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DIABETES

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INSIDE

Review of the 49th Annual Meeting of

EASD 2013

Barcelona, Spain

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31-34 Railway Street
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Welcome

Kelly-Ann Lazarus

Editor, European Medical Journal

Welcome to the inaugural edition of the *European Medical Journal – Diabetes,* which hosts in-depth commentary from the 49th Annual Meeting of the European Association for the Study of Diabetes (EASD), along with up-to-date, peer reviewed papers and interesting new developments in the world of diabetes, outside of the 2013 EASD Congress.

The Annual Meeting of EASD has become the world´s leading international forum for diabetes research not only for individual scientists but also for the pharmaceutical industry worldwide. This year's Congress was held in Catalonia's beautiful city, Barcelona, at the Fira de Barcelona Gran Via exhibition centre, one of the biggest and most modern convention facilities in Europe. Prof Ramon Gomis, Chairman of the Local Organising Committee for the EASD, described Barcelona as being: "an ideal place for hosting the EASD annual meeting, for it has deep roots in cultural, scientific, and intellectual life." Prof Gomis highlighted that: "the city has produced important advancements in research, healthcare, and industry."

The EASD was founded in 1965 and has membership from 130 countries including the US, China, Brazil, and India sending delegates to the 2013 Congress, showing it to be a truly international meeting. Diabetes is a serious condition which, according to the World Health Organization (WHO), affects 347 million people worldwide. Packed full of original research and ideas, this Congress was a forum where ideas and novel therapies being developed by researchers worldwide could be shared; ideas which could answer many questions, and ones which may be able to prevent the disease and enable patients to live a healthier life.

Our 'Congress Review' section highlights the key discoveries and current research being conducted in the field of diabetes as presented at EASD 2013. These include a study which is currently evaluating monozygotic twins, one obese and the other lean, that researchers hope will provide them with important clues with regards to metabolically healthy obesity. Research has also shown that older obese patients who have type 2 diabetes have a lower mortality rate compared to their young counterparts with a lower body mass index. Our Congress Review also covers the concerns raised at the Congress in Barcelona that tighter regulations in European medical device supervision (aimed to improve the safety of patients) will not protect patients with diabetes, as the majority of diabetes equipment falls into Class I or II and is therefore not covered. Further discoveries and up-to-date research are covered in our 'What's New' section, including research into a mobile phone application that could revolutionise the methods of measuring blood sugar levels.

We hope that this will prove to be an exciting and informative read for healthcare professionals within this therapeutic area and acts as a source of information that all diabetes practitioners can look to for future advancements within the field.

Kelly-Ann Lazarus

Editor, European Medical Journal

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SGLT2, sodium-glucose co-transporter-2.

Prescribing information can be found overleaf.

References:

1. FORXIGA®. Summary of product characteristics, April 2013.

2. Bailey CJ, *et al. Lancet.* 2010;**375**:2223–33.

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EASD CONGRESS 2013

MONTJUIC EXHIBITION CENTRE
BARCELONA, SPAIN
23RD-27TH SEPTEMBER 2013

Welcome to the *European Medical Journal* review of the Annual Meeting of the European Association for the Study of Diabetes 2013

EMJ EUROPEAN MEDICAL JOURNAL

EASD CONGRESS 2013

MONTJUIC EXHIBITION CENTRE
BARCELONA, SPAIN
23RD-27TH SEPTEMBER 2013

Welcome to the *European Medical Journal* review of the Annual Meeting of the European Association for the Study of Diabetes 2013

Barcelona, Spain was the setting for the 49th Annual Meeting of the European Association for the Study of Diabetes (EASD), held between 23rd-27th September 2013. A truly beautiful city bursting with personality, combining old traditions with modern ideas, the La Segrada Família being a prominent example of this, it provided an inspiring location for this auspicious event. In addition to the beautiful architecture and the Mediterranean climate, Barcelona is also a city which aims to improve the quality of life of its inhabitants by promoting a healthy lifestyle and preventing disease.

In the last two decades the city has played an active role within the international scientific community as it has made huge advancements in biomedical research. The Mayor of Barcelona, Xavier Trias, described Barcelona as being: "A city that stands at the forefront of healthcare and biomedical research with its world-renowned centres." Building alliances with biomedical societies has meant that the "EASD is leading the paradigm for diabetes research in Europe," said EASD/EFSD President, Prof Andrew J.M. Boulton, in his Presidential address.

This year, around 18,000 participants from 127 different countries attended the Congress, showing it to be a truly international meeting. The mission of the EASD congress is to 'promote excellence in diabetes care through research and education, and championing the need for better research funding within Europe, as well as safeguarding the management of those with diabetes.'

"EASD is leading the paradigm for diabetes research in Europe."

Prof Andrew J.M. Boulton, EASD/EFSD President

"This is the model which we must adopt, not only when dealing with diabetes, but with all diseases: putting patients at the forefront, adopting a more human approach, investing in research and development, and actively involving all stakeholders," said Trias.

A congress such as this enables all healthcare professionals to communicate with peers, colleagues, other scientists, and top-level researchers from all over the world, allowing knowledge and ideas to be shared in a relaxed environment. This year, over 1,300 abstracts were chosen; one discussed how effective a big breakfast, one rich in protein and fat, is for patients with type 2 diabetes compared to a smaller one. Another abstract detailed how sulfonylureas, used as first-line treatment in type 2 diabetic patients, increases the risk of all-cause mortality compared to patients who are treated with metformin.

The debates, symposia, and lectures throughout the Congress were not only original and interesting, but also enlightening, covering both basic and clinical science; all of the events throughout the 5 days reflected the ongoing efforts of both understanding diabetes and preventing it. For all those in attendance, the Congress was a fruitful and rewarding experience, enhancing knowledge, research, and understanding.

Identical twins have different metabolic health

IDENTICAL twins, one obese and the other lean, were evaluated and it was found that half of those assessed were both metabolically healthy, providing researchers with some important clues as to the mechanisms behind metabolically healthy obesity (MHO).

The study assessed 16 pairs of twins aged between 23-36 years old, with a body mass index (BMI) in the range of 20-40. The authors, Dr Kirsi Pietiläinen, Dr Jussi Naukkarinen, and colleagues from the Obesity Research Unit, University of Helsinki, Finland, studied different fat deposits and transcriptional pathways in subcutaneous adipose tissue (SAT) to analyse their relationship with MHO.

The 16 young adult obesity-discordant identical (monozygotic) twin pairs were all examined for detailed characteristics of metabolic health. An oral glucose tolerance test (OGTT) was used to determine how quickly glucose is cleared from the blood.

In eight pairs of twins, the obese twin was as metabolically healthy as their sibling, whereas, in the other half of the population, the obese twin displayed hallmarks of unhealthy obesity - a poorer blood fat profile, higher liver fat, increased insulin production and resistance, and higher blood pressure – all which can lead to diabetes, heart problems, and other complications.

Half of the pairs had around seven-times more liver fat, a 78% increase in insulin production during OGTT, significantly more disturbance in the blood fat profile, and a greater tendency for high blood pressure compared with the lean co-twin.

The authors of the study, have discussed the possibility that the MHO stage may change with age, or with advanced obesity. They suggested: "Weight differences between the groups were similar, but a given weight difference may have different metabolic effects depending on where in the distribution of BMI a pair is located."

Although the study group was small, the authors concluded: "Our results suggest that maintenance of high mitochondrial transcription and lack of inflammation in SAT are associated with low liver fat and MHO." They have also suggested that future studies of MHO may lead to new drugs which may perhaps improve mitochondrial function and prevention of inflammation in adipose tissue.

Sulfonylureas not as effective as previously thought

TYPE 2 diabetic patients who are prescribed sulfonylureas as first-line treatment have a 58% higher risk of all-cause mortality compared to those who are treated with metformin.

As sulfonylureas are commonly prescribed to type 2 diabetic patients in developed countries, "the safety of sulfonylureas needs urgent evaluation because we are potentially increasing the risk of all-cause mortality," according to Prof Craig Currie, an Epidemiologist at Cardiff University, Wales, UK.

He added: "I'm not saying this is a smoking gun. I'm just saying that regulatory agencies and [medical] societies have got to take this seriously and insist that the drug industry commissions studies to evaluate it properly."

As a result of these findings, Prof Currie suggested that this treatment may no longer be appropriate for first-line treatment. Prof Currie said: "Mortality was significantly increased in patients prescribed sulfonylureas as first-line, glucose lowering monotherapy, compared with metformin monotherapy. Whilst residual confounding and confounding by indication may remain, this study indicates that treatment with first-line monotherapy with sulfonylureas should be reconsidered."

The primary endpoint of the study was to assess the effects of sulfonylureas on all-cause mortality. In order to do this the researchers extracted data from the Clinical Practice Research Datalink (CPRD), a data resource comprising of information on around 10% of all patients who are treated in primary care in the UK from 2000 to 2012.

> "The safety of sulfonylureas needs urgent evaluation because we are potentially increasing the risk of all-cause mortality."
>
> *Prof Craig Currie, Epidemiologist, Cardiff University, UK*

The researchers evaluated a total of 76,811 patients who were prescribed metformin monotherapy, and 15,687 patients who were prescribed sulfonylureas, there was a mean follow-up of 3 years in both of these groups. Their research indicated that those patients who were treated with sulfonylureas as first-line therapy were 58% more likely to die from all-cause than those prescribed metformin.

Prof Currie concluded: "Not all general practitioners or other doctors are fully informed about the risks and benefits of commonly used drugs. Failure to identify the higher mortality associated with certain drugs could also be regarded as a failure of the regulatory system."

Breakfast: the most important meal for type 2 diabetics

A BIG breakfast, which is both rich in protein and fat, holds many benefits for patients with type 2 diabetes, including more favourable fasting blood glucose levels and post-meal insulin sensitivity, compared to eating a smaller, low calorie breakfast.

The study enrolled 59 patients, but only 47 completed it. The study analysed the effects of breakfast size and composition on blood glucose control and its association with hormone profile in adults with type 2 diabetes.

Patients were randomised into a big breakfast (BB), and a small breakfast (SB) group. Both groups had a balanced low calorie diabetic diet, however the BB consisted of a higher percentage of protein and fat.

Prof Daniela Jakubowicz, from Tel Aviv University, Israel, said: "A simple dietary manipulation of BB diet rich in protein and fat appears to have additional benefits compared to a conventional low-calorie diet in individuals with type 2 diabetes."

At the end of 13 weeks, in the BB group there were greater HbA1c and systolic blood pressure (SBP) reductions, diabetic medication doses were reduced, and hunger scores were lower, as well as greater fasting glucose. Whereas, in the SB group, a number of participants had their medication dose increased, and there were no reductions in SBP or HbA1c.

"A simple dietary manipulation of BB diet rich in protein and fat appears to have additional benefits compared to a conventional low-calorie diet in individuals with type 2 diabetes."

Prof Daniela Jakubowicz
Tel Aviv University, Israel

Dr Hadas Rabinovitz, from the Hebrew University of Jerusalem, Rehovot, Israel, said: "As the study progressed, we found that hunger scores increased significantly in the SB group while satiety scores increased in the BB group. In addition, the BB group reported a reduced urge to eat and a less preoccupation with food, while the SB group had increased preoccupation with food and a greater urge to eat over time. It is possible that a big breakfast rich in protein causes suppression of ghrelin secretion, which is reflected in enhanced satiety ratings."

More research does need to be conducted in order to confirm and clarify the mechanisms by which a simple diet approach improves satiety and leads to better glycaemic outcomes compared to a conventional dietary approach.

New medical device regulations will not protect diabetes patients

MEDICAL device supervision, believed to improve the safety of patients, has been approved by the European Commission, but the EASD believe that these new proposals are not sufficient in protecting patients with diabetes.

This news, implies the tighter regulation will not cover the extensive array of devices critical for diabetes patients, such as insulin pumps and technology that monitors blood glucose. In conjunction with the European Society of Cardiology (ESC), EASD are requesting a central European Device Agency (EDA) such as the one that already exists for drugs (the European Medicines Agency/EMA).

The European system to approve devices should be more rigorous as currently, to obtain approval of a medical device, manufacturers must be given the Conformité Européenne (CE) mark, provided by 'notified bodies' (NB). These are often private organisations operating within the regulations of the European Union member states where they are based. Once a new device has gone through the NB stage and met specifications, it will receive a certificate for a CE mark and can then be released across Europe.

Dr Deborah Cohen, Investigations Editor at the British Medical Journal (BMJ), reports that this system can be liable to 'notified body shopping' where companies search for NBs they expect will approve their respective device. Also, medical device companies may also receive advice from these NBs of how to get accepted through such a process and thus onto the market.

These changes in regulations concentrate on class three devices, which are highly complex and mostly implantable. The majority of diabetes equipment however, falls into either Class I or II and thus will not be affected. There will be another round of voting this month for the amended proposal; however, it has also been acknowledged that a central EDA has been denied. Dr Cohen added: "It's unclear how these new regulations will impact on the devices involved in diabetes or other Class II devices, though it appears to be good news for those with most complex, highest risk devices, such as hips and other implants."

"It's unclear how these new regulations will impact on the devices involved in diabetes or other Class II devices, though it appears to be good news for those with most complex, highest risk devices, such as hips and other implants."

Dr Deborah Cohen, British Medical Journal, UK

Exercise for healthy genes

EXERCISE can be beneficial to type 2 diabetic (T2D) patients, or those with obesity, as it may be able to alter the genes which are associated with these conditions, and which are present in human adipose (fat) tissue.

Dr Tina Rönn, from Lund University, Malmö, Sweden, said: "In this work we present a link between exercise and altered adipose tissue DNA methylation in candidate genes for obesity or T2D. This study highlights the dynamic feature of DNA methylation, described using a genome-wide analysis in human adipose tissue before and after exercise."

The primary outcome of the study was to evaluate how the DNA methylation pattern (how much the DNA had been chemically altered) in adipose tissue had changed both before and after exercise intervention. The small study consisted of 23 men, with a mean age of 37 years, who, at inclusion had a BMI of 28 kg/m^2. Each of the participants undertook a 6-month exercise intervention.

As a response to exercise intervention the results showed that the activities of some genes were significantly changed by exercise. There were changes in DNA methylation in 18 genes associated with obesity, and in 21 genes associated with T2D. There was also a change in mRNA expression, which may suggest that exercise could impact adipocyte metabolism. Moreover, there was a significant increase for exercise capacity, as well as 'good' cholesterol (HDL cholesterol).

Dr Rönn concluded: "Since we also observed DNA methylation changes in genes important for fat metabolism, which indicates increased fat uptake in response to exercise, these genes could potentially be a target for future drugs."

"Since we also observed DNA methylation changes in genes important for fat metabolism, which indicates increased fat uptake in response to exercise, these genes could potentially be a target for future drugs."

Dr Rönn,
Lund University,
Malmö, Sweden

Diabetes sufferers benefit more from lifestyle advice

A NEW study revealed that lifestyle advice should be the same for those with diabetes as the general public, however, it may be diabetes sufferers who benefit the most from these tips.

