaged using a low mechanical index, but are destroyed if a high mechanical index ultrasound pulse is transmitted. After a high mechanical index pulse is used to destroy microbubbles within the myocardium, the rate of replenishment is dependent upon the presence of intact microvasculature and myocardial blood flow rate. The intensity at which the contrast effects plateaus is dependent on myocardial blood volume. Therefore, areas with impaired perfusion appear dark and patchy. Moir and colleagues[67] used stress myocardial contrast echocardiography to demonstrate reduced myocardial blood flow reserve in diabetic patients in the absence of obstructive CAD.

MP imaging by thallium-201 or technetium-99m sestamibi SPECT is a widely used and well validated tool for evaluating cardiac function and MP (Figure 3, bottom panel). MP defects with stress may be caused by obstructive epicardial CAD or ED of the coronary vasculature, leading to an insufficient vasomotor response and relative hypoperfusion.[64,68] MP defects can be identified in 20-40% of asymptomatic diabetic patients.[69,70] Although prognostic for future cardiac events,[70-72] it may be reversible. The Detection of Ischemia in Asymptomatic Diabetics study[69] demonstrated that inducible myocardial ischaemia in asymptomatic diabetic patients resolved with 3 years of medical treatment (including aspirin, statins, and angiotensin converting enzyme inhibitors) in almost 80% of patients. This is likely due to both improvements in ED and stabilisation of atherosclerotic plaques.

PET has superior sensitivity and specificity compared to SPECT for the assessment of MP to detect underlying CAD.[73,74] It can also provide quantitative measures of myocardial blood flow and coronary flow reserve.[75,76] PET has been used to demonstrate ED in diabetic patients without epicardial CAD.[77-79] Despite these benefits, cardiac PET is still not widely used in clinical practice. MRI MP imaging employs a gadolinium-based contrast agent that can be detected on T1-weighted images as it travels through the cardiovascular (CV) system and into the myocardium. This allows quantification of MP at rest and during maximal hyperaemia induced by a pharmacological stressor. There is limited data on the use of MRI and MP imaging in diabetic patients. A small study found Type 1 diabetic patients with autonomic neuropathy had a significantly lower MP index than diabetic patients without autonomic neuropathy and controls.[80]

CORONARY AS

Some authors consider the diagnosis of diabetes equivalent to pre-existing CAD in terms of predicting future CV events and prognosis.[81,82] Although the effects of CAD on myocardial function do not generally fall within the definition of DHD, they complicate its assessment. Diabetic patients have high rates of silent MI and asymptomatic myocardial ischaemia. Silent MI in diabetic patients was recognised >40 years ago in the Framingham Heart Study.[83] More recently, evaluation of the UK Prospective Diabetes Study showed 326 of 1,967 patients (16.6%) had electrocardiographic evidence of silent MI at baseline.[58] Silent MI in diabetic patients is independently associated with an increased all-cause mortality. In an observational study of 1,899 asymptomatic diabetic patients

without prior CAD or MI, 60% had abnormal stress myocardial contrast echocardiography, and of these, 65% had CAD confirmed on angiography.[84] In that study, the presence of two or more other CV risk factors did not result in more abnormal tests or a higher percentage of confirmed CAD; however, CAD was more diffuse and severe in patients with additional risk factors.

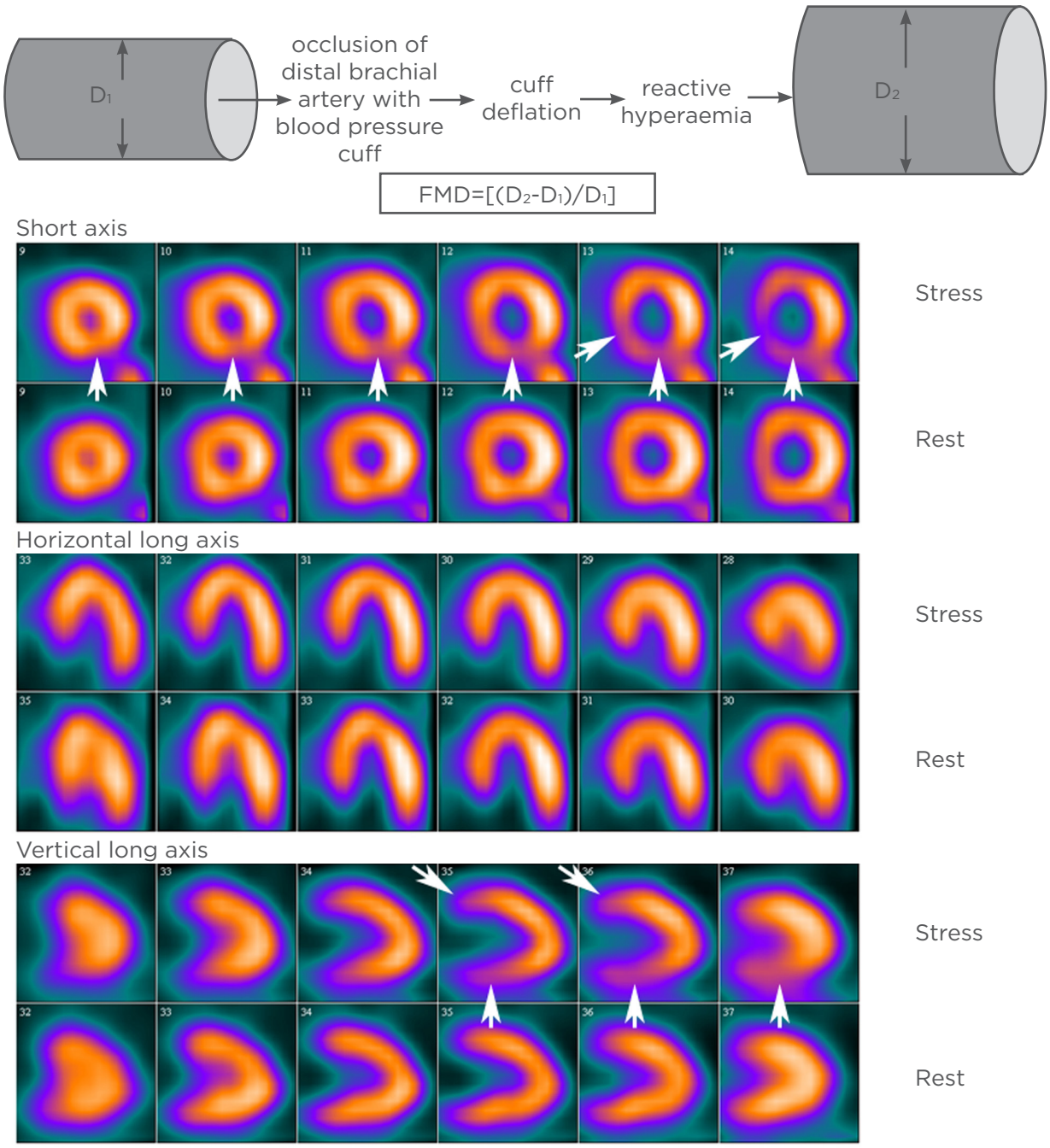

Figure 3: Assessment of flow mediated dilatation (top panel) and myocardial perfusion using gated single photon emission computed tomography at rest and after adenosine stress (bottom panel).
Top: the brachial artery diameter distal to the elbow is measured using ultrasonography (D1). Ischaemia is induced by inflating a distal blood pressure cuff to at least 200 mmHg for 5 minutes. After cuff deflation, the brachial artery diameter is measured every 30 seconds for 5 minutes and the widest diameter recorded is considered the maximal vasodilation achieved during reactive hyperaemia (D2). Bottom: resting images and stress images in the short axis, horizontal, and vertical long axes are depicted. In the current example, no persistent perfusion defects were observed. Reversible perfusion defects were observed in the inferior, inferoseptal, anterior, and anteroseptal regions (arrows).
Permission obtained from Ng et al.[108]

Traditionally, invasive coronary angiography (and its complementary imaging techniques, including intravascular ultrasound, virtual histology intravascular ultrasound, and optical coherence tomography) allowed direct visualisation of coronary AS. However, increasing availability and improved quality of cardiac computed tomography (CT) has led to widespread adoption of this technique to evaluate coronary AS. Coronary artery calcium (CAC) scoring detects calcium present within atherosclerotic plaques. As a marker of AS, CAC scores predict cardiac event risks in both diabetic and non-diabetic patients.[85] Anand and co-workers[86] have demonstrated that in diabetic patients, CAC scores of <10 were associated with very low clinical cardiac event rates and no perfusion abnormalities on MP imaging. CAC score is superior to established CV risk factor models for predicting silent myocardial ischaemia and short-term outcomes.

Cardiac CT angiography (CCTA) can provide detailed information on coronary artery anatomy, and assess both coronary artery atheroma and luminal stenosis (Figure 4). Advances in cardiac CT scanners have led to significant improvements in the accuracy of CCTA for the detection of coronary artery stenosis. The technique is now highly sensitive in detecting AS and has a negative predictive value that approaches 100%. Furthermore, CCTA allows detection of early non-obstructive atherosclerotic plaques without calcium. Compared to non-diabetic patients, CCTA has shown that diabetic patients have higher coronary artery atheroma burden and more extensive coronary artery stenoses.[87,88] All types of plaques (soft, calcified, and mixed) were more common in diabetic patients independent of other CV risk factors.

MD, DD, AND SD

Whether DHD is clinically evident or not, reliable and consistent methods of demonstrating LV DD and systolic dysfunction (SD) are needed to diagnose and assess progression of the disease. Echocardiographic techniques, including tissue Doppler imaging (TDI) and speckle tracking strain/strain rate, remain most useful for this purpose. Similarly, MRI tagging also permits quantification of myocardial strain/strain rate. However, due to the need for complicated image post-processing compared to the ease of echocardiographic speckle tracking strain/strain rate, it has failed to gain significant traction clinically and in research.

