TREATMENT STRATEGIES
DIABETES

Volume 5 Issue 1

- Diabetes and Cardiovascular Risk
- Glucose Monitoring
- Statins
- Type 1 Diabetes
- Type 2 Diabetes Management

Papers include:

49 EASD BARCELONA 2013

Includes a Review of the 49th EASD Annual Meeting

International Diabetes Federation Europe

unite for diabetes

Coming soon…

IDF Europe Study on ...

Access to Quality Medicines and Medical Devices for Diabetes Care in Europe

In the current context of growing concerns regarding access to healthcare, and faced with the significant challenges of addressing long-term care for major chronic diseases such as diabetes, the International Diabetes Federation European Region (IDF Europe) will be publishing a study on Access to Quality Medicines and Medical Devices for Diabetes Care in Europe.

This publication highlights disparities in access to quality medicines and medical devices for diabetes care in the 47 countries of the IDF Europe Region. The study aims to provide evidence to policy makers and stakeholders on the current challenges faced by people living with diabetes in terms of access to the treatment they need.

While national practices do vary and comparable data may be imperfect, the study will tell a compelling story about the need for coordinated action.

Providing the Evidence

Currently, reliable data on the true costs of caring for people living with diabetes is scarce. The issue of having accurate and timely data on diabetes medicines and medical devices thus needs to addressed, as currently decisions are being made in the absence of such information.

Beyond the Short-term

People with diabetes rely on continuous access to medicines and devices to manage their life-long condition. Most diabetes complications, such as heart disease and stroke, kidney failure and foot problems are preventable with a timely diagnosis of diabetes, effective patient and professional education, and comprehensive, multidisciplinary long-term care. This requires sufficient investment to ensure sustainable and uninterrupted access to diabetes medicines and medical devices.

It is imperative that access to diabetes care be seen as an investment to promote a healthier and more productive society, and as a contributor to long-term economic growth.

- The initial findings of the study will be released on 13 November 2013.

- The full study will be available for download as from 4 December 2013.

For more information visit www.idf-europe.org

TREATMENT STRATEGIES DIABETES

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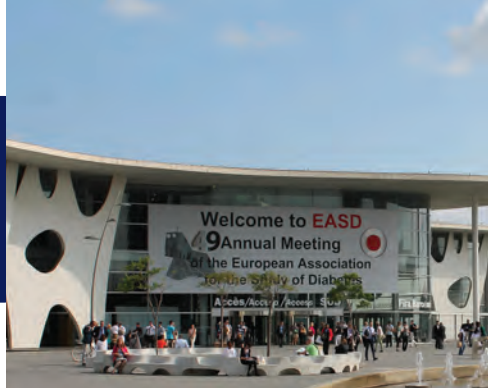

Welcome...

I am pleased to welcome you to the latest edition of *Treatment Strategies - Diabetes*. In this fantastic new edition we have a range of informative articles, as well as an in-depth review of the 49th European Association for the Study of Diabetes (EASD) Meeting.

The Meeting was held from 23 - 27 September, and is the world's leading international forum for diabetes research for both individuals and the worldwide pharmaceutical industry. The event was attended by over 18,000 delegates and covered a broad range of topics including type 2 diabetes, diabetes management and statins. Our review brings you all of the breaking news, research highlights, awards and products that were showcased at the event.

This edition also features a number of interesting and informative papers on subjects such as Type 1 diabetes, glucose monitoring and Type 2 diabetes management. With these papers we aim to bring you new insights into the latest treatment strategies for a number of different diabetic disorders. Indeed, diabetes is becoming an increasingly important area of medicine as more people are diagnosed with the disease. We hope that you enjoy the chosen content.

Here at the Cambridge Research Centre we are always looking for new ways to bring our content to you. This year, in addition to our growing range of interactive eBooks we launched Treatment Strategies TV. Here you will find footage from all of the most important scientific conferences, as well as interviews, symposia proceedings, roundtable events and much more. Additionally, we are excited to bring you our NewsHUB, which collates important news stories, videos, blog posts and more, all in one location. The team are also all active on Twitter and LinkedIn, and please do follow us or join our LinkedIn group to find out more about our upcoming releases.

I hope you enjoy this edition of *Treatment Strategies - Diabetes*, and please do feel free to get in contact with us and let us know your thoughts. We can't wait to bring you our 2014 edition of the publication, which will feature a review of 50th EASD Meeting in Vienna.

Hannah Corby, Chief Sub-editor

The Cambridge Research Centre wishes to thank the following societies for their assistance and involvement in this publication.

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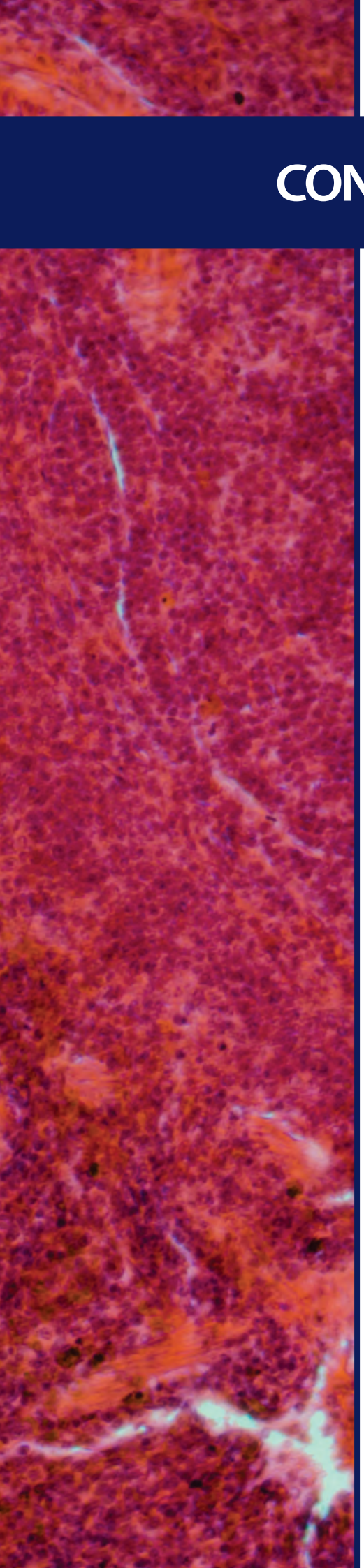

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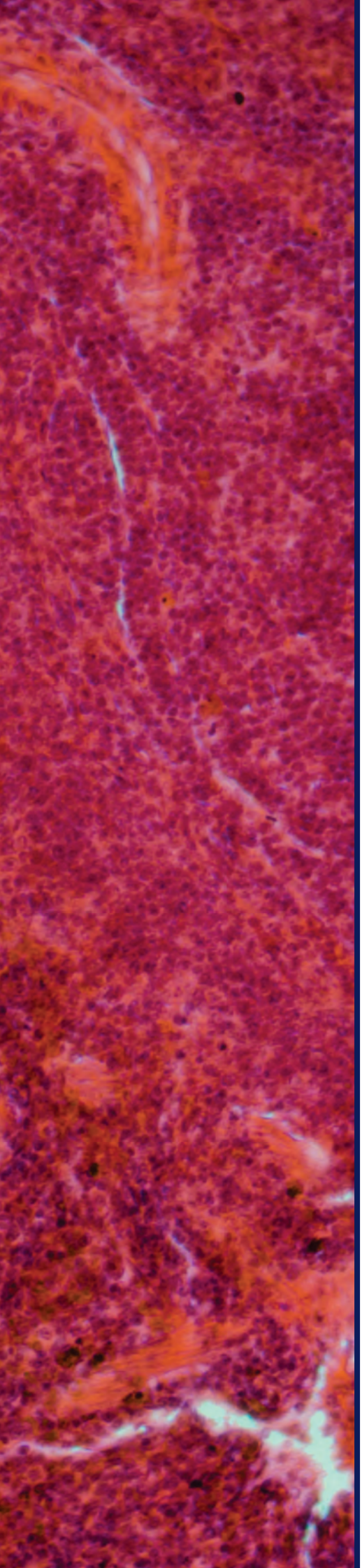

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Foreword

Nigel Lloyd
Managing Director, The Cambridge Research Centre

Welcome to the fifth EASD edition of *Treatment Strategies – Diabetes*. In this edition we are excited to bring you an extensive review of the 49th Annual Meeting of EASD, which we attended in Barcelona this September. This really was a fantastic event which gave some real insights into many areas within the field of diabetes. Our review looks back over the event, and will provide you with all of the breaking news, awards and coverage of the most innovative products that were showcased. A new addition to our review is our poster synopses section, which presents a selection of posters that were presented at the event. We believe that this new feature really adds to the publication, and makes our retrospective review an even more useful tool for our readers.

Diabetes is a lifelong condition which has many consequences for the sufferer. Indeed, in the UK alone there are around 2.9 million people with diabetes, and there is thought to be almost 850,000 people who have undiagnosed diabetes. At EASD 2013, Type 2 diabetes was a much talked about subject area, and is emerging as an important area of research, in particular how to educate young people in how to avoid developing the disease. In this edition of *Treatment Strategies – Diabetes*, Bo Ahren discusses how to manage Type 2 diabetes in his fantastic article 'Strategies to Mitigate the Risk of Hypoglycaemia Associated with the Treatment of Type 2 Diabetes'. In this article he discusses the negative impact which hypoglyaemia can have for diabetes patients, and the importance of selecting the appropriate glucose-lowering medication. Indeed, by reducing the risk of hypoglycaemia, glucose lowering therapy of type 2 diabetes may be improved and more patients will reach their therapeutic target.

Glucose monitoring is very important in the prevention of hypoglycaemia, and is a crucial device in the management of diabetes as a whole. Glucose monitoring reveals individual patterns of blood glucose changes, and helps in the planning of meals, activities, and at what time of day to take medications. In Martin Prázný's paper 'Continuous Glucose Monitoring: Why it is not Enough and What can we Expect of the Closed Loop?' he reveals that continuous glucose monitoring has become the most discussed technological advantage in diabetology in recent years. He then discusses the problems that patients face when using continuous glucose monitoring and, using case studies, talks about the difference that closed loop glucose monitoring can have for the diabetic patient. We have also selected some further reading from previous editions of *Treatment Strategies – Diabetes*, and please do make sure to take a look at these articles if you are interested in this topic.

Type 1 diabetes continues to be an important area of research, and in this edition we have included two papers for you on the subject. Enagnon Kazali Alidjinou and Didier Hober explore enteroviral pathogenesis in their article 'Enteroviral Pathogenesis of Type 1 Diabetes: A Role for Enhancing Antibodies?' Here, they discuss how enteroviruses are thought to be involved in the disease pathogenesis, and they analyse the potential involvement of the facilitation of Coxsackievirus B infection in the viral pathogenesis of Type 1 diabetes. Additionally, Marijana Vučić Lovrenčić's article 'Challenges in Estimating Glomerular Filtration Rate in Diabetic Patients', focuses upon the nephrological aspects of the disease, and writes that appropriate intervention at an early stage of diabetic nephropathy can significantly improve the outcomes for diabetic patients. She discusses the importance of screening for chronic kidney disease and explains more about glomerular filtration rates.

Finally, Henri Tuomilehto looks at how diabetes affects the cardiovascular system in his article 'Obstructive Sleep Apnoea, Type 2 Diabetes and Cardiovascular Consequences.' Here he discusses the growing prevalence of sleep disorders, in particular obstructive sleep apnoea, which has been found to be tightly linked with Type 2 diabetes. His paper focuses on the cardiovascular consequences that this combination of obstructive sleep apnoea and Type 2 diabetes has, and how they can be prevented. We have also selected some papers which also explore

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EASD Annual Meeting 2013

23 - 27 September 2013, Barcelona

49th Annual Meeting of the European Association for the Study of Diabetes

INSIDE...

The Congress

The Exhibition

Treatment Strategies was delighted to attend the 49th Annual Meeting of EASD. In this review, Sara Taheri brings you an in-depth overview of the event, which includes a look at the exhibition hall as well as all of the breaking news, symposia highlights, latest research and more. The review is also followed with a number of poster synopses. This is an exciting addition to the review, as the results of these studies will have a direct impact upon the future of diabetes management.

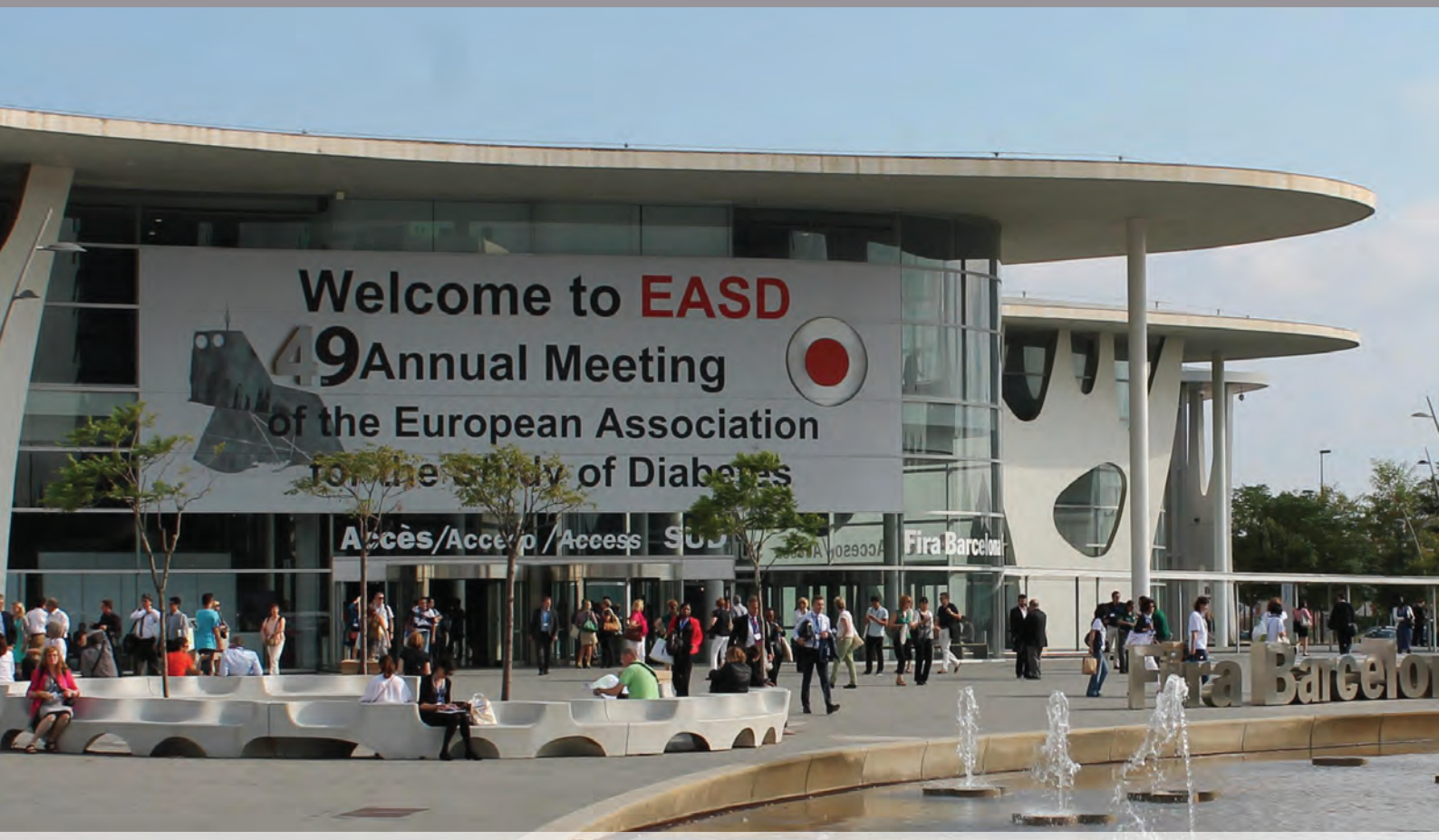
The European Association for the Study of Diabetes (EASD) was founded in 1965 with the mission to encourage and support excellence in diabetes care through research and education.

The EASD has been organising annual meetings since its creation, and over the years these meetings have become the largest international annual conference on diabetes research worldwide. The meetings are still driven by the academic traditions of the founding members. Although guests are welcome to attend, the chairpersons for oral presentations and poster sessions are chosen exclusively from EASD's membership. Indeed, the EASD honourary secretary is solely responsible for inviting speakers and chairpersons for symposia and lectures.

The 49th EASD Annual Meeting was held in the Gran Via exhibition centre of Fira de Barcelona, one of the biggest and most modern convention facilities in Europe. An astonishing 18,000 physicians and scientists involved in basic and clinical research in diabetes from over 120 countries attended the meeting.

The most important advances in all lines of diabetes research were discussed at the event, because although millions of people suffer from diabetes mellitus, there are many aspects of the pathogenesis of diabetes in its two forms which are still unknown. The disease and its complications, including heart disease, blindness and kidney and nervous system damage are acquiring epidemic proportions at a great social and economic cost. Indeed, diabetes is a disease that greatly requires the attention of the scientific community.

Since diabetes is a public health and policy matter the European Medicines



Agency (EMA) and the Directorate General for Research and Innovation of the European Commission were represented, to discuss the future prospects of research funding and the approval of new drugs in Europe.

Patient associations also had a great presence at the meeting. Today, diabetes is considered to be a manageable health problem, with patients playing a leading role in their treatment. Indeed, patients have joined forces and assembled in associations, within which they have become actively involved in pushing health practitioners, hospitals and governments to place a greater emphasis on the human dimension of this disease. The 49th EASD provided a great meeting point for diabetologists and diabetes patients work together to improve education and patient care.

Prof. Andrew J.M. Boulton, the President of the EASD, opened the meeting at the Claude Bernard Hall, welcoming the attendees. Researchers from academia and the pharmaceutical industry around the world then had the opportunity to present new developments in fields such as epidemiology, prevention, therapeutic education, health organisation, and basic and clinical research.

Of the 2321 abstracts received, the Scientific Programme Committee, under the Chairmanship of Prof. Mark Walker, selected 1361 for presentation this year. All abstracts were considered anonymously and were scored by 40 referees. The Programme Committee Members designed the programme and created Oral and Poster Sessions based upon the abstracts.

The scientific programme was comprised of six parallel tracks, which included inspiring symposia, keynote lectures and debates covering basic and clinical science. The scientific programme reflected the on-going efforts to understand, cure and prevent diabetes.

This year the 49th EASD celebrated the 200th birthday of Claude Bernard, and named the main hall in his honour.

The Association awards major prizes annually, including the Claude Bernard Medal, the Minkowski Prize and the Albert Renold Prize Lecture. The recipients of these prizes were then asked to deliver a lecture at the annual meeting.

Furthermore, it was 30 years from the inception and planning of the Diabetes Control and Complications Trial (DCCT), and the final results of the UK Prospective Diabetes Study (UKPDS) presentation, which took place at the 34th EASD annual meeting in Barcelona. In recognition of these two large landmark studies in clinical diabetology two symposia discussed new data resulting from these trials at the 49th EASD. In one symposium, which was chaired by O.B. Crofford and D.M. Nathan, the results of the CCT conducted in patients with type 1 diabetes, which established the modern management theories for this disease, was reviewed and updated. In the other, chaired by A. Adler and I.W. Campbell, the results of the UKPDS on the management of type 2 diabetes were revisited.

Communication and interaction of peers, colleagues and other scientists was facilitated with the Virtual Meeting app and website. The President, Andrew J. M. Boulton, encouraged attendees to download the app and to look through the lectures and posters available on the EASD Virtual meeting website.

Once again, the 49th EASD provided an excellent opportunity for attendees to communicate with peers, colleagues and other scientists both during and after the annual meeting.

EASD Meet in Barcelona

Barcelona is one of the most breathtaking and exciting cities in the world, with a huge number of attractions and historical landmarks. This made it a perfect location for the 49th EASD Meeting.

The "Gothic Quarter" is positioned in the centre of Barcelona's old city. Many of the buildings date back to medieval times, and some from as far back as the Roman settlement of Barcelona.

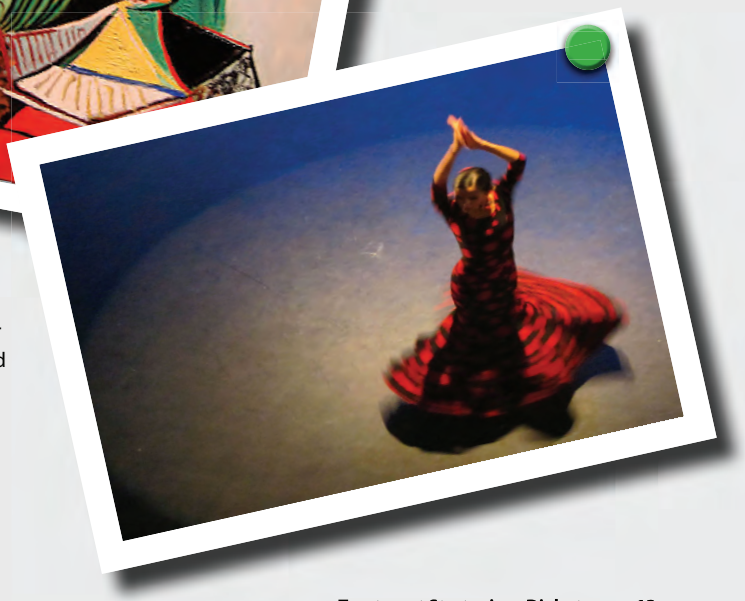
Barcelona also features catalan modernista architecture, which is related to the movement known as Art Nouveau in the rest of Europe. It was developed between 1885 and1950 and left an important legacy in Barcelona. Many of these buildings are World Heritage Sites including several buildings by Antoni Gaudí, Spain's most famous architect.

The city was built north of the mouth of the river Llobregat, and is surrounded by hills of granite and slate. The historical centre lies at the foot of the slate mountain Montjuïc (191 m) on which a fortress was build. South of the mountain (or hill) lies the Montjuic park. Until the 19th century this historical centre was surrounded by walls, which are still standing as the circular and rectangular avenues Rondas and Ramblas. This is both a residential and industrial areas and some parts of the city walls have been preserved.

Las Rambla, the most famous street of Barcelona, is exactly 1.2 kilometres long a big tourist attraction. Laid out in 1766, it follows the contours of the medieval city walls that bounded this part of Barcelona since the 13th century. Because of its central location, the Rambla became a meeting place for all social classes.

At the heart of the city lies the Plaça Sant Jaume, which has been the city's political centre since its inception. The square is the site of the most important buildings in Barcelona and Catalonia, and the palaces of the city council (El Ayuntamiento or Casa de la Ciudad) and the province council (Palacio de la Generalidad) are located here. In Roman times the Plaza Romana or Forum was situated here, however today this is an open space in the middle of the Gothic Quarter.

The Basilica of the Sagrada Família, designed by Antoní Gaudí is the most striking and still unfinished building of Barcelona. Antoni Gaudí began work on the church in 1883 but was not appointed Architect Director until 1884. The facades symbolises Birth (west), Life and Death (east) and the glorification of Christ (south). The eight towers represent the apostles. There are three entrances in the front: faith, hope and love. In the crypt is the tomb of the famous architect Gaudi, who died in 1926. This building is recognised as his best-known work, which is still unfinished but is due to be completed by 2026. He also created remarkable buildings like Casa Batllo with ceramic roofing and Casa Mila.



There are also dozens of museums including one dedicated to Picasso, another to Miró with other major arts exhibitions throughout the year and concerts and shows of different kinds happening all the time.

Barcelona is almost as lively at night as it is during the day and it has a unique, exciting atmosphere, which provided attendees of the 49th EASD with a truly unforgettable experience.

Claude Bernard Lecture

Professor Markku Laakso Awarded the Claude Bernard Prize

The EASD awarded Prof. Markku Laakso the 2012 Claude Bernard Prize. The Claude Bernard Lectureship recognises contributions to the advancement of knowledge in the field of diabetes mellitus and related metabolic diseases.

The Claude Bernard Prize is the most prestigious award of the EASD annual meeting, and Prof. Laakso was chosen for his outstanding contributions to the advancement of knowledge in the field of diabetes.

Prof. Laakso is well recognised in the field of type 2 diabetes, genetics and cardiovascular disease. He applies a variety of approaches and methods that represent the cutting-edge of gene research methods in seeking to unravel the pathophysiology of type 2 diabetes. Prof. Laakso and his team have been exceptionally successful in linking population data with clinical patient studies and animal models, which will help to shed light on the genetic background of type 2 diabetes.

The lecture was entitled 'From one family to 10,000 men: Genes meet phenotypes in diabetes'. "One message is clear: there are also genes associated with insulin sensitivity, not just beta-cell function". Said Prof. Laakso. He explained that the decreasing insulin production is associated with susceptibility genes, and environmental factors which then determine the demand for insulin and the development of diabetes.

Prof. Markku Laakso has been Professor of Medicine at the Department of Medicine, University of Eastern Finland, Kuopio and Chief Physician of the Department of Medicine at Kuopio University Hospital since 1995. Since 2005, he has been Academy Professor at the Academy of Finland and at the University of Eastern Finland, Kuopio. He was Associate Editor for *Diabetologia* from 1997 to1999 and from 2008 to 2013, and a member of Editorial Board for Diabetes Care from 1997 to 1999 and for the Journal of Clinical Endocrinology and Metabolism from 2007 to 2010. His main research interests are cardiovascular complications of type 2 diabetes and genetics of insulin resistance, type 2 diabetes and cardiovascular disease.

He has also received several international awards, including the Novo Nordisk Foundation Award in 2003, Castelli Pedroli Prize (the European Association for the Study of Diabetes) in 2007, and Kelly West Award (American Diabetes Association) in 2008.

The EASD Commemorates Claude Bernard's 200th Birthday

This year the EASD recognised the 200th birthday of Claude Bernard, and named the main hall in his name.

Claude Bernard is considered to be one of the founding fathers of modern physiology and was born on 12 July 1813 in Saint-Julien en Beaujolais in France. His findings were the basis for the understanding of metabolism.

Perhaps his most famous finding was on the glycogenic function of the liver and the cause of diabetes mellitus. In 1848 he published 'de l'origine du sucre dans l'économie animale', where for the first time he described the production of glucose by the liver. He wrote "The digestion of carbohydrates takes place in two steps; first: transformation into glucose, second: glucose is burned in the lung. If this doesn't happen, diabetes occurs." He had to find sugar in the blood and look for the sugar from the vessel of the intestine where it is absorbed to find finally the place where it is burned. To investigate this he gave sweet milk soup to a dog and sacrificed the dog during digestion, he found sugar in the vena hepatica and concluded that all the glucose found in this vein resulted from the sugar the dog had eaten. For a control experiment he chose a dog that was exclusively fed with meat and like before sacrificed this animal during digestion and examined the glucose content of the vena hepatica. He found that although the dog hadn't eaten any sugar the vena hepatica contained sugar.[1] In the article "About the Origin of Sugar", published in 1848[2] he summarised these findings. In this publication, he stated, "Normally there is always sugar in the blood of the heart and the liver. The sugar is formed by the liver; this is independent of the nutrition with sugar or carbohydrates." He then looked into how or in particular in what form the sugar is stored in the liver. In February 1855, Claude Bernard isolated glycogen after numerous experiments.

Throughout his life he was awarded numerous honours, including the Chair of Physiology at the University of Paris (1854), election to the Academy of Medicine (1861) and the Académie Française (1868), a Chair at the Museum of Natural History (1868), and appointment to the Senate upon the personal request of Napoléon III (1869).

Claude Bernard died on February 10, 1878, aged 65, and he was accorded a public funeral, which was bestowed on a man of science for the first time in France. The European Association for the Study of Diabetes honoured Claude Bernard by dedicating a lecture in his name from 1969; the first two recipients, de Duve and Sutherland, were later awarded the Nobel Prize in physiology and medicine.

References
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2. Claude Bernard, introduction à l'étude de la médecine experimentale, Paris, librairie delgrave, 1865

Minkowski Prize

Miriam Cnop Awarded Minkowski Prize

The European Association for the Study of Diabetes presented the Minkowski Prize for outstanding original work of a younger investigator in diabetes research.

The Prize honours pathologist Oskar Minkowski (1858–1931), who determined that diabetes is caused by the suppression of pancreatic substances, which were subsequently found and identified as the hormone insulin. This was the first major breakthrough against the disease, and so he is the namesake of the Oskar Minkowski Award.