Researchers compared lifestyle choices and mortality in diabetes sufferers and those without the disease.

Dr Diewertje Sluik, Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany, led the study on 6,384 people with diabetes and 258,911 without. They used a cohort from the European Prospective Investigation into Cancer and Nutrition (EPIC). Risk factors were modelled against mortality to analyse their association in those with and without diabetes. These factors include; body-mass index, waist/height ratio, 26 food groups, alcohol consumption, leisure-time, physical activity, and smoking.

Lifestyle factors indicated no difference between those with and without diabetes. Whereas, the researchers found overall mortality was 62% higher in people with diabetes. Along with previous nutritional advice, the intake of fruit, vegetables, nuts, seeds, pasta, poultry, and vegetable oil was linked to lower mortality. Higher mortality was thus connected to the intake of margarine and butter. These different foods were given distinct associations with mortality rates, with respect to direction, whilst the levels of these linkages were to different extents between diabetes patients and those without.

Dr Sluik stated; “It appears that the intake of some food groups is more beneficial (fruits, legumes, nuts, seeds, pasta, poultry, vegetable oil) or more detrimental (soft drinks, butter, margarine, cake, cookies) with respect to mortality risk in people with diabetes. This may indicate that individuals with diabetes may benefit more from a healthy diet than people without diabetes. However, since the directions of association were generally the same, recommendations for a healthy diet should be similar for people with or without diabetes.”

Better mortality rates for older obese patients

OLDER patients who have type 2 diabetes and are obese have a lower mortality rate compared to their younger counterparts who have a lower body-mass index (BMI). This finding could suggest that obesity offers metabolic protection from death in older patients with type 2 diabetes.

Data were collected from patients who attended the diabetes service at Hull and East Yorkshire Hospitals National Health Service (NHS) Trust, UK, from 1995 and 2011.

"Previous reports have been limited by statistical power and confounders," said Dr Pierluigi Costanzo, from the University of Hull and York, UK. "In this analysis the relationship between BMI, mortality, and cardiovascular (CV) morbidity was investigated in a prospective cohort, with a long-term follow-up and a large number of events."

A total of 12,025 patients with diabetes – 54% men, 1,761 of these (15%) with type 1 diabetes, the remainder with type 2 diabetes – were enrolled with a mean follow-up of 10 years. The subjects were divided according to BMI quartiles and in age tertiles.

During these 10 years it was found that acute coronary syndrome (ACS) occurred in 9% of patients, cerebrovascular accidents (CVA) occurred in 7%, heart failure (HF) hospitalisations in 6%, there was also a total of 4,125 deaths during this time.

The risk of HF, ACS, CVA, and CV was greater in overweight patients, while in patients with a normal BMI the risks of ACS, and HF were lowest. However, all-cause mortality was lowest (by 25%) in obese subjects compared to normal weight patients. In patients over the age of 67 years, the risk of death was reduced by 18% compared to younger patients with a lower BMI.

Dr Costanzo said: "In this study, in patients with type 2 diabetes, although being overweight was associated with an increased risk of CV events, higher BMIs were associated with a survival benefit, especially amongst older patients. Diabetes induced by the metabolic stress of obesity may be a fundamentally different problem from diabetes that develops in the absence of the stress of obesity. Alternatively, obesity may provide a protective metabolic reserve in older diabetic patients."

In the next stage of the research, information regarding the cause of mortality will be gathered, this will allow the researchers to assess whether there are different causes of death in obese diabetic patients compared with their leaner counterparts.

> "Obesity may provide a protective metabolic reserve in older diabetic patients."
>
> *Dr Pierluigi Costanzo*
> *University of Hull, UK*

Male type 1 diabetes sufferers: more in control of their blood sugar

> "In this analysis of type 1 diabetes data from several countries males were more likely to have a better blood sugar control profile than females. Further work is required to investigate explanations for this finding."
>
> *Prof Sarah Wild, University of Edinburgh, UK*

RESULTS indicating differences in blood sugar control illustrate that men with type 1 diabetes are better at maintaining their sugar levels. However, there is not a significant difference in control between boys and girls.

Professor Sarah Wild, University of Edinburgh, UK, led the study presenting this information, using the International Quality of Care for Type 1 Diabetes (IQoC-T1) Group. There are narrow data providing differences in blood sugar control between the sexes, but Prof Wild explored this issue in the dataset considering patients from 12 countries, totalling 142,260 children and adults with diabetes.

Blood sugar control was analysed over 12 to 24 months, using population-based registers and clinic databases. The proportions of people with HbA1c ≥7.5% (58 mmol/mol) indicates poor blood sugar control.

Researchers discovered the proportions of people with HbA1c ≥7.5% ranged from 64.4% in boys less than 15 years old to 74.0% in women of 15-29 years. The youngest group showed no disparity between boys and girls. Women in the age category 15-29 were 8% more likely to miss the target than men of this age. Women over 30 were shown to be 6% more likely to miss the target than men.

Prof Wild stated: "In this analysis of type 1 diabetes data from several countries males were more likely to have a better blood sugar control profile than females. Further work is required to investigate explanations for this finding." She suggested the root of this could be down to women having lower haemoglobin levels than men, justifying the higher HbA1c levels.

Social deprivation a key factor in diabetic mortality

LEVELS of social deprivation and blood sugar control can be deemed independent risk factors for type 1 diabetics' mortality rates.

Research by the Diabetes Clinical Academic Group at King's Healthcare Partners, UK, analysed blood sugar control, demographics, and health resource utilisation data collected over a 10-year period for a cohort of 1,038 type 1 diabetic patients attending two inner city London specialist diabetes outpatient clinics.

Presented by Dr Stephen Thomas, from the Department of Diabetes and Endocrinology at Guy's and St Thomas' Hospitals NHS Foundation Trust (GSTT), London, UK, the study results revealed that 61% of deceased patients held scores in the poorest 20% of the population range.

"Glycaemic control and social deprivation are independent risk factors for mortality in type 1 diabetes and identify areas where we need to target interventions to improve health outcomes," Dr Thomas said.

Patients attended the service in 2002 and were followed-up until 2010 with their economic status evaluated using the index of multiple deprivation (IMD), a weighted deprivation score derived from a national dataset based on their residential postcode. The group had a mean age at baseline of 42 years, and had been diabetic for an average of 18 years, with 37 deaths having occurred by 2012.

Dr Thomas concluded: "This data analysis is ongoing and offers the possibility of much needed insights into where healthcare outcomes need to be addressed."

Positive opinion for INVOKANA® use in the EU

INVOKANA® (canagliflozin), which was developed by Janssen-Cilag International NV (Janssen), has received a positive opinion recommendation from the Committee for Medicinal Products for Human Use (CHMP). Canagliflozin will help to improve glycaemic control in adults with type 2 diabetes.

The World Health Organization (WHO) estimates that 90% of the diabetes population has type 2 diabetes. If canagliflozin is approved for use in Europe then it will be able to provide a new treatment option for the management of type 2 diabetes in adults.

Prof David R. Matthews, from the Oxford Centre for Diabetes, Endocrinology, and Metabolism, University of Oxford, UK, said: "In Europe, the prevalence of type 2 diabetes continues to be on the rise. Despite there being a number of treatments currently available, many patients are still not able to achieve and maintain long-term control of their blood sugar."

> "Despite there being a number of treatments currently available, many patients are still not able to achieve and maintain long-term control of their blood sugar."
>
> *Prof David R. Matthews*
> *University of Oxford, UK*

Canagliflozin is an oral, once-daily medication which belongs to a new class of medicine called sodium glucose co-transporter 2 (SGLT2) inhibitors. By selectively inhibiting SGL2 canagliflozin is able to promote the loss of glucose via the urine, which in turn, will lower the blood glucose level.

The Phase III clinical programme enrolled more than 10,300 patients in nine studies. The programme evaluated both the efficacy and tolerability of canagliflozin in patients who need further glucose control as a single agent (monotherapy), in combination with metformin, and with other glucose-lowering agents, including insulin.

Jane Griffith, Group Company Chairman of Janssen Europe, Middle-East and Africa, said: "This positive opinion from the CHMP represents a major milestone in Johnson and Johnson's longstanding commitment to diabetes. If approved, INVOKANA® will pave the way for Janssen as part of our goal to develop and provide new therapeutic options for adult patients with type 2 diabetes."

'Bad' variants increase risk of type 2 diabetic mortality

GENETIC variations, KCNJ 11 E23k polymorphism, which are associated with type 2 diabetes and are prevalent in 40% of this population, can be related to an increased risk of cardiovascular mortality by at least 20%.

The aim of this study was to assess whether variants influencing type 2 diabetes and/or glycaemic traits are also associated with an increased risk on total mortality/ cardiovascular mortality. The researchers analysed 30-36 common genetic variants in a total of 3,610 patients.

The results of the study found that the carriers of the 'bad' variant of KCNJ11 E23k had a 42% increased total mortality rate, with a 10% increased risk of overall mortality, and a 44.5% increased risk of cardiovascular disease (CVD)-related mortality. A second meta-analysis included 5,469 patients, of these 820 had CVD-related deaths. The carriers of the 'bad' variant had a 21% increased risk of CVD mortality.

Dr Sami Alkayyali, Lund University, Malmö, Sweden, said: "We demonstrated that the KCNJ11 E23K variant is associated with increased risk of CVD-mortality in patients with type 2 diabetes, and thus, seems to be a common denominator in the pathogenesis of type 2 diabetes and cardiovascular complications."

The next stage in the research is to identify patients who are treated with sulfonylureas who may be at different risks for mortality depending on their genetic background.

IS IT TIME TO TRANSFORM OUR TREATMENT OF TYPE 2 DIABETES?

Summary of Presentations from the Bristol Myers Squibb/ AstraZeneca Alliance Symposium, European Association for the Study of Diabetes (EASD) 49th Annual Congress, Barcelona, Spain, 23rd September 2013.

Chairperson

Michael Nauck,[1] Dídac Mauricio,[2] Anthony Barnett[3]

Speakers

Tina Vilsbøll,[4] Samy Hadjadj,[5] Peter Rossing,[6] Edoardo Mannucci,[7] Harald Darius,[8] Chantal Mathieu[9]

1. Head, Diabeteszentrium Bad Lauterberg, Harz, Germany

2. Chief Physician, Department of Endocrinology & Nutrition, Germans Trias i Pujol University Hospital, Badalona, Spain

3. Professor of Medicine, University of Birmingham, UK

4. Professor of Medicine, Head of the Diabetes Research Division, Gentofte Hospital, Copenhagen, Denmark

5. Department of Diabetology, Poitiers University Hospital, France

6. Head of Research, Steno Diabetes Centre, Professor of Diabetic Angiopathy, Aarus University, University of Copenhagen, Denmark

7. Director, Diabetes Agency of Careggi Teaching Hospital, Florence, Italy

8. Director, Department of Cardiology, Vascular Medicine and Intensive Care Medicines, Vivantes Neukölln Medical Centre, Berlin, Germany

9. Professor of Medicine, Katholieke University, Leuven, Belgium

Disclosure: Speakers participating in this symposium received honorarium from Bristol-Myers Squibb.

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MEETING SUMMARY

This meeting comprised two sessions: the morning session centred around glucagon-like peptide-1 receptor (GLP-1R) agonists and SGLT-2 inhibitors, a new class of glucose-lowering compounds, while the afternoon session focused on new results of cardiovascular safety studies with diabetes medications, with special attention to the SAVOR-TIMI trial of saxagliptin.

Morning Session – Catalysts for Change?

How Can GLP-1 Receptor Agonists and SGLT-2 Inhibitors Help Us Reshape Individualised Diabetes Care?

Addressing the Type 2 Diabetes Pandemic: The Need for Transformational Thinking and Innovative Treatments

Professor Dídac Mauricio

Prof Mauricio began by highlighting the disease burden of type 2 diabetes (T2D) and indicated that previous predictions on prevalence of burden are far behind the reality of the situation. By 2030, there will be more than 500 million people around the world affected by T2D.[1,2] In recent years, diabetes has been estimated to account for 4–13% of national healthcare budgets in Europe,[3] with the estimated average yearly cost per patient at €2,834.[4]

The progressive nature of the disease also contributes to the burden; long-term complications develop that ultimately require additional treatment resources. Examples include macrovascular complications such as cardiovascular (CV) disease, and microvascular complications such as nephropathy, neuropathy and retinopathy.[5] Patients with T2D have a 2 to 4-fold higher risk of coronary heart disease than those without the condition, and 75–80% die due to CV events.[6]

Prof Mauricio discussed the benefit of early therapy in newly diagnosed T2D in reducing long-term complications. In the UK Prospective Diabetes Study (UKPDS), newly diagnosed patients were randomised to receive either conventional therapy (dietary restriction) or intensive therapy (sulphonylurea or insulin, or metformin if >120% ideal body weight). Early intensive intervention provided benefits not only for microvascular disease but also for myocardial infarction (MI).[7] The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) now recommend early, patient-centred treatment in order to manage hyperglycaemia.[8]

Prof Mauricio presented recent European data concerning glycaemic control showing that conventional therapy is suboptimal, and patients receiving more complex treatments are less likely to achieve their target glycated haemoglobin (HbA1c).[9] He stressed that glycaemic control is not the only approach to consider when treating T2D; a multifactorial approach is essential, and comorbidities, efficacy, hypoglycaemia, weight, and cost have to be taken into account.

New Evidence from GLP-1 Receptor Agonist Studies: Their Role in Diabetes Care

Professor Michael Nauck

Prof Nauck started his presentation by giving an overview of the mechanism of action of GLP-1 receptor (GLP-1R) agonists. GLP-1 affects gastric motility and metabolism and reduces appetite; activation/stimulation of GLP-1Rs with GLP-1 agonists could provide a potential avenue for treatment of T2D. Endogenous GLP-1 has a short half-life (<2 minutes) due to degradation and inactivation by DPP-4, requiring GLP-1 analogues to have a longer half-life to be effective.[10] A number of GLP-1R agonists are available, which mainly differ in terms of their pharmacokinetic profile. Exenatide achieves peak plasma concentration 2 hours after injection, while liraglutide maintains high concentrations even after 24 hours.[11,12]

Prof Nauck presented results from the DURATION-1 study where long-acting once-weekly exenatide was more effective at lowering HbA1c and fasting glycaemia than the short-acting twice-daily formulation, but not at lowering body weight.[13] A comparison of the DPP-4 inhibitor sitagliptin and injectable GLP-1R agonist liraglutide showed that the injectable liraglutide was more potent in reducing glycaemia and body weight when compared to sitagliptin.[14]

Prof Nauck highlighted that the results of meta-analyses have shown that there is a higher likelihood of achieving target HbA1c levels with a GLP-1R agonist when compared to insulin, even more so when a longer-acting preparation is used, as was shown with exenatide once weekly in DURATION-3 study up to 3 years.[15] It was Prof Nauck's opinion that the short-acting GLP-1R agonists should be used in combination with long-acting insulin because they show a beneficial effect on postprandial glucose excursions.