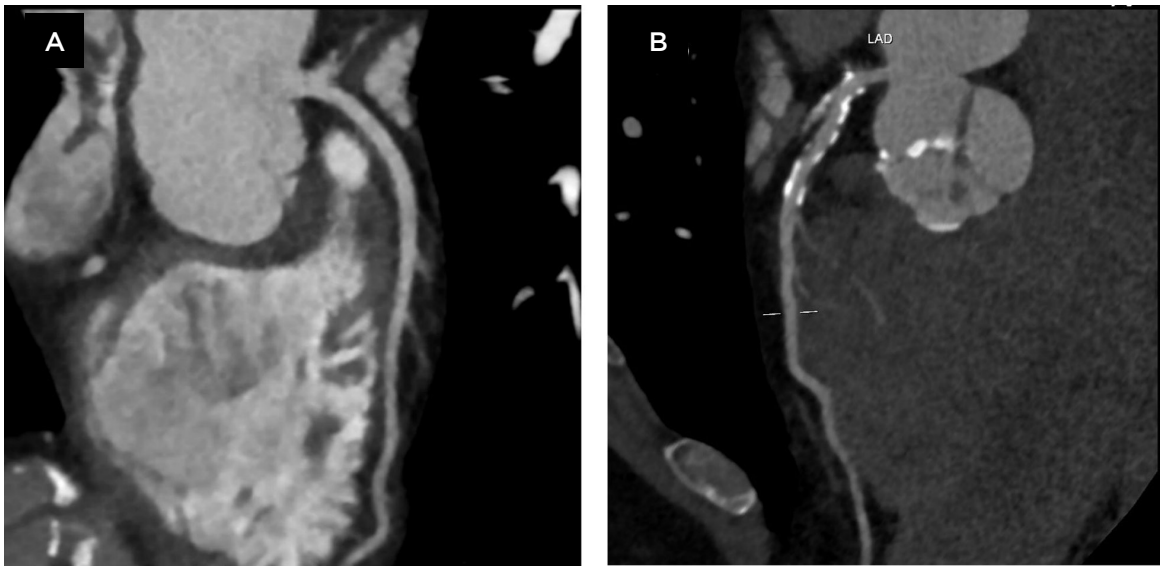

Figure 4: Evaluation of coronary artery disease with cardiac computed tomography angiography in diabetic patients.
A) Curved multiplanar reformation (cMPR) of a left anterior descending artery with no evidence of atherosclerosis. B) cMPR of the left anterior descending artery in a diabetic patient with both calcified and soft plaque in the proximal portion of the vessel.
LAD: left anterior descending artery.

On echocardiography, transmitral inflow patterns and TDI of the peak early diastolic early velocities are used to categorise diastolic function.[89] Interpretation of the transmitral inflow pattern in isolation is limited by its load and age dependency and may be impossible in cases of mitral valve disease. TDI myocardial velocities may be influenced by passive translational motion and tethering effects from surrounding myocardial tissue. Myocardial strain and strain rate imaging (obtained using TDI or speckle tracking) overcome these limitations by providing site-specific quantification of active myocardial deformation.[90-92] Speckle tracking strain is also angle independent. Wang and colleagues[93] have demonstrated in animal models that global strain rate during the isovolumic relaxation time strongly correlates with LV relaxation. The prevalence of DD amongst diabetic patients depends not only on the population studied, but also the sensitivity of the imaging modality employed. Amongst 86 young normotensive diabetics with adequate blood glucose control and no clinically detectable ischaemic heart disease, the prevalence of DD was 47% based on transmitral filling pattern alone[94] but rose to 75% when TDI was also employed.[95] Other groups have reported lower incidence, even when using all available echo parameters.[96,97] The incremental value of using strain and strain rate imaging in the assessment of DD remains unclear.[90]

DHD also affects systolic function. This is particularly evident when sensitive markers of systolic function are used for assessment. Left ventricular ejection fraction (LVEF) has traditionally been the clinical standard of assessing global LV systolic function. However, tissue velocity, strain, and strain rate imaging may be used as more sensitive methods of detecting LV SD. Tissue velocity measurements have been shown to correlate with radionuclide ventriculography in the assessment of global LV function.[98] Strain and strain rate have also been shown to correlate with LVEF by 2D echocardiogram[99] and invasive measures of LV contractility.[100] The sensitivity of tissue velocity, strain, and strain rate imaging makes them useful tools in the assessment of subclinical MD[90-92] and they have been used extensively for this purpose in DHD.[43,101-103] It has been demonstrated that strain and strain rate are significantly reduced in diabetic patients with normal LVEF who have no LV hypertrophy or CAD.[43] Strain and strain rate imaging are also particularly useful to compare within the same individual when assessing response to treatment.[104,105] The site specificity of strain imaging has also allowed regional differences in diabetic MD to be demonstrated, with longitudinal function being impaired early in DHD whilst there is relative preservation of radial function.[101-103,106] These regional variations may account for the initial preservation of LVEF in DHD. Structure and function of the right ventricle may also be affected by DHD. In diabetic patients with satisfactory blood glucose control and without ischaemic heart disease, cardiac MRI has demonstrated right ventricular remodelling and significant impairment of diastolic and systolic function compared to controls.[107]

CONCLUSION

DHD is a significant cause of increased morbidity and mortality. Our understanding of the underlying pathological processes is steadily growing, particularly through the use of multimodality imaging. Multimodality imaging can be used to define and assess both DD and SD in DHD.

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EXERCISE: A POWERFUL TOOL TO MANAGE TYPE 2 DIABETES IN THE AGEING POPULATION

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ABSTRACT

The aim of this paper is to highlight the evidence on the interrelationships between exercise and Type 2 diabetes mellitus (T2DM) in the ageing population. The evidence addressed in the specific literature is presented in three domains: aerobic exercise, resistance exercise, and combined aerobic and resistance exercise. The effects of aerobic exercise are well established, but in the ageing population resistance training could be considered a superior intervention to help glycaemic control; the effects of resistance training on insulin sensitivity are attributable to an increase in muscle mass. Thus, although with resistance training body weight does not change much, the main effect of resistance training on body composition of the elderly should be a shift from fat to muscle mass, and the maintenance of a large muscle mass may reduce obesity related risk factors. Fewer studies have investigated the effects of combined resistance and aerobic training, but from the available evidences it would appear that combined exercise training seems to offer additional benefits if compared with aerobic training alone and resistance training alone.

Keywords: Diabetes, ageing, resistance exercice, aerobic exercise.

INTRODUCTION

In Western society, both medical and social institutions are paying increased attention to the health and well-being of the elderly and the impact that their growing numbers will have on society in future years. Both Europe and the US are facing major changes in population age-balance which is likely to reshape its demographic structure over the next 20 years. In fact, by the year 2050, one-tenth of the world's population will be over 65, and people over 80 are the fastest growing segment of the population, both in the US[1] and in Europe, where the population is projected to reach 517 million in the year 2060. Nearly one-third of the citizens will then be aged 65 or over.[2] According to the importance of this population segment, in recent years a significant amount of new evidence has accumulated regarding the benefits of regular exercise and physical activity for older adults. Among this, there is now a growing body of knowledge supporting the prescription of exercise and physical activity for older adults with chronic diseases and disabilities that started since the publication of the American College of Sports Medicine (ACSM) guidelines on exercise and physical activity for older adults.[3]

Amongst the elderly population, Type 2 diabetes mellitus (T2DM) is a growing problem; this is a metabolic disorder that results in hyperglycaemia due to the body being unable to produce enough insulin or to insulin resistance, and a larger proportion of newly diagnosed diabetics are elderly subjects. Physical activity and exercise are fundamental in preventing and treating T2DM, and since the publication of the American Diabetes Association (ADA) consensus statement,[4] it was highlighted that health benefits occur according to a dose/response relationship: to maximise benefits, diabetic patients should partake in physical activity/exercise programmes that far exceed the minimum level of physical activity recommendations (e.g. 150 minutes per week of moderate intensity physical activity); in fact, additional benefits occur as the amount of physical activity increases through

higher intensity, greater frequency, and/or longer duration. On the other hand, the ACSM guidelines[3] stress the fact that if older adults cannot do 150 minutes of moderate-intensity aerobic activity per week because of chronic conditions, they should be as physically active as their abilities and conditions allow. The aim of this paper is to critically review the recent literature on the effects of exercise and T2DM, with a specific focus on the ageing population.

Structural and Functional Decline with Ageing

Ageing is associated with a number of modifications that encompass the physical, physiological, and psychological domains. We will focus on the physiological domain, considering the age-related modifications that have a relationship with T2DM: specifically, the loss of lean body mass, particularly skeletal muscle, and the progressive increase of body fat mass and those modifications that are due to T2DM, represented by motor nerve impairments. The fact that muscle mass decreases with age has long been known, and this age-related loss of muscle mass appears to be fairly consistent - at a rate of approximately 1–2% per year - over the age of 50 years.[5] This decline in muscle mass occurs in both sedentary and active ageing adults, whilst in healthy young adults, no net change occurs in skeletal muscle due to balance in skeletal muscle protein synthesis and degradation. This age-related reduction in muscle mass and strength is accompanied by a reduction in motor unit number[6,7] by atrophy of muscle fibres, especially the Type 2a, and an associated decline in protein synthesis, particularly myosin heavy chains.[8]

The loss of muscle mass with ageing is clinically important for a number or reasons: it leads to diminished strength and exercise capacity, consequently producing a decline in function, but more importantly in the context of this paper, it is related to a decrease in glucose uptake due to a diminished capacity of glucose storage and an impairment on insulin signalling. Due to the metabolic consequences of reduced muscle mass, it is understood that normal ageing and/or decreased physical activity may lead to a higher prevalence of T2DM. Thus, the greater an individual's total muscle mass, the lower the person's risk of having insulin resistance, the major precursor of T2DM.[9] Biological ageing is also associated with a progressive increase in body fat mass and a loss of lean body mass, particularly skeletal muscle. Visceral fat increases by >300% between the ages of 25 and 65 years, increasing the risk for the development of both T2DM and cardiovascular disease (CVD) in adults with normal body mass index.[10] The distribution of excess fat in the abdominal region modifies the health risk profile, whilst the excess adiposity in the periphery does not appear to increase CVDs.[11]

The above-mentioned modifications have an important role in the progression of T2DM, but they are basically age-related changes in body composition; however, there are also some physiological modifications that could be determined by diabetes itself, specifically the reduced muscle strength associated not only to decreased muscle mass but to muscle quality,[12] leading to diabetic polyneuropathy (DPN). In fact, several reports have shown a relationship between reduced muscle strength and presence and severity of DPN,[13-15] thus suggesting that muscle weakness is a late complication of DPN with motor nerve impairment.[16] It was recently hypothesised that strength deficit with diabetes and the effect of motor nerve impairment are related to contraction speed and to a reduced muscle fibre conduction velocity, and that exercise training may counteract the impairment of neuromuscular function induced by the disease.[17]

THE ROLE OF PHYSICAL ACTIVITY AND EXERCISE

In recent years, the clinical importance of physical activity has become extremely important, both in the general population as well as in the elderly. However, the terms 'physical activity' and 'exercise' denote two different concepts.[18] 'Physical activity' refers to any bodily movement produced by skeletal muscles that results in an expenditure of energy and includes a broad range of occupational, leisure, and daily activities. 'Exercise' refers to planned or structured physical activity. It involves repetitive bodily movements performed to improve or maintain one or more of the components of physical fitness: aerobic capacity (or endurance capacity), muscular strength, muscular endurance, flexibility, and body composition. A considerable amount of literature has been published recently to attempt to identify safe and effective exercise programmes for subjects with T2DM. There are no position stands specifically developed for the elderly with T2DM, but assuming that this is a pathology that is generally developed later in life, even though the onset is now occurring earlier, we can consider as a reference the

latest ACSM-ADA position stand.[19] The most relevant research questions addressed in the recent specific literature, specifically on the benefits of structured exercise and not on those of general physical activity, will be presented in the following sections.