The Oskar Minkowski Award has been awarded annually since 1966, and the winner is invited to pronounce a Minkowski Lecture during the EASD Annual Conference.

Since 1966 the award has been sponsored by the pharmaceutical company Sanofi-Aventis. The prize consists of a certificate and 20,000 euros plus travel expenses. The candidate must be less than 45 years of age on 1st January of the year of award. Self-nomination is also possible.

Miriam Cnop obtained her medical degree at the Vrije Universiteit Brussels. Training in Internal Medicine and Endocrinology, she obtained a PhD for her work on the effects of lipoproteins and free fatty acids on beta cells.

She worked as a postdoctoral fellow in the laboratory of S. Kahn at the University of Washington, before joining the Endocrine Division of the Erasmus Hospital & Laboratory of Experimental Medicine, directed by D. Eizirik, at the Université Libre de Bruxelles. Her group focusses on the role of pancreatic beta cell and apoptosis in the pathogenesis of monogenic and type 2 diabetes, which aims to develop strategies to improve beta cell function and mass. They identified ER stress as a cellular response contributing to free fatty acid-induced beta cell apoptosis. Using small molecules and RNA interference strategies to modulate ER stress response and mitochondrial pathways of cell death, her team is elucidating signal transduction by which free fatty acids induce beta cell apoptosis and searches therapeutic targets to protect beta cells. They also study mutations in genes with a role in ER and mitochondrial function and have demonstrated that beta cell dysfunction and death are central in the pathogenesis of diabetes in Friedreich's ataxia, where frataxin deficiency leads to mitochondrial dysfunction.

Her awards include: Endocrinology Prize by the Belgian Royal Academy of Science 2003, Belgian Novo Nordisk Prize for Diabetology 2004, EASD Rising Star 2005, Belgian Endocrine Society Award 2010, and GB Morgagni Young Investigator Award 2010. She served as Associate Editor and is member of the Advisory Board of *Diabetologia*.

Albert Renold Prize and Lecture

Prof. Patrik Rorsman Awarded the Albert Renold Prize

The Albert Renold Prize and Lecture honours the memory of Albert Renold, the distinguished diabetologist and researcher.

The lecture recognises an individual's outstanding contribution to the advancement of knowledge in the field of research on the islets of Langerhans. Albert Renold was also one of the founding fathers of EASD, serving as Honorary Secretary (1965-1969) and President (1974-1977).

Prof. Philippe Halban chaired the 7th Albert Renold lecture on Tuesday 24th September 2013, where Prof. Patrik Rorsman presented the lecture entitled 'The pancreatic islet: more than the sum of its parts?' Prof. Patrik Rorsman was awarded the 2013 Albert Renold Prize Lecture.

Prof. Patrik Rorsman is a Professor of Diabetic Medicine at the Oxford Centre for Diabetes, Endocrinology & Metabolism and a Medical Tutor of Harris Manchester College.

Patrik Rorsman received his Medical Degree from Uppsala University in his native Sweden where, in 1986, he also received his PhD from the Department of Medical Cell Biology for his thesis Patch-clamp characterisation of pancreatic alpha and beta cells.

Since 2003 he has served as Professor of Diabetic Medicine at the University of Oxford. He has published more than 200 papers dealing with the function of the pancreatic islet cells and has performed pioneering studies on the cellular and molecular regulation of pancreatic islet hormone secretion, the mechanisms that underlie the ability of the different types of islet cell (beta cells, but also alpha cells and delta cells) to sense changes in the plasma glucose concentration, and how these processes become disrupted in diabetes mellitus (T2DM).

He has provided evidence that dysregulation of glucagon and somatostatin secretion contributes to islet dysfunction in T2DM and, by examining the mode of action of sulphonyureas and glucagon-like peptide 1 (GLP-1) analogues on both alpha and beta cells, he has also made important contributions to our understanding of diabetes therapy. A significant recent contribution has been his demonstration of important differences in the functional properties of human and rodent islets.

His achievements have been recognised by several bodies and he has received numerous awards including the EASD Minkowski Prize in 1996.

Anette-Gabriele Ziegler, M.D., Technical University of Munich

Marian Rewers, M.D., University of Colorado School of Medicine

Olli Simell, M.D., Ph.D., University of Turku

JDRF's Prestigious Excellence in Clinical Research Awards

Three scientists were awarded with the Excellence in Clinical Research Award at the meeting, in recognition of their important contributions toward understanding the natural history and pathogenesis of type 1 diabetes (T1D) in children.

The Excellence in Clinical Research Award recognises notable clinical and translational T1D research. The award is named in honour of JDRF's International hairman, Mary Tyler Moore – who has had T1D for over 40 years – and her husband, S. Robert Levine, M.D., for their commitment to JDRF's efforts to find a cure for T1D and improve the lives of those living with the disease through the support of research.

This year's recipients have been researching an area of T1D science that is increasing in importance, which is understanding the natural history of the disease. This understanding is key to slowing or stopping the increasing incidence among children under 14 years of age, which is estimated to rise by three percent annually worldwide.

The three award winners were; Anette-Gabriele Ziegler, M.D., Technical University of Munich, who led the BABYDIAB study; Marian Rewers, M.D., University of Colorado School of Medicine, who led the DAISY study; and Olli Simell, M.D., Ph.D., University of Turku, who led the DIPP study.

"Drs. Ziegler, Rewers, and Simell embody the spirit of this award through their lifetime of work toward better understanding the cause, development, and outcomes of type 1 diabetes," say Ms. Moore and Dr. Levine. "We are proud to present this year's award to these three esteemed researchers, and are thankful for the critical insights they have contributed, and continue to contribute, helping us find the means to reverse the growing incidence and prevalence of this complex disease and create a world without type 1 diabetes."

Drs. Ziegler, Rewers, and Simell followed children from birth to identify risk factors associated with T1D and the development of islet autoantibodies, the markers that indicate the activation of the autoimmune attack on insulin-producing beta cells in the pancreas. T1D occurs when these beta cells are destroyed by the immune system, rendering these patients unable to produce their own insulin.

Their findings have demonstrated that the T1D disease process commonly begins in the first one to three years of life and progresses with a variable time period until the onset of T1D symptoms. Data from the three studies contributed to a larger analysis titled "Seroconversion to Multiple Islet Autoantibodies and Risk of Progression to Diabetes in Children," published in The Journal of the American Medical Association. The global analysis revealed that nearly 70 percent of the 585 young children studied in all three countries who had two or more autoantibodies developed T1D within 10 years. The findings suggest that in certain children the disease process becomes established relatively early in life, which means that interventions to prevent the loss of insulin independence must be instituted at an early age.

"JDRF is grateful for the outstanding leadership and collaborative spirit of Drs. Ziegler, Rewers, and Simell, whose insights have helped to provide our current scientific foundation for the prevention of childhood onset type 1 diabetes," says Richard Insel, M.D., JDRF's chief scientific officer. "Their research has confirmed that type 1 diabetes is a disease process that begins long before clinical symptoms appear. Furthermore, it has defined those children at greatest risk of becoming insulin dependent in the shortest period of time, and who can benefit most from prevention therapies."

The natural history studies created by Drs. Ziegler, Rewers, and Simell also helped to lay the foundation for The Environmental Determinants of Diabetes in the Young (TEDDY) study, a global consortium funded by the National Institutes of Health (NIH) that represents a comprehensive effort to identify environmental origins of T1D. TEDDY is supported through funding from the federally-funded Special Diabetes Program (SDP), which accounts for roughly one third of the federal investment in T1D research performed in the United States.

Dr. Insel said, "We are thankful that these awardees continue to contribute to important type 1 diabetes research, which will be paramount in helping JDRF reach our goal of preventing the disease".

Additional Results from EXAMINE Cardiovascular Safety Outcomes Trial

Takeda, a leading contributor to innovative Type 2 diabetes treatments, presented alogliptin and fasiglifam data. The Fasiglifam Phase 3 Efficacy and Safety Data Also Presented[1]

Alogliptin is a dipeptidyl peptidase-4 inhibitor (DPP-4i) for the treatment of Type 2 diabetes in adults as an adjunct to diet and exercise. DPP-4is are designed to slow the inactivation of incretin hormones GLP-1 and GIP. As a result, an increased amount of active incretins enables the pancreas to secrete insulin in a glucose-dependent manner, thereby assisting in the management of blood glucose levels.

Data from the global EXAMINE (EXamination of CArdiovascular OutcoMes: AlogliptIN vs. Standard of CarE in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome) Cardiovascular (CV) safety outcomes trial indicated that alogliptin did not increase CV ischemic events including all-cause mortality (death from any cause), non-fatal myocardial infarction, non-fatal stroke, and urgent revascularisation due to unstable angina. Alogliptin is a dipeptidyl peptidase-4 inhibitor (DPP-4i) for the treatment of type 2 diabetes in adults as an adjunct to diet and exercise. Additionally, EXAMINE exploratory data presented showed rates of hospitalisation for heart failure were comparable across alogliptin and placebo groups.[2]

The company also presented Phase 3 data on the investigational compound fasiglifam, a potential first-in-class GPR40 agonist for the treatment of Type 2 diabetes, demonstrating the study's primary endpoint of change from baseline in HbA1c at week 24 was met.[3] Study findings showed that fasiglifam significantly improved glycaemic control with low incidence of hypoglycaemia and statistically significant reductions in HbA1c, compared with placebo, at 24 weeks in patients with type 2 diabetes inadequately controlled by diet and exercise.[4]

"As physicians, it is critical that we understand the impact of treating high-risk patient groups such as those evaluated by the EXAMINE trial," said Simon Heller, D.M., EXAMINE Steering Committee member. "Many type 2 diabetes patients today are also living with cardiovascular disease, and these additional findings on heart failure hospitalisations will provide important clinical insights for physicians helping patients manage their diabetes."

Fasiglifam Data

The presentation entitled "Efficacy and safety of fasiglifam (TAK-875), a GPR40 selective agonist, in Japanese type 2 diabetes mellitus patients: a Phase 3, double-blind, placebo controlled, comparative study" includes findings from the CCT-003 study, which evaluated the efficacy and safety of the investigational compound fasiglifam 25 mg and 50 mg, administered once daily before breakfast for 24 weeks, in Japanese patients with type 2 diabetes inadequately controlled by diet and exercise.[6]

"We are pleased to present the Phase 3 findings from this study on fasiglifam, which further help to demonstrate the clinical profile of this potential new option for type 2 diabetes," said Ajay Ahuja, M.D., Vice President, Global Medical Affairs, Takeda. "Takeda has built a strong foundation and maintained a robust focus in diabetes for more than 20 years, and presenting a total of seven abstracts at EASD with the scientific community underscores our dedication to addressing the needs of this growing patient population."

For more information visit; **www.takeda.com**

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2. White, W., Heller, S. (2013). Results from EXAMINE Study Presentation.
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Type 2 Diabetes Treatment with JANUVIA®

MSD, Merck Sharp & Dohme presented seven new studies, including a comparison study of DPP-4 inhibition between patients with type 2 diabetes treated with JANUVIA® (sitagliptin), saxagliptin and vildagliptin.

Sitagliptin is a selective, once-daily DPP-4 inhibitor that increases active GLP-1 and GIP hormones, part of the incretin system that helps regulate blood sugar.[1] Sitagliptin inhibits the DPP-4 enzyme over 24 hours.[1] Sitagliptin was the first approved compound in the DPP-4 inhibitor class of oral treatments, and has been approved in more than 107 countries. To date, more than 58 million prescriptions have been dispensed for the sitagliptin family of products worldwide.[2]

Scientific Abstracts Presented which included:

Sitagliptin

- Comparison of Trough Dipeptidyl Peptidase-4 Inhibition in Patients With Type 2 Diabetes Treated With Saxagliptin, Sitagliptin, and Vildagliptin.
- Effects of 6 Weeks Treatment With Sitagliptin on Counterregulatory and Incretin Hormones During Acute Hypoglycaemia in Patients With Type 1 Diabetes.

Burden of Urinary Tract Infection

- Prevalence of Urinary Tract Infection Among Type 2 Diabetes Mellitus Patients vs. Non-diabetic Patients in Germany.
- Disease Burden of Urinary Tract Infections Among Type 2 Diabetes Mellitus Patients: a US Database Study.

Medication Adherence

- Meta-analysis of Studies Examining Medication Adherence to Oral Antihyperglycaemic Agents in Type 2 Diabetes.

Oxyntomodulin

- Oxyntomodulin Has Significant Acute Glucoregulatory Effects Comparable to Liraglutide in Subjects With Type 2 Diabetes.
- A Long-acting Oxyntomodulin Derivative Exerts Superior Body Weight Lowering to GLP1R Agonism in Monkeys.

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1. JANUVIA Worldwide Product Circular 2012.
2. TRx Monthly May 2013.

Raising Diabetes Awareness with Super Heros

Siemens Healthcare Diagnostics is raising awareness of the prevalence of diabetes among adolescents to healthcare professionals with the help of Marvel Super Hero, Iron Man. Video footage from the comic was being played over the screens at the Siemen's stand and aims to help to promote early diagnosis and treatment to manage diabetes effectively. Diabetes testing can be delivered at the point of care via Siemens' DCA HbA1c test kit and DCA Vantagey Analyser.

"The rate of diabetes among adolescents is a cause for concern. We are proud to team up with Marvel's Iron Man, a Super Hero we feel embodies our passion for innovation, to help raise awareness of the disease among young people," states Hilda Crockett, Regional Business Manager for Point of Care at Siemens Healthcare Diagnostics. "Rapid and comprehensive diagnosis of diabetes helps clinicians to provide early intervention, and the DCA HbA1c test kit and DCA Vantage Analyser enables exactly that, whether in a GP surgery, hospital or clinic."

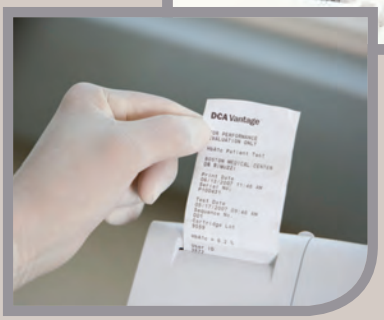
MARVEL CUSTOM SIEMENS

Diagnose Diabetes with In-office Testing

The role of haemoglobin A1c (HbA1c) testing in the management of diabetic patients is established. More recently, the medical community has recognised its clinical utility in the disease's diagnosis. In 2009, several major associations, including the IDF, ADA, and EASD, were part of an International Expert Committee that accepted the A1c test for diabetes diagnosis. In September 2012, the intended use for Siemens DCA® HbA1c test kit[1] was expanded to include new utility as an aid to diagnose diabetes and identify patients at risk for developing the disease.

Advantages of HbA1c Testing

The Expert Committees' decision was based, in part, on several advantages HbA1c testing offers when compared with the current acceptable methods of measuring glucose concentrations by fasting plasma glucose (FPG) or timed oral glucose tolerance tests (OGTT). FPG and OGTT require patients to either fast or inject a glucose beverage and have serial blood draws over three hours. Rather than relying on a single or episodic measurement of glucose levels, the HbA1c measurement represents a degree of glucose exposure over time and is more useful in guiding patient management and therapy adjustment. It is standardised and aligned to the DCCT/UKPDS study, exhibits less biologic variability and pre-analytic instability, and is relatively unaffected by acute (e.g., stress or illness related) fluctuations in glucose levels.[2]



Independent clinical studies have shown that in-office HbA1c testing improves diabetes patient outcomes.[3, 4, 5] Availability of results at the time of visit provides healthcare providers and educators with the opportunity to have meaningful, face-to-face discussions regarding treatment options. From a convenience and scheduling standpoint, it eliminates multiple visits for pre-visit blood draws or post-testing follow-up consultation.

DCA Vantage® Analyser

The DCA Vantage® Analyser helps monitor glycaemic control and detect early kidney disease in environments ranging from the physician's office to remote, point-of-care co-ordinated sites in hospitals and multisite practices. The device enables users to meet lab-quality testing standards with an analyser that speeds and simplifies diabetes tests and delivers accurate,[1] clinically relevant results shown to improve decision-making,[2, 3] patient compliance, and outcomes.[4]

The DCA Vantage® Analyser aims to:

- Manage diabetes patients more effectively.
- Improve workflow in office or clinic.
- Simplify management of diabetes testing in decentralised settings.
- One of just two HbA1c analysers that meet NGSP performance criteria.[1]
- Used by three out of four physicians who perform HbA1c testing in their office.[5]

The device is designed to make consultations easier, and enables physicians to monitor glycaemic control and diabetes complications. Fast, actionable test results enable physicians to determine the effectiveness of a treatment plan, make therapeutic adjustments with confidence, and be more certain whether patients are complying with recommendations.

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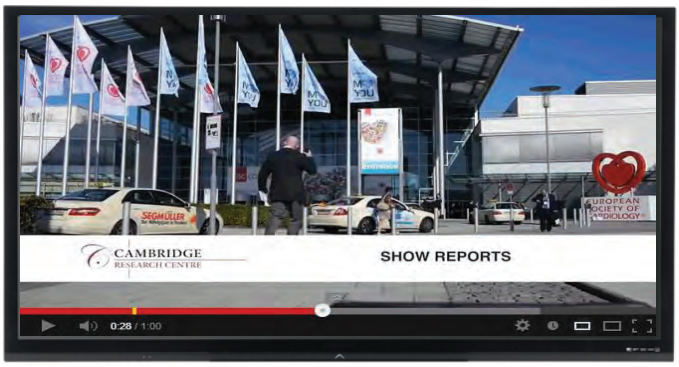

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EndoBarrier® Therapy Efficacy Reinforced

EndoBarrier is a breakthrough device that represents an entirely new class of non-surgical, non-pharmaceutical therapy for the treatment of type 2 diabetes and or obesity. EndoBarrier Therapy helps patients with these diseases achieve rapid and dramatic reductions in blood sugar levels, as well as substantial weight loss.

EndoBarrier is a thin, flexible, tube-shaped liner that forms a physical barrier between ingested food and a portion of the wall of the intestine. Inserted endoscopically (through the mouth without any cutting or scarring of tissue), the EndoBarrier liner prevents the interaction of food with enzymes and hormones in the proximal intestine. In effect, food bypasses the duodenum, but without surgery or permanent changes to the anatomy.

This is a convenient and discreet treatment for people whose diabetes medications are no longer effective and for those who are at risk for serious health complications and want to avoid the progression to daily insulin injections.

In four presentations, GI Dynamics highlighted clinical research findings of data from two patient registries in commercialised markets, clinical research and a meta-analysis of 13 clinical studies.

"Type 2 diabetes requires new treatment options that help patients achieve metabolic control, as existing options are not adequately addressing the needs of patients and physicians," stated David Maggs, M.D., Chief Medical Officer, GI Dynamics. "There is a growing recognition among physicians worldwide of the strong impact that EndoBarrier Therapy can have and where it fits within the existing treatment options for type 2 diabetes and obesity. These data presented at EASD, and data from previous clinical studies, continue to demonstrate and validate the use of EndoBarrier Therapy as part of an effective type 2 diabetes treatment programme."

EndoBarrier Therapy Oral Presentation

During the oral presentation "Interim 12-month results from a post-market clinical trial of DJBL treatment outcomes in subjects with type 2 diabetes and/or obesity," Dr. Julian Teare discussed health improvements achieved through EndoBarrier Therapy in 32 patients. From baseline, patients experienced a one percent decrease in HbA1c, enabling them to achieve better overall glycemic control. In addition, patients achieved a mean weight loss of 26.4 lb (11 kg), along with reductions in blood pressure, cholesterol and triglycerides.

EndoBarrier Therapy Poster Presentations

Additional poster presentations on EndoBarrier Therapy that demonstrated positive treatment outcomes and utility in type 2 diabetes also featured during the meeting. These included:

- Implantation of an endoscopically-deployed duodenal-jejunal bypass liner in obese type 2 diabetes subjects: 8-month follow-up of 10 subjects.
- Six-month follow-up results from a registry observing Duodenal-Jejunal Bypass Liner treatment outcomes in subjects with type 2 diabetes and/or obesity.
- Duodenal-Jejunal Bypass Sleeve for obesity and type 2 diabetes: systematic review with meta-analysis of clinical studies.

"We are very pleased with the progress that we have made in our key European markets and the growing adoption of EndoBarrier Therapy by endocrinologists, as evidenced by the initiation of clinical studies by leading health authorities in France and the United Kingdom," said Stuart A. Randle, President and Chief Executive Officer, GI Dynamics. "The data presented at EASD and the findings from these ongoing studies are designed to help further establish EndoBarrier Therapy as a standard treatment option for type 2 diabetes with local health authorities and in influential treatment guidelines."

For more information, please visit
www.gidynamics.com

ADAMS™ All-in-one Solution for Diabetes Testing

ARKRAY were displaying many of their products, and of particular interest was their Glycated Haemoglobin Analyser, ADAMS A1c HA-8180T, which is a blood glucose test meter.

The ADAMS A1c, HA-8180 is a fully automated Glycohemoglobin (HbA1c) analyser based on HPLC (High Performance Liquid Chromatography). This is an all-in-one solution for diabetes testing and β-thalassemia testing.

The Fastest Measurement of HbA2 in the World

The HA-8180T incorporates unique HPLC column technology to make it the fastest analyzer of HbA2 in the world. The time until first report is 5.4 minutes or less, and in subsequent sample measurements the time taken is just 3.5 minutes.

Highly accurate measurements are obtained thanks to the result of the HPLC measurement principle. The measurement result includes information of each peak and chromatogram. The results are shown in IFCC and NGSP units, which is highly effective for β-thalassemia testing.

The device is equipped with a large-size colour LCD display that shows actual result, and has an easy-to-follow user interface with comments on operational procedure or informs the user about the remaining reagent volume.

There are two types of HA-8180. The HA-8180V is suitable for the measurement of variant Hb and the HA-8180T is highly effective for ß-thalassemia testing.

For more information please visit: **www.arkray.co.jp**

Diasend Promote Easy Communications

Diasend were promoting their standalone system for easy uploading of information from most glucose meters, insulin pumps, CGMs and mobile apps.

The diasend® System consolidates and presents information in clear and structured reports, irrelevant of the device or how the data is stored, providing information that easily shared by patients and healthcare providers. diasend® is used globally in over 15 countries including Europe, the US, Canada, Australia and New Zealand.

diasend® Clinic provides a streamlined approach to disease management with its online solution for healthcare providers. This collects and stores all diabetes patients' data centrally, without having to install any additional software. No matter what type of device, all information is uploaded into a secure diasend.com account which is then immediately made available online. All data from multiple devices will be consolidated and presented in one report.

diasend® is a cloud based system which means that uploaded data can be accessed on any device with internet access. Both patients and care providers can log on using secure accounts at diasend.com, making diabetes management easy and free up valuable resources.

Having partnering with the industries top Electronic Medical Record (EMR) providers, diasend® are taking steps towards setting the standards for better care co-ordination. The EMR interface makes diabetes communications easy by aggregating data from diabetic population's devices into the clinics' EMR. The information from insulin pumps, glucometers, and continuous glucose monitors will be exported from diasend® to the EMR system being used.

With a completely automated electronic exchange from the diasend website to EMRs, the diasend® can reduce costs by eliminating expensive administrative costs.

The interface is also customisable and organisation can specify the types of reports users would like along with the time period that they would like to see them in.

For more information please visit: **www.diasend.com**

Results on Key Proteins in Insulin Sensitisers

Metabolic Solutions Development Company, LLC (MSDC) is a drug discovery and development company investigating novel molecular targets and developing new therapeutics to treat metabolic diseases of aging, especially type 2 diabetes.

On Tuesday 24th September MSDC presented data and insights into mitochondrial target of thiazolidinediones (mTOT) and its role in the development of potentially more useful and novel insulin sensitizers. The poster was entitled 'Study of key proteins in the newly identified mitochondrial target of thiazolidinediones (mTOT): a new target for insulin sensitizers'.

Researchers at MSDC have identified a new drug target through which insulin sensitisers exert their anti-diabetic effects. Insulin sensitisers treat the core problem in type 2 diabetes is insulin resistance, which is a physiological condition in which cells fail to respond to the normal actions of the hormone insulin.

Modification of nutrient utilisation improves cell function and insulin sensitivity mTOT modulators appear to affect the regulation of biochemical pathways essential to maintaining the appropriate level of glucose, a major energy source for cells. Data suggest these new drugs have the potential to improve the body's sensitivity to insulin, lower the percent of calorie-storing "white" fat, increase the production of calorie-burning "brown" fat, preserve the function of pancreatic beta cells (which produce insulin), and protect neurons in the brain (which could be important in treating diseases such as Alzheimer's and Parkinson's disease).

Importance to the Future Discovery and Development of Anti-Diabetic Drugs

Clinical studies in type 2 diabetic patients of MSDC's investigational new drugs, MSDC-0160 and MSDC-0602, demonstrate modulating mTOT could constitute a new approach for the discovery and development of potentially more useful and novel insulin sensitisers.

MSDC-0160 is a novel mTOT Modulator being developed to treat insulin resistance in patients diagnosed with type 2 diabetes. It is a once-a-day, oral insulin sensitiser that works through a newly identified mechanism of action to treat the root cause of type 2 diabetes without the side effects associated with currently marketed insulin sensitisers such as fluid retention, weight gain, and edema.

MSDC-0160 works by modulating a newly defined mitochondrial target called mTOT, which stands for mitochondrial Target of Thiazolidinediones (TZDs). mTOT functions as a molecular "sensor" and "switch" connecting mitochondrial metabolism to important cellular functions are perturbed in metabolic diseases like type 2 diabetes. The new mechanism of action through which MSDC-0160 selectively modulates nutrient sensing pathways, resulting in improved insulin action, lipid oxidation, generation of brown adipose tissue (brown fat), and preservation of beta cells.

New Technologies for Diabetes Measurement and Blood Pressure Monitoring

ForaCare Suisse AG were showcasing the latest in professional diabetes measurement and consumer blood pressure monitoring technology. ForaCare are committed to improving the quality of life for diabetes patients by enhancing the ability of doctors to monitor and care for such individuals.

New products launched by ForaCare at the meeting include the FORA Diamond Blood Pressure Monitor (FORA Diamond Cuff BP), the new iFORA Blood Pressure App (iFORA BP) and the new FORA COMFORT Pro GD40 blood glucose monitor with 5-Electrode Technology.

FORA Diamond Cuff BP offers enhanced patient comfort and faster measurement capabilities, the new iFORA BP allows users to track their morning to night or 7/14/30 day blood pressure trends and share their progress across iOS or Android mobile devices, and the new FORA COMFORT Pro GD40 offers users the highest clinical accuracy for measurement by minimising interference from varying hematocrit levels. The FORA COMFORT Pro GD40 is recommended for hospital/clinic settings, neonatal care, gestational diabetes care and other treatments that require tight glycemic control.

Designed to offer an interactive experience, ForaCare's booth provided product demonstrations to educate EASD attendees first hand on these innovative and easy-to-use products.

"ForaCare Suisse AG is proud to say that our demonstrations of the FORA Diamond Cuff BP were so successful that several doctors expressed an interest in purchasing a cuff directly off the floor," stated Ty-Minh Tan, CEO of ForaCare Suisse AG. "Attendees also appreciated how the iFORA app analyses trends that will empower patients to better manage their health by identifying activities that lead to glucose variations and to share and celebrate their progress over Facebook or email."

ForaCare experts also explained another important feature already implemented on all FORA and FORA Diamond strips, the advanced Superior Sip In (ASSI). ASSI is an enhanced strip technology that builds upon Superior Sip In (SSI) first introduced by ForaCare in 2011. ASSI adds an additional hydrophilic layer to the blood glucose strips, making blood sip-in speed even faster, which increases glucose test precision.

ForaCare is committed to the highest measuring standards and all of their monitoring devices are validated as highly accurate in the industry. FORA Blood Glucose Monitors are validated according to ISO 15197 requirements at an internationally renowned diabetes institute in Ulm, Germany.

For more information, please visit www.foracare.ch

An insulin-independent way to control excess glucose. Remove it.

The **first highly selective** SGLT2 inhibitor that removes excess glucose and its associated calories via the kidney.[1]

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Select FORXIGA®. Effective HbA_{1c} control and secondary benefit of weight loss for your patients with Type 2 diabetes uncontrolled on metformin.[1]

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FORXIGA® is indicated in adults aged 18 years and older with Type 2 diabetes mellitus to improve glycaemic control as: Monotherapy – when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance. Add-on combination therapy – in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.[1]

*FORXIGA® is not indicated for weight loss.