Clinical Experience: How Can GLP-1 Receptor Agonists Improve Daily Life for Patients?

Professor Tina Vilsbøll

Prof Vilsbøll discussed the treatment options for diabetes available in her practice. When she first

decides on a treatment, she has to consider its efficacy with respect to change in HbA1c, change in body weight and risk of hypoglycaemia. Prof Vilsbøll noted that compared to sulphonylureas, thiazolidinedione and insulin, GLP-1R agonists have favourable efficacy outcomes since they reduce both HbA1c and body weight, with low hypoglycaemic risk.[8,16-18]

Prof Vilsbøll asked how GLP-1R agonists could improve daily life. She first looked at their effect on HbA1c, citing a meta-analysis performed in her lab that compared exenatide once-weekly, exenatide twice-daily and liraglutide to all the non-GLP-1R agonists given for more than 20 weeks in clinically-relevant doses. The GLP-1R agonists provided a sustained 0.6% difference HbA1c after 20 weeks.[19] GLP-1R agonists have also been shown to cause a reduced level of hypoglycaemia compared to insulin glargine, especially when on a non-sulphonylurea background,[17,20] and therefore may represent an improvement in treatment in this respect.

Patients with T2D have a 2 to 3-fold increase in risk of pancreatitis, and GLP-1R agonist therapies do not change this risk.[21-29] The European Medicines Association concluded that there are no new concerns for GLP-1 therapies based on the available evidence,[30] and Prof Vilsbøll was of the view that the side-effect profile is acceptable considering the sustained effect GLP-1R agonists have on glycaemic control, body weight, and hypoglycaemia.

An Innovative Treatment Target for Managing Type 2 Diabetes: Evidence from SGLT-2 Inhibitor Trials

Professor Samy Hadjadj

Prof Hadjadj started his presentation by introducing the sodium glucose co-transporter-2 (SGLT-2) inhibitors for the treatment of T2D. Currently, there are many of these drugs in clinical development, with the first-in-class dapagliflozin approved in the EU and canagliflozin approved in the USA.[31] SGLT-2 is expressed in the renal proximal tubule, and causes reabsorption of glucose back into the bloodstream. An SGLT-2 inhibitor such as dapagliflozin inhibits this reabsorption, leading to an increase in glucose excretion and caloric loss. This mechanism is specific to the kidney due to the localisation of SGLT-2 receptors.[32-35]

Prof Hadjadj presented data comparing dapagliflozin to current therapies. Dapagliflozin combined with metformin XR in drug naïve patients provided an even greater reduction up to 2% in HbA1c and body weight compared to metformin alone. In patients with background metformin therapy, these reductions were sustained well beyond the primary endpoint of 24 weeks; at 102 weeks patients treated with the combination therapy had a 0.78% reduction in HbA1c.[36,37] When dapagliflozin is used as part of triple-combination therapy it helps to reduce HbA1c and body weight in patients with T2D.[38] Other combinations of medications, such as empagliflozin in combination with metformin and sulphonylurea produce similar effects.[39]

Prof Hadjadj highlighted that SGLT-2 inhibitors have a low propensity to cause hypoglycaemia. Dapagliflozin in particular is no different to placebo in this respect.[40] Side-effects, such as genital and urinary tract infections, are manageable.[35,41,42] Professor Hadjadj noted that the incidence for bladder cancer was slightly raised in patients treated with dapagliflozin. He commented that this might be explained by a better opportunity to more efficiently diagnose bladder cancer, because the mechanism of action on urine outflow makes it easier to observe haematuria.[43] A meta-analysis for major adverse CV events showed no warning signal for dapagliflozin treatment.[44]

Clinical Experience with Dapagliflozin

Professor Peter Rossing

Prof Rossing outlined the current problems with diabetes disease progression and treatment. It has been shown that progressive loss of glycaemic control occurs in T2D patients, irrespective of treatment.[45] SGLT-2 inhibitors may provide some of the features that are necessary for obtaining good control of glucose and some of the other risk factors. SGLT-2 inhibitors act on glucose, body weight and blood pressure, and have a very low-risk of hypoglycaemia.[42] The SGLT-2 inhibitor dapagliflozin is indicated to improve glycaemic control as both a combination and monotherapy.[42]

Prof Rossing presented case studies. The first case was Anna, a 42-year-old female diagnosed with diabetes. After two years her HbA1c started to rise and her body weight increased. The patient was prescribed dapagliflozin, since she had normal

liver function, preserved renal function, and did not want to risk hypoglycaemia due to her active lifestyle. The patient responded very well to treatment and was happy with the results.

John, a 55-year-old male, who was severely obese and a heavy smoker, did not drastically improve his lifestyle after diagnosis. After metformin administration he lost weight and had a large reduction in HbA1c, but like Anna this control waned after time. Treatment with DPP-4 inhibitors, GLP-1R agonists and insulin were not effective. Despite his slightly lowered GFR, the patient was prescribed dapagliflozin since other prescribing considerations such as liver function and infection history were normal. Dapagliflozin treatment led to a reduction in body weight and HbA1c.

Prof Rossing concluded that better treatment for glycaemia is needed. SGLT-2 inhibitors work in the kidneys and complement the action of metformin and other anti-diabetic drugs. Blocking SGLT-2 reduces blood glucose and has other beneficial effects on body weight and BP, with a low-risk of hypoglycaemia.

Afternoon Session – SAVOR Trial

How May the Largest DPP-4 Inhibitor CV Safety Study Influence Day-to-Day Clinical Practice?

From UKPDS to SAVOR: The Evolving Landscape of CV Outcomes Studies in Type 2 Diabetes

Professor Anthony Barnett

Prof Barnett presented the results of CV risk factor intervention trials from a glycaemia perspective. The UKPDS remains the first large-scale study of intensive versus conventional glucose control in T2D. In this study, over a mean of 10 years the difference in favour of tight control was 0.9% HbA1c, which was associated with a 25% risk reduction for microvascular complications.[45] After a further 10 years, patients from the UKPDS were followed-up; despite the fact that during the interim period there was no effort to maintain treatment and that HbA1c levels were the same between both groups, the intensively-treated patients had significantly improved health outcomes.

Prof Barnett then presented the PROactive study, the conclusions of which are still hotly debated. This study showed that oral pioglitazone reduced the composite endpoint of all-cause mortality, non-fatal MI and stroke in patients with T2D but with increased side-effects, particularly of heart failure.[46,47] Other confounding CV outcomes were also shown in the ACCORD and ADVANCE studies.[48,49] The VADT and ORIGIN study also showed similar results, that glycaemic control had a neutral effect on CV outcomes.[50,51]

Prof Barnett asked what we can conclude from these studies. His suggestion was that there is no one-for-all approach to glycaemic control, and that by increasing risk and rates of hypoglycaemia the benefits of tight glycaemic control may be negated. The current ADA and EASD Joint Position Statement, therefore, recommends an individualised approach to treatment targets.[8] As a result of causing more CV events, an increase in heart failure and MI risk, the thiazolidinedione rosiglitazone was withdrawn in the EU, and the EMA stated that 'a new glucose-lowering agent should preferably show a neutral or beneficial effect on parameters associated with CV risk'.[52-54]

Introducing the Latest CV Safety Studies in Type 2 Diabetes

Professor Edoardo Mannucci

Prof Mannucci started his presentation by discussing the case of rosiglitazone. In 2007, a meta-analysis of rosiglitazone studies suggested that its use could be associated with a relevant increase in the incidence of MI and also possibly CV mortality.[53] As a result of these findings, the Food and Drug

Administration (FDA) imposed new rules for the approval of newly-developed glucose-lowering agents; in particular, drugs must demonstrate CV safety, specifically by showing that they do not increase CV events by more than 30%.[55]

Since the FDA regulations only apply to drugs marketed after 2009, many older drugs that are currently used for treatment would not get approved if developed today. Only two current drugs have shown reliable data from large-scale CV outcome trials: pioglitazone and insulin were shown to be safe in the PROactive and ORIGIN trials, respectively.[46,51] There are a lack of good quality data for the CV safety of metformin, however a meta-analysis of all metformin trials showed that the drug is associated with a significant reduction in the incidence of major CV events,[56] and from this it can be concluded that under current FDA guidelines metformin would likely be approved. Similar results were shown for sulphonylureas and DPP-4 inhibitors.[29]

Prof Mannucci asked the audience about their experience with DDP-4 inhibitors; 10% of the audience's patients were receiving these drugs as secondary prevention after a major CV event. Prof Mannucci concluded by discussing the characteristics of the patients entered into these trials, specifically that those enrolled into large CV outcome trials are not representative of the general population. As such, when considering treatment options, the results of trials such as EXAMINE and SAVOR must be placed into context of the patient population.

Key Findings from the SAVOR Study: The Effects of Saxagliptin

Professor Harald Darius

Prof Darius presented findings from the SAVOR study of the DPP-4 inhibitor saxagliptin, conducted in T2D patients with CV risk. The primary endpoint of the trial was namely CV death, non-fatal MI, and non-fatal ischaemic stroke. The study met this endpoint, meaning that CV risk increase could definitely be ruled out with a very high statistical power.[57] Saxagliptin was not shown to be superior to placebo in terms of efficacy.

The secondary endpoint, which included hospitalisations, came to a rate of 6.6% for saxagliptin and 6.5% for placebo, which again satisfied FDA requirements.[57] In terms of glycaemic control, Prof Darius noted that saxagliptin treatment led to a significant reduction in HbA1c compared to placebo: 7.5% versus 7.8% at year 2. The proportion of patients achieving a HbA1c of less than 7% was also increased in the treatment group. Fewer patients in the saxagliptin group required the addition or increase of any new anti-diabetic therapies, or initiation of insulin therapy for more than 3 months.[57,58]

Saxagliptin neither reduced nor increased the risk of the primary composite endpoint of CV death, MI, or ischaemic stroke in comparison to placebo, in patients with a very high CV risk. In addition, the saxagliptin group experienced an improved glycaemic control, an increased rate of hypoglycaemic events but not hospitalisation for hypoglycaemia, a higher rate of hospitalisation for heart failure, a reduced requirement for insulin or other diabetes medications, a favourable effect on microalbuminuria, and no increased risk of pancreatitis or pancreatic cancer.

The Potential Impact of SAVOR on Clinical Practice

Professor Chantal Mathieu

Prof Mathieu presented her views on the SAVOR trial. A major positive from the trial was that it met its primary safety endpoint, namely no increased risk of CV death, non-fatal MI, and non-fatal stroke. Thus, indicating there was no difference between the treatment and placebo groups (hazard ratio=1.0).[57,58] Another positive outcome was that the trial also met its secondary endpoint (composite primary endpoint plus hospitalisation for heart failure), and in Prof Mathieu's opinion this was an important result, and based on these data she would recommend saxagliptin as a safe drug to use in T2D treatment.

Prof Mathieu suggested that the 0.3% HbA1c difference observed between the treatment and placebo groups may diverge after additional time beyond the current 2-year measurement, since other studies only saw differences after several years of treatment. Prof Mathieu expressed a positive opinion about the safety profile of saxagliptin, in particular regarding pancreatitis and pancreatic cancer.

Prof Mathieu concluded that SAVOR provides an important set of data on the safety and efficacy of this DPP-4 inhibitor, and that the lack of increase in CV risk was a major finding. Stable glucose lowering and the lack of increase in pancreatitis and pancreatic cancer were also important findings. She ended her presentation by polling the audience on whether they were reassured about the use of DPP-4 inhibitors. Two-thirds of the audience were convinced by the data.

How Could We Transform Treatment in Type 2 Diabetes: Which Approach, When and for Whom?

A broader panel discussion then took place involving speakers from both sessions of the meeting. Discussion began by examining the evidence for metformin in the treatment of early stages of diabetes. Prof Mannucci stated that we cannot be sure that metformin is superior to other drugs, despite its effectiveness and safety, and that if another drug was developed that showed clear superiority it would replace metformin as first-line therapy.

The panel then discussed how recent trials such as SAVOR may change treatment strategies. Regarding the concept of treatment individualisation, Prof Barnett stressed that the whole package of treatment must be considered, not just pharmacotherapy. Adherence rates to therapy are very low, and as such, patient needs, lifestyle and attitude must be considered in addition to clinical factors. Prof Mathieu added that cost must be considered as part of this treatment package, since in her opinion sulphonylureas would not be used if they are more expensive.

One question asked whether the results of the SAVOR and EXAMINE trials could be used to generalise for the DPP-4 inhibitors and GLP-1R agonists. It was Prof Vilsbøll's opinion that it is unlikely we will get any surprises in patients having CV heart failure with DPP-4 inhibitor trials.

Prof Mauricio asked the panel for their opinion on the best method for treatment individualisation since phenotyping for patients is currently lacking. Prof Nauck concluded the panel discussion by suggesting that the best method of individualisation is to take into account all of a patient's characteristics, such as obesity and previous efforts at weight loss, since these will inform choices of medication.

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DIABETES MELLITUS AND PERIODONTITIS: SIGNS OF A BIDIRECTIONAL RELATIONSHIP

Pınar Gümüş, Nurcan Buduneli

Department of Periodontology, School of Dentistry, Ege University, İzmir, Turkey

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ABSTRACT

Periodontitis is a multifactorial, irreversible and cumulative condition, initiated and propagated by bacteria and host factors. The multifactorial nature of periodontitis is related with the complex interactions between microorganisms in the microbial dental plaque and host response mechanisms, as well as environmental factors. Progression of periodontal disease is very much dependent on host response. Diabetes mellitus (DM), a complex metabolic disorder characterised by prolonged hyperglycaemia, has long been recognised as one of the leading causes of morbidity and mortality globally. DM is a complex metabolic syndrome that affects both the quality and length of life with major complications. Periodontal disease and diabetes are highly prevalent chronic diseases and inflammation may play a critical role in their relationship. Prospective clinical studies with larger scale and greater statistical power are required to better clarify the mechanisms of possible effects of chronic periodontitis on diabetes.

Keywords: Diabetes mellitus, periodontal disease, saliva, inflammation, serum.

INTRODUCTION

Periodontal tissues consist of four components: gingiva, periodontal ligament, cementum, and alveolar bone (Figure 1). Periodontal diseases are among the most common chronic infectious and inflammatory diseases in the world. Pathogenesis of periodontal diseases has two major aspects: microorganisms and host response. Interactions between microbial plaque and host immune system play a critical role in the initiation and progression of periodontal diseases. Diabetes mellitus (DM) has long been recognised as one of the leading causes of morbidity and mortality globally.[1] This brief review highlights the evidence for a bidirectional relationship between DM and periodontal disease.