Aerobic Exercise

Numerous studies have been published in the past on the effects of aerobic exercise on patients with T2DM, and some specifically involved elderly subjects. Exercise interventions were generally found to reduce glycosylated haemoglobin (HbA1c). In a meta-analysis reviewing exercise intervention of supervised exercise in T2DM individuals,[20] aerobic exercise was seen to have a significant effect on VO_{2max}, and on glycaemic control, while having little effect on body weight. We could say that the effects of aerobic exercise on HbA1c are well established and supported by solid literature, as reported in the latest ACSM-ADA joint position stand.[19] However, the most interesting question to be addressed is not the effect of aerobic exercise itself, but the effects of exercise intensity: vigorous exercise versus moderate physical activity.

To address this, of particular interest is the research undertaken by Mourier et al.[21] In this study, subjects trained for 8 weeks at high-intensity on a cycle ergometer, combining training at 75% of $VO_{2\ peak}$ (continuous for 45 minutes) and interval training (5 cycles of 2 minutes at 85% of $VO_{2\ peak}$ alternating with 3 minutes at 50% of $VO_{2\ peak}$). The results showed a statistically significant elevated effect versus the sedentary control group on: increase in $VO_{2\ peak}$, decrease of HbA1c %, decrease of subcutaneous and visceral abdominal fat, and increase of mid-tight muscle. The effect of exercise intensity was also evaluated on insulin sensitivity; three randomised controlled trials (RCTs)[22-24] and a review[25] compared the effects on insulin sensitivity of different intensities of aerobic exercise training with the same total energy expenditure on exercise. We can conclude by stating that interventions with more vigorous aerobic exercise programmes resulted in greater reductions in HbA1c, greater increase in VO_{2max}, and greater increase in insulin sensitivity.

Resistance Exercise

Skeletal muscle mass is the primary site of glucose disposal, and skeletal muscle that declines each decade after the age of 30[26] may lead to an increasing risk of developing glucose intolerance and T2DM.[27] As mentioned above, the other significant modification that occurs with age is an increase of body fat, specifically of intra-abdominal fat that, if compared to total body fat, correlates better with systolic and diastolic blood pressure, triglycerides, and decreased insulin sensitivity.[27,28] It is also important to consider that intra-abdominal obesity is a well-recognised risk factor for low-grade inflammation.[29,30] Overall, those modifications generate a state of metabolic dysfunction in the skeletal muscle of elderly subjects with T2DM. However, even though ageing has an influence on skeletal muscle loss and all its related consequences, those can be counteracted by exercise training, and mainly by resistance training. Emerging research suggests that resistance training may influence age-related physiological changes and may impose potent and unique benefits in T2DM.

The early studies offering preliminary evidence for the benefits of resistance training with T2DM patients were published 15 years ago, and generally on ageing patients. Eriksson et al.[31] demonstrated that 3 months of moderate-intensity circuit resistance training significantly decreased HbA1c, a reduction mainly due to improvements in lean body mass, as a strong inverse correlation between HbA1c and muscle cross-sectional area post-training. Dunstan et al.[32] randomised 36 overweight older men and women into a progressive resistance training plus moderate weight loss group or a moderate weight loss group which did not execute any specific exercise training. A greater reduction in HbA1c was observed in the training group compared to weight loss alone in the absence of difference for waist circumference or total fat mass between groups.

Similar findings on older adults were reported by Castaneda et al.[33] who randomised 62 patients into either supervised high-intensity progressive resistance training or a nonexercising control group, showing a mean increase in lean tissue mass of 1.2 kg. Also Baldi et al.[34] in another RCT, reported a significant reduction in HbA1c, fasting glucose, and insulin, as well as a significant increase in fat-free mass. Dunstan et al.,[32] Castanedaet al.,[33] and Baldi et al.[34] agree that increases in skeletal muscle mass are related to decreases in HbA1c, and support the hypothesis that resistance training improves glycaemic control by increasing the skeletal muscle storage of glucose. Ibanez et al.[35] demonstrated that, in elderly subjects, resistance exercise reduces

visceral fat. This was followed by numerous other studies highlighting the fact that resistance training has the power to combat musculoskeletal dysfunction in patients with T2DM and improve the overall metabolic health. Recently, a well written review was published[36] that provided an overview on the biochemical mechanistic effects of resistance training on glucose metabolism and discussed the molecular mechanisms that lead to adaptation in skeletal muscle in response to resistance training.

Combined Aerobic and Resistance Exercise

Whether combined resistance and aerobic training offers a synergistic and incremental effect on glycaemic control in individuals with T2DM is an issue that has been addressed by a number of studies,[37-39] even though not specifically designed to address this question with the elderly. Moreover, whether there is an incremental value to combine aerobic and resistance training, as opposed to aerobic or resistance separately, has been addressed in the studies by Cuff et al.[40] and more recently by Sigal and Church.[41,42] Maiorana et al.[37] investigated the effects of an 8-week circuit training programme, combining aerobic and resistance exercise, compared with a non-training period. Muscular strength, oxygen uptake, and exercise test duration increased with training while HbA1c, fasting blood glucose, skin folds, the percentage of body fat, and the waist-hip ratio significantly decreased.

Balducci et al.[38] demonstrated that even low-to-moderate intensity resistance training, combined with moderate aerobic exercise three times a week for a year significantly improved metabolic and lipid profiles, adiposity, and blood pressure. More specifically, compared with a non-exercising comparison group, HbA1c and fat mass was significantly reduced while fat-free mass increased. Additionally, fasting blood glucose, low-density lipoprotein cholesterol, and total cholesterol were significantly reduced, while high-density lipoprotein cholesterol was increased. The findings of this study demonstrate a global improvement in cardiovascular (CV) risk factors with a marked improvement in HbA1c, and highlight the potential benefits of combined training for individuals with T2DM.

Furthermore, these findings also identify that longer-duration and more moderate resistance training may be as efficient as short-term high-intensity programmes at maintaining glucose homeostasis and reducing CV risk factors. The first well designed RCT that aimed to evaluate whether combined resistance and aerobic training offers an incremental value versus either alone or versus a sedentary control group, was DARE (Diabetes Aerobic and Resistance Exercise)[41] followed by HART-D (Health Benefits of Aerobic and Resistance Training in Individuals With Type 2 Diabetes).[42] The primary outcome of both studies was a change in HbA1c from baseline to termination. The hypothesis of the studies was that the decrease in HbA1c would have been greater in the aerobic and resistance training groups than the control group, and would be even greater in the combined exercise training group than the aerobic or resistance training group.

In the DARE study the absolute change in HbA1c was significantly higher in both the aerobic and the resistance training group compared with the control group. Combined exercise training resulted in an additional change in HbA1c that achieved statistical significance if compared with aerobic training alone and with resistance training alone. In the HART-D study, only the combined group showed a significant decrease of HbA1c. One of the most interesting studies was the IDES (Italian Diabetes and Exercise Study),[43] aimed at assessing the efficacy of an intensive exercise intervention strategy in promoting physical activity and improving HbA1c and other modifiable CV risk factors in patients with T2DM. Sedentary patients with T2DM and metabolic syndrome were enrolled in 22 outpatient diabetes clinics across Italy and randomised by centre, age, and diabetes. Interestingly, the experimental group exercised twice a week (combined aerobic and resistance exercise), whilst the control group received structured exercise counselling, which aimed to improve their activity. This exercise intervention strategy was effective in promoting physical activity and improving HbA1c and CV risk profile. Conversely, counselling alone, though successful in achieving the currently recommended amount of activity, was of limited efficacy on CV risk factors, suggesting the need for a larger volume of physical activity in these high-risk subjects.

CONCLUSIONS

Clinical trials and cohort studies have highlighted the role of physical activity in the prevention and treatment of T2DM. Even though the vast majority of the studies were not specifically designed to evaluate the effects of exercise with the elderly, nevertheless, the targeted population involved in those studies was often constituted by elderly

subjects. As a result, a considerable amount of literature has been published in recent years trying to identify safe and effective exercise programmes. The benefits of aerobic exercise are well documented and their effects in patients with T2DM are widely perceived to be beneficial for glycaemic control, weight loss, and the control of lipids and lipoproteins. Some meta-analyses have been particularly useful in summarising and analysing prior research, and the effects of aerobic exercise on HbA1c - the major marker of glycaemic control - have become well established. Well conducted meta-analyses have shown that intensity is a better predictor than exercise volume of both the difference in HbA1c and $V0_{2max}$ between the exercise and the control group. The effect of exercise intensity was also evaluated on insulin sensitivity by means of RCTs that compared the effects on insulin sensitivity of different intensities of aerobic exercise training, with the same total energy expenditure on exercise.

In conclusion, we can say that interventions with more vigorous aerobic exercise programmes resulted in greater reductions in HbA1c, greater increase in $V0_{2max}$, and greater increase in insulin sensitivity. Considering that ageing is associated with a reduction in muscle mass, a progressive increase in body fat mass, and a loss of lean body mass (particularly skeletal muscle), resistance training seems to play a fundamental role. Considering the available evidence, it appears that resistance training could be an effective intervention to help glycaemic control, especially considering that the effects of this form of intervention, as reported in the major RCTs, are comparable with aerobic exercise in terms of metabolic control; but in addition, it provides significant advantages in terms of muscle mass improvement and loss of visceral fat. Thus, although with resistance training body weight does not change much, the main effect of resistance training on body composition of the elderly should be a shift from fat to muscle mass, and the maintenance of a large muscle mass may reduce obesity-related risk factors. Resistance training may serve as a countermeasure of age-associated mitochondrial dysfunction by reducing potentially damaging compounds to mitochondria, and this has important implications for T2DM and the metabolic syndrome.

Whether combined resistance and aerobic training offers a synergistic and incremental effect on glycaemic control in individuals with T2DM is an issue that has been addressed by a number of studies; in general, the results indicate that a combined training programme of strength and aerobics could induce positive adaptations on glucose control, insulin action, muscular strength, and exercise tolerance. Moreover, whether there is an incremental value to combining aerobic and resistance training, as opposed to either separately, is another interesting question that has been addressed by research recently. Combined exercise training seems to determine additional change in HbA1c, which can be seen as significant if compared with aerobic training alone and resistance training alone.