SGLT2, sodium-glucose co-transporter-2.

Prescribing information can be found overleaf.

FORXIGA®▼ 5MG & 10MG FILM-COATED TABLETS (dapagliflozin) PRESCRIBING INFORMATION. Consult Summary of Product Characteristics before prescribing. Presentation: 5mg or 10mg dapagliflozin (as propanediol monohydrate) film-coated tablets. **Indications:** Adults 18 years and older: For patients with type 2 diabetes mellitus to improve glycaemic control: as monotherapy when diet and exercise alone do not provide adequate glycaemic control and use of metformin is considered inappropriate due to intolerance, or in combination with other glucose lowering drugs including insulin when these, together with diet and exercise, do not provide adequate glycaemic control. **Dosage:** Adults: 10mg once daily as monotherapy and add-on combination therapy with other glucose lowering drugs including insulin. Forxiga can be taken at any time of day with or without food. Consider a lower dose of insulin or insulin secretagogue such as a sulphonylurea when used in combination with dapagliflozin to reduce the risk of hypoglycaemia. Children and adolescents: <18 years: Safety and efficacy not yet established. Elderly: ≥65 years: No dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account. ≥75 years: Not recommended. Mild renal impairment: No dosage adjustment. Moderate & severe renal impairment: Not recommended. Severe hepatic impairment: Starting dose of 5mg is recommended, if well tolerated, dose may be increased to 10mg. **Contraindications:** Hypersensitivity to dapagliflozin, or excipients. **Warnings and precautions:** Not to be used in patients with type 1 diabetes mellitus or for diabetic ketoacidosis. Dapagliflozin is not recommended in patients concomitantly treated with pioglitazone and has not been studied with GLP-1 analogues. Use in patients with renal impairment: Not recommended in moderate to severe renal impairment (CrCl <60ml/min or eGFR <60ml/min/1.73m^2). Renal function monitoring is recommended: prior to initiation of dapagliflozin and at least yearly thereafter; prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter; for renal function approaching moderate renal impairment, at least 2 to 4 times per year. If renal function falls below CrCl <60ml/min or eGFR < 60ml/min/1.73m^2, treatment should be discontinued. Use in patients with hepatic impairment: Exposure is increased in patients with severe hepatic impairment. Use in patients at risk of volume depletion, hypotension and/or electrolyte imbalances: Dapagliflozin is associated with a modest decrease in blood pressure, which may be more pronounced in patients with very high blood glucose concentrations. Not recommended in patients receiving loop diuretics or who are volume depleted. Exercise caution in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or elderly patients. Careful monitoring of volume status and electrolytes is recommended in conditions leading to volume depletion, such as acute gastrointestinal illness. In volume depleted patients temporary interruption of dapagliflozin is recommended until volume depletion is corrected. Urinary tract infections: Temporary interruption of dapagliflozin should be considered when treating pyelonephritis or urosepsis. Elderly patients: Elderly patients are more likely to have impaired renal function, be treated with medicines such as anti-hypertensives or diuretics, and be at a greater risk of volume depletion. Cardiac failure: Experience in NYHA class I-II is limited, and there is no experience in clinical studies with dapagliflozin in NYHA class III-IV. Elevated haematocrit: Caution in patients with elevated haematocrit. Urine laboratory assessments: Patients will test positive for glucose in the urine due to mechanism of action. Lactose: Not recommended in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption. **Drug interactions:** Diuretics: Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension. Consider a lower dose of insulin or insulin secretagogue in combination with dapagliflozin to reduce the risk of hypoglycaemia. Dapagliflozin has a low potential for other interactions with commonly used agents in patients with type 2 diabetes. **Pregnancy and lactation:** Do not use during pregnancy or breast-feeding. **Undesirable events:** Refer to SmPC for complete information on side effects. Very common (≥1/10): Hypoglycaemia (when used with SU or insulin). Common (≥1/100 to <1/10): Vulvovaginitis, balanitis and related genital infections, urinary tract infection, back pain, dysuria, polyuria, dyslipidaemia, haematocrit increased. **Legal Category:** POM. **Marketing authorisation number:** EU/1/12/795/002 & EU/1/12/795/007 **Further information is available from:** Bristol-Myers Squibb / AstraZeneca EEIG, Bristol-Myers Squibb House, Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex, UB8 1DH, UK. [FORXIGA] is a trademark of the Bristol-Myers Squibb / AstraZeneca group of companies. **Date of PI preparation:** 04/2013. Approval code: 732UK13PR03937. CV 13 0047

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Bristol-Myers Squibb Pharmaceuticals Ltd. Medical Information on 0800 731 1736 or medical.information@bms.com

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Bristol-Myers Squibb AstraZeneca

Pain-free Insulin Injections with Pen Needles

Pic Solution is the Artsana healthcare brand that specialises in high-quality innovative products that are designed to simplify everyday life.

Pic Solution have one mission, that is to deliver effective easy-to-use solutions at all times which help to improve people's quality of life, including their psychological wellbeing.

Pic Solution has a range of easy-to-use, effective diabetes products delivering precision doses, featuring an exclusive pain-free top-quality needle.

The entire Pic Solution diabetes range is based on innovative technologies and creative, cutting-edge solutions that guarantee outstanding quality for both therapy and in-blood glucose self-testing.
Pic Solution is the only brand to offer diabetic patients the thinnest ever needles for pain-free insulin injections. The accurate triple sharpening of the tip and special treatments ensure that the needle penetrates better, minimising skin trauma and patient discomfort.

31G (with a diameter of just 0.25 mm) is in fact the thinnest needle for insulin syringes and Sensitive 32G (with a diameter of just 0.23 mm) for pen needles. These two products reflect Pic Solution's ability to understand and resolve patients' real needs.

The new pen needles Insupen and new Insumed syringes have been tested in 8 important anti-diabetes centres in Italy. 95% of people who tried them would recommend them to another diabetic patient.
Insupen pen needles have the exclusive Pic Solution needle. It is the thinnest, most pain-free Indolor needle, with an external diameter of 0.23 mm. Its thinner walls enable easier penetration and a high flow, ensuring an even more effective, pain-free treatment for diabetic patients.

For more information please visit :
www.picsolution.com

MyStar Extra®, the First Self-Monitoring Blood Glucose Meter with Estimated A1c

At this years annual EASD meeting Sanofi presented the innovative blood glucose meter MyStar Extra®, the first self-monitoring device that demonstrate robustness and accuracy[1, 2] of estimated A1c value, a key indicator for long-term glucose control.[3, 4]

The haemoglobin A1C (HbA1C) assay has become the cornerstone for the assessment of diabetes control and A1c test results are widely used to guide treatment decisions.[5, 6] MyStar Extra® is a supportive meter designed to help people with diabetes be engaged in their insulin management and treatment plan.[7-9]

The estimated A1c function of MyStar Extra® is based on a new A1c estimation method tracking average glycaemia from self-monitoring data stored in the device. Scientific data presented showed that the estimation procedure used in MyStar Extra® provides accurate estimates of the long-term average blood glucose value.[1, 2] "The major advantage of this method is that it can work with infrequent self-monitoring data, for example fasting blood glucose readings and occasional daily profiles, and still provide reliable estimations where other techniques could fail. In-silico studies confirmed that the dynamical estimation procedure of MyStar Extra® tracks accurately the changes in average glycemia underlying the changes in A1c," said Prof. Boris Kovatchev.

Fasting plasma glucose (FPG) trends and a three-day FPG average provided MyStar Extra® is especially convenient for people starting on or already using insulin as it provides additional blood glucose information on overall glucose control such as three-, seven- and thirty-day fasting plasma glucose averages and fasting plasma glucose trends. The three-day FPG average is an important parameter for insulin titration.[10]

Experts agree support and motivation is key to improving diabetes self-care "People with diabetes need to actively manage their diabetes to achieve good blood sugar control. Support and guidance through new technologies in self-monitoring of blood glucose can increase patients' motivation to stay on track – and motivation is very important in a chronic disease like diabetes. What's more, several studies have shown that ongoing feedback of one's A1c may really help people to see the value of diabetes self-care and ultimately improve diabetes control", said Dr. William Polonsky.

At the Sanofi press briefing experts agreed that simple illustrations of therapy progress can contribute to improved diabetes care and better health outcomes for diabetics, particularly for people using insulin. "At Sanofi, our aim is to truly understand the needs of people with diabetes and to provide efficient, simple tools and guidance that help improve living with and treating diabetes", said Pierre Chancel, Senior Vice President, Sanofi, Global Diabetes. The upcoming launches of MyStar Extra® and MyStar SylkFeel® underscore Sanofi's commitment to provide innovations and integrated solutions to enhance diabetes self-care."

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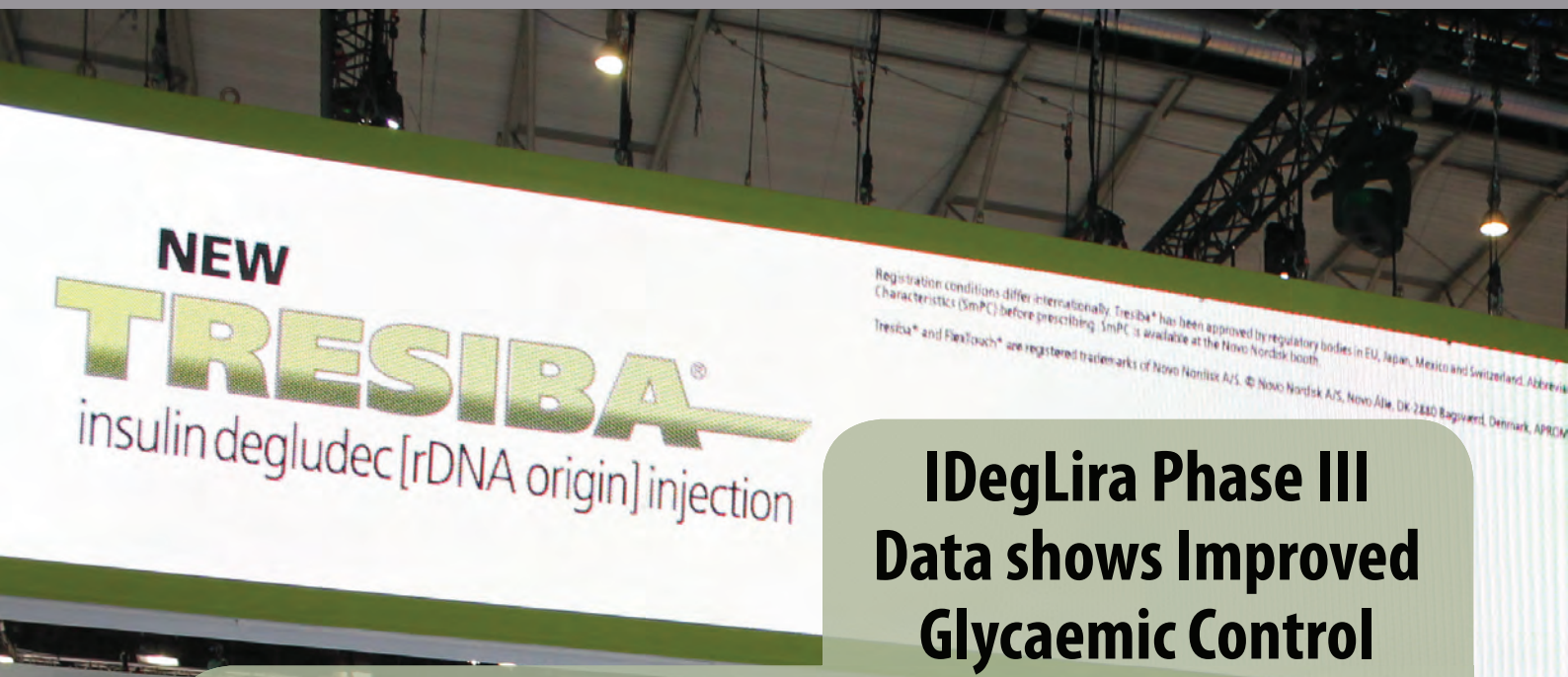

IDegLira Phase III Data shows Improved Glycaemic Control

IDegLira improves glycaemic control throughout the day compared to insulin degludec or liraglutide alone, with a low rate of hypoglycaemia and no weight gain compared to insulin degludec.

IDegLira is a combination of Novo's Victoza (liraglutide), a GLP-1 analogue, and Tresiba (insulin degludec) in a single-injection delivery device for type 2 diabetes. Tresiba was EU-approved in January 2013. Victoza is both US- and EU-approved.

Phase 3 data from the investigational therapy IDegLira [Tresiba® (insulin degludec)/Victoza® (liraglutide injection)] were presented from the DUAL™ I trial show IDegLira demonstrates a statistically significant greater reduction in blood sugar levels HbA1c compared to insulin degludec or liraglutide alone, with no weight gain and a low rate of hypoglycaemia compared to insulin degludec in adults with type 2 diabetes. These results were also supported by data showing once-daily IDegLira provides statistically greater reductions in post-prandial glucose following all three main meals of the day (breakfast, lunch and dinner) compared to insulin degludec.

IDegLira is a once-daily, single-administration basal insulin/GLP-1 analogue combination being developed for the treatment of type 2 diabetes in adults.

"The efficacy of IDegLira demonstrated by the DUAL™ I data is exciting. It combines the clinical advantages, yet mitigates the principal side effects of insulin degludec and liraglutide," said Prof. Stephen Gough, University of Oxford and Oxford University Hospitals NHS Trust, lead investigator of the study. "DUAL™ I shows how patients can achieve an average final HbA1c of 6.4% with no weight gain and a low rate of hypoglycaemia."
The DUAL™ I trial evaluated IDegLira in people with type 2 diabetes inadequately controlled on oral antidiabetic (OAD) medications compared to insulin degludec or liraglutide (1.8 mg) alone:[1]

- IDegLira showed a statistically significant mean HbA1c reduction of 1.9% (from baseline of 8.3%), achieving its primary endpoint of superiority versus liraglutide and non-inferiority versus insulin degludec (-1.3% and -1.4%, p<0.0001, respectively).
- 81% of patients treated with IDegLira reached the HbA1c goal of <7%, and 70% reached ≤6.5% versus liraglutide alone (60% and 41%, respectively) and insulin degludec alone (65% and 48% respectively).
- IDegLira resulted in a mean weight reduction of -0.5 kg and a 32% lower rate of confirmed hypoglycaemia versus insulin degludec (p<0.0001; 1.8 versus 2.6 events per patient per year) whereas liraglutide was associated with less hypoglycaemia and greater weight reduction.

The effects of IDegLira on fasting and postprandial glucose levels resulted in a substantial overall improvement in glycaemic control as compared to its individual components.[2] IDegLira reduced the postprandial increments significantly more than insulin degludec following all three main meals. The reduction in postprandial increments seen for IDegLira and liraglutide were similar.[2] Furthermore, IDegLira resulted in significantly better control of postprandial blood glucose following a standardised mixed meal compared to insulin degludec.[3]

The most frequently reported adverse events seen with IDegLira in the DUAL™ I trial are consistent with its individual components.

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Weight Loss Combined with Dapagliflozin Contributes to Changes in Haemoglobin A1c

AstraZeneca and Bristol-Myers Squibb presented results on Dapagliflozin and weight loss. According to the results of a pooled analysis weight loss With Dapagliflozin contributes to changes in haemoglobin A1c and blood pressure for patients with type 2 diabetes.

"Weight loss is actually a very powerful tool when it comes to reducing cardiovascular risk factors, and SGLT2 [sodium-glucose transporter 2] inhibition seems to be a good help on the way to achieve these weight losses," stated lead author C. David Sjöström, MD, PhD, AstraZeneca, Mölndal, Sweden. "Dapagliflozin causes a continuous loss of calories through the kidney during treatment, providing a retained weight loss over time", he added.

Dr. Sjöström and colleagues pooled data from 7 phase-3 studies that included patients who underwent both dapagliflozin monotherapy and combination therapy (dapagliflozin with metformin, sulphonylurea, thiazolidinedione, insulin; n = 1,066). The placebo pool included 988 patients.

Across the pooled studies, the adjusted mean changes from baseline over 24 weeks demonstrated the expected benefits of dapagliflozin.

The change in HbA1c with placebo (-0.60%) was significantly improved with dapagliflozin (-1.10%). Similarly, systolic blood pressure (SBP) and diastolic BP showed significant improvements over placebo with dapagliflozin (-3.68 mmHg, -1.79 mmHg).

This was paralleled by a significant -2.02 kg weight loss over placebo for dapagliflozin.

The researchers carried out adjusted linear regression modelling to determine the contribution to the changes in HbA1c and blood pressure that were directly related to the dapagliflozin-induced weight loss. This analysis included covariates (gender; baseline age, smoking, anti-hypertensive medicine, HbA1c, estimated glomerular filtration rate, weight, and SBP and DBP); study assignment; treatment; and possible treatment interactions.

Three dependent variables were determined, with beta values for per-kg weight changes as HbA1c 0.028% (P< .0001), SBP 0.606 mm Hg (P< .0001), and DBP 0.253 mm Hg (P< .0001).

For HbA1c, for example, overall weight losses of 3 kg and 5 kg would contribute to 8% and 13%, respectively, of the total reduction in HbA1c upon dapagliflozin treatment. Similarly, for SBP, these weight losses would contribute to 37% and 49%, respectively, and for DBP, 32% and 44%, respectively, of the total reduction in blood pressures upon dapagliflozin treatment.

"There is an added benefit of weight loss during dapagliflozin treatment that contributes to the overall changes in HbA1c and blood pressure levels after 24 weeks of treatment," Dr. Sjöström concluded.

Baseline characteristics showed that just under 50% of subjects were male, and had an overall mean age of 55 to 56 years, duration of type 2 diabetes of 6.3 years, weight of 88.4 kg, body mass index of 31.8, HbA1c of 8.3%, and SBP/DBP of 130.5/79.5 mmHg.

The majority of patients with type 2 diabetes are overweight or obese, and it is known that weight loss can improve glycaemic control, lipid profile and blood pressure; guidelines recommend weight loss.

Omnipod, a Continuous Insulin Delivery System

Ypsomed, distributor of the Omnipod and other diabetes care products under the brand Mylife Diabetescare in Europe, were displaying devices including the new smaller OmniPods that began shipping earlier this year.

With no tubes, no bulky device and no regimented schedules, the OmniPod makes managing diabetes easy. The tubing-free OmniPod is now even smaller, lighter and more discreet than ever.

The OmniPod® Insulin Management System is an innovative continuous insulin delivery system that provides all of the proven benefits of continuous subcutaneous insulin infusion (CSII) therapy in a way no conventional insulin pump can. The System's innovative design and features allows the patients to live their life and manage diabetes with unprecedented freedom, comfort, convenience, and ease.

The long-term health benefits of better blood glucose control are well-known. Maintaining near-normal blood glucose levels can help you live a longer, healthier life with fewer diabetes- related complications. The OmniPod System also has many practical, everyday benefits, including convenience, freedom, flexibility, and ease of use. Continuous insulin delivery most closely mimics the insulin release of a healthy pancreas. Since the landmark 10-year Diabetes Control and Complications Trial (DCCT), the long-term health benefits of maintaining near-normal blood glucose levels have been widely recognised.
Continuous insulin delivery at preset rates eliminates the need for injections and the interruptions that come with them. In addition, with the OmniPod System, insulin delivery can be changed with the press of a button to adapt to snacks or unexpected changes in daily routine.

The OmniPod System is a great option for people with diabetes who require insulin, working much like the pancreas of a person without diabetes by delivering insulin in two ways:

- A small, constant, background supply of insulin (called a basal rate) is delivered automatically at a programmed rate, throughout the day and night.
- An extra dose of insulin (called a bolus) can be delivered when needed to match the carbohydrates in a meal or snack or to correct a high blood glucose.

Wearing an insulin pump like the OmniPod offers some distinct benefits over managing diabetes with daily injections. For the body, it's more like insulin delivery from a healthy pancreas. Patients can achieve tighter blood glucose control and improve your A1C – without needing to add injections.

For more information visit: **www.myomnipod.com**

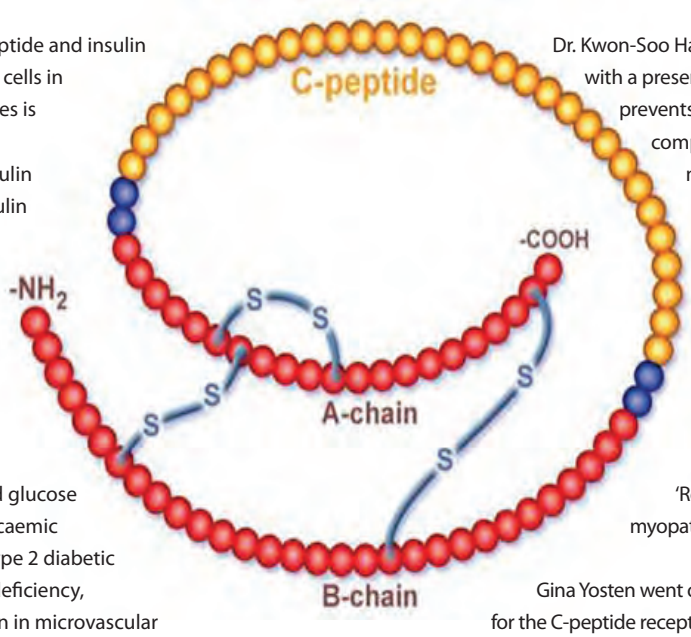
New Developments in C-Peptide for Treating Diabetic Peripheral Neuropathy

At the 49th EASD Annual Meeting Cebix Incorporated chaired a symposium on 'C-Peptide and the Pathophysiology of Diabetes – New Developments'.

On Monday 23rd September Cebix executive Dr. John Wahren, and Dr. Nigel Brunskill from the Department of Infection, Immunity and Inflammation at the University of Leicester chaired the symposium in which the latest developments on C-Peptide and the Pathophysiology of Diabetes were discussed.

Cebix is focused on the treatment of diabetic complications including those affecting the function of nerves, kidneys, and eyes. Cebix's candidate drug Ersatta™ is a long-acting form of C-peptide, a naturally-occurring peptide that is formed when insulin is cleaved from pro-insulin.

In healthy individuals, C-peptide and insulin are co-secreted by the beta cells in the pancreas. Type 1 diabetes is characterised by the body's inability to produce pro-insulin and consequently both insulin and C-peptide. Because C-peptide deficiency has only recently been implicated in vascular microcirculation dysfunction, treatment for type 1 diabetes is currently limited to intensive insulin therapy and frequent blood glucose monitoring to optimise glycaemic control. Type 1 and some type 2 diabetic patients have a C-peptide deficiency, which can cause a reduction in microvascular circulation, resulting in progressive damage to the nerves, retina and kidneys.



Ersatta™ is a disease-modifying replacement peptide for the treatment of complications associated with diabetes. Ersatta is a long-acting form of C-peptide that has the potential to reduce the chronic complications of diabetes, including progressive damage to the nerves, kidneys, and retina.

Cebix has been granted fast track status by FDA for Ersatta for treating diabetic peripheral neuropathy. Cebix have recently completed a 72-subject phase 1/2 clinical trial evaluating Ersatta in patients with type 1 diabetes. The trial validated Ersatta's benign safety profile and once weekly administration, and provided favourable initial results in improved nerve conduction velocity (a measure of peripheral neuropathy).

Cebix has launched an international 240-subject phase 2b trial in early 2013 measuring nerve conduction velocity as the primary endpoint. While Ersatta is initially being developed for peripheral neuropathy, the drug has potential in autonomic neuropathy, retinopathy, nephropathy, and erectile dysfunction, all long-term complications seen in both type 1 and type 2 diabetic patients.

Dr. Kwon-Soo Ha began the symposium with a presentation entitled 'C-peptide prevents development of diabetic complications by inhibiting ROS-mediated intracellular events'.

This was followed by a presentation on 'C-peptide regulated pathways adapting beta cells to stress' by Dr. Patrizia Luppi, who was followed by Dr. Sumia Essid's presentation entitled 'Reversal of statin-induced myopathy by C- peptide'.

Gina Yosten went on to present on "Searching for the C-peptide receptor" and the Biophysical properties and molecular interactions of C-peptide were discusse by Dr. Mikael Landreh.

Dr. Alexander Chibalin discussed the C-peptide mediated intracellular signalling and new findings of this in his presentation, and the lhe last presentation of the symposium was entitled 'Development and early findings for a long-acting C-peptide,' which was given by Dr. Joel Martin.

For more information, visit www.cebix.com

Dulaglutide Results Show Improved Patient Health Outcomes

Eli Lilly and Company presented Phase III clinical trial data for Dulaglutide

In addition to reductions in HbA1c (hemoglobin A1c) levels and weight at 26 and 52 weeks with dulaglutide,[1] dulaglutide-treated patients reported significant, positive improvements compared to baseline across several patient-reported indicators of diabetes management, including:

- Satisfaction with treatment and rates of perceived hyperglycaemia as measured by the Diabetes Treatment Satisfaction Questionnaire (DTSQ);

- Weight-related self-perception (Impact of Weight on Self-Perception (IW-SP) and Ability to Perform Physical Activities of Daily Living Questionnaires (APPADL)); and

- Perceived current health status (EuroQoL 5-Dimension Questionnaire (EQ-5D)).[2]

"Patients' perception of how diabetes treatment may affect their lives is an important consideration when choosing a medication. We are pleased that in this study, patients treated with dulaglutide reported improvements in several patient- reported outcome measures," said Gwen Krivi, Ph.D., Vice President, Lilly Diabetes product development. "These results, coupled with dulaglutide's positive clinical data, suggest that, if approved, our investigational once-weekly GLP-1 may be an attractive treatment option for patients with type 2 diabetes."

The patient-reported outcomes from the AWARD-1 trial, a randomised, 52-week, placebo-controlled comparison of the effects of dulaglutide and exenatide twice-daily on glycaemic control in patients with type 2 diabetes on metformin and pioglitazone. The primary objective of the study was to evaluate whether dulaglutide, dosed once-weekly, was superior to placebo in reducing HbA1c from baseline at 26 weeks.

Clinical results from the AWARD-1 trial showed that treatment with dulaglutide led to improvements in HbA1c levels and weight reductions.[1] Dulaglutide-treated patients also demonstrated significant improvements compared to baseline and exenatide twice-daily in perceived hyperglycaemia scores (using DTSQ) at 26 and 52 weeks.[2]

Patients in the study noted significant improvements in weight-related self-perception (IW-SP) compared to baseline at 26 weeks, which persisted through one year of treatment. These improvements were not significantly different between all treatment groups.[2] There were no significant differences in the ability to perform physical activities of daily living (APPADL) between dulaglutide-treated patients compared to baseline, placebo or exenatide-treated patients.[2]

Treatment with dulaglutide, as well as with exenatide twice-daily, led to significant improvements in perceptions of current health status (EQ-5D) compared to baseline at 26 weeks; these improvements with dulaglutide as well as exenatide twice-daily were also significant compared to placebo. Significant improvements were also seen compared to baseline at one year, with no significant differences between dulaglutide and exenatide twice-daily.

Dulaglutide is one of several diabetes molecules in Lilly's late-stage pipeline, with a number of potential medicines in development for diabetes and its related conditions. Lilly expects to submit dulaglutide to regulatory authorities in 2013.

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Tanita Presents Body Composition Analysers

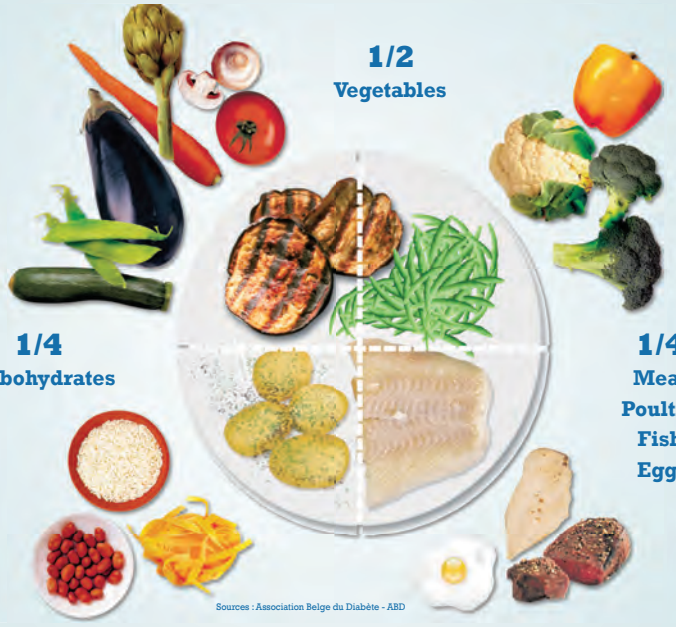
Tanita is a world leader in the field of Precision Electronic Scales and Body Composition Analysers. An ethical healthcare product manufacturer, their objective is to research and bring to market technologies that facilitate health monitoring, both for professionals and for the health-conscious public.