SEARCH STRATEGY

A literature search of the last thirty years was performed using the ISI and PubMed database from 1980 to 30 April 2013, with the following search strategy: ("periodontitis" OR "periodontal disease") AND ("diabetes mellitus") AND ("treatment" OR "interaction" OR "metabolic control") AND ("saliva" OR "gingival crevicular fluid" OR "serum"). The search was limited to the English language. *In vitro* studies on cell cultures, experimental studies on animal models, polymorphism studies, studies particularly investigating possible role of various therapeutic agents such as subantimicrobial-dose doxycycline, anti-inflammatory agents, and studies focused only on smoking were excluded from the present review. Titles and abstracts were screened and the full text of publications was obtained for the selected articles. In addition, the reference lists of review papers were hand searched.

DEFINITIONS OF PERIODONTITIS AND DIABETES MELLITUS

Healthy gingiva has a pink colour and firm consistency with no sign of inflammation (Figure 2). Periodontitis is characterised by gingival inflammation and alveolar bone resorption. Gingival inflammation is visualised by gingival

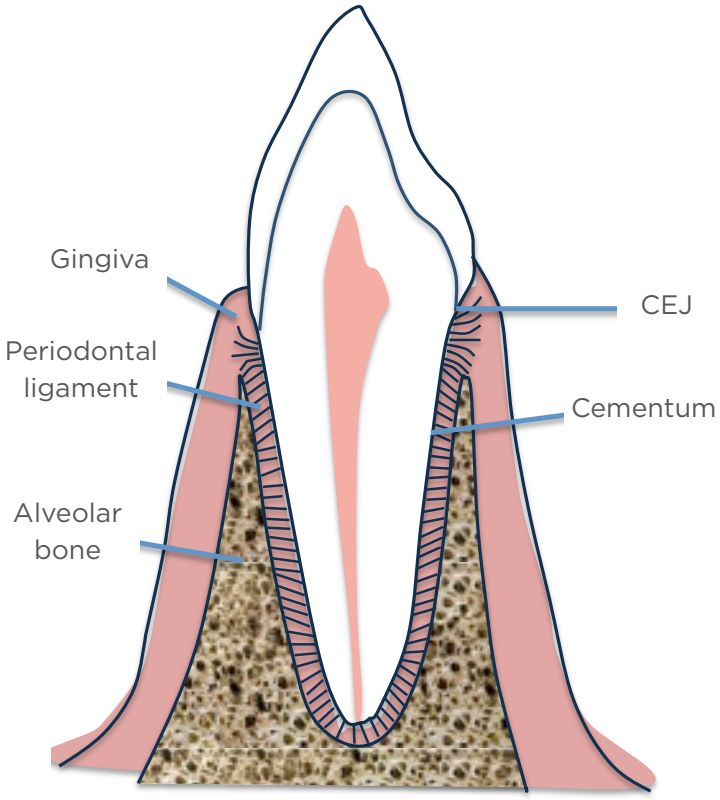

Figure 1. Diagram of healthy periodontal tissues namely; gingiva, periodontal ligament, cementum, and alveolar bone.
The cementoenamel junction (CEJ) is at the base of the sulcus, the periodontal ligament fibres are all intact lying between cementum on the root surface and the alveolar bone. Thus, there is no attachment loss and no pocket when probed with a periodontal probe. Pocket depth (PD) is the distance between the free gingival margin and the base of the sulcus/pocket in millimetres. Clinical attachment level (CAL) on the other hand shows the distance from the CEJ to the base of the sulcus/pocket.

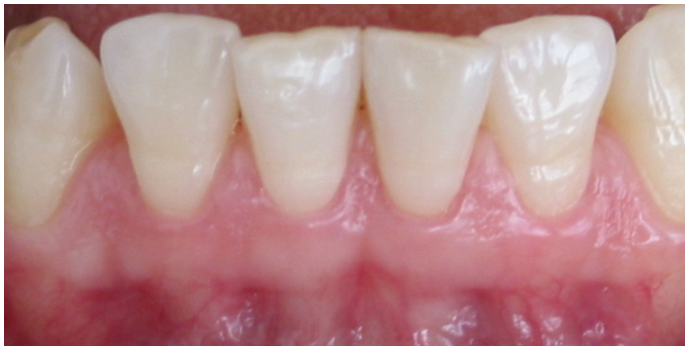

Figure 2. Clinical picture of healthy teeth and periodontium.
Inflammation-free gingiva is characterised by a coral-pink colour, there is no sign of oedema or bleeding and the gingiva is tightly surrounding the tooth.

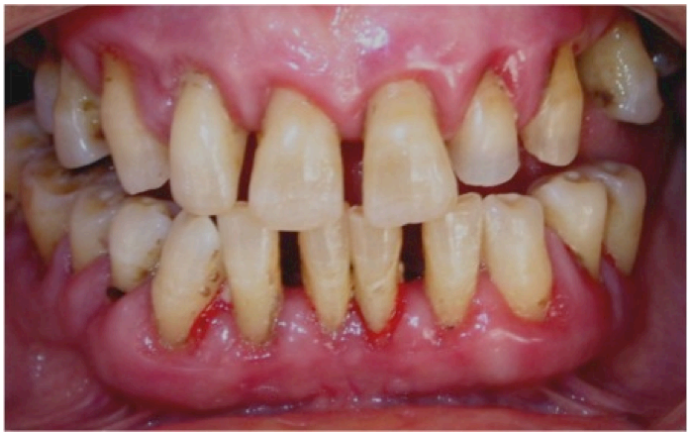

Figure 3. Clinical picture of a case of severe chronic periodontitis with type 2 diabetes mellitus.
Note the pronounced gingival inflammation, bleeding, and swelling, but also gingival recession. There is visible plaque accumulation at the necks of the teeth and calculus deposits are also easily detectable. The upper anterior teeth had migrated due to severe periodontal destruction and lost their contacts with each other.

reddening, oedema, and bleeding on probing (BOP) with a periodontal probe (Figure 3). Alveolar bone resorption can be detected radiographically and also clinically by measuring the probing depth and clinical attachment level (CAL) in millimetres by a periodontal probe. The World Health Organization reported that severe chronic periodontitis leading to tooth loss was found in 5-15% of most populations worldwide. Periodontitis is a chronic local oral infection regarded as triggering not only a local but also a systemic immuno-inflammatory response.[2] More than 500 different bacterial species are able to colonise the oral biofilm and up to 150 different species of bacteria are possible in any individual's subgingival plaque. Systemic diseases and conditions may affect the onset and course of periodontal disease or vice versa.

DM is a complex metabolic syndrome that affects both the quality and length of life with major complications, which is caused by either a deficiency in insulin production or an impaired utilisation of insulin. Type 1 DM is caused by progressive autoimmune destruction of pancreatic insulin-producing ß cells. Type 2 DM describes a metabolic disorder of multiple aetiology,

characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action or both.[1]

EPIDEMIOLOGY

Clinical and epidemiological studies have reported higher prevalence and increased severity of periodontitis in diabetic patients.[3-5] It was reported that type 2 DM patients are 2.8 times more likely to have periodontitis,[6] and 4.2 times more likely to have significant alveolar bone loss[7] than systemically healthy individuals. Indeed, periodontal disease has been proposed to be the sixth complication of DM[8] with evidence showing a correlation between poorer glycaemic control and worsening periodontal health.[9,10] Higher gingivitis index and gingival recession in diabetic patients compared to the systemically healthy controls were reported.[11] Higher gingival index and attachment loss were also associated with HbA1c levels in diabetic patients.[12] HbA1c correlated positively with percentage of sites that bleed on probing and sites exhibiting probing depths ≥5 mm.[13] The best predictor for severe periodontal disease in subjects with type 2 DM has been reported to be smoking followed by HbA1c level.[14] Diabetic patients commonly present with xerostomia[15] and lower salivary flow rates compared to the systemically healthy controls. Thus, there is substantial information supporting a close association between DM and periodontitis.[16]

INTERSECTIONS IN PATHOGENIC MECHANISMS

Diabetes-associated susceptibility traits for periodontitis include neutrophil dysfunction, abnormal cross-linking and glycosylation of collagen, defective secretion of growth factors, cytokines and subsequent impaired healing. Reactive oxygen species have a role in periodontal diseases as well as diabetes. Prolonged inflammation, such as periodontitis, is a source of reactive oxygen species and can compromise the antioxidant capacity of serum and tissues.[17] Significantly higher salivary glutathione peroxidase and reductase activities with lower mean glutathione level was reported in DM patients.[18] Oxidative stress burden was increased in serum and saliva resulting in different redox state of DM patients from that of normoglycaemic control subjects.[19] Reduced salivary glutathione concentrations were noted in type 1 DM patients as a sign for careful follow-up of these patients in regards to periodontal disease.[20] Moreover, gene expression of antioxidant enzymes in gingival tissue was up-regulated in the poorly-controlled diabetic group with periodontitis.[21]

DM-induced changes in immune cell function also up-regulate proinflammatory cytokines from monocytes/polymorphonuclear leukocytes and down-regulate growth factors. This creates a predisposition to chronic inflammation, progressive tissue breakdown, and diminished tissue repair capacity. DM patients have elevated levels of advanced glycation end-products (AGEs) in their gingival tissues that may be associated with a state of enhanced oxidant stress, a potential mechanism for accelerated tissue injury.[22] AGEs can interact with specific receptors on cells, such as macrophages, impairing chemotactic and phagocytic function of polymorphonuclear leukocytes and stimulating the production of matrix metalloproteinases and IL-1ß.[23] Monocytes from DM patients produce significantly greater amounts of IL-1ß, and prostaglandin E2 (PGE2) than non-diabetic controls.[24,25] These proinflammatory cytokines may partially explain the increased severity of periodontitis in diabetic patients.

The level of metabolic control has a central role in the intersection of periodontitis and DM. Decreased metabolic control in type 2 DM resulted in increased serum triglycerides, and all clinical periodontal measurements and gingival crevicular fluid (GCF) levels of IL-1ß showed a trend to increase as diabetic control diminished.[26] Type 1 DM patients with periodontitis exhibited significantly higher GCF levels of IL-1ß and PGE2.[25] Elevated GCF IL-1ß was associated with poor glycaemic control in type 2 diabetic patients with untreated periodontitis.[27,28]

On the other hand, adipokines, like leptin, resistin and adiponectin, highly activate cells releasing TNF-α and IL-6.[29] This, in turn, stimulates greater hepatic C-reactive protein (CRP) synthesis which may also increase insulin resistance.[30,31] Inflammatory and infectious stimuli such as lipopolysaccharides and cytokines increase leptin levels in the acute phase.[32] Adiponectin plays a significant role in regulating glycaemia, lipidemia, endothelial dysfunction, and proinflammatory mechanisms.[33] Low serum concentrations of

adiponectin have been reported to be linked with decreased insulin sensitivity.[34] A low plasma adiponectin concentration is associated with a decrease in whole body insulin sensitivity in humans.[35]

Function and activation of endothelial cells are also impaired in DM.[36] Adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin, play key roles in leukocyte adhesion to arterial endothelial cells.[37] Serum concentrations of soluble ICAM-1 (sICAM-1) and other adhesion molecules were increased in DM patients.[38,39] Periodontitis patients have higher serum sICAM-1 levels than periodontally-healthy individuals.[40] Elevated serum levels of TNF-α, IL-6, CRP, leptin, sICAM-1, and decreased adiponectin levels in diabetic patients with periodontitis may eventually act to aggravate insulin resistance and deteriorate glycaemic control.

PERIODONTAL TREATMENT AND DIABETES

Effects of periodontal treatment on clinical periodontal parameters, systemic mediators, and glycaemic control were evaluated in well or poorly-controlled type 2 diabetic as well as systemically healthy periodontitis patients.[35] The poorly-controlled diabetic group exhibited significantly decreased HbA1c levels 3 months after completion of non-surgical periodontal treatment. Increased adiponectin levels may at least partially explain the significant improvement in glycaemic control by non-surgical periodontal treatment in the DM group.[35] These findings corroborate the previous studies demonstrating significant improvements in HbA1c levels and clinical periodontal parameters following non-surgical periodontal treatment.[41-46] Almost no change in the HbA1c percentage in the well-controlled diabetics with non-surgical periodontal treatment in contrast to the significant improvement in the poorly-controlled diabetics have been reported.[47] This may be regarded as further proof of the beneficial effects of periodontal treatment in the glycaemic control of type 2 DM. While their current medical therapies are efficient in the well-controlled diabetics, the 1.5% improvement in glycaemic control of the poorly-controlled diabetics with periodontal treatment may correspond to significant improvement in general health.[47] It may be suggested that the deeper the baseline peritoneal dialysis (PD) is, the longer follow-up period is required for proper periodontal healing as well as significant decrease in HbA1c level. The risk of diabetic complications were strongly associated with previous hyperglycaemia in type 2 diabetics and any reduction in HbA1c is likely to reduce the risk of complications.[48] Therefore, periodontal treatment may be regarded as a means of reducing HbA1c levels, eventually helping the overall management of diabetic patients.[49]

In a study reporting better HbA1c levels in people with better tooth brushing self-efficacy, it was suggested that motivation and instruction on better oral hygiene is important in diabetic patients especially those with poor metabolic control.[50] The importance of prevention of oral diseases for a better systemic health was also emphasised recently.[51] Poorly-controlled diabetics have been reported to exhibit significant reductions in PD, peritonitis incidence (PI), and BOP following mechanical periodontal treatment.[41,42,52-55] Higher PI and BOP levels have been reported in poorly-controlled diabetics, 1 and 3 months after periodontal treatment compared to baseline.[53,54] Poor glycaemic control was suggested to have contributed to higher BOP scores in the poorly controlled group. It is likely that microvascular changes due to prolonged hyperglycaemia create a tendency for bleeding in these patients despite the similar plaque scores with the well-controlled group.

Increased serum levels of proinflammatory cytokines like TNF-α, IL-6, CRP, and sICAM-1 may play a role in insulin resistance and deteriorate glycaemic control in diabetic patients. Such an increase in serum levels of inflammatory cytokines may be one of the mechanisms by which infection by Gram-negative bacteria promotes atherosclerosis in diabetic patients.[56] Intervention trials suggest that periodontal therapy, which decreases the intraoral bacterial bioburden and reduces periodontal inflammation, can have a significant impact on systemic inflammatory status. Reports suggest that periodontal therapy is associated with improved glycaemic control in many patients with both diabetes and periodontal diseases.[57] TNF-α, IL-6, CRP, and sICAM-I concentrations tended to decrease in the poorly-controlled diabetics following periodontal treatment.[35] These decreases may at least partially explain the significant improvement in HbA1c level. Recently, the

possibility of a direct relationship between the severity of periodontitis and diabetic complications has been discussed in a workshop and it was concluded that moderate-to-severe periodontitis is associated with increased risk for macroalbuminuria, end-stage renal disease, calcification of atherosclerotic plaques, carotid intima-media thickness and cardio-renal mortality.[58]

Moreover, the participants with the most severe periodontitis at baseline exhibited approximately 5-fold greater increase in HbA1c levels over 5 years, and the authors suggested that severe periodontitis predicts the progression of DM.[59]

Non-diabetic patients had more healthy sextants and diabetic patients showed a higher variability in salivary-IgA levels as compared with non-diabetic patients.[60] Serum levels of high-sensitivity CRP, TNF-α, IL-6, fasting plasma glucose, HbA1c, fasting insulin decreased and adiponectin increased 3 months after periodontal treatment in type 2 DM patients and periodontal treatment may improve glycaemic control, lipid profile, reduce serum inflammatory cytokine levels, and increase serum adiponectin levels in poorly controlled type 2 DM patients.[61] Levels of high-sensitivity CRP and stem cell factor in serum and GCF were reported to be increased in patients with periodontitis and DM.[62]

SPECIFIC MOLECULES IN THE INTERACTION

The strongest relationship was found between the intensity of periodontal pathology markers and the activity of β-glucuronidase of neutrophilic leukocytes in patients with type 1 DM and periodontitis.[63] It was speculated that if periodontal impairment is severe, DM possibly causes a faster destruction of periodontal tissues, increasing the risk of periodontitis.