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WHO GETS DIABETIC MACULAR OEDEMA; WHEN; AND WHY? PATHOGENESIS AND RISK FACTORS

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ABSTRACT

Diabetic macular oedema (DMO) presents an enormous rise in the last decades with an increasing number of diabetic patients. It has a negative impact on the health-related quality of life beside the related visual loss. Additionally, it incurs more health centre visits, higher health costs, and lower working performance. Therefore, early diagnosis and preventive measures gain more and more importance in the management of DMO. Risk factors for DMO can be divided into systemic and ocular risk factors. The leading systemic risk factors include age, type and duration of diabetes, insulin use, and glucose regulation. Hypertension, nephropathy, hyperlipidaemia, anaemia, cardiovascular disease, smoking, and amputation are other risk factors reported. In addition, susceptibility in cases with endothelial nitric oxide synthase polymorphism and vascular endothelial growth factor C634-G polymorphism has been reported. The severity of diabetic retinopathy, microaneurysm turnover, cataract surgery, incomplete vitreous detachment, and peripheral retinal ischaemia are among ocular risk factors. Though avoiding changes in the metabolic memory related to hyperglycaemia in the early period seems to be the most efficient treatment, nowadays close follow-up of patients with high risk and effort to control the modifiable risk factors seems to be the ideal treatment.

Keywords: Diabetic macular oedema, risk factors, hyperlipidaemia, hypertension, cataract.

INTRODUCTION

The modified dietary changes and Western type lifestyle leads to an enormous increase in the incidence of diabetes. It is estimated that there were 347 million people affected by diabetes worldwide in 2011 and this is expected to double by 2030.[1,2] This alarming rise in the number of diabetic patients is accompanied by the rapid increase in the number of patients affected by its microvascular complications, diabetic retinopathy (DR) and diabetic macular oedema (DMO). DMO is the most common cause of visual acuity decrease in diabetic patients. About one diabetic patient in four can be expected to develop DMO in a lifetime.[3]

According to statistics, 40% of people with diabetes have retinopathy, and diabetes is the leading cause of new blindness in adults 20–72 years of age.[4] In 2012, DMO was estimated to affect approximately 21 million cases worldwide which constitutes 7% of all people with diabetes.[5] Comparing the prevalence of DMO between Type 1 and 2 diabetes mellitus (T1DM and T2DM), 14% of people with T1DM have DMO, while it affects only 6% of people with T2DM. However, since the number of T2DM cases significantly outnumbers that of T1DM, there are more T2DM patients with DMO.[6]

In addition to visual loss, the negative impact of DMO on the diabetic population, especially on patient health-related quality of life (QoL), is a serious issue as well. Patients with DMO consume significantly more healthcare resources, incur higher costs, and have a low work efficiency compared to diabetic patients without retinal complications. The yearly number of ophthalmological examinations of diabetic patients are 3-times higher than controls. The health costs are 30% higher in DMO cases compared to diabetic patients without retinopathy.[7,8]

As these data show, visual disability from diabetes is a significant public health problem which is largely preventable, and the QoL can be preserved if managed with timely intervention. Therefore, determining the risk factors, close follow-up, early diagnosis, and taking preventive precautions for patients at higher risk to prevent the visual disability related to DMO has gained more importance despite encouraging and hopeful developments for the treatment of DMO in the pipeline.

DMO can be seen at any stage of DR, either nonproliferative or proliferative, with two types: focal oedema (FO) arising from microaneurysm (MA) leakage, and diffuse oedema related to increased capillary permeability. Focal macular oedema has been defined as an area of retinal thickening less than two disc areas in diameter, not affecting the centre of the macula. Diffuse macular oedema has been defined as having two or more disc areas of retinal thickening with involvement of the macular centre. FO has been reported to be more common than diffuse DMO and associated with better visual acuity, less severe retinopathy, and less macular thickening. The decision for treatment is based on the criteria of clinically significant macular oedema (CSMO) defined by the Early Treatment for Diabetic Retinopathy Study (ETDRS) in 1985 with clinical exam or colour fundus photographs. According to their definition, one of the following three criteria should be fulfilled:

1. Any retinal thickening within 500 μm of the macular centre.

2. Hard exudates within 500 μm of the macular centre with adjacent retinal thickening.

3. Retinal thickening at least one disc area in size, any part of which is within one disc diameter of the macular centre.[9-11]

In recent years optical coherence tomography, which has allowed assessment of early DMO, including subclinical DMO, has become an adjunctive tool in addition to colour fundus photography and fundus fluorescein angiography (FA) to determine its classification and thus its management strategy.[12]

Diabetes affects all cell types in the retina including neurons, glial cells, and blood vessels. Chronic hyperglycaemia initiates a complex series of responses including activation of protein kinase C, activation of aldose reductase, formation of advanced glycation end products, increased hexosamine pathway flux, and activation of renin-angiotensin system. These together induce overproduction of reactive oxygen species, which increase oxidative stress leading to retinal damage. The structural changes related to hyperglycaemia are thickening of the capillary basement membrane, loss of microvascular pericytes, MA formation, and breakdown of the blood-retinal barrier which initiates the DMO. Furthermore, vascular endothelial growth factor (VEGF) and other inflammatory cytokines such as tumour necrosis factor and interleukin 1β, insulin-like growth factor, hepatocyte growth factor, and histamine also contribute to vascular permeability by disrupting the tight junction proteins in the endothelium.[13-15]

Under normal conditions the inner retina is continuously dehydrated by glial cells such as Müller cells, and the outer retina is kept dry by pumping of retinal pigment epithelium. Special water channels called 'aquaporins' enhance permeability of membranes and mediate rapid and extensive fluid exchange.[16] Intraretinal fluid collection may develop as a result of enhanced fluid leakage due to breakdown of the blood-retinal barrier and by the impaired removal of fluid from the retinal tissue to systemic circulation. The permeability of the retinal capillaries increases approximately 12-fold but the activity of the pigment epithelial pump increases only 2-fold in diabetes, and in the macular centre there is no venous side of vasculature and water can leave the extravascular space only via action of the retinal pigment epithelial pump.[17]

Generally, fluid collection develops in interstitial spaces (extracellular fluid, vasogenic oedema) causing cellular compression or it may collect within cells (intracellular, cytotoxic oedema) resulting in cellular swelling. Vasogenic oedema can be explained by Starling's law. According to Starling's law, oedema will form if the hydrostatic pressure gradient between vessel and tissue is increased or the osmotic pressure gradient is decreased.[18] The increased capillary permeability in diabetes enables leakage of macromolecules, predominantly albumin, from the blood into the tissue interstitial space. This accumulation of albumin in the tissue increases the osmotic pressure difference between tissue and blood, which pulls water into the interstitial space.[19] VEGF is the primary cytokine responsible for the increased permeability of retinal capillaries which makes it an essential target in the treatment of DMO.[20] VEGF is controlled

by oxygen tension in the tissue; its production is induced by hypoxia. Reducing the VEGF concentration in the retina seems to be the ideal way to reduce the leakage of plasma proteins from the blood into the tissue interstitial space.[18]

Intracellular oedema leakage will not be seen on FA, as the fluid is intracellular and can be explained by hypoxia-induced K+ channel disturbances. The redistribution of K+ channels results in a net accumulation of K+ ions within cells, building an osmotic gradient. This gradient drives water from the blood and vitreous into the glial cells via aquaporins, and causes glial swelling oedema and cyst formation.[21] A prevailing view is that cyst formation secondary to macular oedema is formed by swollen and dying Müller cells. When present, these cysts are predominantly located in the inner nuclear layer and Henle fibre layer.[22]

DMO: WHO, WHEN, AND WHY?

The answer of this question is multifactorial, including systemic or ocular factors. Systemic factors include age, duration and type of diabetes, and insulin use. According to the Wisconsin epidemiologic study of DR10 data, cumulative DMO risk increases with age in 25 years. In cases with duration of disease >20 years, DMO prevalence is 32% for patients younger than 30 years at the time of diagnosis and using insulin. For patients who are older than 30 years at the time of diagnosis with either T1 or T2DM, the prevalence of DMO is 38% for insulin users and 18% for non-insulin users.[23] ETDRS group reported the incidence of DMO for 10 years follow-up as 20.1% in T1DM cases, 25.4% in insulin-dependent T2DM patients, and 13.9% in non-insulin-dependent T2DM patients.[24]

There are not so many studies evaluating DMO prevalence and its correlation with the disease duration in Europe. From the 775 patients participating in the Exeter Diabetic Retinopathy Screening Programme in the United Kingdom, 6.1% were diagnosed to have DMO at the time of screening. This ratio is 11.5% for T1DM cases, 4.1% for non-insulin-dependent T2DM patients, and 9.1% for insulin-dependent T2DM patients.[25] The Epidemiology of Diabetes Interventions and Complications research group found that at 4-year follow-up, patients in the Diabetes Control and Complications Trial (DCCT) who received intensive insulin treatment showed better retinopathy outcomes than those receiving conventional treatment.[26] However, insulin treatment is always associated with higher DMO incidence. Previous studies could not detect a direct association with insulin use and DMO, and proposed that DMO incidence was higher among insulin users as those are usually uncontrolled patients with severe DR, and strict glucose regulation with insulin resulted in decrease in DMO incidence with time.[7,23] However, recent studies proposed that insulin causes impairment of the blood retina barrier by increasing binding of hypoxia-induced factor to the VEGF promoter region. In the long term, insulin demonstrated positive effects on DMO due to its anti-inflammatory, antiapoptotic, oxidative stress diminishing effects.[27,28] DCCT[15] and the United Kingdom's Prospective Diabetes Study[16] reported an increase in DMO in T2DM cases with especially >3% decrease in glycated haemoglobin (HbA1c), but no progression was detected in patients without retinopathy at the beginning.[29] Therefore, close follow-up is recommended for cases starting insulin treatment.