Extensive research has been carried out to establish the relationship between excess body fat, heart disease, diabetes and certain cancers; Tanita introduced the world's first Integrated Body Fat Scale to medical research professionals in 1992. Using this same technology, Tanita then developed the world's first Body Fat Monitor Scale for personal use in 1994.

With the mission to help people enjoy healthier lives, they have become the world leader in this area and have set the gold standard for Bio-electrical Impedance Analysis (BIA) scales and monitors. Backed by extensive clinical research and a Medical Advisory Board of independent researchers and consultants, its products are trusted by physicians, clinicians and health and fitness experts worldwide.

Today, Tanita continues to lead the way in the scale category for both its personal and professional models. Recent innovations include being the first to market with 'segmental body composition analysis' - differentiating between fat and muscle in each limb - and an impressive array of radio wireless products that employ ANT+, Bluetooth and Wi-Fi protocols for remote monitoring and trend analysis.

Ingredients for a healthy lifestyle



A healthy lifestyle reduces the risk of developing diabetes and its complications.
It is also essential for diabetes management and care.

world diabetes day
14 November

International Diabetes Federation Europe

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Non-invasive Glucose Monitoring Devices

The developer of the GlucoTrack® model DF-F non-invasive blood glucose measurement device Integrity Applications, Inc, presented and exhibited at the 2013 EASD meeting.

Integrity Applications is a medical device company focused on the design, development and commercialisation of non-invasive glucose monitoring devices for use by people with diabetes. Integrity Applications have developed the GlucoTrack model DF-F non-invasive glucose monitoring device, which is designed to help people with diabetes obtain blood glucose level measurements without the pain, inconvenience, incremental cost, and difficulty of conventional (invasive) spot finger stick devices.

The company exhibited its CE Marked GlucoTrack® model DF-F non-invasive glucose monitoring device, designed for spot measuring, at the event.

In addition, Avner Gal, Chief Executive Officer of Integrity Applications, presented a poster titled "Presenting a Truly Non-invasive Glucose Monitor for Home Use" on Thursday, 26th September in a conference session titled "New Devices for Glucose Monitoring and Insulin Delivery."

Mr. Gal said, "Attendance at EASD is vital for every company involved in the development of new technology intended to help patients with diabetes. We are eager to take this opportunity to present our GlucoTrack® DF-F blood glucose monitoring device to the distinguished attendees of this meeting, and we look forward to detailing its features and benefits to them in person."

For more information please visit **www.integrity-app.com**

Weight Loss and Caloric Modulation

Arena Pharmaceuticals presented phase 3 clinical trial data for BELVIQ® (lorcaserin HCl) at the 49th EASD Annual Meeting which were focused on discovering, developing and commercialising novel drugs that target G protein-coupled receptors, or GPCRs, to address unmet medical needs. Arena Pharmaceuticals presented a poster entitled 'Weight Loss and Caloric Modulation'. The poster looked at Lorcaserin HCl Phase 3 Trials in Obese and Overweight Patients.

Lorcaserin helps overweight people with type 2 diabetes lose weight. It has serotonergic properties and acts as an anorectic. It has been approved by the US Food and Drug Administration for chronic weight management, and is available by prescription in the United States. Lorcaserin is believed to decrease food consumption and promote satiety by selectively activating serotonin 2C receptors in the brain though the exact mechanism of action is not known.

For more information visit www.arenapharm.com

Personalised Diabetes Management with Roche

Roche Diabetes Care held a symposium entitled 'Personalised Diabetes Management - the Journey to More Efficient and Effective Solutions', which was chaired by Antonio Ceriello, Hans DeVries, and Rolf Hinzmann on Monday 23rd September.

The Symposium consisted of five presentations on the following topics; Information matters – translating glucose data into clinical value; Continuous glucose monitoring – clinical applications for high performance sensors; Expand the options – insulin dosing and delivery; Use the data – reality, opportunities, and future options of mobile health; Act and react – a structured feedback loop involving patients and healthcare providers.

Dr. Matthias Axel Schweitzer, Roche Diabetes Care Mannheim, Germany, gave the first presentation entitled 'Information matters – translating glucose data into clinical value', in which he discussed the diabetic patients need for glucose information in order to manage the daily tasks of their progressing, chronic disease. He explained that this information serves as a foundation for the patient's use of available tools, services, and medical devices. Although evidence suggests that these can be applied successfully, he highlighted that they must be tailored to meet individual medical needs, patient wishes, and the abilities of both the healthcare team and the patients themselves.

Dr. Schweitzer then explained that using glucose information to personalise diabetes management in a convenient, effective, and progressively automated, eliminates the burden of diabetes therapy and improves its quality, making this an increasingly promising reality in the treatment of diabetes.

'Continuous glucose monitoring – clinical applications for high performance sensors' was the title of the following presentation given by Dr. J. Hans DeVries from the Academic Medical Center, University of Amsterdam, The Netherlands. In his presentation Dr. J. Hans DeVries discussed how continuous glucose monitoring has been demonstrated to improve glucose control by reducing the number of hyperglycaemic and hypoglycaemic events alike in type 1 diabetes. He cited a recent meta-analysis[1] which showed a meaningful reduction in HbA1c depending on baseline HbA1c and frequency of sensor use. The first report for which has been recently received showing a decrease in severe hypoglycaemia in patients who are unaware of their blood glucose levels without measuring. This should spur more widespread reimbursement across the globe. With further improvements in accuracy, which was also recently reported,[2] continuous glucose monitoring is now coming of age.

Dr. Iain Cranston, from the Queen Alexandra Hospitalin Portsmouth, UK, followed on with a presentation entitled 'Expand the options – insulin dosing and delivery'. Dr Cranston explained that over recent years there has been much research published on continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM) and the drive towards "closed loop care". Nevertheless, it remains the case that the great majority of individuals with type 1 diabetes manage the disease using flexible dose multiple daily injections (MDI) and self-monitoring of blood glucose (SMBG) levels to guide decision-making.

To improve outcomes for individuals on multiple daily injection (MDI) therapy, Dr. Cranston suggested that it is necessary to improve the way SMBG data is utilised so that it is a more effective advisory processes for flexible insulin-dosing MDI regimens. In particular Dr. Cranston spoke of the impact of bolus advisory meter use in structured care programmes, with reference to the recently published ABACUS[3] data.

This presentation was followed by 'Use the Data – Reality, Opportunities, and Future Options of Mobile Health' by Dr. Irl B. Hirsch, Professor of Medicine, University of Washington, USA. Dr. Hirsch started his presentation with the evolution of diabetes data monitoring technology over the years. He discussed how these devices were used to assess the reliability of the patient's written logbooks, and then went on to explain that over time, glucose meter downloads have become more sophisticated, with powerful analysis allowing both clinicians and patients to recognise patterns which are not appreciated with the traditional pen and paper approach.

Despite these advancements, Dr. Hirsch explained that unfortunately the barriers to downloading meters, now in addition to pumps and continuous glucose monitoring devices, has resulted in underutilisation of this technology, even in areas where computers, smart phones, and WiFi are plentiful. While the time required to utilise the tools for data download and analysis is

considered too great for many clinicians (and patients), early studies have shown some improvement of glucose control. These trials, however, are small and non-definitive. On the other hand, clinicians who consistently use this technology to assist patients generally find it invaluable. Importantly, payers are now beginning to require some data download for a variety of reasons, including documentation of the number of strips required for individual patients. It is quite likely that payers will want to see more detailed data in the future.

This last point is likely what will push this "diabetes data explosion" into the world of mobile health. Even if that is the case, "mhealth" could potentially have other downstream benefits for diabetes care. The ultimate goal is to take this relatively simple technology, which is used in everyday life, and utilise it in the world of diabetes in order to make diabetes management more efficient and to improve outcomes.

Last but not least, Dr. Oliver Schnell, Forschergruppe Diabetes e.V. at the Helmholtz Center, Munich, Germany gave his presentation 'Act and react – a structured feedback loop involving patients and healthcare providers'. Here, Dr. Schnell discussed how diabetes provides a pertinent case of chronic disease management with a particular focus on patient self- management.

Dr. Schnell explained that despite advances in diabetes therapy, many people with diabetes still fail to achieve treatment targets, thus remaining at risk of complications. He went on to describe a six-step cycle[4] for personalised diabetes (self-) management and collaborative use of structured blood glucose data, which tailors therapy to individual patients and can help therapy adherence and treatment outcomes:

1. The patient receives structured education and training to perform Structured Testing.
2) Well thought-out self-monitoring of blood glucose is conducted to monitor the patient's glycaemic status.
3. Electronic devices or software tools can easily collect and document blood glucose monitoring data directly from the blood glucose meter. This can be done by the patient or by a nurse or medical assistant. This information may be stored in personal health records and viewed by patients, as well as by care providers with the consent of the patient.
4. Analysis of the data comes with a graphic presentation that illustrates the findings in an easy-to-digest manner. With increasing data, predictive modeling algorithms may be personalised to create best-fit, tailored care models to achieve targets.
5) Treatment is chosen based on the characteristics of the individual patient and his/her self-management blood glucose profile to achieve individual treatment goals and to improve the medical outcome-and thus quality of life for the patient.
6) Treatment efficacy should be assessed on a regular basis, approximately 3-6 months after the change in therapy has been initiated.

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EFSD and Diabetes Research Programmes in Europe

To encourage diabetes research in Europe, the EASD created its own non-profit Foundation the European Foundation for the Study of Diabetes (EFSD) in 1999.

The EASD executive committee is also the executive committee of EFSD, which is under the close supervision of the EASD Council and the General Assembly of the EASD.

The EFSD actively supports high quality research in diabetes across Europe by liaising with both non-governmental and governmental agencies. EFSD endeavours to support research to find a cure for diabetes and associated complications, and to prevent their onset whilst also increasing awareness.

The Foundation has now become a significant European funding agency for diabetes research as it strives to enhance awareness of the severity and magnitude of this disease in Europe.

Together with numerous funding partners the foundation runs an increasing number of partnership programmes. The current partners of the foundation supporting the research of diabetes in Europe include; AstraZeneca / Bristol-Myers Squibb; Boehringer Ingelheim; Chinese Diabetes Society; Janssen; Japan Diabetes Society; Juvenile Diabetes Research Foundation; Lilly; Merck Sharp & Dohme; Novartis; Novo Nordisk and Sanofi.

janssen

Janssen:
EFSD and Janssen Programme for the Study of the Role of the Kidney in Diabetes is intended to stimulate and accelerate European research in understanding the role of the kidney in diabetes. The emphasis of the programme is on renal glucose handling and metabolism, and in particular its physiological and pathophysiological role in type 2 diabetes.

EFSD and Janssen Rising Star Fellowships aim to identify promising and innovative young researchers developing research activities in Europe. Selected candidates have the opportunity to present an overview of their past and on-going research activities during a multi-disciplinary research symposium at the EASD Annual Meeting. Candidates are invited by EASD to present a lecture and receive a commemorative diploma with a research fellowship of Euro 30,000 for their institution.

MERCK SHARP & DOHME

Merck Sharp & Dohme:
EFSD and MSD have established a European Research Programme on novel therapies for type 2 diabetes with joint funding. This programme is intended to encourage and accelerate European research to identify and get an understanding of novel therapies for the treatment of type 2 diabetes.

Boehringer Ingelheim

Boehringer Ingelheim:
EFSD and Boehringer Ingelheim have established a new partnership called the EFSD and Boehringer Ingelheim European Diabetes Research Programmes. These consist of two elements, each with a different focus: Regulation of Secretion and Function of Non-Insulin Peptides from the Endocrine Pancreas for basic research projects; Mechanisms Relating Renal Dysfunction to Cardiovascular Disease in Type 2 Diabetes for clinical/translational research projects.

NOVARTIS

Novartis:
EFSD and Novartis have established a partnership called the EFSD/Novartis European Research Programme in Microvascular Complications of Diabetes This aims to encourage European basic and clinical research that focuses on microvascular complications of diabetes.

novo nordisk®

Juvenile Diabetes Research Foundation and Novo Nordisk:
EFSD, JDRF and Novo Nordisk European Programme in Type 1 Diabetes Research has been renewed, this aims to promote research targeted at finding a cure for type 1 diabetes and its complications.

EFSD, JDRF and Novo Nordisk Research Fellowships in Type 1 Diabetes. The objective of this Research Fellowships is

Lilly

to support young investigators engaged in research focused on type 1 diabetes and its complications.

Lilly:
The EFSD/Lilly European Diabetes Research Fund was created to promote increased European diabetes research and to increase public awareness and political understanding of the magnitude and burden of the disease.

EFSD/Lilly Mental Health and Diabetes Programme focuses on European research aimed at clinical research into improved care of patients with diabetes and mental diseases including all forms of depression, schizophrenia and alzheimer's disease.

EFSD/Lilly Research Fellowships objective is to encourage research in the field of metabolism and complications of diabetes, and to promote medical education within these areas.

Chinese Diabetes Society and Lilly:
EFSD, CDS and Lilly Programme focuses on collaborative research endeavours between European and Chinese research centres and/or individual investigators. The objective of these fellowships is to provide the opportunity for young researchers in china to visit a European institution.

AstraZeneca/Bristol-Myers Squibb:
The EFSD European Diabetes Research Programme in Cellular Plasticity Underlying the Pathophysiology of Type 2 Diabetes is supported by an educational grant from AstraZeneca/Bristol-Myers Squibb. Investigations into cellular plasticity of the diabetes disease process are welcomed in this programme.

To encourage research projects aimed at advancing knowledge of macrovascular complications of diabetes EFSD together with an educational grant from AstraZeneca/Bristol-Myers Squibb has established a Clinical Diabetes Research Programme in Macrovascular Complications of Diabetes.

EFSD, supported by an educational grant from AstraZeneca/Bristol-Myers Squibb has established a European Diabetes Research Programme in Patient Education to encourage projects in this area.

Novo Nordisk A/S:
EFSD and Novo Nordisk Partnership for Diabetes Research in Europe is a programme which accepts applications from all fields of clinical and basic research.

Sanofi:
A new partnership, the EFSD and Sanofi European Research Programme's objective is to encourage new projects aimed at advancing current knowledge. The programme is intended to stimulate European research focusing on innovative approaches to treat type 1 and/or type 2 diabetes through an increased understanding of the underlying pathophysiological processes.

EFSD and Sanofi Programme for collaborative clinical diabetes research between European and non-European countries plan is to initiate a collaboration between European clinical research in rapidly developing countries who would benefit from the collaboration with research institutes in Europe.

Japan Diabetes Society:
EFSD and JDS Reciprocal Travel Research Fellowships, of which there are up to four, are fellowships of Euro 50,000 each. This fellowships aims to encourage collaborative research between Europe and Japan in the field of diabetes. Applicants are accepted from Japan to travel to Europe and also from Europeans to travel to Japan.

Additionally, EFSD also runs the following programmes:

EFSD Clinical Research Grants in Diabetes is an independent programme to stimulate clinical research into all aspects of diabetes.

EFSD New Horizons Collaborative Research Initiative, which was created to promote inter-regional collaboration in diabetes research throughout Europe and rebalance the uneven funding that has historically been distributed.

EFSD Research Programme in Diabetes and Cancer aims to promote investigations to identify an association between diabetes and increased morbidity and mortality in certain cancers.

EFSD Albert Renold Fellowships is a programme supported by an unrestricted educational grant from Merck Sharp & Dohme (MSD). A Fellowship for Young Scientists, this programme enables young scientists to travel and stay at other institutions to learn different scientific techniques related to diabetes research. Either the home or the host institution must be based in Europe or an associated country.

For more information visit: www.europeandiabetesfoundation.org

The Associations' Village Exhibition Area

The Associations' Village is a special exhibition area, organised by the EASD in collaboration with IDF Europe. This provides attendees the opportunity to connect with international diabetes associations, societies and study groups exhibiting at the annual meeting.

Represented association, society and study groups each had their own stand to display current activities and highlight the work and practices they are undertaking.

The Associations' Village provided a multinational networking platform with the aim to further increase and facilitate the exchange of knowledge and experiences among diabetes associations. It also aimed at providing physicians and researchers from all over the world information on the existing professional and patient associations.

At the Associations' Village visiting physicians and researchers had the opportunity to learn about diabetes in a variety of different countries, speak with colleagues and get the latest information on diabetes research from all over Europe.

Direct Scientific Exchange: EASD Poster Sessions

At the Annual EASD Meeting poster presentations are thought of as equal to that of oral presentations.

The posters are mounted in the morning of the first day and are displayed throughout the duration of the meeting, and are removed on the last day.

For first-rate and direct scientific exchange all posters were presented at six one hour Poster Discussion Sessions which were held on Tuesday, Wednesday and Thursday from 12:30 to 14:45, when no other scientific sessions were taking place.

During the Poster Presentation Sessions, the presenting author was present or if not, had made arrangements for somebody with knowledge of the displayed work to be present at the poster.

Posters were also available via EASD Virtual Meeting where participants were able to discuss and comment on the posters using the Virtual Conference Tool.

Early Phase of Metformin Action in Dietary Obese Mice: Lack of Involvement of AMP-Activated Protein Kinase and Possible Interaction with n-3 Fatty Acids

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Long-chain n-3 polyunsaturated fatty acids (omega-3) of marine origin, mainly eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3), exhibit beneficial effects on health. They act as natural hypolipidaemics and they could prevent development of cardiovascular disease in humans. In mice, but not in humans, omega-3 could counteract development of insulin resistance and type 2 diabetes (T2D). We have shown previously that omega-3 prevented impairment of hepatic insulin resistance in mice fed a high-fat diet (HFD), which was dependent on functional AMP-activated protein kinase (AMPK).[1] Metformin (1,1-dimethylbiguanide) is the most widely prescribed drug to treat hyperglycaemia in individuals with T2D and it is recommended, in conjunction with lifestyle modifications (dietary measures, weight control and physical activity), as a first-line oral therapy. This antidiabetic drug with blood glucose-lowering effect also has beneficial impact on lipid metabolism. The precise mechanism of metformin action still remains unknown. Existing data suggest that metformin lowers glycaemia via mild suppression of mitochondrial complex I activity, leading to a decrease in hepatic glucose production and concomitant AMPK activation.[2, 3] However, it was shown, that metformin exhibit glucose-lowering effect even in liver-specific AMPK-deficient mice.[4] This suggests that AMPK-independent mechanisms of metformin action may also exist. We sought to learn whether pre-treatment of dietary obese mice with omega-3 could enhance early phase of metformin action, and whether AMPK is involved.

Adult insulin resistant obese mice fed HFD for 6 weeks were randomly assigned either a HFD diet or the diet containing omega-3 concentrate replacing 15% (wt/wt) of dietary lipids (HFD+F). At the end of this dietary intervention, which lasted for two weeks, mice were treated either with single high (400mg/kg body wt.) or low (60mg/kg body wt.) dose of metformin or placebo (saline) by means of oral gavage and 30 minutes later on, the mice were subjected to oral glucose tolerance test (OGTT).

Results showed that both omega-3 and high dose of metformin significantly decreased glucose levels 30, 45 and 60 minutes after the glucose load when compared to saline-treated mice. The incremental area under the glucose curve (AUC) in the treated mice was also significantly lower than in the control animals. Omega-3 tended to augment the metformin action, but the effect was not statistically significant. Similar results were observed in mice subjected to the low dose of metformin, which elicited a relatively weak effect on glucose tolerance, while a trend for the additive effect of metformin and omega-3 was apparent at 60 minutes following the glucose load.

Hepatic AMPK activity assessed 30 minutes after the administration of metformin (400 mg/kg body wt.) did not differ between the sub-groups. To further investigate the involvement of AMPK in metformin action, an additional experiment was performed, in which the low dose of metformin and HFD-fed mice lacking α2 subunit of AMPK (as well as their wild-type controls) were used. However, no effect of the AMPK ablation on metformin effect was observed.

In conclusion, we demonstrated acute dose-dependent hypoglycaemic effects of both omega-3 and metformin during OGTT in dietary obese mice. Omega-3 lowered the glycaemic response to glucose challenge, while showing a trend for additive improvements of glucose tolerance when combined with a low dose of metformin. AMPK was not essential for the acute blood glucose-lowering effect of metformin.

Possible AMPK-independent interactions between omega-3 and metformin regarding their effects on glucose homeostasis are likely and require further characterisation.

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Petra Kucharikova, Bc. has been working at the Department of Adipose Tissue Biology at The Institute of Physiology Academy of Sciences of the Czech Republic, v.v.i., in Prague since 2011. Currently, she is finishing her MSc studies at the Faculty of Science of Charles University in Prague. Her thesis is focused on insulin sensitivity and the effects of combined dietary and pharmacological intervention. She will finish her MSc studies in 2014.

Poster Synopsis

Specific Changes in Plasma Lipidome in Obesity and Type 2 Diabetes are Associated with Physical Inactivity and Muscle Mitochondrial Function

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Introduction

The world faces the pandemy of obesity and type 2 diabetes (T2D). T2D is characterised by insulin resistance at the level of many tissues, including skeletal muscle. Muscle insulin resistance and decreased muscle mitochondrial content & function[1] are closely related and causally linked to a physically inactive lifestyle. Thus, regular exercise is the most powerful physiological stimulus capable of increasing both biological effect of insulin and mitochondrial content & function, promoting oxidation of lipids.[2]

Dyslipidemia plays a central role in linking obesity to T2D. Plasma lipidome contains a broad range of different lipid species which could modify metabolism. Nevertheless, up-to-date detailed information on plasma lipidome composition, regulation and function in obesity and T2D is still scarce, although a few clinical studies point at distinct plasma lipid profile associated with metabolic disease.

In our study, we investigated the interrelation of plasma lipidome with skeletal muscle mitochondrial content/function and physical activity in middle aged lean healthy (Normal Glucose Tolerance, NGT) (n=28; 23.2±2.2 kg.m^{-2}), overweight/obese (NGT) (n=29; 30.4±2.8 kg.m^{-2}), pre-diabetic (Impaired Fasting Glucose/Impaired Glucose Tolerance) (n=24; 31.3±3.2 kg.m^{-2}) and T2D men (n=15; 31.4±3.9 kg.m^{-2}).

Material and Methods

Volunteers underwent a complex metabolic phenotyping including the assessment of insulin sensitivity (euglycemic hyperinsulinemic clamp), glucose tolerance (oGTT), adiposity & fat distribution (MRI) and hepatic lipid content (1H-MR spectroscopy). Physical activity was monitored with accelerometers and with standardised questionnaire. Samples of *m. vastus lateralis* were obtained by needle biopsy and expression of peroxisome proliferators-activated receptor-gamma coactivator 1-alpha (PGC1-α) and mitochondrial DNA (mtDNA) content were determined by qRT-PCR. The activity of cytochrome C oxidase (COX) was measured by oxymetry in permeabilised muscle fibers. Plasma lipidome was analysed by mass spectroscopy.

Results

Individuals with type 2 diabetes preferred low intensity physical activity, which was clearly reflected in a significantly reduced time dedicated to moderate and high intensity physical activity, as objectively assessed by accelerometers (40% reduction compared to lean). Higher body weight was generally associated with a decreased leisure time index (based on self-evaluation by a questionnaire) (r=-0.375, p<0.001, n=96). Similarly, diabetes was associated with a decrease in mitochondria-related parameters: (i) PGC1-α mRNA (the coordinator of mitochondrial biogenesis) (p<0.01, compared to lean), (ii) mtDNA content (the marker of mitochondrial number) (p<0.05, compared to overweight/obese NGT) and (iii) activity of mitochondrial enzyme (COX, mitochondrial function) (p<0.05, compared to overweight/obese NGT). Overall, decreased physical activity was correlated with impaired metabolic phenotype (lower insulin sensitivity, increased adiposity, hypertrophic adipocytes) and decreased PGC1-α gene expression.

A complex plasma lipidomic analysis included determination of lipid species with different chain length and saturation. Most lipid species (phosphatidylcholines, cholesteryl esters, phosphatidylinositols, phosphatidylethanolamines) were upregulated in pre-diabetes and/or T2D and negatively correlated with physical activity and PGC1-α mRNA. However, a great majority of lysophosphadidylcholine (LPC) species were downregulated with pre-diabetes and diabetes and some LPCs had positive associations with physical activity, muscle PGC1-α mRNA and COX activity. Importantly, LPC 18:1 and 18:2 were found to be decreased in the metabolically healthy obese compared to lean healthy individuals, before the onset of metabolic disease (p<0.001). LPC 18:2 has recently emerged as a putative biomarker and an independent risk factor of pre-diabetes and/or T2D, predicting the impairment of glucose tolerance up to 7 years before disease onset.[3,4] In our population, LPC 18:2 was strongly

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negatively correlated with several clinical phenotypes of obesity, including BMI (r=-0.73, p<0.001, n=86), adiposity (r=-0.70, p<0.001, n=83), adipocyte diameter (r=-0.57, p<0.001, n=83), fasting glycemia & insulinemia (r=-0.35, p<0.001, n=86; r=-0.36, p<0.001, n=86) and it was positively associated with insulin sensitivity (r=0.40, p<0.001, n=85).

Conclusion

Type 2 diabetes is accompanied by physical inactivity, reduced muscle mitochondrial biogenesis and function and specific changes in plasma lipidome. This suggests that physical inactivity might also contribute to the pathogenesis of T2D by regulating plasma lipid composition. Furthermore, discovery of early specific lipid biomarkers of T2D risk might help to identify individuals at high-risk for metabolic disease development, greatly increasing the chances to delay or prevent disease onset.