Diabetic patients exhibited significantly higher mean salivary levels of alkaline and acid phosphatase, osteopontin, and osteocalcin than healthy controls.[64] Substance P, a potent proinflammatory neuropeptide present in sensory neurons, is important in initiating and sustaining inflammation. Serum substance P levels were higher in the poorly-controlled diabetic group than in well-controlled patients; within the poorly-controlled group, patients with severe attachment levels had the highest circulating substance P levels.[65]

Lipid peroxidation (LPO) evaluated by malondialdehyde in plasma and GCF is increased in diabetes and may be related to modulation of inflammatory response. Significant correlations between LPO markers and periodontal parameters suggest a direct relationship between these two entities.[66]

Plasma adrenomedullin level is elevated in pathophysiological conditions such as arterial hypertension, acute coronary syndrome, renal diseases, DM and periodontal diseases. Type 2 DM patients with/without periodontitis had significantly higher periodontal clinical indices than the non-diabetic control groups. Chronic periodontitis and type 2 DM group had significantly higher total adrenomedullin level.[67]

Human β-defensins (hBD-1 and hBD-3) have strong antibacterial action against various microorganisms, especially periodontal pathogens. Patients with type 2 DM and chronic periodontitis had worse clinical periodontal parameters, they also had significantly higher GCF levels of total hBD-1 and hBD-3 than systemically healthy patients with periodontal disease.[68]

Toll-like receptor (TLR) 2, 3, 4, and 9 levels in gingival tissue were higher in individuals with diabetes, possibly due to an exacerbated inflammatory reaction.[69] Levels of osteoclastogenesis-related factors (soluble receptor activator of nuclear factor-kappa B ligand [sRANKL] and osteoprotegerin [OPG]) have been evaluated in GCF from poorly or well-controlled type 2 diabetes and chronic periodontitis before and after periodontal therapy. Levels of sRANKL and RANKL/OPG ratios were higher in poorly-controlled group at baseline and after therapy.[70]

Visfatin, a human pre-B cell colony-enhancing factor is secreted by the adipocytes of the body that induces the production of IL-1β, TNF-α, and IL-6 during infection and inflammation. The mean visfatin concentration was increased in both serum and GCF in type 2 DM patients with chronic periodontitis.[71]

CONCLUSION

In conclusion, it is uncertain which of the hypothesised mechanisms or combinations of mechanisms is directly responsible for the detrimental effects of diabetes on periodontal

health or vice versa. Prospective clinical studies with a larger scale are required to better clarify the mechanisms of possible interactions between these two entities. It is quite clear that especially poorly-controlled DM increases the risk for periodontitis, whereas there is ever-increasing evidence which shows adverse effects of periodontal disease on DM onset and progression. Existing evidence suggests that improvement of patients' awareness on oral health should be an integral part of the routine prevention and treatment protocol of DM. This can be best achieved by a closer collaboration between dentists and physicians and referral to a dentist is highly suggested after diagnosis of DM.

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AMBULATORY BLOOD PRESSURE MONITORING AND CIRCADIAN RHYTHM OF BLOOD PRESSURE IN DIABETES MELLITUS

Elena Matteucci, Ottavio Giampietro

Dietology Unit, Department of Clinical and Experimental Medicine, Pisa University, Italy

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ABSTRACT

Systolic and diastolic blood pressures display a circadian rhythmicity that can be assessed by 24-hour ambulatory blood pressure monitoring and analysed using the cosinor procedure. Altered characteristics to the circadian rhythm of blood pressure, which may result in adverse health outcomes, have been observed in both prediabetes and diabetes. We have investigated the circadian variability of blood pressure in patients with type 1 and type 2 diabetes. Chronobiologically interpreted ambulatory blood pressure monitoring uncovered not only midline estimating statistic of rhythm (MESOR)-hypertension and circadian hyper-amplitude-tension, but also circadian ecphasia (an odd timing of the daily blood pressure swing). Diastolic blood pressure acrophases were found to be phase shifted to earlier along the time axis only in patients with diabetes, but not in those with essential hypertension. Several mechanisms, from changes in nutrient-dependent signalling pathways to diabetic autonomic neuropathy, can contribute to alterations of circadian time structures in diabetic people. The chronology of blood pressure changes in animal models of diabetes and hypertension suggests that a chronobiological approach to the diagnosis of blood pressure disorders could offer advantages, but longitudinal studies in humans are needed to determine its potential relevance in hypertension associated with diabetes.

Keywords: Ambulatory blood pressure monitoring, circadian rhythm, midline estimating statistic of rhythm, acrophase, type 1 diabetes mellitus, type 2 diabetes mellitus, essential hypertension.

INTRODUCTION

Systolic and diastolic blood pressures display a circadian rhythm with a surge at the end of the night on arousal. The term 'circadian rhythm' refers to a periodically repeated sequence of events occurring in cycles of approximately 24 hours. Chronobiology is the study of biological rhythms. Time series of blood pressure measurements can be analysed by the cosinor (e.g. cosine and vector) method where a model consisting of cosine curves with known periods can be fitted by least squares to the data as an estimate of the pattern of the smooth rhythm.[1] The midline estimating statistic of rhythm (MESOR) is the value midway between the highest and lowest values of the cosine function best fitting to the data, the amplitude is half the value of the range of oscillation, and acrophase is the time at which the peak of a rhythm occurs.[2] Chronic circadian misalignment has been implicated in the development of metabolic and cardiovascular diseases, which in turn can modify intrinsic circadian rhythmicity.[3,4] The central circadian clock is located in the suprachiasmatic nuclei of the anterior hypothalamus in the brain of mammals, but similar clock oscillators have been found also in peripheral tissues. The biological clock regulates metabolic responses; on the other hand, metabolism, food consumption, timed meals, and nutrients feed back to the circadian system (Figure 1).[5] Time-related changes in cardiovascular parameters, such as blood pressure and heart rate have long been known, but only 24-hour ambulatory blood pressure monitoring (ABPM) has enabled an accurate

assessment of circadian blood pressure patterns. Many indices can be derived from ABPM recordings: average daytime, night-time, and 24-hour blood pressures (calculated by the arithmetic mean of all measurements and/or by the mean of hourly averages in the respective periods) are the most commonly used variables in clinical practice.[6] Otherwise, MESOR is a rhythm-adjusted mean based on the parameters of a cosine function fitted to the raw data and differs from the arithmetic mean when the data are not equidistant and/or do not cover an integer number of cycles.[1]

ABPM IN DIABETES MELLITUS

The guidelines of the American Diabetes Association do not recommend the use of ABPM for the management of hypertension in diabetes.[7] However, this tool was superior to the traditional clinic measurement in many respects: higher reproducibility, absence of placebo and white coat effect, better correlation with organ damage and cardiovascular events, and possibility to estimate heart rate variability.[4,8]

MESOR and mean of systolic and diastolic blood pressure were found higher in diabetic patients

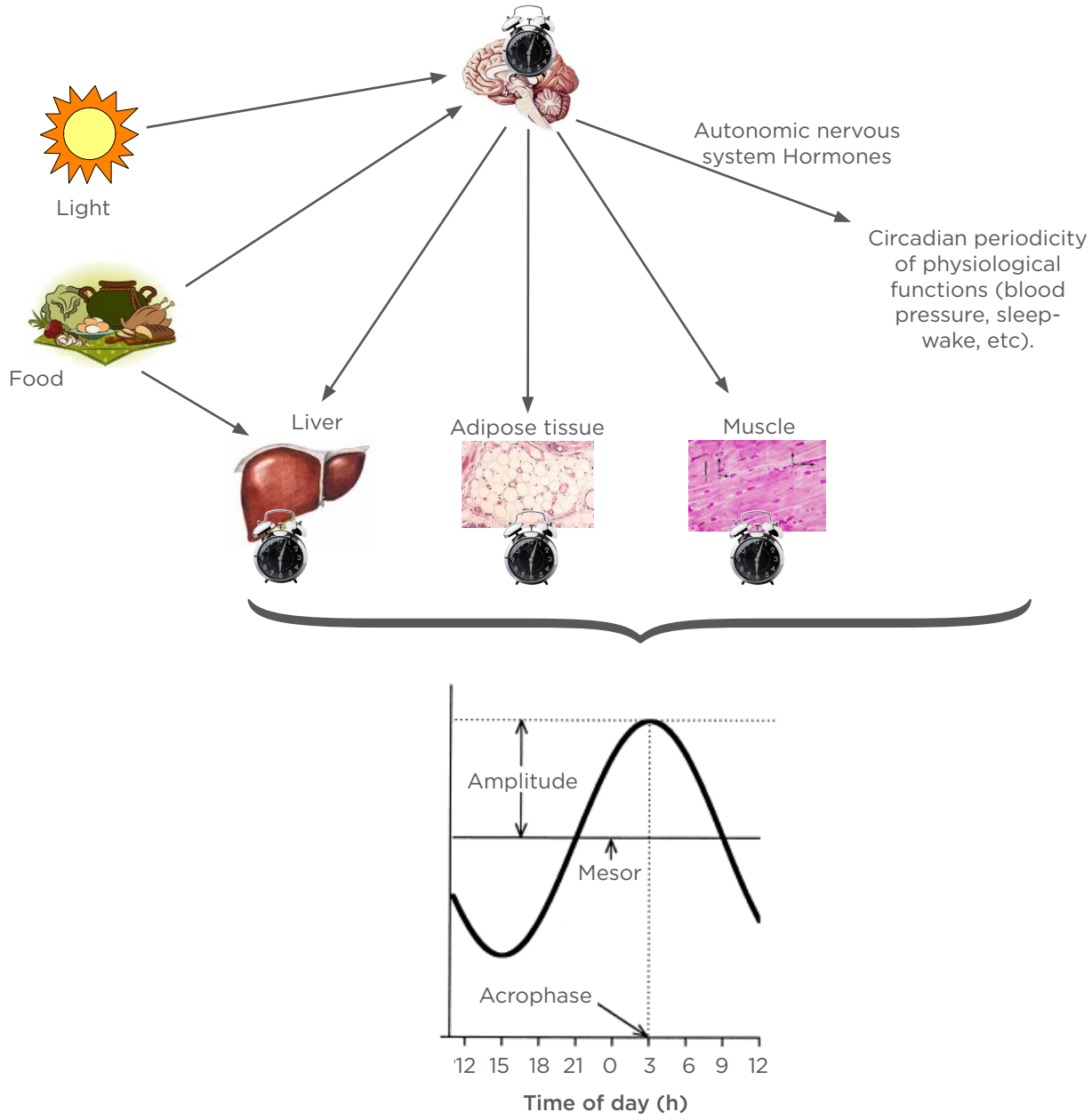

Figure 1. Central and peripheral clocks with some of their resetting signals.
Adapted from Froy et al.[4]

than in healthy subjects with a high prevalence of increased night time blood pressure (so-called non-dipping profile). This could reflect the presence of autonomic neuropathy and/or breathing-related sleep disorders, such as obstructive sleep apnoea in obese subjects with type 2 diabetes (Figure 2).[4,9] So far, few researches have evaluated abnormalities in blood pressure circadian patterns in diabetes mellitus using cosinor approach and a classification system based on the phase and amplitude of the human circadian rhythm.[10,11] After an average 4-year follow-up in 325 patients with type 2 diabetes, Nakano et al.[12] found that the circadian

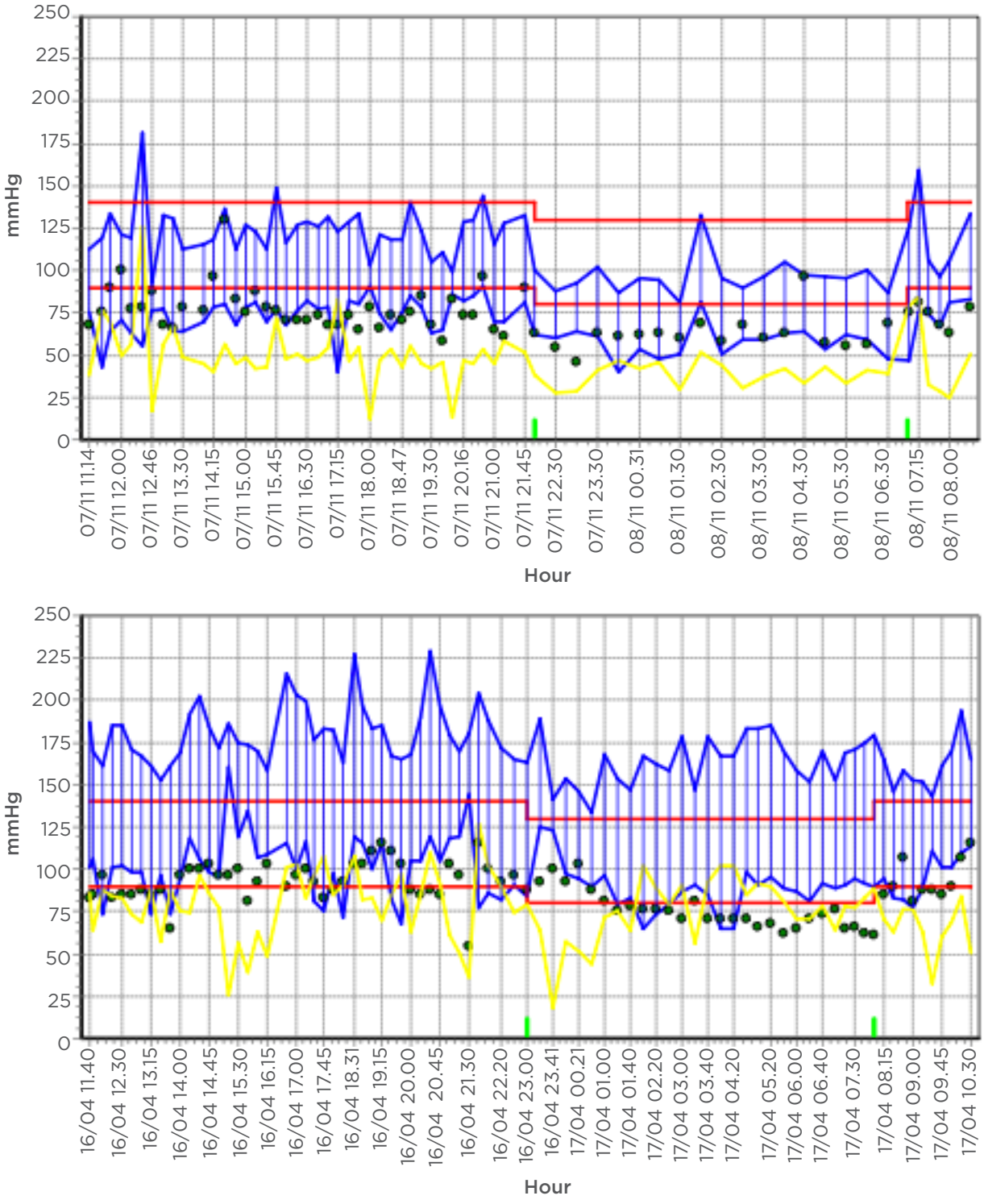

Figure 2. Example graphs from 24-hour ambulatory blood pressure monitoring report of a normotensive patient (upper panel) and a non-dipper hypertensive patient with type 1 diabetes and diabetic nephropathy (lower panel).

blood pressure patterns (analysed by the cosinor method) exhibited a statistically significant adjusted relative risk for fatal and nonfatal events.