In addition to DM type, duration, and insulin use, the degree of metabolic control, dependent on blood glucose and HbA1c level, is the most important risk factor for DMO.[30] The 4th and 7th year follow-up data of DCCT[15] group showed that patients receiving intensive insulin treatment presented slowdown of DR progression, which continues even after the intensive treatment has been stopped. Similarly, the endothelial dysfunction related to poor glucose regulation in the first 5 years of the disease persists after normoglycaemia.[31] The study of Madsen-Bouterse et al.[32] showed persistence of mitochondrial DNA damage even after normoglycaemia following 6 months of poor glucose regulation. These findings bring up the 'metabolic memory' concept which is a result of oxidative stress, advanced glycosylation end products, and epigenetic changes related to chronic hyperglycaemia in diabetes. It also emphasises the importance of preventing these stationary metabolic memory changes by early diagnosis and intensive glucose regulation.[33] Despite positive effects of DM regulation in the early period, the treatment itself may sometimes have some risks. For example, the thiazolidinediones which were increasing the insulin sensitivity were claimed to increase DMO risk in some studies.[34] However, recent studies proved that they induce neither clinical nor subclinical DMO.[35]

DMO prevalence has been studied in many ethnic groups as well. Black and Hispanic patients seem to be more prone to DMO compared to Chinese and Caucasian patients.[36] The three population study (Los Angeles Latino Eye Study, Projecto VER, Beaver Dam Eye Study) of Varma et al.[37] found higher prevalence of DR among Hispanics after eliminating the traditional risk factors. In the United States, the cross-sectional Veterans Affairs Diabetes Trial examined the association between ethnicity and DMO and found that Hispanics (18%; OR 2.30) and African-Americans (15.6%; OR 2.30) have a greater prevalence and risk of DMO than non-Hispanic whites (6.3%), even after adjusting for confounding risk factors.[38] These ethnic risk factors can be explained by predisposition to conventional risk factors, insulin resistance, and difference in anthropometric measurements truncal obesity, difference in health service facilities, genetic predisposition, and epigenetic changes. There is no difference among both sexes for DMO.[37,38]

There are several other systemic risk factors mentioned in other studies, including high blood pressure, nephropathy, hyperlipidaemia, anaemia, cardiovascular disorders, and high basal metabolic index.[24,39] Asensio-Sanchez et al.[40] reported age, high HbA1c, high blood pressure, smoking, high-density lipoprotein (HDL) cholesterol levels and low-density lipoprotein (LDL)-cholesterol levels, proteinuria, and microalbuminuria as the significant systemic risk factors for DMO. The Veterans Affairs Diabetes Trial[26] claimed young age, early-onset DM, long duration of disease severity of DR, and high HbA1c as high risk factors in addition to urine albumin/creatinine ratio and amputation as associated risk factors.[38] Congestive heart failure, renal failure, and hypoalbuminaemia are among the situations where DMO increased due to either increased hydrostatic pressure or decreased osmotic pressure.[41]

High blood pressure increases have been demonstrated to increase DMO incidence 3-fold. The majority of the studies found high systolic blood pressure more risky. There are also some others claiming high diastolic blood pressure is more risky.[5,7,42,43] This effect is proposed to be related to impaired retinal autoregulation, accelerated endothelial damage and VEGF, and VEGF receptor increase due to vascular tension in retinal endothelium.[44] According to Stefánsson,[32] arterial hypertension raises the hydrostatic pressure in the capillaries which, in turn, increases the fluid leakage. Improvement of DMO has been reported after successful treatment of hypertension.[19] Nephropathy also showed a close relationship with DMO - especially gross proteinuria in the late-onset, insulin-dependent group - increasing the risk severely.[7,23,45] The study of Romero et al.[46] also showed a decrease in diffuse macular oedema after dialysis. No correlation could be assessed between microalbuminuria and DMO. Dyslipidaemia is known to be an important risk factor for DMO.[47] Hyperlipidaemia has been reported as a risk factor first by Dornan in 1982.[48] This has a special importance in DMO cases, as further progression of exudates to the foveal centre resulted in subretinal fibrosis and associated visual loss. Several studies demonstrated a strong relationship with lipid exudates and serum cholesterol and LDL levels.[49-51] Miljanovic et al.,[52] in a prospective study, showed an increase in serum lipids, especially total/HDL cholesterol ratio and triglyceride, to be independent risk factors for both clinically significant DMO and retinal hard exudates. However, CSMO was not found to be correlated with the lipid profile in a recent study by Kamoi et al.[53] A more detailed study comparing the influence of serum lipids on clinically significant versus non-CSMO revealed high serum LDL, non-HDL cholesterol, and cholesterol ratios related to non-CSMO and total cholesterol related to CSMO. The body mass index was also found to have a negative effect on DMO.[51]

The increase in blood viscosity and changes in the fibrinolytic system in hyperlipidaemia are proposed to cause hard exudates.[54] The influx of triglycerides into the cell membrane gives rise to fluidity change and leakage of the plasma content into the retina.[55] Additionally, high lipid levels cause endothelial dysfunction leading to blood retinal barrier impairment as proved by animal studies.[56] The lipid lowering drugs, atorvastatin, have been shown to decrease DMO in two small studies, which also confirm that statins may be an adjunctive medication for the management of DMO. The recently published FIELD[57] (Fenofibrate Intervention and Event Lowering in Diabetes) and ACCORD[58] (Action to Control Cardiovascular Risk in Diabetes) studies indicate that use of fenofibrate for 5 years - which increases the HDL cholesterol, apolipoprotein (Apo) A1 levels, and decreases triglyceride and Apo B levels - lowers the need for laser treatment both in DR and DMO.[59] Owing to this, the management plan for DMO warrants evaluation and inclusion of all risk factors. In addition to these modifiable risk factors, one can

also have unmodifiable risk factors like genetic predisposition. For example, endothelial nitric oxide synthase gene polymorphism may give rise to a change in enzyme expression which may play a role in blood-retinal impairment; therefore, it is assumed to be a risk factor for DMO.[60] The C634-G polymorphism of VEGF, which is the major cytokine responsible for increased permeability, is also thought to be a risk for DR and DMO. Individuals carrying the 634-C allele present more transcription compared to those carrying 634-G allele.[61]

Among ocular risk factors for DMO, severity of DR is the major one. DMO can accompany every stage of DR. The incidence is 3% for mild non-proliferative DR, 38% for moderate non-proliferative DR, and 71% for proliferative DR.[7] In a recent study, increased activity of microvascular disease in the macular region has also been demonstrated to increase the rates of MA turnover and is associated with higher risk for development of CSMO.[62] Retinal arteriolar haemodynamic changes related to blood pressure, age, and duration for DM may also be associated with DMO.[63] Guan et al.[63] noted an increase of arterial circulation and vascular rigidity, especially in the maximum-minimum velocity. Klein et al.[64] reported association of DR progression risk with retinal vein thickness in a recent study.

Besides microvascular complications of DM, vitreous also plays a role in vascular permeability increase under the effect of various factors. Nasrallah et al.[65] declared that DMO is detected in 20% of DR patients with posterior vitreous detachment and in 55% of DR patients with attached hyaloid. These findings supported the role of vitreous traction in DMO pathogenesis. Hikichi et al.[66] detected spontaneous resolution of DMO in 55% of patients with vitreomacular detachment and 25% of patients with vitreomacular attachment longer than 25%. The promising results of vitrectomy as a treatment for DMO is further proof for the role of the vitreous in DMO pathogenesis. Stefánsson[18] suggested that vitrectomy clears VEGF and other cytokines from vitreous, and replacement of vitreous gel with saline facilitates oxygen transport to ischaemic retina. He further explained the effect of traction on retinal oedema by Newton's third law: a force is always met by an equal and opposite force in the retina and this tends to pull the tissue apart and lowers the tissue pressure in the retina. The lowered tissue pressure increases the difference between the hydrostatic pressure in the blood vessels and tissue, and this contributes to oedema formation. However, it is still a matter of debate whether DMO forms a rich environment due to cellular proliferation or vitreoschisis exacerbates DMO.

The wide field angiogram enabled the identification of another risk factor for DMO: the peripheral retinal ischaemia. The RaScal study[67] clearly demonstrated that DMO patients receiving peripheral laser plus ranibizumab treatment showed less recurrence and a decrease in central foveal thickness compared to patients who received macular laser plus intravitreal triamcinolone acetonide. Intraocular surgeries, such as for cataracts, may also have an exacerbating effect on DMO; this is presumed to be related to an exacerbation of the existing chronic inflammation in DMO.[68,69] There are also some protective ocular factors for DMO, such as axial length. Man et al.[70] reported that long axial length is protective for both DR and DMO.

CONCLUSION

Regarding its negative impact on vision and thus QoL, the prevention and treatment of DMO is an important issue that warrants proper and on-time management. Various treatment modalities have to work in synergy and supplement each other for ideal treatment. Intraocular injection of anti-VEGF antibodies can remove VEGF from the retina, and steroids may reduce permeability.

Laser and vitrectomy can increase retinal oxygen tension and thereby reduce VEGF production. Posterior vitreous detachment and vitrectomy can increase diffusion and convection in the vitreous and increase clearance of VEGF and other cytokines from the retina. The hydrostatic gradient between microcirculation and tissue may be reduced by either decreasing the hydrostatic pressure in microcirculation by reducing the arterial blood pressure or by releasing vitreoretinal traction; thus, increasing the tissue pressure. Improved retinal oxygenation through laser treatment or vitrectomy also constricts the retinal arterioles, increases their resistance, and reduces hydrostatic pressure in microcirculation. The Diabetic Macular Edema Treatment Guideline Working Group suggested the use of anti-VEGF therapy for a centre involving patients with a visual acuity <20/32 and laser photocoagulation for patients with a visual acuity >20/32 or DMO not involving the centre. Additional treatment modalities are usually applied in an individualised algorithm; however, close follow-up and control of the modifiable risk factors are of the utmost importance in the treatment of each individual with DMO.

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One pen needle making one big difference to diabetics

Interview with Mr Richard Walker and Mr Richard Simmonds from Owen Mumford.

Rich Simmonds

Rich Walker

THE BACKGROUND

Mr Richard Walker, Global Product Manager for Drug Delivery, and Mr Richard Simmonds, Head of Global Marketing, from Owen Mumford, Woodstock, Oxfordshire, UK, spoke to the *European Medical Journal* exclusively about the Unifine® Pentips® Plus device, as well as the challenges which face the European healthcare system.

All of the products designed, manufactured, and produced by Owen Mumford aim to provide greater safety, convenience, and comfort for patients. The company's philosophy is to improve quality of life, encourage patient compliance, prevent infection, and reduce healthcare costs and they have, on all counts, achieved this with their new Unifine Pentips Plus device.

What would you say are the Challenges Facing the European Healthcare System Currently? And what is Owen Mumford doing to overcome these Challenges?

"*Well certainly, relevant to diabetes, a key problem is the explosion in numbers*," replied Mr Simmonds; Owen Mumford focuses on "*making products easy to use so that patients and healthcare professionals require minimal training, because that is the thing that really costs healthcare systems money when you have to train, and allowing patients to be independent and manage their disease, therefore reducing the total cost of treatment,*" as well as reducing any complications.