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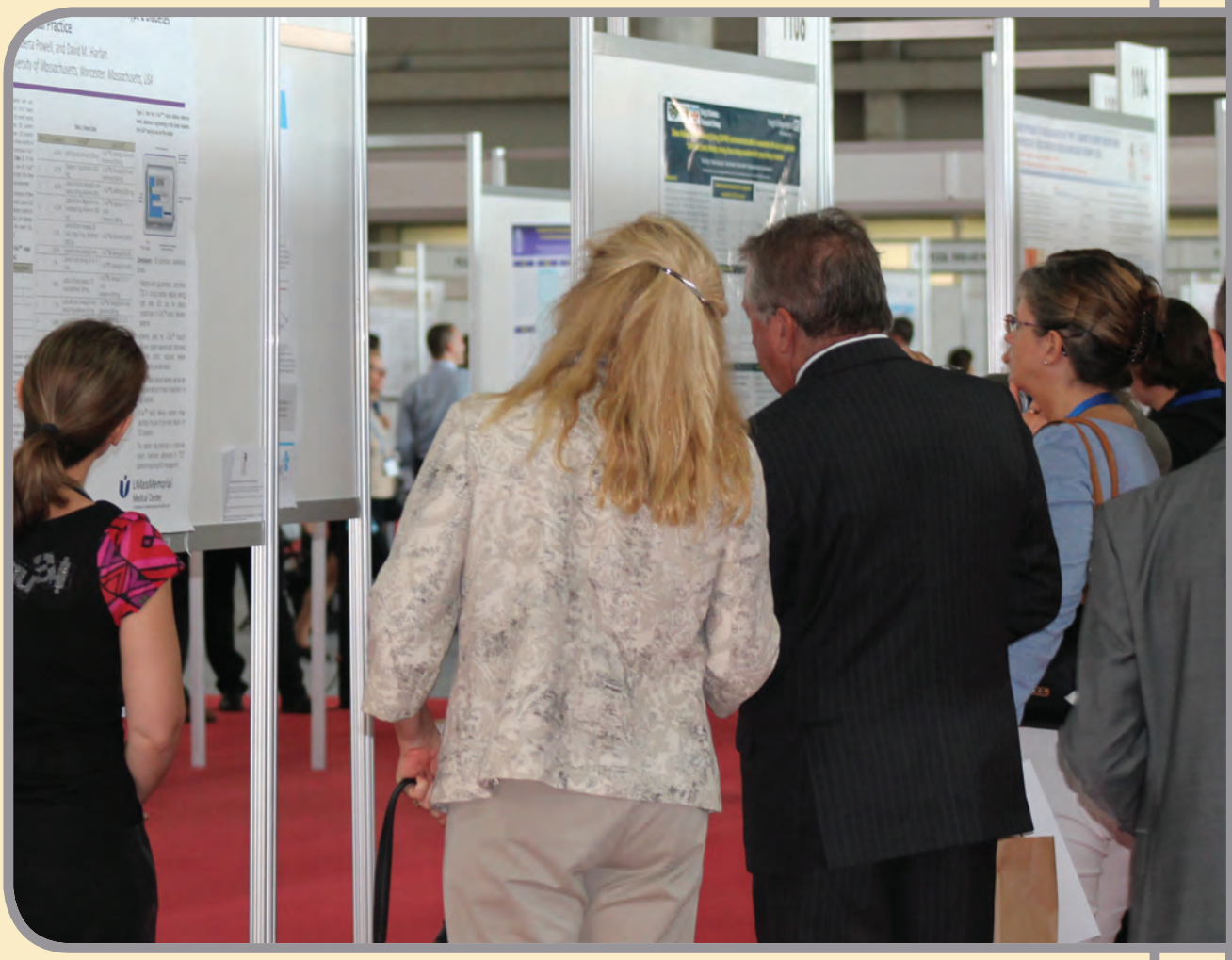

Poster Synopsis

Obesity and the Inflammation of Fat Tissue of Children

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Obesity is characterised by an accumulation of adipose tissue (AT) in order to store excess energy, which is associated with an increased secretion of pro-inflammatory adipokines[1] and gives rise to a state of chronic, low-grade inflammation.[2, 3]

The Influence of Inflammatory Cells on Adipose Tissue

It has previously been shown that a low-grade inflammation state is accompanied by an increase in the number of macrophages.[4, 5] In general, macrophages play an important role in the immune system and tissue homeostasis by clearing pathogens and old or dead cells.[6] Hirasaka *et al.*[7] showed that an excessive infiltration of macrophage into AT worsens insulin sensitivity in rodents, whereas a decrease in the amount of macrophages leads to inhibition of obesity-induced insulin resistance.[8] Recent studies have demonstrated that multiple intracellular signalling pathways are activated in adipocytes during adipocyte hypertrophy, which leads to an increased secretion of cytokines, and chemokines.[9, 10, 11] So far, little is known about the alterations of macrophage recruitment at the level of adipose tissue during the ontogenic development of adipose tissue and obesity. Therefore, it is of central importance to understand the pathogenesis of obesity in children.

Macrophage Recruitment in Adipose Tissue of Children

To investigate the development of obesity in children and associated changes in AT biology, the Childhood Adipose Tissue biobank was established. Since the initiation of the project, 207 subcutaneous AT samples from 171 Caucasian children (106 lean, 16 overweight, 49 obese) who underwent selective surgery were collected. Children were 0 to 18 years old and free of severe diseases. The following exclusion criteria have been defined: type 1 or type 2 diabetes, generalised inflammation, cardiovascular or peripheral artery disease, malignant disease and genetic syndromes. Anthropometric data, including age, gender, pubertal stage, height, weight, and medical history were recorded before surgery. To investigate the occurrence of macrophages in AT from children, immunohistochemical analyses for CD68 (specific macrophages marker) were performed. Preliminary analyses indicate that macrophage recruitment already occurs in obese children. The mechanisms leading to the recruitment in the obese state are not completely understood. There is evidence that hypertrophy and local hypoxia play an important role in this setting.[12] This might lead to a rupture of the plasma membrane, dilatation of the endoplasmic reticulum and release of cell contents to the extracellular space, where they evoke inflammatory responses.[13-15]

Heterogeneity of Macrophages

Macrophages can show a high plasticity and heterogeneity as a respond to a multitude of stimuli that they receive from their micro-environment.[16] Therefore, they can be classified into pro-inflammatory M1 and anti-inflammatory M2 macrophages. Obesity induces a phenotypic switch from an anti-inflammatory M2 polarised state to a pro-inflammatory M1 state.[17] Preliminary analyses indicate that a shift in the M1/M2 ratio on mRNA level of the previously described M1 (CD86) and M2 (CD163/D206) markers could not be observed in children.

With this project, we strive for a better understanding of how AT alterations occurring with the development of obesity in children. New therapeutic strategies, which suppress the obesity induced inflammatory response, could contribute to the prevention of type 2 diabetes and cardiovascular diseases.

D. Rockstroh studied biology at the "Freie Universität Berlin" and finished with a diploma degree. She achieved her diploma thesis at the Max-Planck Institute for molecular genetics Berlin. Since September 2010 she has been working on her doctoral project, which is focused upon adipose tissue development and the progression of obesity in children in order to understand obesity development and associated comorbidities during childhood, adolescence and adulthood.

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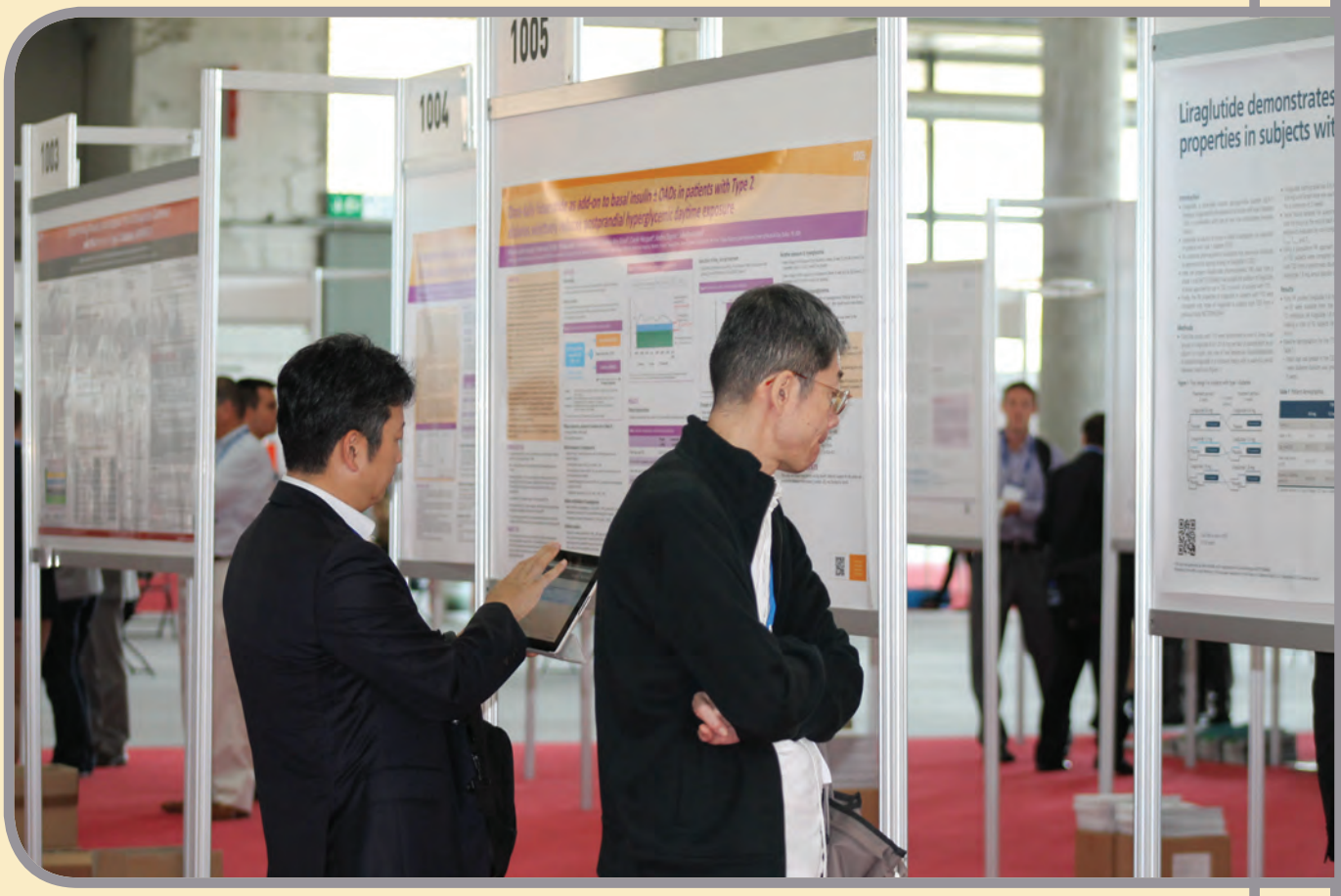

Poster Synopsis

Effect of Omega 3/ALA Supplementation on Inflammatory Markers and ER Stress in Diabetic Rats

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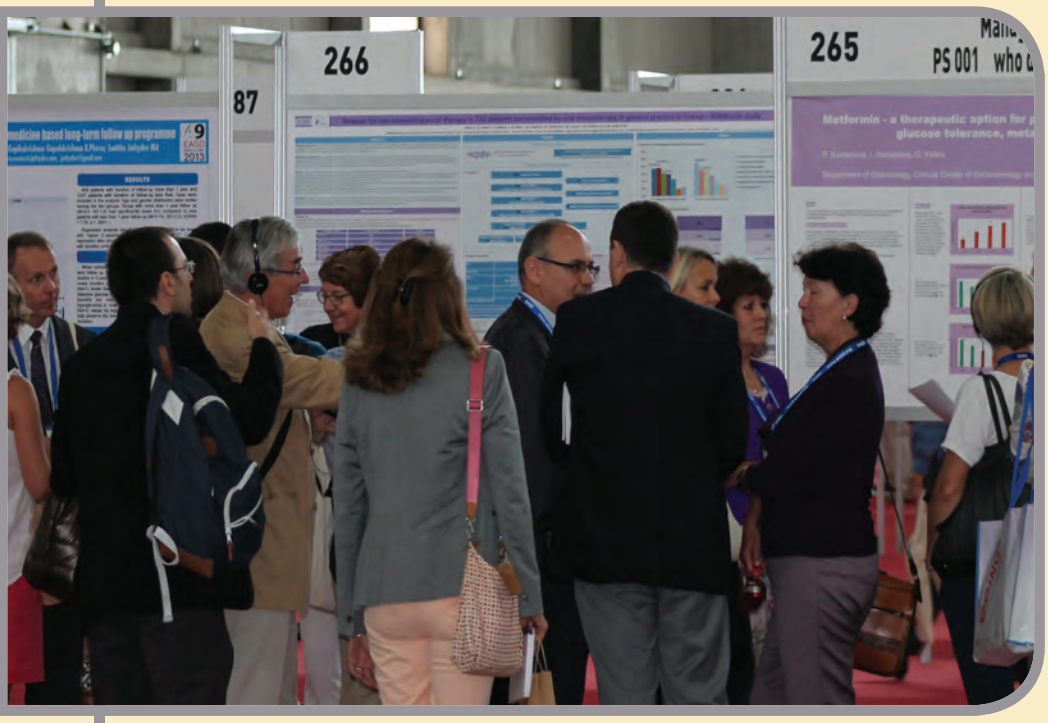
A state of chronic and sub-clinical inflammation is often observed in diabetic patients, and more recently it has been associated with activation of the endothelium reticulum stress (ERS). Previous studies have shown that polyunsaturated fatty acids ω3 eicosapentaenoic acid (EPA; C20:5n-3) and docosahexaenoic acid (DHA; C22:6n-3) can modulate gene expression of transcription factors such as NFkB and PPAR, which can contribute to reduce inflammation and insulin resistance (IR) in laboratory animals, but little is known about the effect of ω3 α-linolenic acid (ALA; C18:3n-3). The ω3/ALA is the primary fatty acid of the n-3 pathway found in seeds oils, notably those of flaxseeds and chia.



The aims of this study was to evaluate the effects of ω3/ ALA supplementation on sub- clinical inflammatory process, control of glucose and lipid metabolism and activation of ERS in animal models of diabetes mellitus.

We studied 40 wistar rats (150g), divided into four groups: control, control+ω3, diabetes and diabetes+ω3. Induction of diabetes was performed using 40mg/kg of streptozotocin iv and diabetes mellitus was diagnosed after demonstration of hyperglycaemia (glucose >11mmol/L) 7 days after the streptozotocin infusion. Animals in the control+ω3 and diabetes+ω3 groups received supplementation of 3g of ω3/ALA from flaxseed, daily for a period of 8 weeks. The ω3/ ALA was added to the diet and the animals had food and water *ad libitum*.

Measurements of serum glucose, lipid profile serum cytokines (TNF-α, IL-6 and INF-γ) and body weight were performed before the beginning of the supplementation (T1) and by the end of this period (T2). Data of liver and epididimal fat weight were collected no T2.

The diabetes+ω3 group had lower liver ($p<0.001$) and greater epididimal adipose tissue ($p=0.04$) weight in relation to the diabetes group, besides no difference in total body weight. There was no difference on the total liver lipid between the groups, as shown in Table 1. On the other hand, the control+ω3 group showed increased liver ($p=0.001$), epididimal ($p<0.001$) and body weight ($p<0.001$) (table). Diabetes+ω3 group showed lower glucose ($p=0.01$) and triglyceride ($p<0.001$) levels on T2 compared to

Maria Cristina Foss-Freitas has been a Faculty member at the Ribeirao Preto Medical School-São Paulo University since 2008. She finished her specialisation in Internal Medicine and Endocrinology and Metabolism in 2001 at the same school, where she now works as a Professor of Medicine. She is also engaged in clinical practice and research on inflammation and diabetes, and is interested in evaluating the metabolic effect of nutrients such as omega 3 and BCAA in hyperglycaemia and insulin resistance situations.

	CONTROL		CONTROL+ω3/ALA		DIABETES		DIABETES+ω3/ALA	
	T1	T2	T1	T2	T1	T2	T1	T2
Body Weight (gr)	169.1±17.7	283.5±42.5	168.7±10.5	336±71.7 *	146.9±11.2	245.3±1.2*	158.5±11.7	225.4±0.3
Glucose (mg/dL)	153.6±17.2	100.3±9.9	141.1±8.3	92.8±6.3	471.7±54.4	517.4±67.7	482.6±35.7	431.4±58.4*
Total Cholesterol (mg/dL)	78.7±12.5	57.7±6.9*	70.1±10.4	55.4±10.0*	74.7±7.6	91±17.7*	79.2±13.6	91±14.4
Triglycerides (mg/dL)	70.7±15.7	86±22.7	68.5±21.7	114.5±30.1*&	75.8±8.8	216.8±49.7*	71.9±29.5	89.4±39.5&
Serum TNF-a (pg/mL)	40,1±21,6	21,2±12,7	32,4±12,8	18,6±18,0	13,0±7,9	30,6±5,5	29,3±28,1	30,3±13,4
Serum IL-6 (pg/mL)	105,9±38,4	81,4±25,3	116,1±36,9	95,7±23,1	44,1±28,3	37,5±17,6	74,9±31,7	50±35,3
Serum INF-g (pg/mL)	739,1±190,8	542,0±237,7	694,4±159,7	634,9±170,0	598,3±186,6	402,4±236,7	636,1±121,9	378,3±174,7*

Table 1. Body weight and serum levels of fasting glucose, lipids and Serum cytokines level from streptozotocin induced diabetic rats (Diabetes and Diabetes+ω3/ALA) and control animals (Control and Control+ω3/ALA) supplemented or not with 3 gr/day of omega 3/ALA.

Abbreviations. ω3: Ômega 3; ALA: alpha-linolenic-acid; T1: pre-treatment; T2: end of supplementation treatment; TNF-a: tumor necrosis factor-alpha; IL-6: interleucin-6; INF-g: interferon-gamma; * p<0.05 T1xT2; & p<0.05 Control or Diabetes group T2 x Control or Diabetes+ω3/ALA group T2.

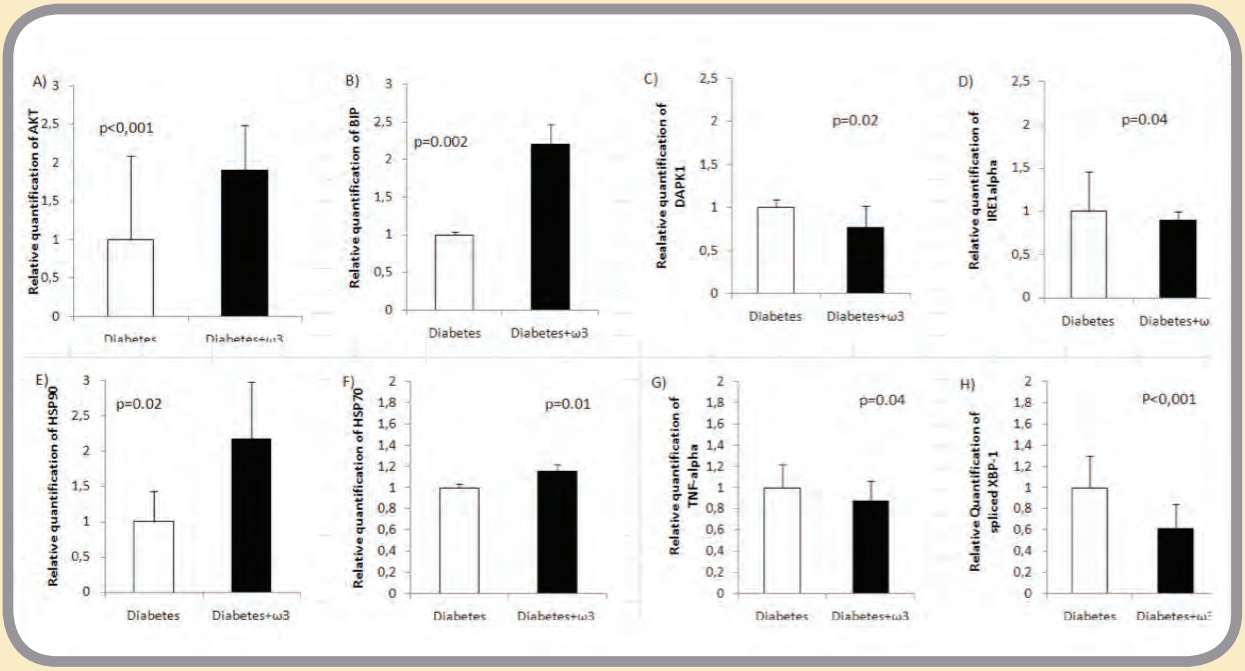


Figure 1. Relative quantification of immunoblot of liver total protein extract after supplementation or not with 3 gr/day of omega 3/ALA in streptozotocin induced diabetic rats (Diabetes and Diabetes+ω3/ALA). Data are presented in relative quantification and SEM.

Diabetes group, but no difference in total cholesterol. Serum levels of TNF-α and IL6 were lower in the diabetic groups compared to the control groups but the ω3/ ALA supplementation did not determine significant changes. However, the diabetic+ω3 group showed a decrease in the INF-γ serum levels after the supplementation period, as shown in Table 1. We also observed that diabetes+ω3 group had increased expression of BIP (p=0.002), AKT (p<0.001), HSP90 (p=0.02) and HSP70 (p=0.01). Concomitantly there was a decrease in the expression of spliced XBP-1 (p<0.001), IRE1 alpha (p=0.04), DAPK1 (p=0.02) and TNF-alpha (p=0.04). There were no difference in the expression of PERK, GADD153, unsliced XBP-1 and IL-6, as shown in Figure 1.

Our data supports that daily supplementation of 3 gr of ω3/ALA was able to reduce blood glucose and triglyceride in diabetic rats associated to a reduction in systemic inflammation as observed.

Poster Synopsis

C-peptide Levels not Affected by Duration of Diabetes in a Telemedicine Based Long-term Follow-up Programme

Jothydev Kesavadev

Chairman & Managing Director, Jothydev's Diabetes Research Centre, Trivandrum, Kerala

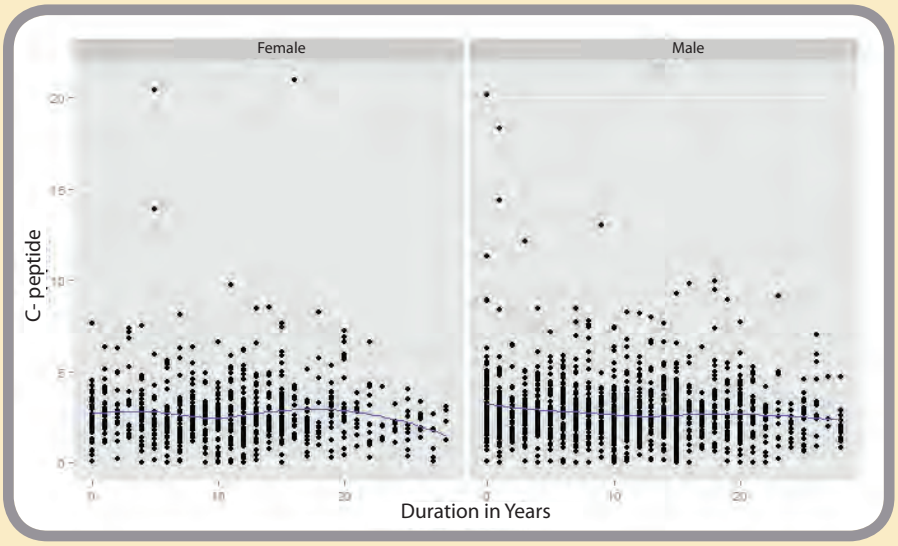
In the natural history of the progression of type 2 diabetes the initial hyperinsulinaemia culminates in near total decline in the beta cell function over several years. The eventual loss of beta cell function and associated insulin secretary deficiency is more rapid when HbA1c levels consistently remain high. Since the mid-1970s, C-peptide has been used as a surrogate marker for monitoring the course of type 1 and type 2 diabetes and determining the effects of interventions designed to preserve and improve residual β-cell function. In our centre, subjects registered under telemedicine based long-term follow-up care Diabetes Tele Management System (DTMS®) maintains near normal metabolic targets being followed up frequently via a multi-disciplinary trained diabetes team. DTMS® involves unique software & trained multi-disciplinary diabetes team members communicating with patients through phone/email for slow, steady titration of drugs combined with frequent tele-counselling precluding physical visits to the hospital. The team consists of physicians, trained dieticians, pharmacists, nurses, diabetes educators and psychologist. Each tele-consultation offers an opportunity for education, interactive communication and trouble shooting. The frequency of education via telephone/internet is again decided based on individual requirements. The follow-up programme via the telephone or internet precludes physical visits to the hospital and has been proven to be cost effective, as well as helping to maintain individualised HbA1c targets without significant hypoglycaemia.

A cross-sectional analysis of 2076 T2DM patients aged above 20 years was performed. 37% of these patients were female. The mean age was 51.7 years SD 11.9 and C-peptide mean was 2.725 SD 1.7. A1c mean was 8.8 SD 2.1.

829 patients which had a duration of follow-up of more than 1 year and 1247 patients which had a duration of follow-up of less than 1 year were included in the analysis. Age and gender distribution were similar among the two groups. Group with more than 1 year follow up (M=8.4, SD-1.8) had significantly lower A1c compared to new patients with less than 1 year follow-up (M=9.1%, SD=2.2), $t(2009) = 7.25$, $p < .0001$. Regression analysis also indicated that A1c tends to be lower with higher C-peptide ($R2=0.01$, $F(4,819)=2.7$, $p=0.02$).

Linear regression also showed no significant change of C-peptide levels with duration under care, as shown in the figure below.

When compared with newly enrolled patients, patients on long-term follow-up and maintaining a low HbA1c value showed no decline in C-peptide levels while on DTMS® based care. However, newly enrolled patients with long-standing diabetes and higher HbA1c levels had relative low C-peptide levels. The benefits of intensive glucose lowering with proven, both short- and long-term benefits are restricted by the serious consequences of hypoglycaemia in routine diabetes care. Maintaining near normal HbA1c values by regular follow up via DTMS® based care may help preserve the beta cell function even after decades of onset of diabetes.



Dr. Jothydev Kesavadev is an alumnus of Govt. Medical College, Trivandrum and Mayo Clinic, Minnesota, USA. He has several national and international presentations and publications to his name. His research mainly focuses on cost effectiveness of telemedicine in diabetes, insulin pumps and continuous glucose monitoring. He has been a speaker at the American Diabetes Association (ADA), International Diabetes Federation (IDF) and Advanced Technologies and Treatments for Diabetes (ATTD). He has also presented at the European Association for the Study of Diabetes (EASD). He dedicates his time entirely to diabetes and streamlines his activities in 4 different areas: research, patient care, mass education and community work.

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Statins and New Onset Diabetes: Getting to the Heart of the Matter

Introduction

The satellite symposium entitled, "Statins and New Onset Diabetes: Getting to the Heart of the Matter" was held during the 49th Annual Meeting of the European Association for the Study of Diabetes (EASD) on Monday 23rd September 2013 in Barcelona, Spain. The Congress was chaired by Prof. Henry N. Ginsberg, Irving Professor of Medicine and Director, Irving Institute for Clinical and Translational Research, Columbia University, New York, USA.

Introduction

Henry N. Ginsberg
(Irving Institute for Clinical and Translational Research, Columbia University, USA)

Despite major advances in the treatment of cardiovascular disease, it remains the most common cause of death globally, and is on the increase.

Statins are prescribed to millions of patients diagnosed with raised cholesterol levels. In the EUROASPIRE study, the prevalence of raised total cholesterol (TC: >4.5 mmol/L) was assessed in cardiology clinics among patients who had cardiac events across many European countries between 1995-6 and 2006-7, and it was found that there was an overall decrease from 94.5% in 1995-6 to 46.2% in 2006-7.[1] This was believed to be largely due to the utilisation of statins. The EUROASPIRE database also looked at the prevalence of diabetes over the same time period and found an overall increase from 17.4% to 28%. This has been thought to be due to an increase in the incidence of obesity, decrease in physical activity and a move away from traditional to more Western diets in many countries.

The metabolic syndrome associated with insulin resistance imparts a high risk of atherogenesis, with a decrease in high density lipoprotein (HDL) levels and an increase in triglyceride (TG) and small dense low density lipoprotein (LDL) levels.[2]

The ACCORD study examined the effects of combination lipid therapy in type 2 diabetes mellitus (T2DM). They reported an annual rate for the first occurrence of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes of 2.2% for patients treated with simvastatin plus fenofibrate versus 2.4% for patients given simvastatin plus placebo.[3] Sub-group analysis indicated a possible interaction according to lipid subgroup, with a possible benefit for patients with both a high baseline TG level and a low baseline level of HDL-cholesterol (HDL-C) (p=0.057 for interaction).

The Cholesterol Treatment Trialists (CTT) meta-analysis showed that statin therapy reduced the risk of occlusive vascular events regardless of whether a patient had T2DM or not.[4] However, the rates were higher if a patient had T2DM. Therefore, although the relative risk reduction was the same, the absolute risk in diabetes patients was higher.

The Emerging Risk Factors Collaboration, using data from over 300,000 patients, assessed major lipids and apolipoproteins in vascular risk.[5] It was shown that TG were a univariate predictor of cardiovascular disease. However, when the data were adjusted for non-lipid factors such as body mass index (BMI), age, blood pressure and smoking history, and also adjusted for HDL-C and non-HDL-C, TG were not predictors. By contrast, HDL-C and non-HDL-C (in opposite directions) were predictive of

Statins and New Onset Diabetes: Getting to the Heart of the Matter
Kowa Pharmaceuticals Europe Sponsored Satellite Symposium at the 49th Annual Meeting of the European Association for the Study of Diabetes (EASD), Barcelona, Spain, 23rd September 2013

Chair: Henry N. Ginsberg, Irving Institute for Clinical and Translational Research, Columbia University, New York, USA

Chair's Introduction
Henry N. Ginsberg, Irving Institute for Clinical and Translational Research, Columbia University, New York, USA

Pitavastatin in Cardiometabolic Disease: Therapeutic Profile
Lluís Masana, Vascular Medicine and Metabolism Unit, University Hospital "Sant Joan". Rovira and Virgili University Reus, Spain

Pitavastatin and Incident T2DM
Masato Odawara, Department of Diabetology, Metabolism, and Endocrinology, Tokyo Medical University, Tokyo, Japan

Statin Diabetogenicity: Guidance for Clinicians
Kausik K. Ray, Cardiovascular Sciences Research Centre, St. George's University of London, UK

Opportunities and Challenges in Managing Cardiometabolic Disease
Henry N. Ginsberg, Irving Institute for Clinical and Translational Research, Columbia University, New York, USA

cardiovascular disease risk.