Since normotensive non-diabetic siblings of patients with type 1 diabetes had abnormal blood pressure response to exercise testing that was associated with indices of metabolic syndrome and increased oxidative stress,[13] we investigated the circadian variability of blood pressure in patients with type 1 diabetes, their healthy siblings, and healthy control subjects who had no first-degree relative with type 1 diabetes.[14] Secondary aims of the study were to explore the influence of cardiovascular autonomic function and erythrocyte electron transfer activity on the ambulatory blood pressure profile. For this purpose, autonomic function was assessed using four standardised autonomic function tests and erythrocyte transplasma ferricyanide reductase activity was measured as the erythrocyte velocity of ferricyanide reduction.[15,16]

24-hour ABPM in type 1 diabetes families showed evidence that: 1) systolic blood pressure, MESOR and pulse pressure were higher in patients with type 1 diabetes; 2) diastolic blood pressure acrophase was 3 hours earlier in the diabetic than in normal subjects, and diastolic blood pressure ecphasia was more pronounced in patients with lower heart rate variability during deep breathing test; 3) non-diabetic siblings of patients with type 1 diabetes, who showed signs of reduced insulin sensitivity, had larger circadian amplitude of systolic blood pressure and higher ambulatory arterial stiffness index. Thus, not only diabetes but also prediabetes seemed to be associated with abnormal circadian blood pressure variability; 4) daytime systolic blood pressure was positively, independently associated with body mass index and erythrocyte transplasma ferricyanide reductase activity. This transplasma membrane electron transport system transfers reducing equivalents from intracellular reductants, such as NADPH, to extracellular oxidants, such as ferricyanide, and protects cells against oxidative damage. Transplasma membrane electron transfer systems have been found in all tested cells (including endothelial cells) and implied in antioxidant defence, cell growth, redox signal transduction, etc. The redox activity of the endothelial surface is likely to be involved in modifying the redox status of other bloodborne substances, thus influencing blood composition and vascular and organ function.[15,16] Our finding confirmed, in a clinical setting, the proposed role of transplasma membrane electron transport systems in vascular pathobiology.[14]

Recently, in order to compare the circadian rhythm characteristics of blood pressure among different groups, we have retrospectively evaluated ABPM records in normotensive control subjects, patients with type 1 and type 2 diabetes, and patients with essential hypertension who were well matched regarding age, gender, and body mass.[17] The MESOR of systolic and diastolic blood pressure was higher in patients with type 1 diabetes, type 2 diabetes, and essential hypertension. Diastolic blood pressure ecphasia was present only in the diabetic individuals: the acrophase of diastolic blood pressure occurred 4 hours earlier than normal in type 1 diabetes, whereas 2 hours earlier in type 2 diabetes. In a multiple-regression analysis, only HbA1c and systolic blood pressure acrophase were statistically significant and correlated with diastolic blood pressure acrophase. We concluded that altered circadian timing of diastolic blood pressure characterises diabetes mellitus and correlates with the previous 2-3 months of glycaemic control.[17]

CHANGES IN CIRCADIAN RHYTHMS

Due to the feedback loop between components of circadian and metabolic cycles in mammals,[18] changes in nutrient-dependent signalling pathways typical of diabetes may affect cardiovascular rhythmicity through transcriptional and non-transcriptional mechanisms. Indeed, evidence has linked cellular metabolism, epigenetic state, and the circadian clock: NAD+ is considered a critical signalling metabolite with effects on epigenetic state.[18] In this regard, our finding of a relationship between daytime systolic blood pressure and erythrocyte transplasma membrane electron transport activity that maintains appropriate intracellular NADH/NAD ratios is noteworthy.[14] The coupling mechanisms between core clock circuitry and metabolism should include NAD-dependent enzymes, redox and/or temperature-dependent transcription factors, nutrient-sensing transcriptional regulatory proteins, and protein kinases.[19]

Additionally, the pineal hormone melatonin that is involved in the phasing of circadian rhythms appears to have an antagonistic relation with

insulin.[20] For example, the circadian rhythm of insulin secretion can be phase-shifted by melatonin, polymorphisms of the melatonin MT2 receptor locus have been associated with type 2 diabetes, and increased melatonin levels in type 1 diabetic rats are normalised by insulin therapy. Catecholamines, which decrease insulin levels and stimulate melatonin synthesis, might control insulin-melatonin interactions.[20] Finally, diabetic autonomic neuropathy can contribute to the changes in the time structures of melatonin[21] and blood pressure.[22]

Health Impact of Circadian Blood Pressure Rhythm Alterations

Follow-up studies demonstrate that ambulatory blood pressure predicts target organ damage and cardiovascular prognosis in diabetic patients.[4] Non-dipping, defined as a nocturnal blood pressure fall ([awake blood pressure mean - asleep blood pressure mean]/awake blood pressure mean x 100) of less than 10%, is considered one of the most relevant features of abnormal circadian variability. While the adverse prognostic implications of a blunted day-night blood pressure dip (independent of the average 24-hour blood pressure) have recently been confirmed, those of the morning blood pressure surge are still debated.[23] However, adopting a chronobiological approach to the diagnosis of blood pressure disorders could offer advantages in explaining differential outcomes and deserves more thorough investigation.[10]

Moreover, a classification in term of 'dipping' may not match chronobiological analysis or it may even be misleading.[11,24] The following concordances between studies on animals and humans suggest the clinical meaning of the chronobiological approach. By recording via telemetry the arterial blood pressure in an animal model of spontaneous type 1 diabetes mellitus, changes in circadian cardiovascular and autonomic functions were detected. These included: 1) a phase shift by the second diabetic month in which the diurnal blood pressure peak shifted from the mid-afternoon to late-afternoon but the amplitude of the rhythm was reduced, and 2) a phase shift in the peaks and dips (with the night-time having the lowest dip) by the ninth month that could mark the beginning of irreversible impairment of autonomic and cardiovascular function.[25]

Analogously, patients with type 1 diabetes mellitus showed diastolic blood pressure ecphasia that was more pronounced in those with lower heart rate variability.[14] Furthermore, in longitudinal studies using animal models of hypertension, an increase in the circadian amplitude of blood pressure preceded MESOR hypertension,[26] just as observed in non-diabetic siblings of type 1 diabetic patients who showed signs of reduced insulin sensitivity associated with a circadian hyper-amplitude-tension.[14]

CONCLUSION

Unfortunately, the exact prognostic values of changes in blood pressure MESOR, amplitude, and acrophase remain undetermined. To determine the potential relevance of these parameters in hypertension associated with diabetes, follow-up studies are required that 1) use and compare multiple procedures for the analysis of blood pressure time series, 2) evaluate target organ damage, and finally 3) implement personalised antihypertensive therapy by timing along the circadian scale.

Glossary[2]

Acrophase: Measure of timing of a rhythm in relation to a defined reference time point selected by the investigator (e.g. local midnight for circadian rhythms); used for data which can be described by the fitting of a mathematical model, e.g. a cosine curve, and represents the crest time of the cosine curve best fitting to the data; may be expressed in (negative) degrees as the lag from the acrophase reference (360°C=1 period) or in calendar time units (e.g. hours and minutes for circadian rhythms, days or months for infradian rhythms).

Amplitude: The measure of one half of the extent of the rhythmic change estimated by the mathematical model (e.g. cosine curve) best fitting to the data (e.g. the difference between the maximum and the rhythm-adjusted mean (MESOR) of the best fitting curve).

Chronobiology: The science of investigating and objectively quantifying phenomena and mechanisms of the biological time structure, including the rhythmic manifestations of life.

Circadian ecphasia: an odd timing outside reference limits of the circadian rhythm of blood pressure.

Circadian hyper-amplitude tension (CHAT): condition defined by an excessive circadian amplitude of blood pressure, above a threshold approximated by the upper 95% prediction limit of clinically healthy peers matched by gender, age and ethnicity.

Circadian: About 24 hours. The term describes rhythms with an approximately 24-hour (>20 to <28) cycle length whether they are synchronised with a 24-hour periodic surrounding or not.

Cosinor procedure: A mathematical-statistical method of describing a rhythm by determining by least squares technique the cosine curve best fitting to the data and exploring the presence of a rhythm by examining the null hypothesis for amplitude in an F-test. If a rhythm can be described by this procedure the cosinor yields a rhythm-adjusted mean (MESOR), an amplitude as measure of the extent of the rhythm, and an acrophase as indication of its timing with variance estimates for each.

MESOR: Midline Estimating Statistic of Rhythm. The value midway between the highest and the lowest values of the (cosine) function best fitting to the data. The MESOR is equal to the arithmetic mean only for equidistant data covering an integral number of cycles.

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MORTALITY IN PATIENTS WITH PAD WITH RESPECT TO GLYCAEMIC STATUS: A REVIEW

Iren D. Hjellestad,[1] Torbjørn Jonung[2,3]

1. Department of Medicine, Haukeland University Hospital, Bergen, Norway
2. Department of Vascular Surgery, Haukeland University Hospital, Bergen, Norway
3. Department of Clinical Sciences, University of Bergen, Bergen, Norway

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ABSTRACT

Peripheral arterial disease (PAD) is a manifestation of atherosclerosis. Atherosclerosis is a chronic inflammatory process and nonenzymatic glycation is a process of major interest in relation to how risk factors promote atherogenesis. A strong association between diabetes mellitus (DM) and PAD has been established, and the association is related to the duration of DM. Previous studies have revealed a higher prevalence of DM in patients with PAD compared to general populations and populations at risk of developing DM. The typical dyslipidaemia found in patients with PAD is similar to that found in patients with insulin resistance, and an association of HbA1c with atherogenic dyslipidaemia is described. HbA1c has been described as a predictor for DM and of micro and macrovascular disease. 5-year all-cause mortality in PAD is 19–37% and 10-year all-cause mortality is 42-54%. The mortality in PAD increases with age, with the severity of the peripheral vascular disease, and with the coexistence of PAD with coronary artery disease and DM. Patients with DM, defined by glucose criteria, and PAD have an increased mortality compared with patients with PAD alone. Recent studies have shown an association of HbA1c levels with vascular complications and death in patients with DM. No studies could be found that aimed to validate HbA1c against glucose criteria as a predictor for mortality in patients with PAD. Further studies on patients with PAD and DM are needed to identify which is the best diagnostic method to predict mortality in PAD with respect to glycaemic status: the glucose parameters or the HbA1c.

Keywords: Peripheral arterial disease, mortality, diabetes mellitus, glycaemic status, HbA1c.

INTRODUCTION

Peripheral arterial disease (PAD) and diabetes mellitus (DM) represent a major public health challenge. The prevalence of PAD in general populations is reported to be 2.5-20%[1-10] and it is increasing with age.[2,11,12] In populations at moderate-to-high risk of developing PAD, the prevalence of PAD is 23-41%.[13-16] Individuals with DM have twice as high prevalence of PAD as normoglycaemic individuals.[12,17-19] DM is rapidly increasing in prevalence affecting 285 million people worldwide (2010).[20] Patients with PAD are multimorbid and of high age.[21] PAD varies in severity and clinical expression, and about one-third of patients with PAD are asymptomatic.[11,17] DM and smoking are two main risk factors for PAD[22] and patients with PAD are also likely to have coronary artery disease (CAD) and cerebrovascular disease. Cardiovascular diseases are the leading cause of death globally and accounted for 12.9 million deaths (one-fourth of all deaths) in 2010. 1.3 million deaths were due to DM.[23] CAD and cerebrovascular disease are the main causes of death in patients with PAD.[24] The increased cardiovascular risk in patients with PAD appears to be independent of classic risk factors.[25,26]

Despite the high prevalence and mortality in patients with PAD and the strong association between PAD and DM, PAD is underrepresented in diabetes research compared with CAD. The aim of this article is to review the risk of mortality in patients with PAD with respect to glycaemic status.

METHODS

A PubMed search on titles with the words "atherosclerosis pathophysiology", "endothelial dysfunction in diabetes", "peripheral arterial disease and diabetes mellitus", "distribution of peripheral arterial disease", and "peripheral arterial disease", "vascular disease", and a combination of the two latter with "prevalence" AND "mortality" was performed. Additional related citations were identified from reference lists of articles already included for review.

DEFINITIONS

Definition of Peripheral Arterial Disease

PAD is a manifestation of atherosclerosis, a chronic inflammatory process in the arteries causing both stenotic disease and weakness of the arterial wall, presented as aneurysms. Atherosclerosis occurs focally in the arteries with predilection sites proximally in the arteries and at bifurcations.[27] The clinical diagnosis of PAD is based on a resting Ankle-Brachial Index (ABI) <0.9. A reduction in post-exercise ABI is required as a confirmative test in the presence of symptoms and with a normal resting ABI or in individuals at risk of PAD but with a borderline or normal ABI.[26,28] Current guidelines recommend annual inspection of the foot and palpation of peripheral pulses in the femoral, popliteal and pedal vessels. PAD screening with an ABI, and if normal repeated test every 5 years is recommended in patients with DM >50 years of age.[29]

Definition of Diabetes Mellitus and Intermediate Hyperglycaemia

DM is a group of metabolic diseases resulting from defects in insulin secretion, insulin action or both. Traditionally, the diagnosis of DM has been based on glucose criteria defined by fasting plasma glucose (FPG) ≥7.0 mmol/l or a 2-hour post glucose load value of ≥11.1 mmol/l.[30] The International Expert Committee of Diabetes (2009), the American Diabetes Association (2010), and the World Health Organization (WHO) (2011) implemented an HbA1c value of ≥48 mmol/mol (6.5%) as a new additional diagnostic criterion for the diagnosis of DM.[29,31,32] Limitations in the use of HbA1c as a diagnostic criterion for DM include conditions with abnormal red cell turnover and rapidly evolving diabetes. HbA1c is not approved for the diagnosis of gestational diabetes.[29] Furthermore, HbA1c provides no information about the fasting glycaemic state or the postprandial glycaemic state.