Mr Simmonds continued by adding: "*In terms of our research and development programme, we have a razor sharp focus on continuing to improve usability for people managing long-term complications,*" and the one thing all of their products have in common is "*that they are absolutely ruthlessly focused on making it easier for the patients; we have a pipeline full of new innovations which are all focused around patients managing their long-term complications and making it easier for them.*"

UNIFINE PENTIPS PLUS

"*The idea was to have a pen needle that was easier to use and more convenient,*" commented Mr Walker. Features of the product include a shorter, thinner needle which is able to reduce penetration force and allows for a more comfortable injection experience. It also encourages frequent needle change, and ensures that the correct insulin dose is dispensed.

"*Unifine Pentips Plus is unique in the fact that it has a built-on chamber, a separate chamber; essentially, you could call it a dual chamber product, where there is a dedicated remover attached to every Unifine Pentips Plus and that adds to ease of use and convenience of the product,*" Mr Walker highlighted.

"*When it comes to removing needles [users] know they should remove a needle after each injection, but they did not have anywhere to put the used needle. So having a remover always available to hand with*

your new needle adds to the convenience for the person using the product," Mr Walker continued.

Testing Compliance

A UK-based study, which included a sample size of 59 people with either Type 1 or Type 2 diabetes, assessed the needle changing behaviour of these persons over a period of 8 weeks, using the Unifine Pentips Plus, and compared it to their current pen needle device.

"*They spent 4 weeks recording their current behaviour using their current pen needle, and after 4 weeks... they were then given the Unifine Pentips Plus,"* said Mr Walker.

"*They spent another 4 weeks using Unifine Pentips Plus and we then got the results and were able to compare behaviour, particularly needle-changing behaviour, between the two products. The results did show that there was a 61% increase in the rate of compliance, and when we say compliance we are referring to using a new needle for each injection; it basically supported our belief in the product that behaviour would change by using Unifine Pentips Plus,"* emphasised Mr Walker.

Mr Simmonds highlighted: "*What we are really excited about is that it is allowing patients to become more compliant and more adherent with what their current healthcare professional wants them to do."*

"*What we are trying to do is to get away from the idea that the healthcare professional needs to wag their finger and nag patients to do what they are told, but instead just make it more convenient and easier for them to be compliant, so that the patient just wants to [adhere to it]. One of the key things that came out of the study was that we did not need to train patients to do this, we effectively just gave them a few words of encouragement, from the pharmacist, the box with the instructions, and then left them alone, and that was enough to change their behaviour,"* explained Mr Simmonds.

PRODUCTS TO BENEFIT PATIENTS

"*The main benefits are that if you leave a pen needle on your pen and reuse it there are several things that can happen; one of them is that the needle will obviously get blunted the more times that you use it and using needles that are not sharp as they were when they were first used causes more tissue damage, so there is research that shows the repeated use of used needles can increase lipodystrophy... which can affect the efficacy of your dose, so it can cause irregular absorption of the insulin,"* there is also an increased risk of infection and additional problems when injecting which can contribute to increased healthcare costs Mr Walker said.

Mr Walker also highlighted: "*At EASD we have healthcare professionals attending, and they were all very positive towards Unifine Pentips Plus. When you look at the product it is not immediately obvious of the benefits, but when you demonstrate it to healthcare professionals it is immediately, widely accepted as being an improvement on standard pen needles and it would help their patients change their needle more frequently."*

"*One of the unique things about us is that we take a concept right from an idea on a scrap of paper through to a product which we take to market... But we also know that all the clever features that the research and development guys build into a product are nothing unless the patient actually values them and uses them. So what we try to do differently, I think, is to understand the end user needs right from the beginning. So we do not just do things because an engineer tells us we can, we do them because a patient says that they want them, need them, or will use them,"* Mr Simmonds expressed.

COMPANY SUCCESS

Owen Mumford have won a number of awards throughout their 62-year history, including The World Economic Forum's Global Growth Company 2014 award. Mr Simmonds believes this reflects: "*First of all our innovation, and secondly our ability to export UK-produced ideas and products to the rest of the world."*

"*The first thing it means to us as a company is it's a recognition of the things that we are doing and we have clearly been successful in doing that. From my own personal point of view, it is just good to see that somebody else recognises the good stuff that we are doing,"* continued Mr Simmonds.

Mr Walker proudly concluded: "*We are being recognised for our effort to improve the outcome as far as we can for our customers."*

Maternal antidepressants: health risk for babies

PREGNANT women taking antidepressants during pregnancy may be predisposing their infants to Type 2 diabetes mellitus (T2DM) and obesity in later life.

Up to 20% of women in the USA are prescribed an antidepressant during pregnancy, when they are most vulnerable to the illness. Obesity and T2DM are on the rise in young children, and it is widely argued that lifestyle, high calorie foods, and reduced physical activity are to blame.

Maternal antidepressants may also be contributing to the epidemic, suggests a study by Dr Alison Holloway, Associate Professor of Obstetrics and Gynaecology, Division of Reproductive Biology, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada.

"While it is known that these drugs can increase the risk of obesity in adults, it is unknown whether a woman's antidepressant use during pregnancy increases the risk of metabolic disturbances in her children," Dr Holloway commented.

Therefore, the aim of the study was to determine whether maternal exposure to antidepressants is related to the development of fatty liver, something commonly seen in obese offspring.

Regarding the results, Ms Nicole De long, Division of Reproductive Biology, commented: "We have demonstrated for the first time in an animal model that maternal use of a class of antidepressants called selective serotonin reuptake inhibitors, or SSRIs, resulted in increased fat accumulation and inflammation in the liver of the adult offspring, raising new concerns about the long-term metabolic complications in children born to women who take SSRI antidepressants during pregnancy."

The study does not suggest that women should altogether avoid antidepressants during pregnancy, but there may be risks associated with antidepressants that have not been previously identified. This research may help to identify children who may require specific interventions in order to prevent obesity and T2DM in later life.

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"While it is known that these drugs can increase the risk of obesity in adults, it is unknown whether a woman's antidepressant use during pregnancy increases the risk of metabolic disturbances in her children."

Dr Alison Holloway,
Division of Reproductive Biology,
McMaster University,
Hamilton, Canada

Gut changing diabetes circumstances

"People have been talking about turning one cell into another for a long time, but until now we had not gotten to the point of creating a fully functional insulin-producing cell by the manipulation of a single target."

Dr Domenico Accili,
Russell Berrie Foundation,
Columbia University Medical Center,
New York City, USA

SWITCHING off a single gene can retrain the cells within an individual's gastrointestinal (GI) tract and convert human GI cells into insulin-producing ones, new research shows, which is welcoming news to diabetes sufferers.

For almost two decades, researchers have been trying to make surrogate insulin-producing cells for Type 1 diabetes patients. Now, scientists have data which suggest that cells lost by the disease may be easily replaced through the re-education of existing cells, rather than through the transplantation of new cells (created from embryonic or adult stem cells).

Dr Domenico Accili, Professor of Diabetes, the Russell Berrie Foundation, Columbia University Medical Center, Columbia University, New York City, New York, USA, explained: "People have been talking about turning one cell into another for a long time, but until now we had not gotten to the point of creating a fully functional insulin-producing cell by the manipulation of a single target."

Though the cells do not yet have all the functions of naturally occurring pancreatic beta cells, previous research by the team has shown that mouse intestinal cells can be transformed into insulin-producing cells; the latest work demonstrates that this technique also works in humans.

The researchers were able to change the gut cells' function by deactivating the *FOXO1* gene. Firstly, they created a tissue model of a human intestine with human pluripotent stem cells, and then, through genetic engineering, they deactivated any functioning *FOXO1* within the intestinal cells. After 7 days, some cells had begun to release insulin and, importantly, only in response to glucose.

"By showing that human cells can respond in the same way as mouse cells, we have cleared a main hurdle and can now move forward to try to make this treatment a reality," Dr Accili added.

Healthy obesity: fact or fiction?

LINKS between obesity and diabetes may need to be revised, since approximately one-quarter of individuals who are categorised as obese may not suffer from metabolic diseases (MDs) such as Type 2 diabetes.

The increased risk of MDs can be attributed to increased levels of a molecule called heme oxygenase-1 (HO-1), suggesting HO-1 blockers to be a promising counteractive therapy.

"The results indicate that HO-1 is in fact necessary for the development of MD and call for a re-evaluation of numerous findings in the field," said Dr Harald Esterbauer, Associate Professor of Biochemistry and Clinical Biochemistry, Clinical Department of Medical and Chemical Laboratory Diagnostics, Medical University of Vienna, Vienna, Austria. "The study also reveals HO-1 as a candidate biomarker for the stratification of metabolically healthy and unhealthy obesity and provides a framework for selective, personalised therapy."

Although the exact process is unclear, it was suggested that a maladaptive immune response - metabolic inflammation - may play a role in the factors which determine if obesity could potentially lead to poor metabolic health.

The results revealed that increased levels of HO-1 in liver and fat biopsies were seen in obese, insulin-resistant individuals, compared with their obese, metabolically healthy counterparts. Also, tests on mice revealed that deletion of the HO-1 gene in macrophages led to decreased inflammation; deletion of the same gene in the liver and macrophages of mice fed a high fat diet also triggered improved metabolic health.

"Our findings show that HO-1 is among the strongest predictors of metabolically unhealthy obesity in humans, and it could have a high prognostic value for detecting disease onset," said Dr J. Andrew Pospisilik, Department of Epigenetics, Max Planck Institute of Immunobiology and Epigenetics, Freiburg, Germany. "This could allow clinicians to use targeted interventions to prevent disease progression specifically in obese individuals who show early signs of Type 2 diabetes."

"The study also reveals HO-1 as a candidate biomarker for the stratification of metabolically healthy and unhealthy obesity and provides a framework for selective, personalised therapy."

Dr Harald Esterbauer,
Clinical Department of Medical and Chemical Laboratory Diagnostics,
Medical University of Vienna,
Vienna, Austria

Polycystic ovary syndrome contributing to Type 2 diabetes

"Our research found that there is a clear link between PCOS and diabetes. However, PCOS is not a well-recognised diabetes risk factor and many young women with the condition do not get regular diabetes screening even pre-pregnancy, despite recommendations from the Australian PCOS evidence-based guidelines."

Prof Helena Teede, The School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

SIGNIFICANT populations of women diagnosed with polycystic ovary syndrome (PCOS) - a hormonal disorder - who are young and not overweight, are at high-risk of developing Type 2 diabetes mellitus (T2DM).

This thought-provoking revelation was the outcome of a large-scale epidemiological study, entitled the Australian Longitudinal Study of Women's Health, and led by Prof Helena Teede and Dr Anju Joham, Department of Epidemiology and Preventive Medicine, The School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia.

"Our research found that there is a clear link between PCOS and diabetes. However, PCOS is not a well-recognised diabetes risk factor and many young women with the condition do not get regular diabetes screening even pre-pregnancy, despite recommendations from the Australian PCOS evidence-based guidelines," said Prof Teede.