The TNT study has also shown that HDL-C levels in patients receiving statins are a strong inverse predictor of cardiovascular events.[6] Interestingly, when the analysis was stratified according to LDL-C levels, the relationship remained significant.

When it comes to the trials of statin therapy, there have been conflicting findings on the risk of development of T2DM in patients given statins. An analysis of 13 statin trials with 91,140 participants, of whom 4,278 (2,226 assigned statins and 2,052 assigned control treatment) developed diabetes during a mean of 4 years, showed that statin therapy was associated with a modest 9% increased risk for incident T2DM.[7] The risk of developing T2DM was highest in trials with older participants, but neither baseline BMI nor change in LDL-C concentrations accounted for the residual variation in risk. This study concluded that statin therapy was associated with a slightly increased risk of development of T2DM, but the risk was low both in absolute terms and when compared with the reduction in coronary events.

The challenge for clinicians is to balance the need for lipid lowering versus the risk of developing T2DM in patients with hypercholesterolaemia.

Pitavastatin in Cardiometabolic Disease: Therapeutic Profile

Lluís Masana
(University Hospital "Sant Joan". Rovira and Virgili University Reus, Spain)

Statins differ with respect to their ring structure and substituents, and these differences affect their pharmacological properties. Pitavastatin differs from other statins in that it has a cyclopropyl group on the base structure. This cyclopropyl group contributes to a more effective inhibition of the HMG-CoA reductase enzyme to reduce cholesterol production, and affords effective LDL-C clearance and reduction of plasma cholesterol at a lower dose.[8] The difference in structure affords pitavastatin a high degree of lipophilicity, oral absorption and bioavailability, which negates concerns regarding food or drug-drug interactions.[9]

The goal of statin therapy is to reduce LDL-C levels. European Society of Cardiology (ESC)/ European Atherosclerosis Society (EAS) guidelines have proposed an estimation of the distance from the lipid target that can easily be obtained, as shown in Table 1.[10] Once the distance from a target is determined, then by interpolation from the known dose-response of statins, the best target dose for the best statin to help reach the lipid goal can be identified. A high-risk patient with an LDL-C value greater than 170 mg/dl requires a reduction in LDL-C levels by more than 40%. Based on the ESC/EAS guidelines, after the withdrawal of simvastatin 80 mg, only atorvastatin, rosuvastatin and pitavastatin have approved doses that can achieve mean reductions of ≥45%.

Other contributing factors, such as glucose, HbA1c, obesity and glomerular filtration rate (GFR) values will impact on the LDL-C reduction needed, and will also impact on TG and HDL-C levels. Therefore, It is also important to know the impact of statins on HDL-C levels.

Pitavastatins have shown a unique HDL raising impact compared with other satins.

In a sub-analysis of the 2-year LIVES study, pitavastatin 1 to 4 mg/day significantly increased HDL-C levels by 5.9% in all subjects and by 24.6% ($p<0.0001$) in those with a low baseline HDL-C.[11] Pitavastatin has also demonstrated around a three times increase in HLD-C levels versus atorvastatin.[12]

It has been suggested that elevations in HDL-C and decreases in LDL-C levels might slow the formation of atherosclerotic plaques and may reduce the residual cardiovascular risk by increasing the rate of cholesterol efflux from cells. Of particular interest for pitavastatin were the results from a meta-analysis of different statin studies and the impact on plaque volume. It was found that, whilst the plaque volume change induced by a 1% reduction in LDL-C showed little difference using a number of different statins (atorvastatin, pravastatin,

Starting LDL-C		% Reduction to reach LDL-C		
mmol/L	~mg/dL	<1.8 mmol/L (~70 mg/dL)	<2.5 mmol/ (~100 mg/dL)	<3 mmol/L (~115 mg/dL)
>6.2	>240	>70	>60	>55
5.2–6.2	200–240	65–70	50–60	40–55
4.4–5.2	170–200	60–65	40–50	30–45
3.9–4.4	150–170	55–60	35–40	25–30
3.4–3.9	130–150	45–55	25–35	10–25
2.9–3.4	110–130	35–45	10–25	<10
2.3–2.9	90–110	22–35	<10	-
1.8–2.3	70–90	<22	-	-

Table 1. Percentage reduction of LDL-C requested to achieve goals as a function of the starting value.

pitavastatin, rosuvastatin, simvastatin), pitavastatin delivered the greatest reduction in plaque volume per 1% increase in HDL-C.[13]

There has been some concern raised regarding the impact of statin use on the development of diabetes. A recent study has shown that pitavastatin 4 mg has no effect on glycaemic parameters in metabolic syndrome at 6 months.[14] In addition, HbA1c levels were shown to decrease after 104 weeks of treatment with pitavastatin in people with diabetes in the LIVES study.[11]

Diabetic patients treated with statins frequently require polypharmacy. Therefore, drug-drug interactions are also a key concern. Most statins are metabolised through cytochrome p450, isoform 3A4. As around 30% of these patients are on 3A4 inhibitors at the same time, this has the potential for drug-drug interactions.[15] The unique structure of pitavastatin reduces the potential for these drug-drug interactions.[16] Pitavastatin's cyclopropyl group diverts the drug away from metabolism by CYP3A4 and allows only a small amount of clinically insignificant metabolism by CYP2C9.

As with all drugs, it is important to be aware for the potential of adverse events (AEs). Only 10.4% of pitavastatin-treated patients experienced adverse events (AEs), of which approximately 84% were mild and around 1% was severe.[17] Increases in blood creatine phosphokinase (2.7%), alanine aminotransferase (1.8%), myalgia (1.1%), aspartate aminotransferase (1.5%) and gamma-glutamyltransferase (1.0%) were the most common AEs. Only 7.4% of patients discontinued pitavastatin due to AEs.

Three out of four patients on pitavastatin achieve LDL targets, including the elderly population.[18-20] Pitavastatin has also shown beneficial effects on GFR and albuminuria.[11, 21, 22]

In the CIRCLE study, which compared the efficacy of different statins on serum lipid levels and the association between those changes and cardiac events in patients after percutaneous coronary intervention, each statin significantly prevented major adverse cardiac events (MACE) compared with no statin.[23] However, pitavastatin was found to be the most effective.

Based on the available data for pitavastatin, it can be seen that a wide range of patients are suitable for therapy. These include patients with the need for 40% or higher reductions in LDL-C levels; those who have acute coronary syndrome with coronary lesions; those with low HDL-C levels; those on more than one medication; the elderly; and patients who are either diabetic, pre-diabetic or have chronic kidney disease.

Pitavastatin and Incident T2DM

Masato Odawara

(Tokyo Medical University, Japan)

The incidence of T2DM and pre-diabetes is on the increase across the world, and Japan is no exception.[24, 25] It is known that statins reduce the risk of cardiovascular disease in Western countries. To see if the same was true for the Japanese community, the MEGA study examined the impact of diet plus pravastatin versus diet alone on lipid levels in a group of this population with hypercholesterolaemia.[26] The study demonstrated a 33% (p=0.01) decrease in cardiovascular risk with the introduction of statin therapy. Sub-analysis found that statin therapy was also equally or more effective in diabetic patients with hypercholesterolaemia. However, there is a concern regarding the potential for some statins to induce T2DM. In the Jupiter trial, rosuvastatin therapy was associated with an increased incidence of new onset T2DM versus placebo.[27] In contrast to this, a sub-analysis of the WOSCOP data found that treatment with pravastatin reduced the incidence of T2DM by 30% versus placebo. However, this study used a non-classical definition of T2DM, including an increase of 36 mg/dL in fasting blood glucose as a criterion, due to study data limitations.

In order to establish if any relationship existed between statin use and development of diabetes, a meta-analysis of several statin trials was carried out.[7] The study found that, across 13 trials for atorvastatin, simvastatin, rosuvastatin, pravastatin and rosuvastatin, statin therapy was associated with a modest 9% increased risk for incident diabetes with little heterogeneity between trials. Meta-regression showed that the risk of developing diabetes with statins was highest in trials with older participants, but neither baseline BMI nor change in LDL-C concentrations accounted for the residual variation in risk.

In Japan, J-PREDICT is a recently completed open-label, randomised, controlled, parallel-group comparative study to evaluate the effect of pitavastatin versus lifestyle modification on the risk of diabetes in a target population of 1,240 subjects with impaired glucose tolerance over 5 years.[28] This is the first study evaluating the incidence of diabetes as a primary outcome in a prospective manner. Early results show that the cumulative incidence rate of T2DM as defined in the primary endpoint was significantly reduced (p=0.041) by 18% with pitavastatin (HR 0.82 (95% CI: 0.68-0.99)) versus lifestyle modification alone.[29]

Statin Diabetogenicity: Guidance for Clinicians

Kausik K. Ray

(St. George's University of London, UK)

It is important to establish whether or not hyperglycaemia has a negative impact on cardiovascular risk. In people who develop T2DM over the age of 40 years, the average number of years of life lost is around 6-7, mostly from vascular disease.[30] If T2DM develops later in life, it has less of an impact. In another study, that included 528,877 participants, T2DM was found to double the risk of vascular disease after adjusting for age, sex, cohort, systolic blood pressure, smoking and BMI.[31] However, cardiovascular disease risk from diabetes is not explained by conventional risk factors. Dysglycaemia (below 7mmol/L) is a modest cardiovascular risk factor,[31] and early onset T2DM is equivalent to previous MI and no diabetes in terms of cardiovascular

risk.[32] A meta-analysis of randomised controlled trials has shown that, although intensive compared with standard glycaemic control significantly reduces coronary events without an increased risk of death, a greater benefit was achieved by 4 mmHg systolic blood pressure lowering (-12.5% cardiovascular events) and by a 1 mmol/L lower LDL-C reduction (-8.2%), compared with a 0.9% lower HbA1c (-2.9%).[33] Another study has shown that although the oral hypoglycaemic, rosiglitazone, substantially reduces incident T2DM, there appeared to be little or no effect on cardiovascular events.[34]

When it comes to lipid lowering, the CTT analysis showed that a reduction in LDL-C, regardless of the initial lipid profile or other presenting characteristics, is associated with a clear reduction in cardiovascular events.[35] In fact, per mmol/L reduction in LDL-C, there was a 21% reduction in any major vascular event ($p<0.0001$). A follow-up CTT analysis found that statin therapy reduced cardiovascular event risk irrespective of diabetes status.[4] In a more recent CTT meta-analysis of data from 170,000 participants in 26 randomised trials, more intensive lowering of LDL-C resulted in definite further reductions in the incidence of heart attack, of revascularisation, and of ischaemic stroke, with each 1.0 mmol/L reduction, resulting in a decrease in the annual rate of these major vascular events by just over a fifth.[36]

Regarding the safety of statins, there is no evidence of an overall increased risk of cancer or at any particular site.[37] In the PROVE-IT study, no significant differences in safety parameters in the very low LDL groups were reported, including muscle, liver, or retinal abnormalities, intracranial haemorrhage, or death.[38]

As we have seen earlier, statins can increase the risk of dysglycaemia, and this risk increases with increasing age.[7] However, a recent meta-analysis of statin trials has shown that, although intensive statin therapy is associated with a higher incidence of new-onset T2DM, it is also associated with fewer major cardiovascular events. In absolute terms this analysis found that there was 1 additional case of T2DM for every 498 patients treated for 1 year compared with 1 fewer patient experiencing a cardiovascular event for every 155 patients treated for 1 year. This would suggest that there is a net cardiovascular benefit in high-risk individuals strongly favouring statin therapy. However, the long-term consequences are unclear, particularly with regard to microvascular disease.

Opportunities and Challenges in Managing Cardiometabolic Disease

Henry N. Ginsberg

(Irving Institute for Clinical and Translational Research, Columbia University, USA)

Cardiovascular disease and T2DM are a growing burden on healthcare systems. In the management of patients with cardiometabolic disease, statins are used with the understanding that a slightly increased risk of diabetes is outweighed by the cardiovascular benefits of the drugs. Although meta-analyses of the major clinical trials indicate that statin-associated risk of developing diabetes is a class effect, further studies are needed to determine whether all statins carry the same risk of increasing incident diabetes. For the present, physicians should continue to use statins with confidence, but should monitor for the development of diabetes, especially in high-risk patients.

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Obstructive Sleep Apnoea, Type 2 Diabetes and Cardiovascular Consequences

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Introduction

Sleep disorders have become a public health concern in modern society, affecting millions of people. Besides causing subjective discomfort, such as excessive daytime sleepiness, sleep disorders have been associated with an increased morbidity and mortality.[1] Obstructive sleep apnoea (OSA) is one of the most common sleep disorders, and has become a major burden on our healthcare system over the last few years. OSA mostly affects the middle-aged work force, causing a major negative impact on public health.[2] Furthermore, OSA has also been found to be tightly linked with metabolic abnormalities, particularly Type 2 diabetes (T2D), and cardiovascular morbidity.[3]

Symptoms and Epidemiology of OSA

The recurrent upper airway obstruction and the resulting interruptions in breathing during sleep characterised by OSA are manifested as loud snoring, pauses in breathing, and sleep fragmentation. Due to the sleep fragmentation, OSA is often accompanied by daytime symptoms; fatigue, lack of concentration, irritation, morning headache, impotence, deterioration of an individual's quality of life and working capacity.[4, 5] However, symptoms and knowledge about OS may vary greatly between individuals. Furthermore, humans tend to adjust to their situation despite it being less than ideal. Thus, a majority of OSA patients live their everyday life without knowing that they actual suffer from a serious disease. The prevalence of OSA has increased significantly over the last two decades. Recent estimates of moderate to severe OSA are 10% among 30-49 year-old men, 17% among 50-70 year-old men, 3% among 30-49 year-old women and 9% among 50-70 year-old women.[6] Since excessive daytime sleepiness is the main reason for patients seeking medical help, this suggests that a great number of patients (up to 80-90%) remain undiagnosed.[7]

Henri Tuomilehto was appointed as Adjunct Professor in 2009 at University of Kuopio, Finland. He is currently the Head Physician of Oivauni Sleep Clinic, Kuopio and Tampere, Finland. Dr. Tuomilehto founded the Kuopio Sleep Apnoea group in 2004 when starting the first randomised study evaluating the effects of lifestyle intervention in patients with obstructive sleep apnoea (OSA). It is one of the landmark studies examining the effects of weight loss in OSA. Currently, his main research project is "Early Prevention of Diabetes Complications in Europe": a multi-centre study on obesity, metabolism and obstructive sleep apnoea.

Pathophysiology and Risk Factors for OSA

The pathophysiology of OSA is complex and most likely multifactorial, consisting of a combination of predisposing anatomical factors and impaired neuromuscular compensatory responses.[8] However, obesity is considered to be the most important risk factor for OSA, and a BMI > 29 increases the risk for OSA 10-fold. It has been estimated that 60–90% of all patients with OSA are obese.[9] Weight gain increases the possibility for the development of OSA in previously healthy people, and accelerates the progression of earlier diagnosed OSA, particularly in patients who are already overweight.[10, 11] The other major predisposing factors for OSA are male gender, age and certain anatomical factors e.g. large tonsils, prominent uvula, mandibular micrognathia and nasal deformities.[12] Due to all these factors, the airspace of the naso- and oropharynx decreases and there is a narrowing of the upper airways, thus increasing the risk of OSA in the supine position and a loss of neuromuscular compensation at the onset of sleep.

OSA and T2D

In clinical work, the association between T2D and OSA should be firmly kept in mind. Patients with OSA are found to have an increased risk for T2D (approx. 40% of people with OSA will have T2D), but the incidence of new T2D or different stages of hyperglycaemia in people with OSA is not known.[3, 13] The severity of OSA also seems to be linked with worsened insulin resistance and glucose control in diabetes.[14] On the other hand, it has been demonstrated that patients with T2D may have a very high prevalence (60-85%) of OSA.[3, 13] Both conditions are chronic diseases that progress from mild sleep disordered breathing or hyperglycaemia to more severe condition over a varying period of time, which may be surprisingly short in the case of weight gain and lack of effective treatment. The studies examining these associations have unfortunately, thus far, consisted

of only small sample sizes (n=60-200).[3, 13] The main proposed mechanisms causing the association include hypoxaemia and sleep fragmentation, which may alter glucose and insulin metabolism by elevating chronic inflammation and sympathetic activity. However, the exact underlying mechanisms leading to these associations are still not fully understood, but it is most likely that they are multifactorial and highly influenced by the common feature of obesity, and in particular central obesity.[3, 13, 14] Thus, there exists a

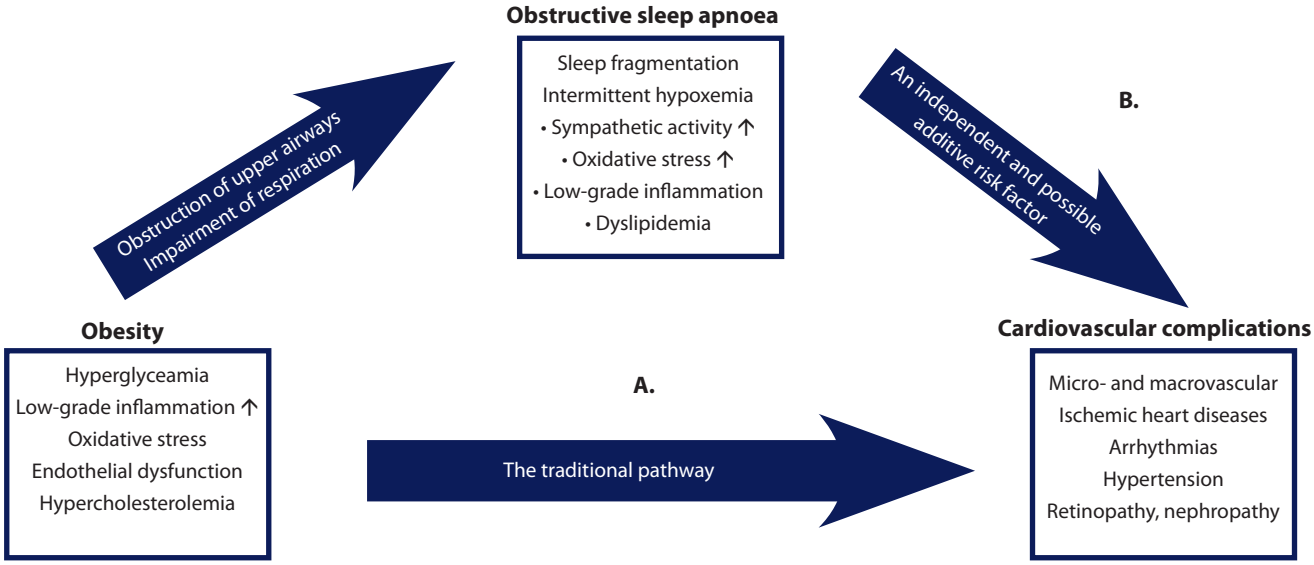

Figure 1. The major mechanisms for cardiovascular complications in obese patients. In hyperglycaemic patients with OSA both A (traditional) and B (related to OSA) pathways are activated.

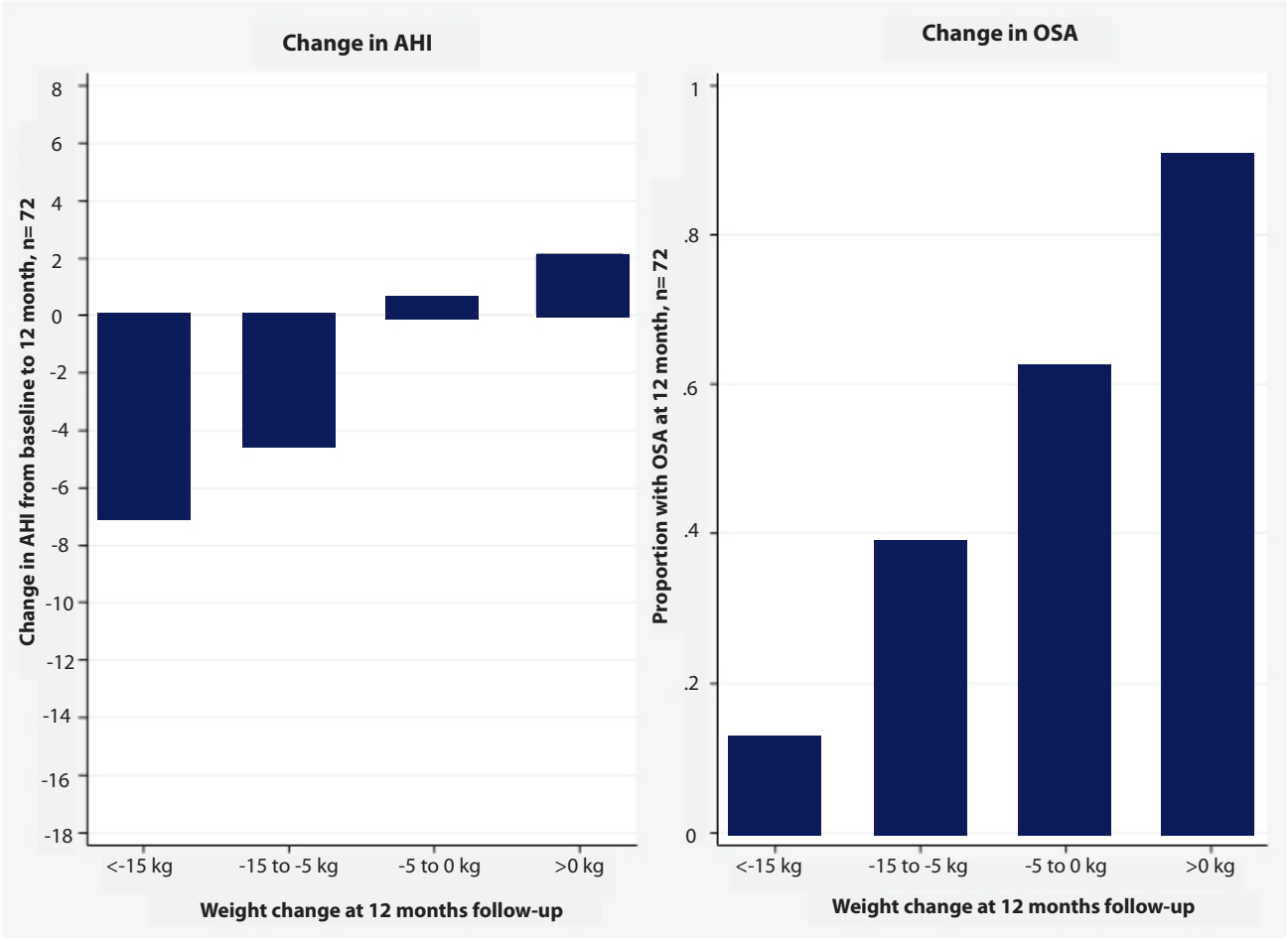

Figure 2. Changes in apnoea-hypopnoea index (AHI) in relation to changes in body weight, and the proportion of patients (%) with OSA (AHI>5) in relation to the weight change categories <-15 kg, -15 to -5kg, -5kg to 0kg, and >0kg at the 12-month follow-up. Reprinted with permission of the American Thoracic Society. Copyright © American Thoracic Society. Tuomilehto H *et al. Am J Respir Crit Care Med* 2009;179:320-7. Official Journal of the American Thoracic Society.

need to improve our knowledge on the association between cardiometabolic syndrome and OSA, and the effect of weight loss in all co-morbidities related to obesity.

OSA, T2D and Cardiovascular Consequences

A linear relationship exists between hyperglycaemia and microvascular complications. For instance, impaired glucose tolerance is associated with a 40% of increased mortality and the risk of both microvascular and macrovascular complications.[15] T2D leads to both macro- and microvascular complications that are responsible for most of the associated excess morbidity and mortality. While macrovascular complications such as cardiovascular disease are the most frequent cause of excess mortality, microvascular complications such as retinopathy and nephropathy are responsible for much of the excess morbidity.[16] OSA is also an important risk factor for increased mortality. This is particularly due to coronary artery disease and even mild OSA is associated with increased activation of the inflammatory system and a risk for cardiovascular morbidity, although the risk is more frequently associated with more severe degrees of the disease.[17, 18] Our study group has demonstrated that sleep disturbances may predict a progression from pre-diabetes stages to T2D.[19] However, it is still unclear whether sleep disorders, such as OSA, further increase the risk for micro- (i.e. endothelial dysfunction, retinopathy, nephropathy) or macrovascular complications in people with hyperglycaemia. If so, and considering the suggested high prevalence of OSA linked to T2D, it would be essential to find the risk group and properly treat OSA in people with hyperglycaemia.

Furthermore, little is known about the associations between different stages of OSA and hyperglycaemia, particularly in the early phases of the diseases. Also, reliable scientific evidence on the effect of treating these conditions with healthy diet and increased physical activity, and the effect that this has on the development of cardiovascular complications is lacking. Often these conditions are present in the same individual, and it has been suggested that the co-existence of OSA, obesity, insulin resistance, hypertension and dyslipidaemia may have a more widespread impact on the cardiovascular complications than these conditions could on their own[20] (Figure 1). The consensus statement of International Diabetes Federation (IDF) urges action to raise awareness and recommends that all healthcare professionals involved with T2D or OSA should be educated about the links between the two conditions and trained in their care. Further research is needed to better understand the links between the two conditions and improve treatment and care.[21]

Treatment for OSA

The gold standard for treating patients with OSA is nasal continuous airway pressure (CPAP). It has been found to be effective for removing the abnormal respiratory events, as well as reducing the cardiovascular morbidity and mortality related to OSA.[18, 22] Therefore, CPAP is a first-line treatment for patients with more severe OSA and/or when the disease is accompanied with significant impairment in daytime performance. However, adherence (60-80%) to the treatment may sometimes be a major limitation, particularly in early, mild-moderate symptomatic stages of the disease (the largest subgroup approx. 70-80% of all OSA patients). Moreover, there is little evidence about the possible beneficial metabolic effects of CPAP.[20]

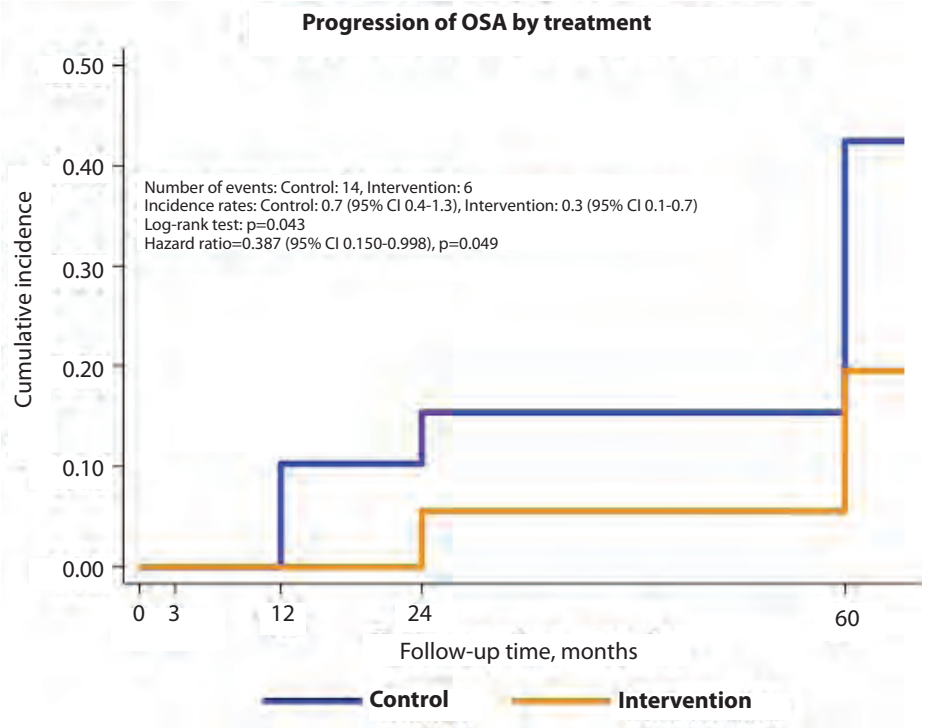

Figure 3. Progression of OSA by treatment group during the post-intervention follow-up period. Kaplan-Meier estimate of probability of progression of OSA. The difference between the survival curves was tested with the log-rank test. The COX proportional hazard model was used to estimate the hazard ratio for the progression of OSA. Reprinted with permission of the JAMA Internal Medicine. Copyright © American Medical Association. Tuomilehto H *et al. JAMA Intern Med* 2013, Apr 15.