According to WHO (1999) criteria, intermediate hyperglycaemia is defined as impaired glucose tolerance, (FPG <7.0 mmol/L and a 2-hour-value between 7.8 mmol/L and 11.1 mmol/L) and impaired fasting glucose (fasting glucose value between 6.1 mmol/L and 7.0 mmol/L with a normal 2-hour-value).[30] Two intermediate HbA1c ranges have been suggested to be used to identify individuals at high-risk for developing DM: 39-46 mmol/mol (5.7-6.4%) (American Diabetes Association) and 42-46 mmol/mol (6.0–6.4%) (the International Expert Committee).[29,33] The WHO has not yet made a statement on HbA1c levels and intermediate hyperglycaemia.

PATHOPHYSIOLOGY

Atherosclerosis

Atherosclerosis is a chronic inflammatory process initiated and facilitated by risk factors such as DM, smoking, hypertension, hyperlipidaemia, obesity, prior inflammatory states, and elevated plasma homocysteine concentrations.[34] The initiation of atherosclerosis takes place due to alterations in the interaction between the endothelium of the artery wall, the haemodynamics of the arterial flow and the blood composition. Strain applied on the endothelial cells by these alterations causes an activation of the endothelium. A factor of major importance for the maintenance of these alterations and the development of atherosclerosis is endothelial dysfunction. Endothelial dysfunction occurs as an imbalance between the normal endothelial function and the hyperfunction of the activated endothelium.[27,35] Endothelial dysfunction is characterised by functional changes in the endothelial cells

affecting vasoconstriction, vasodilatation, growth of vascular smooth muscle, inflammation, and haemostasis, by altering the normal production of nitric oxide (NO), growth factors, adhesion molecules, cytokines, chemokines, and prostacyclins. Lipoprotein particles adhere to the endothelium as a result of the action of adherence molecules, and accumulate in the intima layer of the arterial wall. Chemical modifications of the lipoproteins lead to the recruitment of mononuclear leukocytes and the formation of foam cells. Smooth muscle cell proliferation, accumulation of extracellular matrix, and cell death contributes to the expansion of the atherosclerotic lesion. Finally, neovascularisation and calcification of the atherosclerotic lesion occur.[27,34,35]

Diabetes and Endothelial Dysfunction

Oxidation and nonenzymatic glycation are two processes of major interest in relation to how risk factors promote atherogenesis. In situations with sustained hyperglycaemia, nonenzymatic glycation of lipoproteins is likely to occur. The glycation of low density lipoproteins (LDL) may act as a strain on the endothelium and thereby start a cascade of alterations which may lead to endothelial dysfunction.[35] DM promotes atherosclerosis not only by increased glycation of LDL, but also by affecting the endothelium in the direction of endothelial dysfunction, by dyslipidaemia, and decreased NO bioavailability because of insulin deficiency or defective insulin signalling in endothelial cells.[36] Apoptosis of vascular smooth muscle cells in advanced lesions results in plaque instability and precipitation of clinical events.[37]

ASSOCIATION BETWEEN GLYCAEMIC STATUS AND PAD

A strong association between DM and PAD has been established, which is related to the duration of DM.[38] Previous studies have revealed a higher prevalence of DM in patients with PAD[2,21,39,40] compared to general populations[41-43] and populations at risk of developing DM.[44] A prevalence of pathologic glucose metabolism of 55% and a frequency of diabetes of 29% was found in Norwegian vascular surgery patients defined by the glucose tolerance test.[21] Likewise, Johansen et al.[40] found a prevalence of pathologic glucose metabolism in 57% of patients with PAD. Leibson et al.[38] revealed a co-existence of DM and PAD at 32.5% in out-clinic patients.[38] The Cardiovascular Health Study revealed a relative risk (RR) at 4.05 for DM in patients with PAD defined as ABI <0.9.45. Ogren et al.[17] reported a 29% prevalence of PAD in men with DM compared with 12% in men without DM. The diagnosis of DM was based on a history of DM or FPG ≥6.1 mmol/L. The overall prevalence of PAD in the National Health and Nutrition Examination Survey (1999-2002) was 5.1%, and the prevalence of PAD in participants with DM was 7.5% for HbA1c values <7% and 8.8% for HbA1c values ≥7%. Hyperglycaemia is associated with increased risk of PAD independent of other risk factors.[46]

The typical dyslipidaemia found in patients with PAD is similar to that found in patients with insulin resistance, thus emphasising the association between the two conditions.[23] In 118 participants aged 65–95 years, Martins et al.[47] found an association of HbA1c with atherogenic dyslipidaemia. The distribution and severity of PAD in patients with DM differs from non-diabetic populations. PAD in patients with DM is multisegmental, progresses at a more rapid rate to occlusion, is more likely to proceed to amputation, and has a higher mortality at a younger age compared with non-diabetic patients. The vascular disease presents at a greater severity in the profunda femoris artery and in the arterial segments below the knee in patients with DM. No significant differences in the severity of the vascular disease in the aorta, the iliac arteries, or the superficial femoral arterial segments are seen in patients with DM compared with patients without DM.[48-50] Studies have shown inconsistent results regarding abdominal aortic aneurysms and DM. A tendency toward a negative hazard ratio regarding abdominal aneurismal disease in DM is described, but further studies are needed to investigate this association.[51]

Differences in the Prevalence of DM and Intermediate Hyperglycaemia Among Patients with PAD by HbA1c Values Compared with Oral Glucose Tolerance Test Results

Most studies that investigated the use of HbA1c values against the oral glucose tolerance test (OGTT) as a diagnostic tool for DM, have found reduced prevalence by HbA1c criteria compared with the OGTT criteria. The studies also showed discordance between OGTT and HbA1c values

suggesting that the two methods define different patient categories.[41-44,52,53] In concordance with these results, a recent study on Norwegian vascular surgery patients found that the OGTT and the HbA1c categorised different individuals with DM and intermediate hyperglycaemia. The total prevalence of pathologic glucose metabolism was substantially higher based on HbA1c values than based on the OGTT.[54]

HbA1c and Cardiovascular Disease

HbA1c has been described as a predictor for DM and of micro and macrovascular disease.[55,56] Studies have shown inconsistent results regarding HbA1c and the prediction of cardiovascular disease. A meta-analysis on glycosylated haemoglobin and cardiovascular disease in patients with DM described a corresponding 26% increased risk of PAD for every 1% increase in HbA1c levels.[57] Pradhan et al.[58] found a multivariable adjusted RR of 1.0–1.6 of HbA1c with the incident of cardiovascular events, and concluded that the association largely could be explained by co-existent traditional risk factors. A recent study from van der Heijden et al.[59] (The HOORN study) found that individuals with DM type 2, but not individuals with intermediate hyperglycaemia are at increased risk for a recurrent cardiovascular event compared with individuals with normal glucose metabolism. Cederberg et al.[60] concluded that HbA1c level range of 5.7-6.4% predicted a 10-year risk of developing DM type 2, but cardiovascular disease only in women at HbA1c ≥6.5%. In patients with CAD but without DM, no correlation was found between HbA1c levels and the presence of CAD.[52] In individuals with DM type 2, overweight and high cardiovascular risk, a high baseline HbA1c level was associated with a high cardiovascular and all-cause mortality risk. Crude incidence rates for all-cause mortality increased with the elevation of baseline HbA1c levels.[61]

MORTALITY IN PAD

Patients with PAD have the highest rate of cardiovascular death and major cardiovascular events among patients with cardiovascular disease.[62,63] The excess mortality in patients with PAD compared with patients without PAD is mainly due to cardiovascular death.[22,25,64]

Overall Mortality

5-year all-cause mortality in PAD is 19-37%[4,65,66] and 10-year all-cause mortality is 42-54%.[65,67,68] The mortality in PAD increases with age, with the severity of the peripheral vascular disease and with the coexistence of PAD with CAD and DM.[25,69,70] Mortality is reported to be higher in males than females.[25]

Mortality in PAD Related to Glycaemic Status

Diabetes-associated vascular complications are responsible for 75% of the deaths associated with diabetes.[71-73] DM increases the risk of death from coronary heart disease independent of coexisting risk factors, and the risk increases with the duration of DM. Patients with DM but without prior myocardial infarction have the same risk of subsequent myocardial infarction as patients with a prior infarction but without DM.[72,74,75] A longitudinal study on PIMA Indians found that medial arterial calcification in patients with DM was related to impaired vibration perception, long duration of DM and high plasma glucose concentrations. Patients with DM and medial arterial calcification had 1.5-fold the mortality rate and 5.5-fold the amputation rate compared with patients with DM but without medial arterial calcification.[76] Ogren et al.[17] stated that both DM alone and PAD alone were associated with an increased rate of mortality. No statistically significant increase in mortality was seen among patients with DM and PAD compared with DM alone.[17] In hypertensive adults without cardiovascular disease at baseline, 6-years mortality was 31% in patients with DM and a low ABI, whereas 12% in patients with DM and a normal ABI. In patients with DM, the RR of mortality for those with a low ABI was 2.74. The RR of mortality in patients without DM and with a low ABI was 2.26.[45] The results from Pasqualini et al.[77] reported a 4-year overall mortality to be 34.3% from all causes and 19.5% from cardiovascular causes. The prevalence of DM, based on FPG ≥7.8 mmol/L or current treatment with insulin or oral hypoglycaemic agents, was significantly higher in the critical ischaemia group compared with the intermittent claudication group. Patients with critical limb ischaemia had an excess risk of 3.40 for overall mortality. The prevalence of DM among patients alive at follow-up compared with patients dead at follow-up was the same in the two groups.[77]

Barzilay et al.[78] aimed to determine the long-term survival and predictors of mortality in patients >50 years of age, with and without DM and with coexistence of PAD and CAD (263 DM, 1137 non-DM) for a mean follow-up at 12.8 years. Patients with DM had a significantly higher mortality rate compared with non-diabetics. The presence of DM was an independent risk factor for mortality. In patients with PAD and DM, CAD was especially severe and prognosis was poor.[78] In a retrospective cohort study of patients with an ABI <0.9, Collins et al.[79] reported a 44.5% mortality. Of the total cohort 61.3% had DM. The authors hypothesised from the results that glucose control defined by HbA1c ≤7.0 or FPG ≤140 mmol/mol was protective against death with a hazard ratio of 0.74, p=0.004. As the authors outpoints, these findings should be evaluated in a prospective study.[79]

Leibson and associates[38] studied patients registered at the Mayo Clinic who had PAD, DM or both at baseline. Results showed that individuals with both PAD and DM have twice as high-risk of death as individuals with PAD alone. Progressors of PAD were at increased risk of death compared with non-progressors. The increased risk was only significant for individuals with DM.[38] Recent studies have shown an association of HbA1c levels with vascular complications and death in patients with DM. Results from the ADVANCE study found a 38% risk of macrovascular events and a 38% risk of death for every 1% rise in HbA1c level above 7%. Stratton et al.[80] found a reduction in risk of amputation or death from PAD of 43% per 1% reduction in HbA1c concentration in the UKPDS 35.[80,81] Takahara et al.[82] aimed to investigate prognostic factors in 278 patients undergoing percutaneous transluminal angioplasty for critical limb ischaemia. HbA1c levels were associated with major amputation but no association was found between HbA1c levels and mortality.[82]

CONCLUSION

DM is an established risk factor for micro and macrovascular disease, and a strong association between DM and PAD has been shown. Patients with DM, defined by glucose criteria, and PAD have an increased mortality compared with patients with PAD alone. Recent studies have shown an association of HbA1c levels with vascular complications and death in patients with DM. No studies could be found that aimed to validate HbA1c against glucose criteria as a predictor for mortality in patients with PAD. Further studies on patients with PAD and DM are needed to identify which is the best diagnostic method to predict mortality in PAD with respect to glycaemic status: the glucose parameters or the HbA1c.

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Revolutionary new mobile app for diabetics

A MONITORING system in the form of an app for mobile phones could completely alter the management of diabetes. 'Cloud' internet technology enables the app to measure blood sugar levels, recorded by sensors in real time.

With the rate of UK diabetes sufferers increasing, and already 1 in 10 adults being affected, this could revolutionise the methods of maintaining adequate health for those with the disease.

Approximately 10% of the NHS budget is spent on the direct treatment of diabetes. A large proportion is then used to deal with further complications, such as kidney failure, nerve damage, blindness, and amputations. Many patients may have appointments every 6 months to have their blood sugar levels analysed with reports on how well they have been controlled in the previous months.

This new personal health monitoring system is being trialled by diabetic athletes and could prevent marathon runners and long-distance cyclists from 'hitting the wall', where sugar levels are depleted and blood sugar drops.

Researchers from the Universities of Newcastle and Northumbria, UK, trialled the personal monitoring system at sporting events, where participants wore a small sensor linked wirelessly to their mobile phones. Most of the 100 athletes involved had diabetes, and raced from Brussels to Barcelona, completing a 2,100 km course with a cumulative climb of 22,000 m. The monitors picked up chemical changes to record glucose in the body fluid when inserted under the wearer's skin through a small wire. It can be worn for up to 10 days and costs around £40.

> "It is really about demonstrating how much things most of us carry in our everyday lives, mobile phones, hold the potential to help living with diabetes."
>
> *Prof Mike Trenell, Newcastle University, Newcastle upon Tyne, UK*

Prof Mike Trenell of Newcastle University, Newcastle upon Tyne, UK stated: "It is really about demonstrating how much things most of us carry in our everyday lives, mobile phones, hold the potential to help living with diabetes. We can enable patients to make real-time context-based decisions to improve their diabetes control."

Sugar: "the most dangerous drug of the times"

SUGAR is the most dangerous drug of this era, according to Paul van der Velpen, Managing Director of GGD Amsterdam, the Netherlands.

In an opening statement, the Head of Amsterdam's Public Health Service, Mr van der Velpen, warned that the obesity epidemic is expanding, and as a result, healthcare costs will inevitably increase. The government wants these costs under control and seeks to cut them where possible.

"Just like alcohol and tobacco, sugar is actually a drug. The use of sugar should be discouraged. And users should be made aware of the dangers," Mr van der Velpen wrote.

"This may seem exaggerated and far-fetched, but sugar is the most dangerous drug of the times and can still be easily acquired everywhere."

He argued there should be regulations regarding the amount of sugar that can be consumed, similar to salt regulations, and that health insurers should finance the addiction therapy for their obese clients. Manufacturers of sports drinks were not safe from criticism either, the director stated that drinks which contain a lot of sugar should have legal action taken against them for false advertisement.