The study comprised of over 6,000 women, including 500 diagnosed PCOS sufferers, all of whom were monitored throughout a 9-year duration. The age range of the women was 25-28 years from the start of the study in 2003. According to Prof Teede, this age range represents a woman's peak reproductive years where there are significant ramifications from undiagnosed diabetes and this can be a risk factor for both mothers and babies.

In women with PCOS the incidence and prevalence of T2DM were 3 to 5-times higher; additionally, obesity, which is a key trigger for T2DM, was not a significant trigger in this subgroup of women.

Prof Teede added: "Currently diabetes screening guidelines recommend screening over 40 years of age. This may need to be reconsidered in women with PCOS. We clearly need more research in PCOS, with better screening, prevention, and treatments."

Research into novel medication for the improvement of health in women with PCOS will be further investigated, with volunteer recruitment shortly underway.

Microchip magnifies Type 1 diabetes diagnosis

REVOLUTIONARY development of an inexpensive, portable, microchip-based test for diagnosing Type 1 diabetes mellitus (T1DM) could have significant implications for patient care on a global scale.

"With the new test, not only do we anticipate being able to diagnose diabetes more efficiently and more broadly, we will also understand diabetes better – both the natural history and how new therapies impact the body," said Dr Brian Feldman, senior author, Assistant Professor of Pediatric Endocrinology, Department of Pediatrics, Brian Feldman Laboratory, Stanford School of Medicine, Stanford University, Stanford, California, USA.

T1DM occurs when there is an attack by an individual's own antibodies on insulin-producing cells in the pancreas, resulting in the lack of insulin production - a hormone needed for sugar processing. Detection of the auto-antibodies by the microchip can distinguish the difference between T1DM and T2DM, leading to better patient categorisation.

Early detection of the auto-antibodies can be beneficial to T1DM patients in the long-term, since the early administration of new therapies can hypothetically halt autoimmune attacks and possibly preserve some insulin production.

The detection of antibodies is utilised using a fluorescence-based method where the glass plates forming the base of the microchip are coated with nanoparticle-sized islands of gold, intensifying the fluorescent signal. The microchip will cost approximately $20 USD (£12, €15) to produce, and can be utilised in up to 15 tests.

The test also has the potential to detect T1DM in close relatives, allowing doctors to track their auto-antibody levels before symptom onset. Due to its low cost, the potential for a large-scale population screening could be on the horizon with the development of the microchip.

The researchers have filed for a patent to use the microchip, they are also currently involved in the launching of a start-up company to serve as solid ammunition for FDA approval.

"With the new test, not only do we anticipate being able to diagnose diabetes more efficiently and more broadly, we will also understand diabetes better – both the natural history and how new therapies impact the body."

Dr Brian Feldman, Department of Pediatrics, Brian Feldman Laboratory, Stanford School of Medicine, Stanford, USA

Sleep apnoea increases diabetes risk

"After adjusting for other potential causes, we were able to demonstrate a significant association between OSA severity and the risk of developing diabetes."

Dr Tetyana Kendzerska, Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada

PATIENTS who experience obstructive sleep apnoea (OSA) are likely to be at a higher risk of developing diabetes in later life than those who do not, Canadian research highlights.

8,678 adults with suspected OSA, without diabetes at baseline, underwent a diagnostic sleep study between 1994 and 2010, and were followed through May 2011 using provincial health administration data to examine the occurrence of diabetes. Their OSA severity was measured with the apnoea-hypopnoea index (AHI), which indicates extensity based on the number of complete and partial cessations of airflow per hour of sleep.

During the follow-up, 1,017 subjects developed diabetes. Patients classified as having severe OSA (AHI >30) had a 30% higher risk of developing the disease than those classified as not having OSA (AHI <5). Meanwhile, patients with mild (AHI 5-14.9) and moderate (AHI 15-30) OSA had a 23% increased risk of developing the condition.

Other risk factors of diabetes included AHI during rapid eye movement sleep and the measures of the physiologic consequences of OSA, including oxygen desaturation, sleep deprivation, and activation of the sympathetic nervous system, as indicated by a higher mean heart rate during sleep.

The study showed some limitations, including a lack of data on some potential confounders such as family history of diabetes and race, and a possible misclassification of some participants due to the limitations of the administrative health data used.

"After adjusting for other potential causes, we were able to demonstrate a significant association between OSA severity and the risk of developing diabetes," said Dr Tetyana Kendzerska, Institute of Health Policy, Management and Evaluation, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada.

"Our findings that prolonged oxygen desaturation, shorter sleep time, and higher heart rate were associated with diabetes are consistent with the pathophysiological mechanisms thought to underlie the relationship between OSA and diabetes," Dr Kendzerska added.

The evolution of diabetes therapy

DIABETES medicine costs healthcare payers more than any other disease, and this spending is predicted to significantly increase with the number of people diagnosed expected to reach 552 million by the year 2030.

If these costs are to be managed, makers of drugs and medical devices need to start providing solutions that will allow patients to better control their diabetes, preventing debilitating nerve damage and cardiovascular disease; which is exactly what MannKind, Apple, and Novo Nordisk are currently trying to do.

Afrezza®, designed by MannKind, seeks to change the way in which diabetics receive their medication. Having been approved by the FDA, the insulin is distributed via an inhaler, giving sufferers more options for mealtime insulin and potentially improving glycaemic control.

As well as this, Apple have recently discussed the potential for a device that includes sensors and a glucometer, with the FDA. This caused much excitement amongst Apple fans who speculated that such features could be incorporated into a potential iWatch; the agency would regulate the software used to collect and read blood sugar levels.

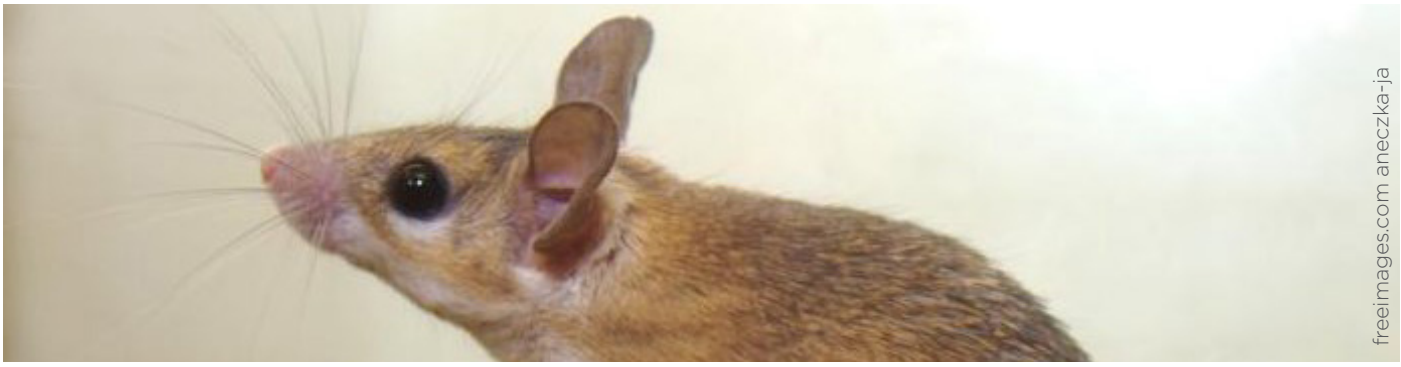
Together, these three creative products seek to innovate and revolutionise the treatment of diabetes.

Finally, whereas MannKind's focus is on launching an insulin inhaler, Novo Nordisk believes a bigger opportunity exists for the drug in tablet form, and the appeal of this is highly significant. Few patients are completely comfortable with injecting themselves with insulin, and eliminating this has become an important focus for drug makers; Novo plans to invest $3.7 billion (USD) in developing tablet alternatives.

Together, these three creative products seek to innovate and revolutionise the treatment of diabetes; the fact that Apple is asking questions about the disease supports the notion that mobile devices can increasingly provide features designed to help users in monitoring their overall health.

This information could go a long way toward helping patients maintain their medication and, ultimately, manage their disease.

Of mice and men: new diabetes gene discovered



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> "It is very exciting to see that we can now translate research results from one species to another. To me, a new age for biology, and soon medicine, has just begun."
>
> *Prof Johan Auwerx, Director of the Laboratory Integrative Systems Physiology, Lausanne, Switzerland*

MICE and humans share a pathological process which contributes to the onset of Type 2 diabetes (T2D); this discovery comes from the combined efforts of three European research teams.

Investigators studied both the genome and the 'phenome' of a family of 183 mice. According to Prof Johan Auwerx, Director of the Laboratory Integrative Systems Physiology, École Polytechnique Fédérale, Lausanne, Switzerland: "By comparing the metabolism of twins subjected to different life conditions and with a different diet, it is possible to exactly assess the influence of the environment on the expression of certain genes and the way this affects clinical features, and the risk for developing diseases."

Researchers have since added new analytical evidence to the combination of genotypic and phenotypic information from years of previous investigation, and it is now possible to quantify the presence of hundreds of proteins from a single sample, establishing what experts call an individual's 'proteome'.

Combining a mouse's genome, phenome, proteome, and metabolome, researchers identified a specific gene whose presence is important in the onset and development of T2D; mice consuming high-fat diets are likely to develop the disease regardless of whether or not this gene is active.

Interestingly, diabetic mice had low urinary levels of the metabolite 2-aminoadipate, the concentration of which varies depending on the presence of the gene, but not in relation to the creature's body fat, thus proving to researchers that the gene, and not the diet, regulates protein expression.

"Thanks to this innovative approach that connects several layers of information, we were able to identify a urinary marker that can easily detect the presence of a case of diabetes," said Prof Auwerx. "It is very exciting to see that we can now translate research results from one species to another. To me, a new age for biology, and soon medicine, has just begun."

The key to coping with diabetes

"We would like to encourage patients to be able to share their thoughts and experiences about having diabetes with family members and other trusted individuals."

Prof Heather Stuckey, lead qualitative investigator of the study, Penn State Harrisburg, Harrisburg, USA

COPING with psychological challenges faced by individuals with diabetes can be made easier with a positive outlook and social support; greater understanding of psychological, emotional, and social obstacles suffered by diabetes patients could vastly improve health outcomes.

The second study of its kind, the Diabetes Attitudes, Wishes, and Needs study has performed the largest analysis of personal accounts of subjects living with the disease; whilst a previous investigation, in 2001, revealed that 41% of adult sufferers had poor psychosocial wellbeing.

In the latest study, researchers administered online, telephone, and in-person questionnaires to 8,596 individuals living with both Type 1 and 2 diabetes across 17 countries.