One must keep in mind that obesity is the most important risk factor for both OSA and T2D, and in fact most OSA patients (> 70%) and diabetics are obese.[3, 9] In the first randomised study on the topic, our study group has recently demonstrated that lifestyle intervention can be a curative treatment in moderately obese patients with mild OSA[23] (Figure 2). Later, this finding has been supported by two other RCTs; one on diabetic patients and another on patients with moderate-severe OSA with CPAP treatment.[24, 25] It has been reported that it is more difficult to improve OSA by weight reduction than to develop or further deteriorate OSA by more weight gain.[10] This finding clearly highlights the importance of

maintaining a normal body weight by providing general information to the public via prevention programmes, or in the case of individuals who are overweight, committing them to early control of their condition and more active treatment. However, regardless of promising results in terms of symptoms of OSA and the undoubted cardiometabolic benefits of changing lifestyles, weight reduction as a treatment of OSA is still fiercely underrated.[26]

OSA is a chronic, progressive disease, and it is well-documented that severe OSA is associated with an increased risk for cardiovascular morbidity and mortality. Furthermore, the vast majority of people with OSA still remain undiagnosed. Intervention through lifestyle changes has already been successfully used in the prevention of Type 2 diabetes,[27, 28] and also in larger scale in the implementation programmes for the prevention of Type 2 diabetes in clinical settings.[29] There are no national programmes for screening OSA or preventing the progression of the disease, as there are for T2D. Just recently we demonstrated, in the first study, long-term evidence that a healthy lifestyle i.e. changes in diet according to the current recommendations and increased physical activity along with weight reduction, can result in marked improvements of OSA in overweight patients that are sustained even four years after the cessation of the active intervention, and the progression of the disease prevented[30] (Figure 3).

Based on the statement of IDF, weight reduction should be the primary treatment strategy, and the primary aim of research should be the implementation of interventional studies that analyse the effects of various therapies for OSA in people with T2D, particularly focusing on cardiovascular outcomes, and the mechanism linking OSA with T2D.[16] Thus, there is a definite need for larger, well-controlled trials on the effects of different lifestyle programmes among OSA patients to determine the overall efficacy of different treatment modalities and their long-term succession before larger scale programmes may be implemented in clinical settings, as has been the case for the prevention of T2D.

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Continuous Glucose Monitoring: Why it is Not Enough and What Can We Expect of the Closed Loop?

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Introduction

Continuous glucose monitoring (CGM) is one of the most discussed technological advantages in diabetology in recent years. It can be compared to the start of the era of personal blood glucose meters in the 1980s, the difference being that CGM provides glucose monitoring at a higher qualitative level. Continuous glucose monitoring brings new therapeutical and educational possibilities for both patients and physicians. The continuous aspect of glucose measurement provides a complex insight into the glucose metabolism in patients with diabetes and enables them to connect common daily activities with glucose excursions, which was previously often incomprehensible and problematic. This gives patients a chance to avoid certain activities in order to prevent undesirable blood glucose changes and/or to adjust their lifestyle to minimise its impact on blood glucose levels. CGM also helps patients to reach their target glucose range without increasing the risk of hypoglycaemia during self-management and facilitates the delivery of better support to the patients from healthcare professionals. New possibilities have arisen based on the recent advantages in the development of the closed-loop systems for insulin delivery. Currently, patients with diabetes still need to put a lot of energy into monitoring blood glucose, calculating carbohydrates, precisely dosing insulin and balancing their physical activity with all of the aforementioned factors. Closed-loop systems have the potential to rid them of this burden and return the lost spontaneity to their lives. This may be, in fact, one of the most significant contributions of the industry to diabetology since the first clinical use of insulin in 1922.

Martin Prázný is an Associate Professor of Internal Medicine at 1st Faculty of Medicine, Charles University in Prague. He works in a diabetes research group at 3rd Department of Internal Medicine, traditionally aimed at endocrine and metabolic diseases. During his PhD studies, he published several original papers in the field of microvasculature, endothelial function and oxidative stress in patients with diabetes and other endocrine disorders. For many years, he has utilised the advances of technologies in diabetes. Recently, his research group has become more involved in clinical research in Type 1 diabetes. With better availability and reliability of continuous glucose monitoring, he investigates the role of glycaemic variability in glycaemic control and diabetes complications. He has also launched a series of postgraduate education courses on CGM use in the Czech Republic to bring this technology to healthcare professionals and to patients.

Type 1 Diabetes and SMBG

It has repeatedly been shown that self-monitoring of blood glucose (SMBG) with personal blood glucose meters significantly improves the metabolic control of diabetes in Type 1 diabetic patients. The degree of improvement is related to the frequency of SMBG.[1] Frequent measurement of blood glucose facilitates precise insulin dosing and is a prediction of blood glucose levels. However, this requires a lot of concentration on the glucose trends and keeping in mind not only the last measured value but rather a whole series. For some patients, especially for those with high glycaemic variability, it is extremely difficult to connect these series of results into a continuous line and predict the future development of glycaemia. For these patients, many of their blood glucose values are difficult to comprehend, and this lack of understanding prevents them from administering the precise insulin dosing. Imprecisions in insulin substitution then often lead to hyperglycaemia and, more importantly, to hypoglycaemia.

Hypoglycaemia and the Fear of it

Hypoglycaemia is currently the main obstacle in reaching the target glucose range safely with insulin[2] and is also a significant direct cause of mortality in patients with diabetes. Some authors estimate that about 6-10% of overall mortality of patients with Type 1 diabetes are related to hypoglycaemia,[3] a high number for an iatrogenic complication. Fear of hypoglycaemia is often present in patients with recurrent severe hypoglycaemia and may negatively impair their quality of life. Unsatisfactory diabetes control due to fear of hypoglycaemia, on the other hand, seems to be a more significant problem in patients on multiple daily injections (MDI) than in those treated with insulin pumps (CSII).[4] Sensor-augmented insulin pump (SAP) treatment improves the fear of hypoglycaemia significantly,[5,6] while the benefit on HbA_{1c} is preserved. It was shown in several studies that CGM reduces the total time spent in hypoglycaemia,[7,8] however, the effect of CGM or SAP on the frequency of hypoglycaemic episodes is still unclear. This may imply that even if CGM or SAP would not prevent hypoglycaemic episodes, it can significantly reduce their

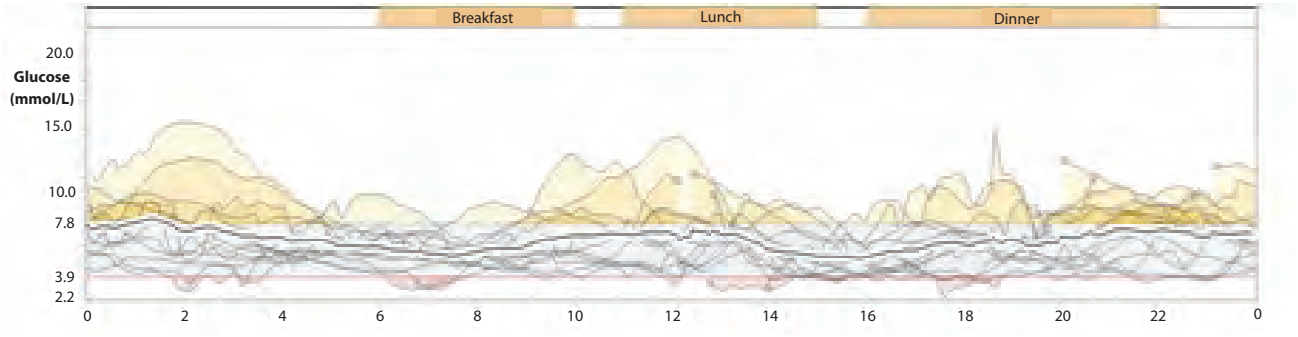

Figure 1. CGM record of well controlled patient with Type 1 diabetes.

duration. This may be very important in the prevention of hypoglycaemia-induced seizures.[9] In addition, it was shown that SAP also reduces glycaemic variability in patients with Type 1 diabetes with HbA_{1C} less than 8% (DCCT) in the STAR 3 study.[10]

Precise Insulin Dosing with CGM

Precise insulin dosing, a low count of hypoglycaemic events and excellent glycaemic control are the targets of diabetes treatment for all patients. However, only a minor percentage of patients achieve this. Most patients perform SMBG up to 4-6 times per day, and even the most dedicated rarely use it more frequently. For patients with Type 1 diabetes, frequency of SMBG may also predict the probability of long-term CGM benefit.[11] An example of a well-controlled patient is given below. Her CGM record is shown in Figure 1.

This patient is 62 years old and has had diabetes for 28 years. Her main motivation for keeping tight glycaemic control is proliferative retinopathy and preventing it from worsening. She uses a sensor-augmented insulin pump. In addition, she is performing SMBG with an average frequency of 6.4 times per day. The mean sensor glucose is 6.6±2.1 mmol/L, total mean insulin dose 24.9±3.7 U/day and 63% of the total dose is given in boluses. The total daily count of boluses is 9 at average, and the bolus calculator is used 4 times/day (patient usually makes small adjustments to the recommended dose – the dose suggested by the calculator is decreased by the patient by approximately 0.8 U/day and increased by 1.3 U/day). To cover carbohydrate intake, this patient needs 7.2 U/day and 2.8 U/day is injected to correct glycaemia to the target range. Her postprandial glucose control after dinner can be seen in Figure 2. Mean dose of insulin before dinner is 3.4 U. Mean blood glucose before dinner is 6.3 mmol/L and after dinner 7.2 mmol/L – the postprandial glucose peak is thus less than 1 mmol/L. The overall frequency of self-reported hypoglycaemia is low, and minor hypoglycaemia occurs usually 2 times in a week. This is well-recognised by the patient. No severe hypoglycaemia was reported in the last three years. The HbA_{1C} of this patient is 49 mmol/M (IFCC), which is equivalent to 6.6% (DCCT).

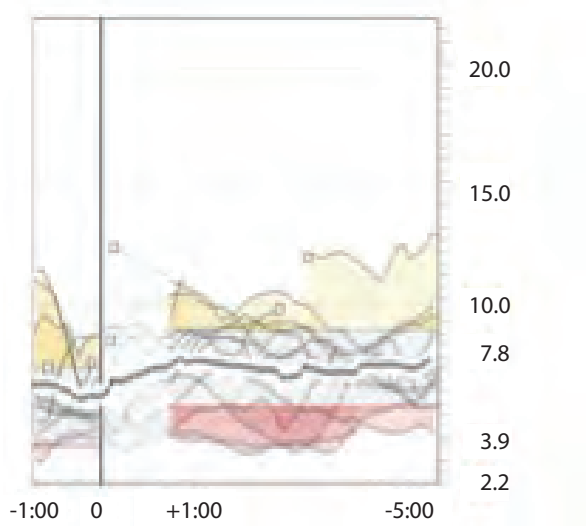

Figure 2. CGM record of postprandial control after the dinner.

Efficacy of Sensor-augmented Pump Therapy

In accordance with this case report, it has recently been concluded in a meta-analysis that CGM may improve diabetes control in patients with Type 1 diabetes, especially in insulin pump users.[12, 13] In patients using SAP, a significant improvement in glucose control was persistent for 3 years.[5] The efficacy of the SAP is dependent of the time spent on the glucose sensor[7] and is based on a combination of advantages of both sensor and the pump. The pump enables precision tuning of the insulin therapy for very insulin-sensitive patients. This is sometimes not possible with insulin pens which, at best, give insulin in half-unit steps. Continuous glucose monitoring not only shows patients their current glucose levels but also warns them when they reach their high and low glycaemic threshold. Moreover, CGM devices or sensor augmented pumps calculate the rate of change in glucose concentration and show glycaemic trends. These systems can give a warning to the patient when the rate of glucose rises or the fall is too swift. The predictive alarms are triggered in advance so that patients have some time left to react; to adjust the insulin dose, carbohydrate intake and/or physical activity to prevent hyperglycaemia or hypoglycaemia.

Patient Burden with Sensor-augmented Pump

It is clear that well-controlled patients need to adjust insulin doses precisely, plan their future activities and keep an eye on their blood glucose at all times. However, these activities consume patient time, psychical resources, limits their freedom, spontaneity and negatively impacts their common daily activities. Nevertheless, patients treated

with insulin rate their insulin treatment positively. They understand that insulin has a positive impact on their long-term health status.[14] Patients using modern technologies like sensor-augmented pumps pay more attention to their diabetes care then patients on multiple daily injections. Patients on pumps and sensors spent an extra 2 hours per week on diabetes-related care during pump initiation and an extra 1 hour per week after initiation than the patients on MDI.[15] Despite patients and caregivers reporting satisfaction with SAP treatment (related to a therapeutic efficacy, convenience and level of interference with daily activities) in the STAR 3 trial,[16] some patients exhibited symptoms of burn-out: lifestyle non-adherence, omitting SMBG, sensor use and sometimes also insulin treatment. In the INTEPRET study, patients used glucose sensor for 37% in the first 3 months of the 1-year follow-up compared to 27% in the 3 last months.[6] As was shown by Beck *et al*. and confirmed in the meta-analysis of Pickup *et al*., the efficacy of CGM or SAP is positively associated with the time spent on the sensor.[7, 11] The loss of patients' adherence to the sensor use is therefore alarming.

Current Advances in Closed-loop Systems

Previous studies have shown that closed-loop systems are feasible, at least when the glycaemic control is not disturbed by food intake or exercise. Closed-loop systems were used overnight with promising results in children with Type 1 diabetes.[17, 18] However, the ultimate challenge for the closed-loops system is represented by careless operation, independent of the patient's food intake and physical activity. Recent results of a 36-hours uninterrupted closed-loop basal insulin delivery (2 nights and one day) in 12 adolescent Type 1 diabetes published by Elleri *et al*. showed excellent data from this point of view. Patients applied boluses before main meals but not before snacks. They were also exposed to moderate exercise under controlled conditions twice a day that was not announced to the control algorithm. The percentage time spent in the target range was increased by closed-loop insulin delivery to 84% (vs. 49% during the control visit). In 17 of 24 nights during closed-loop insulin delivery patients reached 100% time spent in the target range. Nine hypoglycaemic events (5 of them related to exercise) were observed during closed-loop test comparable to the control visit (10 events).[19] In another study involving 11 adolescents and 27 adults published by Breton *et al*.,[20] the authors tested two modular closed-loop attitudes. Standard control to range (sCTR) was designed to prevent extreme glucose excursions and enhanced control to range (eCTR) aimed to control glycaemia to the near-normoglycaemia range (3.9-10 mmol/L). All subjects were hospitalised for 22 hours and their regimen included meals, overnight rest and 30 minutes of exercise. sCTR increased the time in near normoglycaemia from 61 to 74%, while the time spent in hypoglycaemia was reduced. Glycaemic variability was reduced overnight. eCTR improved mean blood glucose from 7.7 to 6.7 mmol/L without increasing hypoglycemia. Patients in eCTR settings reached 97% time in near normoglycaemia and 77% time in the optimal glycaemic control.

Low Glucose Suspend

Currently, there is only one feature of the close-loop implemented in a commercially available device. The low glucose suspend function is an optional tool in the insulin pump for a temporary discontinuation of insulin delivery in a case when the hypoglycaemic alarm is not responded by the patient. Insulin delivery is restarted after two hours to prevent rebound hyperglycaemia. The use of low glucose suspend function was associated with a reduction of hypoglycaemia in children and adolescents in a real-life setting.[21] It also reduced nocturnal hypoglycaemia in high-risk adult Type 1 diabetic patients.[22] Moreover, this function was well-accepted and rated by these adult patients.

Conclusions

Patients with Type 1 diabetes have a profit from frequent monitoring of their blood glucose. Awareness of their glycaemia facilitates their qualified decision about the optimal dose of insulin. Continuous glucose monitoring is a useful tool for better self-management of the patients. However, it still does not prevent natural burn-out of diabetic patients resulting from the necessary attention paid to the glucose values and insulin adjustments. Closed-loop systems are feasible at this moment and the first results from clinical studies attempting to model a real-life situation (daytime, food and exercise) show excellent efficacy. However, it will take some time and thorough testing of efficacy and safety before these systems will reach commercial availability. Low glucose suspend of the insulin pump, the first commercially available and commonly used feature based on the closed loop, reduces hypoglycaemia and is well-accepted by the patients. It may suggest how the fully functional closed-loop systems will be welcomed by the patients and helpful in reducing the diabetes burden.

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Further Reading

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Monitoring, Assessment, and Control of Blood Glucose Fluctuations in Diabetes

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Diabetes is a complex of disorders, characterised by a common final element of hyperglycaemia. Intensive treatment with insulin and with oral medication to maintain nearly normal levels of glycaemia markedly reduces chronic complications in both type 1 and type 2 diabetes mellitus (T1DM, T2DM), but may risk symptomatic hypoglycaemia and potentially life-threatening severe hypoglycaemia. Therefore, hypoglycaemia has been identified as the primary barrier to optimal diabetes management. Thus, people with T1DM and T2DM face a life long optimisation problem: to maintain strict glycaemic control without increasing their risk for hypoglycaemia. However, the struggle for tight glycemic control could result in large blood glucose (BG) fluctuations over time. This process is influenced by many external factors, including the timing and amount of insulin injected, food eaten, physical activity, etc. In other words, BG fluctuations in diabetes are the measurable result of the action of a complex dynamical system, influenced by many internal and external factors. This article looks at different methods of glucose monitoring, including the artificial pancreas, self-monitoring and continuous glucose monitoring.

Continuous Glucose Monitoring

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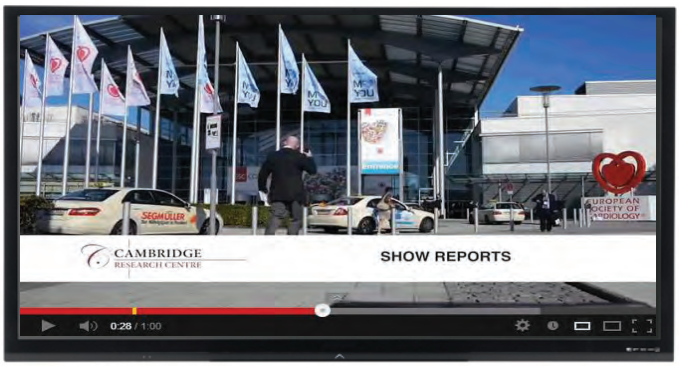
Most patients with type 1 and insulin treated type 2 diabetes test their capillary blood glucose multiple times a day and base decisions about food intake and insulin dose adjustment on these results. These capillary readings only provide a "snapshot" of information about blood glucose. The advent of continuous glucose monitoring (CGM) has allows patients as well as health care providers to gain information about the direction and rate of change of glucose, which can help patients make more appropriate decisions. High or low blood glucose alarms can warn them of impending glucose excursions, allowing corrective action and helping keep blood glucose concentrations within acceptable limits.

CGM has been shown to improve glucose control in patients with type 1 diabetes without any increase in hypoglycaemia. There have been demonstrable improvements in quality of life, particularly in fear of hypoglycaemia. Data on the ability of CGM to reduce hypoglycaemia in those with impaired awareness is emerging, as is the value of this technology in managing pregnancy in diabetes. However, the promise of continuous glucose monitoring extends beyond the current applications with alarms and real- time displays. It paves the way for the development of closed-loop artificial pancreas systems that will control insulin delivery on the basis of information obtained from the sensors and help patients maintain optimal glycaemic levels with minimal if any risk of hypoglycaemia. The first generation of these devices is already available, which suspends insulin delivery if the patient fails to respond to a hypoglycaemia alarm, and future versions that control blood glucose overnight are in advanced stages of testing.

Continuous glucose monitoring has provided a step-change in diabetes management, just as home glucose monitoring did three decades previously, and will help many more patients gain control over their diabetes.



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Enteroviral Pathogenesis of Type 1 Diabetes: A Role for Enhancing Antibodies?

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Introduction

Type 1 diabetes (T1D) is an autoimmune disease resulting from the loss of functional insulin-producing pancreatic islet beta cells. Enteroviruses (EV) belonging to the Picornaviridae family, and especially Coxsackievirus B (CVB), are thought to strongly contribute to the multifactorial process leading to the development of T1D.[1-4] Although it is well known that the disease results from an autoimmune destruction of pancreatic beta cells, the role of CVB in the process is not entirely clear, even if various mechanisms have been reported.[3-5] During a viral infection, enhancing antibodies in contrast to neutralising antibodies can play a potentiating role and increase the infectivity of target cells. The antibody-dependent enhancement (ADE) of the infection has been reported for various viruses. The ADE of the infection can then contribute to the pathogenesis of virus-induced diseases.[6, 7]

In this chapter, the mechanism of the ADE of CVB infection will be described; and its implications on the role of CVB in the pathogenesis of T1D will be analysed.

The Antibody-dependent Enhancement of CVB Infection

Enhancement of viral infectivity by antiviral antibodies depends beyond the virus, on the quality and quantity of several factors including target cells and antibodies.

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Cells and Receptors

CVB can infect a large range of cells. It is generally understood that the virus entry follows the binding to its cellular receptor, the Coxsackie and Adenovirus Receptor (CAR). The most common process to CVB internalisation into cells is similar to macropinocytosis. However, several findings indicated that the mechanism of the entry of CVB into the cell depends on the cell type. Indeed, CVB can enter in cells that express Fc receptors (e.g. those of the immune system, such as macrophages, monocytes, B-cells and granulocytes), when bound to CVB-specific antibodies.[8] This virus entry, dependant on FcR, is the most described of ADE mechanisms. In this scenario, immune complexes constituted by virus-bound antibodies recognise at least one of the receptors for the Fc part of antibodies on the cell surface, providing a bridge that enhances the attachment of viruses to the cells.[6, 7] The ADE phenomenon has been described with various viruses that replicate in monocytes and macrophages.[9] Using peripheral blood mononuclear cells, it was shown that CD14+ monocytes were target cells in the ADE of CVB4 infection.[10] The ADE of CVB infection was also observed in murine macrophagic cell lines J774.1 and P388D1.[11] Previous studies by our team reported that the ADE was dependent on FcγRII and FcγRIII. In addition, CAR (Coxsackie and Adenovirus Receptor), the cellular receptor of CVB, was also needed,[10-12] unlike some viruses for which ADE enables emancipation from their cellular receptor for infection. For these viruses, primary non-susceptible cells could then be infected if they express Fc receptors.[7]

Antibodies

Several factors such as the class, the concentration and the epitope specificity of the antibody seem to be essential for ADE of CVB4 infection. Antibodies involved in the facilitation of CVB4 infection have been identified as IgG antibodies directed against VP4, a viral capsid protein. The target amino acid sequence of these antibodies was shown to be localised between amino acids 11 and 30 of the VP4 protein (69 amino acids in total).[13, 14] According to X-ray crystallography datas obtained at – 196°C, VP4 is buried in the capsid and is not accessible at the virion surface; however it is thought that in physiological conditions, conformational changes may expose a part of this protein, making it

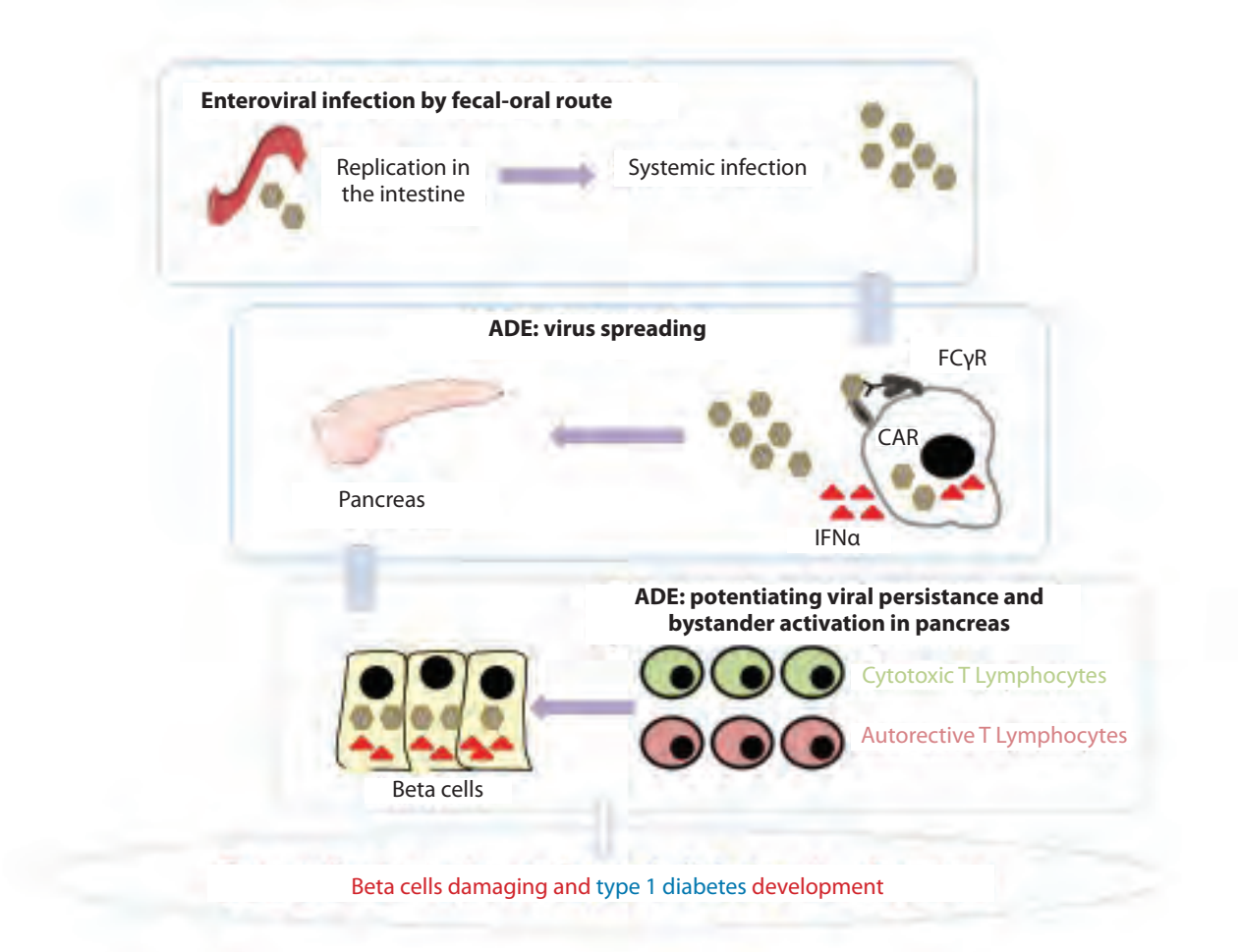

Figure 1. Role of enhancing antibodies in the enteroviral pathogenesis of Type 1 diabetes. The enteroviruses are transmitted by an oral route. After primary replication in the intestine, the viruses can spread to the circulation and to target organs such as the pancreas. The antibody dependent enhancement (ADE) of the infection can amplify the replication and the dissemination of the viruses. In the pancreas of subjects with a genetic predisposition, the ADE of enteroviruses infection can damage beta cells through two possible mechanisms: the persistance and the bystander activation of an autoimmune destruction of beta cells.

recognisable by enhancing antibodies. Enhancing antibodies against VP4 protein also seem to be type-specific because no cross reaction was observed between CVB3 and CVB4.[13]

Moreover, studies using plasma or serum for ADE demonstrated that facilitation was observed at higher dilutions. Indeed, it was reported that at sub-neutralising concentrations, the infection may be enhanced. At high concentrations of neutralising antibodies most of the binding sites of the virion are blocked, while in sub-neutralising conditions, available Fc portion of a neutralising antibody on one side and unoccupied viral proteins on the other side may allow enhancement of infectivity. Nevertheless, assuming that enhancing antibodies are different from neutralising ones, with different epitopes, it is conceivable that at low concentrations of neutralising antibodies, epitopes of enhancing antibodies are further exposed.[6, 7]

ADE of CVB Infection as a Possible Mechanism Involved in the Pathogenesis of T1D

The ADE of a viral infection does not only facilitate virus entry but also modifies innate and adaptive intracellular antiviral mechanisms and enhances the viral replication.[9] The results of the facilitation of CVB infection have been described in the literature through studies using cell culture systems and animal models, and a link has been strongly suspected with T1D development in humans.