New hope for experimental diabetes treatment

SCIENTISTS have found that the self-destructive immune reaction against insulin-making cells causing type 1 diabetes could be slowed down using experimental DNA-based therapy. The research, published in *Science Translational Medicine* is a preliminary step towards formulating a treatment for the condition.

Dr Lawrence Steinman, Professor of Neurology and Neurological Sciences, Pediatrics, and Genetics, Stanford University, USA, and his colleagues injected 26 volunteers with placebos weekly, while another 54 received the experimental treatment. In patients with diabetes, rogue CD8 T cells attack proinsulin, a protein on beta cells, thereby sabotaging insulin production as the proinsulin cannot become insulin after modification.

The experimental treatment contained replacement DNA for the gene-encoding proinsulin. The patients who were treated in this way for 12 weeks appeared to make altered proinsulin proteins that signalled the immune system to destroy the rogue T cells, and as a result, the number of T cells decreased after 5 months. Stabilisation and improved insulin production were shown in the patients after 12 weeks, hinting that the therapy might halt beta cell destruction. However, the two changes were not permanent.

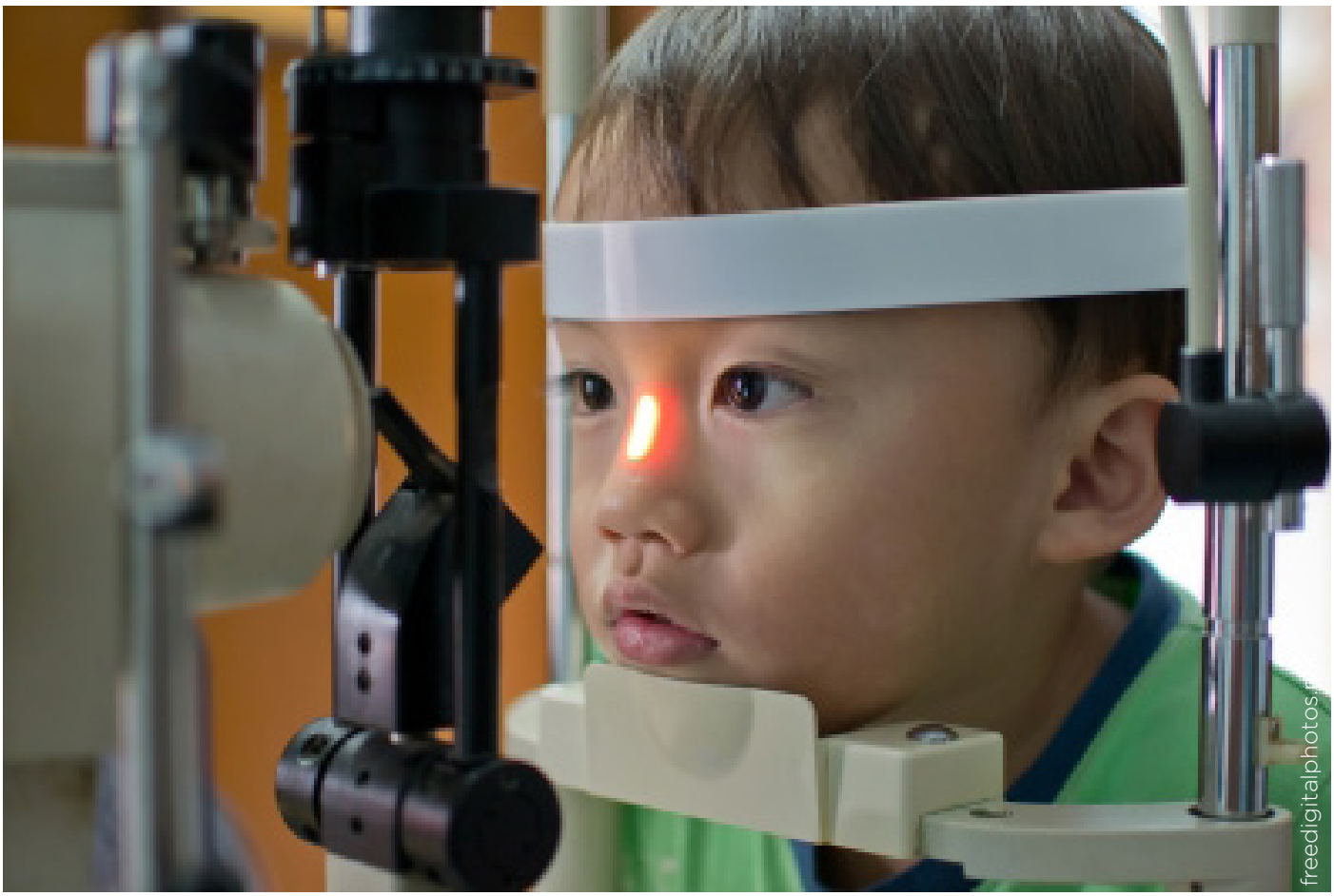
NICE new treatment for diabetic macular oedema

CHRONIC macular oedema that is considered unresponsive to other available therapies can be treated by fluocinolone acetonide intravitreal implant (ILUVIEN®, Alimera Sciences) according to new recommendations made by the National Institute for Health and Care Excellence (NICE).

The central part of the retina, the macula, is responsible for colour visualisation and acuity. The abnormal growth of new retinal blood vessels in diabetics leads to the development of diabetic macular oedema. The reduction in the amount of connective tissues around the capillaries leads to an increased amount of vascular endothelial growth factor (VEGF), causing the blood retinal barrier to become more permeable. This, in turn, leads to a build-up of excess fluid and swelling, which causes visual impairment.

Fluocinolone acetonide intravitreal implant is recommended as a treatment option if used in an eye along with intraocular (pseudophakic) lenses, and the manufacturer makes it available to the NHS under the terms agreed with the Department of Health for a patient access scheme.

Prof Carole Longson, Health Technology Evaluation Centre Director, NICE, UK said: "Around 14% of people with diabetes in the UK have diabetic macular oedema, which can cause blurred or double vision in those affected. NICE is, therefore, pleased to be able to recommend fluocinolone for some people with this condition in final draft guidance."



Power of light heals diabetes

LIGHT can be used to heal diabetes in mice via a transparent gel that comprises of genetically modified light-sensitive cells. With further research, this new implantable gel could possibly treat disease and monitor toxins in humans.

Lead author Dr Myunghwan Choi, Harvard Medical School, Boston, USA, explained the initial issue with this kind of treatment: "Light is a great tool to interface with biological systems, but there is a fundamental problem. It gets scattered when it hits tissue, and at depths much thinner than our skin."

The team designed an implantable gel to avoid this problem. Light was shone into the mouse at the gel using a fibre optic cable attached to its head. Through a series of reactions, the light triggers the cells in the gel to produce a compound that stimulates the secretion of insulin, which in turn, leads to the stabilisation of blood glucose levels. The research team also monitored for cadmium poisoning that fluoresced when the mouse was under stress from the toxin.

"The promise is there," Prof Fiorenzo Omenetto, Biotechnologist, Tufts University, Medford, Massachusetts, USA agreed. "The tough thing here is the presence of a large implant and a fibre sticking out of your head. Not something I'd want if I were diabetic."

More work will be conducted into making the implant more user friendly. Dr Choi mentioned: "We are thinking of adding a micro-LED with a wireless power receiver [to the gel implant]."

This research is still in its infancy, but the ultimate goal is to reduce the need for doctors to carry out multiple injections and blood tests to monitor or treat patients with diabetes.

"The tough thing here is the presence of a large implant and a fibre sticking out of your head. Not something I'd want if I were diabetic."

Prof Fiorenzo Omenetto, Biotechnologist, Tufts University, Medford, Massachusetts, USA

Sugar linked to type 2 diabetes

A NEW study led by Dr Sanjay Basu, Assistant Professor of Medicine at Stanford University, California, USA found that obesity is not the only driving factor of the development of type 2 diabetes and has identified excessive sugar intake as a cause.

Data from the United Nations Food and Agricultural Organization and the International Diabetes Federation were used to target certain aspects (omitting obesity), such as the availability of foods in 175 countries, and the prevalence of diabetes in adults respectively.

Researchers discovered a connection between the availability of sugar in the diet and level of diabetes. For each additional 150 calories of sugar, approximately the amount in a 355 ml can of sweetened soft drink, that were available per person per day, the prevalence of diabetes rose 1% in the population.

When they concentrated on an additional 150 calories per person daily from different sources, they found a 0.1% rise in the proportion of diabetes. Dr Basu noted: "There are likely a number of ways sugar may contribute to the development of diabetes, such as increasing insulin resistance and inflammation."

"There are likely a number of ways sugar may contribute to the development of diabetes, such as increasing insulin resistance and inflammation."

Dr Sanjay Basu,
Assistant Professor of Medicine,
Stanford University,
California, USA

These new data do not however justify completely that sugar is the causality of diabetes, having only found an association between the two factors. It should also be acknowledged that this information purely applies at a population level, and thus does not predict an individual's risk of developing the disease.

Another significant disadvantage of this study was that it was unable to provide details of distinct differences between types of sugar, such as high-fructose corn-syrup or natural sugar.

Dr Joel Zonszein, Director of the Clinical Diabetes Center at Montefiore Medical Center, New York, USA said: "Type 2 diabetes is a complex disease. Eating a lot of sugar is not good, especially the sugar substitutes like fructose and sucrose. But, I wouldn't underplay the importance of exercise and calorific intake. And you have to have individuals who have a genetic abnormality first before you can have type 2 diabetes."

Innovative gene therapy for type 1 diabetics

"Gene therapy does not represent a 'cure' for type 1 diabetes because it does not regenerate beta cells, but rather could lead to an effective long-term treatment."

Dr Fatima Bosch, Center of Animal Biotechnology and Gene Therapy, Barcelona, Spain

THE FIRST large scale study to analyse gene therapy in the treatment of animals with type 1 diabetes indicates that it could be effective after providing benefits for more than 4 years in dogs without causing hypoglycaemia.

A previous study suggested this same outcome when mice were used. This new research marks another leap towards testing this procedure in humans.

Dr Fatima Bosch, Director of the Center of Animal Biotechnology and Gene Therapy, Barcelona, Spain stated: "If something works well in large animals, we have reason to believe, based on previous experience in the field of gene transfer, that it is likely we will see a similar outcome in humans."

Five lab dogs were injected using an adenoassociated virus (AAV) vector, which originates from a non-pathogenic virus and is able to infect cells in the canines' skeletal muscle with insulin and glucokinase. These two genes remain in this location for a long duration as these muscle cells do not divide, implying that the dogs only require one injection as the genes continue to perform their tasks of releasing low levels of insulin and glucokinase. This suggests they may aid in glucose uptake monitoring, responding to increases and decreases in glucose levels for years.

As a result of this trial, the dogs treated maintained normal blood glucose levels without exhibiting hypoglycaemia for more than 4 years.

Researchers explained both genes were needed in order to achieve such effective results, and would not be attainable with just one. The next action will involve testing this operation on different breeds of dogs with type 1 diabetes, where they live with families as opposed to dogs treated in the lab. This will enable researchers to measure the different doses required for various sizes and situations, and thus adjust accordingly. When they can determine by means of adapting the therapy to these cases, they will be prepared to test this treatment on humans.

Dr Bosch mentioned: "Gene therapy does not represent a 'cure' for type 1 diabetes because it does not regenerate beta cells, but rather could lead to an effective long-term treatment."

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The World Diabetes Congress 2013

2nd-6th Dec 2013

Melbourne, Australia

The International Diabetes Federation is the global voice for people with diabetes and those at risk. Around 20 years after the World Diabetes Congress in Japan, the Western Pacific region is again in the global health spotlight, and this is why Melbourne was chosen to host the World Diabetes Congress in 2013. Events such as this present an enormous opportunity to come together and share the most recent evidence and best practice to support improvements in diabetes care, treatment, and prevention.

The 7th International Conference on Advanced Technologies & Treatments for Diabetes (ATTD 2014)

5th-8th Feb 2014

Vienna, Austria

The Congress will attract an international audience of researchers and clinicians, as well as developers from the medical technology industry. Since the inaugural meeting in 2008, gatherings have grown dramatically. ATTD 2014 will build on the success of previous annual meetings and present the latest technological advances in treatment of diabetes and related conditions.

International Cardiometabolic Syndrome Eastern Mediterranean Congress

27th Feb-2nd Mar 2014

Kyrenia, Cyprus

Sedentary lifestyle and high-calorie diet caused by modern-day life are the most important factors in the emergence of cardiometabolic syndrome, affecting individuals of all ages. The rapid rise of obesity, physical inactivity, smoking, stressful lifestyles, diabetes, and cardiovascular diseases, brings into question the necessity of serious social measures. One of the most important aims of the Congress is to draw together stakeholders in the scientific arena for interdisciplinary collaboration in the fight against cardiometabolic syndrome.

Annual Congress of the French Society of Diabetes (SFD 2014)

11th-14th Mar 2014

Paris, France

The annual conference of the Société Francophone du Diabète (SFD - French-speaking Diabetes Society), has become a forum for all those involved in diabetes, from doctors, healthcare professionals, researchers and students, to industrial partners and patient associations. In recent years, it has attracted more than 4,500 participants. Visitors come to listen, exchange information, learn more about the disease, make their debut as a speaker or simply meet with fellow French-speaking colleagues.

The 3rd Latin America Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy)

13th-16th Mar 2014

Panama City, Panama

Bringing to the forefront the crucial issues and debates facing clinicians and patients in Latin America, the Congress enables an interaction which benefits both the professionals as well as the patients, accomplishing the goal of CODHy to bridge gaps between the expansion of information and its consolidation in clinical practice.

International Congress on Obesity (ICO)

17th -20th Mar 2014

Kuala Lumpur, Malaysia

The health burdens which are related to obesity are rapidly increasing in Asia, more than anywhere else in the world, and this problem can no longer be ignored. The ICO Congress will be a unique experience for anyone interested in obesity to share their experiences and knowledge in order to find practical solutions to prevent the escalation of this epidemic.

The 3rd International Conference on Prehypertension & Cardio Metabolic Syndrome

27th-30th Mar 2014

Warsaw, Poland

The Conference will aim to deal with all aspects related to early diagnosis, including innovative technologies, and treatments, and will bring together professionals from the fields of hypertension, nephrology, endocrinology, internal medicine, cardiology, and more.

The 50th European Association for the Study of Diabetes (EASD 2014)

15th-19th Sept 2014

Vienna, Austria

Though emerging as the largest international annual conference on diabetes research worldwide, the EASD is still driven by the academic tradition of the founding members: to promote excellence in diabetes care through research and education. Encouraging co-operation with industry and other institutions conducting and funding diabetes research, the EASD is host to over 7,000 members from over 100 countries - including scientists, physicians, laboratory workers, nurses, and students.

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