Results showed that approximately half of those with diabetes had negative social, psychological, and emotional illness related experiences; subjects reported anxiety, depression, and hopelessness about their health.

Additionally, participants experienced social misunderstanding in regards to their illness, with one in five also having experienced workplace discrimination, including job loss.

When asked about their successes with the condition, it appeared that personal resilience, due to a positive outlook, as well as support from family, friends, and healthcare professionals were of the greatest help in dealing with diabetes challenges.

Several messages emerged from the study for anyone suffering with (or living with a sufferer of) the disease; for example, many people with diabetes are reluctant to share their challenges as they do not wish to be perceived as a burden to others.

Prof Heather Stuckey, lead qualitative investigator of the study, Assistant Professor of Medicine, Penn State Harrisburg, Harrisburg, Pennsylvania, USA, said of the findings: "We would like to encourage patients to be able to share their thoughts and experiences about having diabetes with family members and other trusted individuals," continuing: "We believe that will relieve some of the stress that people experience and will improve living with diabetes."

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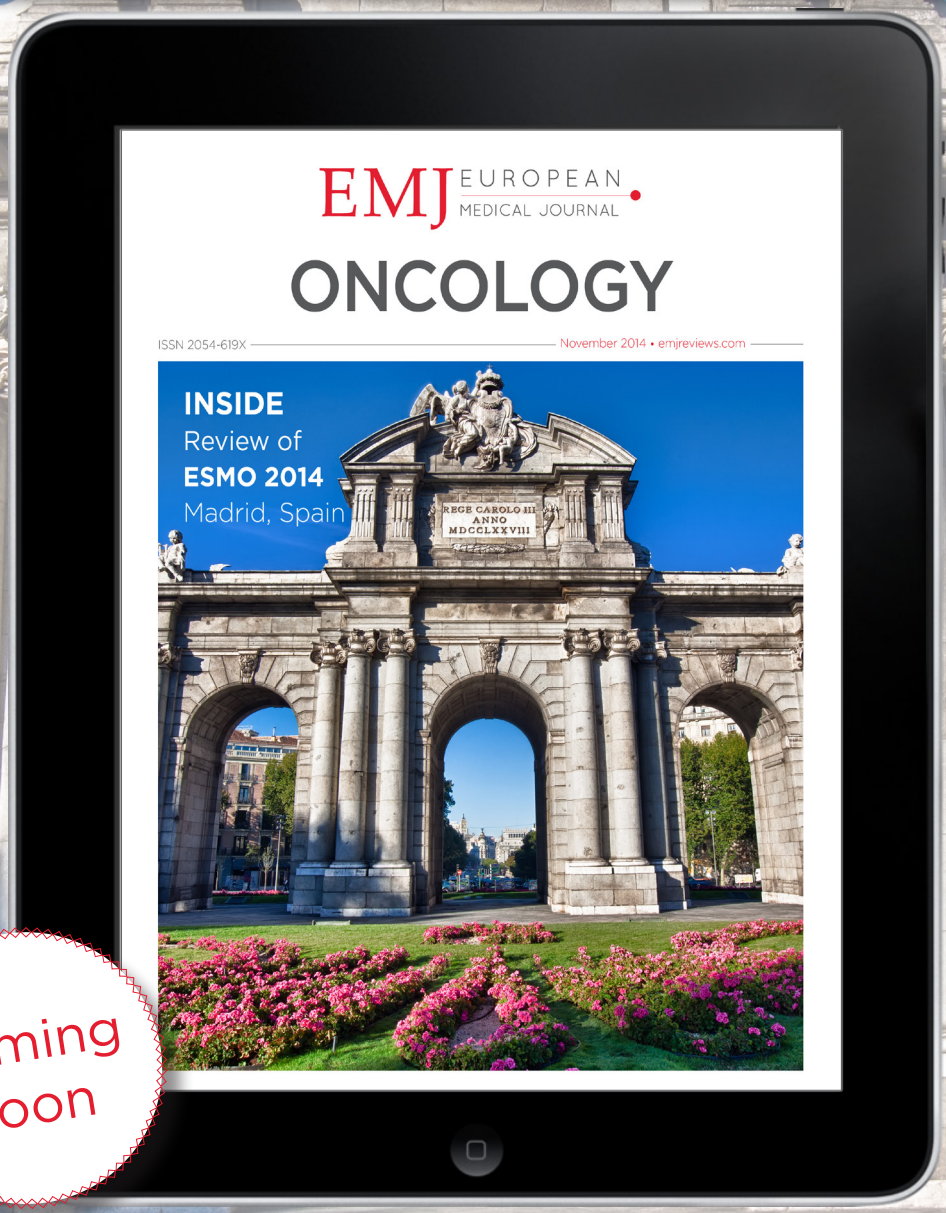

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Featured Suppliers

Diabetes

Responsible for the development of some of the world's most important drug products in fields ranging from diabetes care to veterinary medicines, Bayer HealthCare is a key innovator in the manufacturing of pharmaceutical and medical products. The Bayer subdivision's aim is to create state-of-the-art, groundbreaking products to improve the lives of patients worldwide. It aims to accomplish this through its consumer care, medical innovations, and pharmaceutical divisions, addressing some of the great challenges in the modern era. The company has bases in 5 continents, with approximately 55,300 people working for the subgroup in over 100 countries.

Boehringer Ingelheim (BI) is a group of companies heavily focused on the research, development, manufacturing, and marketing of potentially life-altering pharmaceuticals. The group has over 46,000 employees and 140 affiliated companies distributed worldwide. BI has made clear its vision of 'value through innovation', which is also central to the company's corporate strategy. By carrying out key research projects in the development of innovative drugs, the company has a strong focus in the main therapeutic areas of cardiovascular diseases, respiratory diseases, diseases of the central nervous system, metabolic diseases, virological diseases, and oncology.

Merck aspires to be the world's number one pharmaceutical company, improving the lives of people worldwide through a strategy involving the production, development, and marketing of innovative medicines, vaccines, biological therapies, consumer care, and animal health products. Merck currently employs a diverse workforce and has built its global empire on projects carried out with the utmost attention to ethics and integrity. Their numerous past achievements include the discovery of statins for treating high cholesterol, as well as unearthing the existence of vitamin B1 and a range of cold remedies and antacids.

Novartis AG has one outstanding mission: to discover, design, and deliver cutting edge healthcare to patients worldwide. Founded in 1996 and based in Basel, Switzerland, this world-leading pharmaceutical company has consistently produced medical breakthroughs, developing innovative products for patients and consumers. A host of innovative pharmaceuticals, generics, vaccines, and consumer health products have provided pain relief and boosted patient quality of life since the company's inception. Operating in 140 countries, the seismic ambitions of Novartis have attracted a total of 135,000 associates, including top experts in research and development.

Takeda is currently the largest pharmaceutical company in Japan, and is one of the main global healthcare players. The company has based its philosophy on the concept of 'Takeda-ism' (integrity, fairness, honesty, and perseverance), which has been developed over the company's 230-year lifetime. Following this, Takeda carries out its activities through the company slogan: "Strive towards better health for people worldwide through leading innovation in medicine." The Osaka-based firm has over 30,000 employees in more than 70 countries and regions worldwide.

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Diabetes in Older People – Challenges, Controversies, and Complexities

19th November 2014

London, United Kingdom

Diabetes consultants and trainees, members of multi-disciplinary diabetes teams, and GPs are all urged to attend this event. The interactive programme featured throughout the day will cover key topic areas including: 'acute diabetes emergencies in the older person', 'glycaemic management – controversies and challenges', and 'diabetes and dementia – mechanisms of association, and care of the older person – can they benefit from new technologies?'

International Conference on Diabetes and Metabolism 2015

23rd-24th February 2015

London, United Kingdom

This event provides a premier interdisciplinary forum for researchers, practitioners, and educators to present and discuss the most recent innovations, trends, concerns, practical challenges encountered, and solutions adopted. It also brings together leading academic scientists, researchers, and research scholars to exchange and share their experiences and research results concerning all aspects of diabetes and metabolism.

The 8th International Diabetes in Pregnancy (DIP) Symposium – Diabetes, Hypertension, Metabolic Syndrome and Pregnancy

15th-18th April 2015

Berlin, Germany

Over 1,300 healthcare professionals, from more than 70 countries, are expected to attend this event. During the event, data concerning management protocols to ensure the optimal outcome of pregnancies complicated by diabetes, hypertensions, and metabolic syndrome will be presented. Controversial topics, innovations, and clinical and laboratory revelations will all be discussed in detail, allowing this sub-specialty to come of age.

7th International Symposium on the Diabetic Foot

20th-23rd May 2015

The Hague, the Netherlands

Renowned specialists within this field are joining together to discuss the prevention, diagnosis, and treatment of lower extremity problems in diabetes. This unique multidisciplinary symposium aims to cover and provide attendees with the latest scientific developments from both basic research and clinical insights. There will be a number of interactive workshops and poster presentations which will provide information for daily clinical practices.

75th Scientific Sessions American Diabetes Association (ADA) 2015

5th-9th June 2015

Boston, USA

Fighting against the deadly consequences of diabetes, this meeting brings together nearly 18,000 participants – including more than 14,000 clinicians and researchers from over 117 countries, making this event the largest diabetes meeting in the world. Timely and significant advances in basic science and the prevention, diagnosis, and treatment of diabetes will be discussed in a number of symposia, oral abstract sessions, and discussions.

8th International Conference on Diabetes and Obesity

2nd-3rd July 2015

Riga, Latvia

The topics discussed during this event will include the latest therapeutic innovations, new pathways which will allow the development of new pharmaceutical treatments, and discussions concerning how to prevent diabetes and obesity through the use of natural ingredients. Diabetes and obesity are multi-factorial problems, therefore a multi-disciplinary understanding and approach is paramount throughout the course of the event.

51st European Association for the Study of Diabetes Annual Meeting (EASD) 2015

14th-18th September 2015

Stockholm, Sweden

The aim of the EASD annual meeting is to promote excellence in diabetes care through research and education, while also encouraging and supporting research within this field. The meeting embraces scientists, physicians, laboratory workers, nurses, and students from all over the world, all interested in diabetes and other related disciplines. The high quality of scientific research presented at the meeting is attested to by the increasing participation.

World Diabetes Congress

30th November-4th December 2015

Vancouver, Canada

With a vast amount of symposia, poster discussions, oral presentations, meet-the-expert sessions, and teaching lectures, this Congress promises to deliver the latest information in both basic and clinical science. The goal of this meeting is to drive change at all levels, from local to global, to prevent diabetes and increase access to essential medicines. To achieve this, best practice in diabetes policy and management will be encouraged.