Effects of Enhancement of CVB Infection

Our group early reported the effects of facilitation of CVB infection using monocyte-enriched peripheral blood mononuclear cells (PBMC). It was clearly demonstrated that incubation of CVB with diluted plasma or non-neutralising anti-CVB4 IgG antibodies before inoculation to PBMC resulted in a production of high amounts of interferon α (IFNα) while inoculation of the virus alone led to a very weak production of IFNα. This enhanced production of IFNα is undoubtedly linked to an increase of CVB infection as shown by viral RNA and protein detection in cells.[10, 12]

Similar results were obtained using the THP-1 monocytic-like cell line which expresses FcγR I, II and III receptors.[15]

The effects of the facilitation of CVB infection by antibodies were also

evaluated *in vivo*. Enhancement of CVB3 infection in A/J male mice were observed following inoculation of the virus in presence of anti-CVB2 IgG antibodies. An increase of up to 1000-fold of the viral load was noted in blood and in target organs such as the heart, pancreas, and spleen. Worsen histopathologic aspects were also observed in the exocrine pancreas and in the heart.[11] Experiments by Kishimoto *et al*. on C3H/He male mice were also very conclusive. After a first immunisation with CVB3, the second inoculation yielded different results according to the titer of anti-CVB3 antibodies in mice. While mice with high titers of anti-CVB3 antibodies were fully protected from the myocarditic strain of CVB3, those without anti-CVB3 antibodies presented a moderate myocarditis with a slight T cell and macrophagic infiltration in the myocardium, which was accompanied by moderate viral titers and by a weak increase in the concentration of the chemoattractive cytokine MIP-2 in blood. In mice with weak titers of anti-CVB3 antibodies, the inoculation of CVB3 resulted in an exacerbated and sometimes lethal myocarditis with a strong T cell and macrophagic infiltration in the myocardium, which was accompanied by elevated viral titers in this organ and a marked increase in the concentration of MIP-2 in blood.[16]

Suggested Scenario for the Role of Enhancing Antibodies in the Enteroviral Pathogenesis of T1D

The outcome of a viral infection depends on the virus and the host factors, namely the immune system; and this interplay is well demonstrated by the ADE phenomenon. The results of ADE *in vivo* can be an escape from immune system and an increase of infectivity in the target organ, but it can also amplify the immune response.[6, 7] Based on the previous reports on ADE of CVB infection and given that numerous studies have shown a more frequent detection of CVB in type 1 diabetic patients, it is highly tempting to suspect the enhancement of CVB infection as a mechanism contributing to induce or to aggravate T1D. This issue will be addressed through two hypotheses:

• The enhancement of CVB infection can contribute to the spreading of virus in the body and especially in the pancreas.

After transmission by faecal-oral route, the primary replication of CVB occurs in the intestine. The detection of enterovirus in the mucosa of small intestine of T1D patients has been reported.[17, 18] From the gut, a systemic infection can lead to dissemination of the virus to other target organs. In developed countries where T1D incidence is rapidly increasing, there is a decrease in the prevalence of enterovirus infection. This low prevalence of enteroviral infections in rich areas results in low levels of anti-enterovirus antibodies in the population.[1] The picture is then compatible with a favourable situation to ADE, as described above. Data from studies in humans also suggested such association. IFNα, which was shown to be a marker of ADE of CVB *in vitro*, was detected more frequently and at higher levels in the blood of diabetic patients than in the blood of healthy individuals,[19] and enteroviral RNA was present in the blood of patients with detectable IFNα. When whole blood or PBMC from diabetic or healthy patients were inoculated with CVB4, higher amounts of IFNα were detected in the culture supernatant fluid of cells from diabetic patients.[20] Moreover, anti-VP4 antibodies which were shown to be involved in the ADE of CVB4 infection were found more frequently and at higher concentrations among diabetic subjects.[21]

• The enhancement of CVB infection is involved in the process leading to the destruction or the damaging of pancreatic beta cells.

The pancreas is a main target for enteroviruses. Many strains of CVB are naturally pancreatotropic or can become pancreatotropic through adaptation to pancreatic tissue.[22, 23] Enterovirus components were detected in pancreas biopsy samples of diabetic subjects and especially in islets beta cells.[24, 25]

Several mechanisms have been proposed to explain the role of CVB in the alteration of pancreatic beta cells. ADE of CVB infection is thought to potentially contribute to two of these hypotheses - the 'viral persistance' and the 'bystander activation'.

An enhanced infection of monocytes, macrophages and other immune cells with CVB which can result in an increased and possibly continuous virus production may play a role in the infection of beta cells and in the persistence of CVB in these cells. Thus, the infection of beta cells can damage or disturb these cells, and may contribute to an activation of immune system by prolonged presentation of viral antigens and self antigens to T lymphocytes.[26] On the other hand, the bystander activation is a scenario in which enterovirus infection could induce a very important local inflammation in beta cells with an increased expression of stress markers, phagocytosis and self-antigens presentation.[27] The inflammation is deleterious by itself to beta cells as shown by *in vitro* experiments and studies in animals;[28] but will also promote recruitment and activation of existing autoreactive T cells. The ADE, by potentiating the immune response, can aggravate these effects leading to damage of pancreatic islets.

Conclusion

There are abundant data in the literature supporting a role for enteroviruses, and especially CVB, as an environmental factor in the development of T1D, at least in some genetically susceptible individuals. However the molecular mechanisms of the enteroviral pathogenesis of the disease are still fuelling debate. In so far as the ADE of CVB infection can amplify the effects of the virus *in vitro* and *in vivo*, this process may play a role in the complex relationship between enteroviruses and T1D. Further studies are needed to investigate this hypothesis.

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Challenges in Estimating Glomerular Filtration Rate in Diabetic Patients

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Introduction

The prevalence of diabetes mellitus, as well as diabetes-related complications is increasing worldwide.[1] Diabetic nephropathy has become the most common single cause of end-stage renal disease, seriously affecting both patient outcomes and economical resources of healthcare systems.[2] There is a substantial body of evidence which emphasises that appropriate intervention (intensive diabetes and hypertension management) at an early stage of diabetic nephropathy can significantly improve the outcomes for diabetic patients.[3, 4] Thus, screening for chronic kidney disease in asymptomatic patients remains one of the most important tasks in diabetes management.

Urinary albumin excretion rate within range 30-299 mg/24h ("microalbuminuria") has been identified as a sensitive marker of glomerular basal membrane damage at an early stage of diabetic nephropathy.[2] However, despite the fact that screening for microalbuminuria had been the recommended procedure in diabetes care for many years, undiagnosed chronic kidney disease is still common in diabetes.[5, 6] There is an accumulating body of evidence which suggests that a significant loss of kidney function, assessed as glomerular filtration rate (GFR) decline is not uncommon in diabetic patients without overt albuminuria, implicating a complementary, rather than consecutive relationship between renal function impairment and glomerular membrane damage in the pathogenesis of diabetic kidney disease.[5, 7]

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Current guidelines regarding diabetic nephropathy screening include the testing of urinary albumin excretion and the measurement of serum creatinine in all adults with diabetes regardless of the degree of urine albumin excretion.[2] The serum creatinine should be used to estimate GFR and stage the level of chronic kidney disease (CKD), if present. Current staging of CKD according to GFR values is presented in Table 1.[8]

Glomerular Filtration Rate Assessment

An ideal marker of glomerular filtration is a physiologically inert, not protein-bound molecule that is freely filtered by the glomeruli, not secreted by the tubuli, and not synthetised, transported or metabolised by the kidney.[9] Among the very few substances fulfilling these criteria, a plant polysaccharide inulin is considered to be the gold standard, whereas a radiograhic contrast iohexole and various radionuclides (125I-iothalamate, 51Cr-EDTA or 99mTc-DTPA) represent some suitable alternatives. These procedures are complex, costly, time- and labour-consuming, and involve exogenous administration of substances and the collection of samples followed by the appropriate analytical quantitation of the applied marker. Furthermore, measurement of GFR by either of the procedures may suffer from inaccuracies related to specimen collection protocols, and different procedures may yield substantially different results. Consequently, glomerular filtration rate measurement is not a suitable tool for the routine assessment of kidney function and screening for chronic kidney disease.

Serum creatinine has been used as a marker of kidney function for many years due to practical reasons, despite serious drawbacks originating from both biological and analytical limitations.[10] Being significantly influenced by nutrition habits, muscular mass, age, gender and ethnicity, and partially secreted and reabsorbed by the tubuli, creatinine is far from an ideal marker of glomerular filtration. While intra-individual variability of creatinine is low (5.3%), reference intervals are relatively wide, and a significant loss of kidney function may occur in many individuals whose creatinine levels are still well within reference intervals.[9, 10] Moreover, the clinical reliability of creatinine has been burdened with analytical issues, particularly non-specificity of the most commonly used Jaffe alkaline picrate method and a lack of standardisation. Recent efforts regarding

GFR category	GFR (ml/min/1.73 m²)	Classification
G1	≥ 90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

Table 1. Staging of Chronic Kidney Disease by the GFR categories.[8]

global standardisation of creatinine measurement with calibration traceable to the definitive isotope dilution-mass spectrometry method (IDMS) have improved precision and harmonisation of results between laboratories. However, the problem of non-specificity bias remained with re-calibrated Jaffe alkaline picrate methods, while specific, enzymatic creatinine assays are still scarcely used due to the higher costs.[11]

Creatinine clearance, although a more sensitive marker of glomerular filtration than serum creatinine, requires a cumbersome 24h urine specimen collection, with a large proportion of collection-associated errors. Even with appropriate specimen collection, creatinine clearance does not accurately reflect kidney function due to variable and substantial tubular secretion, while high intra-individual variation (11-15%) may significantly flaw clinical interpretation of results.[9, 12]

Creatinine-based Estimates of Glomerular Filtration Rate

The need for practical, accurate and reliable surrogate marker of kidney function has long been identified, and led to the development of various predictive equations for eGFR derived from serum creatinine values (eGFRCreat, Table 2).

The first predictive equation, enabling estimation of creatinine clearance from serum creatinine adjusted for age and weight was published by Cockroft and Gault in 1976 (C-G equation,[13]). The equation was derived and validated in a population of hospitalised patients, mostly males. Further validation revealed an inherent weakness in the equation leading to a significant over- and underestimation of creatinine clearance in overweight/obese and lean patients, respectively.[14] Despite these limitations, the potential to estimate GFR by a relatively simple calculation from serum creatinine and anthropometric measures attracted a lot of attention and C-G equation had been of value for evaluating kidney function in clinical settings in the past. Today, it is still prescribed by FDA for kidney-function assessment necessary for appropriate drug-dosing, but it should be stressed that that C-G equation has not been re-expressed and is not accurate for use with standardised creatinine methodology used in most of the clinical laboratories worldwide.[9, 12]

Modification of Diet in Renal Disease (MDRD) Study, conducted in a large cohort of patients with CKD, among other objectives, aimed to develop a predictive equation for eGFR from plasma creatinine.[15] 125I-iothalamate served as a reference method for measured GFR. Age, gender, plasma creatinine and race (white or black) were identified as the most prominent predictive variables of GFR, and these were included in a 4-variable equation, which was re-expressed after standardisation of creatinine measurement by calibration traceable to IDMS reference method.[16] As MDRD-equation required no information on body weight, it was convenient for an automated eGFR reporting with routine creatinine requests, and was subsequently recommended as the preferred eGFR-equation in the Kidney Disease Outcome Quality Initiative Clinical Practice Guidelines for Chronic Kidney Disease (K/DOQI-CKD) in 2002.[17] Poor performance at normal plasma creatinine concentrations and lack of validation data in specific populations (healthy individuals, children, pregnant women, elderly), as well as in regard to the extremes of body weight, were some of the most highlighted limitations of the

Equation	Estimated parameter
Cockroft-Gault:[13] $\frac{(140-age) \times mass\ (kg) \times k}{SCr\ (\mu mol/L)}$ *k=1,23 for males and 1,04 for females*	Creatinine Clearance (ml/min)
4-variable MDRD:[15] $186 \times [SCr\ (\mu mol/L) \times 0{,}011274]^{-1{,}154} \times [age(years)]^{-0{,}203} \times [0{,}742\ \text{if female}] \times [1{,}212\ \text{if black}]$	GFR (ml/min/1,73m²)
4-variable MDRd re-expressed to standardised creatinine:[16] $175 \times [SCr\ (\mu mol/L) \times 0{,}011274]^{-1{,}154} \times [age(years)]^{-0{,}203} \times [0{,}742\ \text{if female}] \times [1{,}212\ \text{if black}]$	GFR (ml/min/1,73m²)
CKD-EPI:[18] Female, SCr≤62 µmol/L: $144 \times (SCr/62)^{-0{,}329} \times 0{,}993^{age} \times 1{,}159$ (if black) Female, SCr>62 µmol/L: $144 \times (SCr/62)^{-1{,}209} \times 0{,}993^{age} \times 1{,}159$ (if black) Male, SCr≤80 µmol/L: $141 \times (SCr/80)^{-0{,}411} \times 0{,}993^{age} \times 1{,}159$ (if black) Male, SCr>80 µmol/L: $141 \times (SCr/80)^{1{,}209} \times 0{,}993^{age} \times 1{,}159$ (if black)	GFR (ml/min/1,73m²)

Table 2. Creatinine-based surrogate markers of GFR.

MDRD equation. Due to the inaccuracy at higher GFR levels, a cut-off for reporting was set at 60 ml/min/1,73m^2 and it was recommended for the results above the cut-off to be reported as >60 ml/min/1,73 m^2, rather than respective calculated value.[17] This seriously compromised clinical usefulness of MDRD-equation in monitoring kidney function and possible progression of renal impairment at earlier stages of CKD (Table 1).

In order to overcome these limitations, CKD-Epidemiology Collaboration Group (CKD-EPI) in 2009 proposed a new equation, with improved accuracy at GFR levels >60 ml/min/1,73m^2.[18] CKD-EPI equation was derived from data obtained in six studies including different patient populations. Due to the equation-design (logcreatinine modelled as a 2-slope linear spline with gender-specific knots and age, race and gender on the natural scale), there are actually four different equations (males, females, above and below creatinine knot value, respectively), and different factors are used for Caucasians and for African-Americans, respectively (Table 2). CKD-EPI equation provides not only a more accurate estimation of GFR at higher levels, which is particularly interesting in diabetic patients with hyperfiltration, but has been shown to have a significant influence on estimated prevalence of CKD in comparison to MDRD-equation.[19-22] Considering these advantages, CKD-EPI equation has been assigned as the recommended equation for automated eGFR reporting in recently issued Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.[8]

Cystatin C and eGFR

Cystatin C is a low-molecular mass basic protein, produced at a constant rate by nucleated cells, and eliminated by glomerular filtration. The decrease in glomerular filtration rate is reflected by an elevation of plasma cystatin C levels. In comparison to creatinine, cystatin C is much less affected by gender, age, race and body mass and it was suggested to be a better surrogate marker of GFR. Several cystatin C-based eGFR (eGFRCys) equations have been proposed and validated in different patient populations, including diabetic patients, with conflicting results regarding its superiority over creatinine-based eGFR.[23-25] Apart from practical advantages of eGFRCys for which no information on age, gender and ethnicity are required, the lack of analytical standardisation and significant influence of some common clinical conditions (thyroid dysfunction, malignancies, inflammation) on plasma cystatin C levels indicates that more evidence should support the general use of this promising marker of eGFR. KDIGO Clinical Practice Guidelines suggest that eGFRCys may be used for confirmation of CKD in adult patients with eGFRCreat 45-59 ml/min/1,73m^2 (Stage G3a) where no other markers of kidney damage (albuminuria, urinary sediment abnormalities) have been detected. If used, plasma cystatin C should be assayed with a method traceable to the international standard reference material, and eGFRCys calculated by either 2012 CKD-EPI cystatin C or 2012 CKD-EPI creatinine-cystatin C equation.[8]

GFR and Diabetes: Controversies and Challenges

Kidney function is seriously and diversely affected by diabetes. Early type 1 diabetes is commonly associated with an elevated GFR, as a consequence of severe hyperglycaemia. It is still unclear whether this phenomenon, called hyperfiltration, reflects only deranged glucose homeostasis or is involved in the early pathogenesis of diabetic nephropathy, preceding albuminuria.[26] A substantial proportion of newly-diagnosed type 2 diabetic patients were found to have hyperfiltration as well, whereas a much lower prevalence was demonstrated in patients with a longer duration of diabetes.[27] Regardless of the mechanisms involved, accurate and reliable method for GFR estimation over the wide range of GFR is particularly needed for the diabetic population.

The accuracy of creatinine-based GFR equations has been constantly questioned in many studies conducted in various sub-populations of patients with different types of diabetes and stages of CKD and albuminuria.[28-31] Both under- and overestimation of eGFR in comparison to mGFR with different creatinine-based equations, including CKD-EPI were documented, dependent on the study design and a comparator method[25, 32, 33] However, discrepancies between measured and estimated GFR are reflecting physiological differences between actual glomerular function and serum creatinine levels, that are influenced by other factors as well and, more specifically, by hyperglycaemia in diabetic patients. Also, a lack of standardisation and inaccuracies of the methods for measurement of GFR are often overlooked as confounding factors when analysing and interpreting these discrepancies. CKD-EPI equation, offering less biased estimation of GFR than MDRD equation, within a wide range of creatinine levels, may be used as a recommended tool for routine eGFR monitoring in diabetic patients. However, clinicians should be aware that mathematically derived eGFR result enables by default a comparison of the patient to the study-population from which the equation was defined and all potential limitations should be carefully considered when interpreting results of eGFR. There is not sufficient evidence at the moment proving cystatin C-derived eGFR might offer any advantage over CKD-EPI eGFR in assessment of kidney function in diabetic patients.

In conclusion, while it is not questionable that all eGFR equations suffer from imperfections, an ongoing search for more accurate surrogate markers of kidney function is of utmost importance, as GFR measurement is neither suitable nor available for the recommended routine screening of diabetic nephropathy.

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Strategies to Mitigate the Risk of Hypoglycaemia Associated with the Treatment of Type 2 Diabetes

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Introduction

Glucose-lowering therapy of type 2 diabetes carries a risk of hypoglycaemia.[1, 2] This is especially so in patients aiming at intensified treatment strategies for a tight glycaemic control.[3] In fact, hypoglycaemia is the limitation to the success of such a strategy.[4, 5] Fear of hypoglycaemia may also lead to the deterioration of glycaemic control and is a cause of clinical inertia. Strategies to mitigate the risk of hypoglycaemia are therefore of importance, and such strategies should include both increased awareness of the condition, education of patients, relatives and healthcare providers as well as selecting glucose-lowering medications which carry a low risk of hypoglycaemia.

Definition of Hypoglycaemia

The American Diabetes Association defines hypoglycaemia as when plasma glucose is ≤3.9 mmol/l.[6] Most patients feel the symptoms of hypoglycaemia when glucose is <≈ 3.4-3.6 mmol/l, because in this range the glucose counter-regulation is initiated.[7] In clinical trials, 3.1 mmol/l is commonly used as criterion for hypoglycaemia. Hypoglycaemia is subdivided into grade 1 hypoglycaemia (mild hypoglycaemia), an event which is self-treated by the patient, and grade 2 (severe) hypoglycaemia, in which the patient requires the assistance of another person.[8]

Causes and Risk Factors for Hypoglycaemia

The most common cause for hypoglycaemia is glucose-lowering medication, which increases circulating insulin in a glucose-independent manner, as is performed by sulfonylureas and exiogenous insulin therapy.[9] Several other factors, however, contribute to the risk for hypoglycaemia. Such factors include delayed or missed meal intake or the ingestion of smaller meal than planned, or a prolonged fasting period. Increased physical activity is also a risk factor for hypoglycaemia, because it increases insulin sensitivity. Other risk factors are delayed glucose counter-regulation, as for example by drug or alcohol consumption or concomitant medication with ACE inhibitors or beta-blockers. Some patient groups are particularly vulnerable for hypoglycaemia, such as elderly patients and patients with long duration of diabetes, renal dysfunction, hypoglycaemia unawareness and cognitive dysfunction.[10]

Consequences of Hypoglycaemia

Hypoglycaemia results in acute symptoms, such as tachycardia, shakiness, anxiety, irritability and hunger. These symptoms are mainly caused by the sympatho-adrenal glucose counter-regulatory response and initiated at glucose levels ≈3.4-3.6 mmol/l. More severe hypoglycaemia (usually <3.0 mmol/l) also creates neuroglycopenia, which causes problems in concentration, weakness and dizziness, headaches, confusion and sometimes blurred vision, slurred speech or seizure, loss of consciousness and coma.[10] Severe hypoglycaemia is also associated with increased mortality.[11]

An important consequence of hypoglycaemia is the fear of another hypoglycaemic event.[12] This may result in a reduced quality of life, particularly if the events are repeated.[10, 13, 14] Fear of hypoglycaemia may also diminish adherence to dietary and medication therapy, with a deterioration of glucose control as a consequence. For example, many patients who have experienced hypoglycaemia, and especially nocturnal hypoglycaemia, may have a desire to have a higher glucose at bed time. Fear of hypoglycaemia is also a cause of clinical inertia, i.e., the failure to advance therapy in patients who are not sufficiently controlled.[15]

Hypoglycaemia also results in defence eating, the so-called snack defence, to prevent hypoglycaemia, which in turn results in weight

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gain. This weight gain may worsen insulin resistance, which may further contribute to the deterioration of glucose control and the overall risk for macrovascular complications.

Besides these acute consequences, hypoglycaemia is also by itself an independent risk factor for macrovascular complications. This increased risk for cardiovascular diseases in patients who have experienced hypoglycaemia has several mechanistic causes. These causes include cardiovascular changes initiated by noradrenaline, which is locally released from sympathetic nerves during hypoglycaemia. This may increase heart rate and result in myocardial ischaemia and prolong the QT time on ECG. These are all proarrhythmic causes and may cause sudden death, angina and myocardial infarction.[16-18] Increased thrombotic tendency with decreased thrombolysis, endothelial dysfunction with reduced vasodilatation and inflammation due to cytokine release have also been reported in association with hypoglycaemia.[16] Another long-term risk is the development of cognitive dysfunction and dementia, which by themselves are also risk factors for hypoglycaemia.[19, 20] It is thus obvious that both in the short and long-term, hypoglycaemia has negative implications.

High Cost of Hypoglycaemia

Hypoglycaemia is associated with a high cost for the patient, the healthcare system and the society at large. This is due to the increased number of visits to the healthcare system after hypoglycaemic episodes, the cost for emergency care (ambulance, emergency wards, hospitalisation), an increased use of strips for glucose monitoring and the use of glucagon injections, low productivity and absence from work and accidents.[10, 21] Added to this may be the cost of diabetes complications due to the deterioration of glucose control and the increased risk of cardiovascular diseases, which may be a consequence of hypoglycaemia. The total cost is huge and health economic models should be developed to further study this.[10]

Mitigation of the Risk of Hypoglycaemia

Strategies to mitigate hypoglycaemia are important in the glucose-lowering therapeutic approach in type 2 diabetes. One important strategy is to increase the awareness of hypoglycaemic risk, and several risk factors exist which are of particular importance in the vulnerable patient groups. The education of patients, relatives and healthcare providers is also important in regard to symptoms and risk factors for hypoglycaemia. Indeed, educating people about the symptoms which are not always associated with hypoglycaemia, such as, for example, confusion in elderly subjects is particularly important. Education in the consequences of hypoglycaemia is also essential and should include teaching that weight gain, deterioration of glycaemic control and increased risk for cardiovascular diseases are consequences of hypoglycaemia and that a fear of hypoglycaemia may underlie clinical inertia. A third strategy to mitigate the risk of hypoglycaemia is to consider the risk of hypoglycaemia and its complications when selecting the optimal glucose-medication for each individual patient.

Glucose-lowering Medication and Risk of Hypoglyacemia

Metformin

First-line pharmacological glucose-lowering therapy in most guidelines is metformin, which carries a low risk of hypoglycaemia. For example, in the UKPDS study, it was shown that the incidence of hypoglycaemia in patients treated with metformin was 0.3% per year.[22] Therefore, as a pharmacological monotherapy, metformin is a good choice from the perspective of hypoglycaemia risk. Since metformin increases the insulin sensitivity, however, it may be associated with hypoglycaemia when used in combination with agencies that increase the absolute insulin levels, such as sulfonylurea or exogenous insulin.

Sulfonylurea

In patients in whom metformin as monotherapy is insufficient to adequately reduce glycaemia, a common add-on is with a sulfonylureas. They have been shown to have good glucose-lowering ability, but they are associated with an increased risk of hypoglycaemia. There are two mechanistic reasons for the increased risk of hypoglycaemia associated with sulfonylureas. One such mechanism is the glucose-independent stimulation of insulin secretion.[23] This also leads to hyperinsulinaemia when glucose levels are low, which increases the risk for and the duration of hypoglycaemia. Another mechanism, which is important for older sulfonylureas like glibenclamide, is that these sulfonylureas diminish the glucagon counter-regulation to hypoglycaemia.[24] This aggravates a hypoglycaemia episode. The exact hypoglycaemic risk with sulfonylureas has been difficult to establish because it is different in different studies. In the UKPDS study, patients who were treated with sulfonylurea had a risk for mild hypoglycaemia of 20% per year and of severe hypoglycaemia of 1-2% per year.[22] Yet another study showed an annual risk of severe hypoglycaemia in patients treated with sulfonylurea of ≈0.8%.[25] Furthermore, another study reported that hypoglycaemia occurred in 16% of patients with type 2 diabetes treated with sulfonylureas over a mean period of 7 months[26] and The UK Hypoglycaemia Study Group reported that 39% of patients with type 2 diabetic treated with sulfonylurea had hypoglycaemia during a 8-10 months study period.[1] Severe hypoglycaemia due to sulfonylurea also carries a ≈9% risk for mortality as shown in one study.[11] What is important from a clinical point of view is that the risk of hypoglycaemia is different with different sulfonylureas. Thus, the newest types of sulfonylureas (gliclazide, glimepiride and glipizide) have a lower risk of hypoglycaemia than the first and second generations of sulfonylureas (tolbutamide, glibenclamide).[27, 28]

Thiazolidinediones

Thiazolidinediones have been used as a second- or third-line therapy since the end of the 1990s; their main mechanism is to increase insulin sensitivity in muscles, adipose tissue and the liver.[29] The risk for

hypoglycaemia during treatment with thiazolidinediones is similar as for metformin and lower than for sulfonylureas. For example, in the ADOPT study, treatment with rosiglitazone, metformin and glibenclamide as monotherapy was compared over a four-year study period, and it was found that hypoglycaemia occurred in ≈10% of patients on rosiglitazone, ≈12% of patients on metformin and ≈39% of patients on glibenclamide.[30]

Alpha Glucosidase Inhibitors

Alpha glucosidase-inhibitors reduce glucose by inhibiting the glucose uptake into the circulation after meal ingestion. They are used either as monotherapy or as add-on to metformin. Since they do not increase insulin levels, their risk for hypoglycaemia is low.[31]

Incretins

Incretin therapy is based on the glucose-lowering action of the gut incretin hormone glucagon-like peptide-1 (GLP-1) and is used either as injectable agonists activating the GLP-1 receptor[32] or as oral tablets inhibiting dipeptidyl peptidase-4 (DPP-4) which is the enzyme that inactivates GLP-1.[33] Both GLP-1 receptor agonists and DPP-4 inhibitors have a low risk for hypoglycaemia which in many studies is the same as after placebo treatment. This has been demonstrated when incretin therapy is added to metformin[34-40] or to insulin.[41-46] The low hypoglycaemia risk with incretin therapy is explained by the glucose-dependent mechanism of GLP-1 to stimulate insulin secretion[47] and that GLP-1 or DPP-4 inhibition does not compromise the glucagon counter-regulation to hypoglycaemia.[48-50]

Insulin

Insulin treatment may be carefully targeted to avoid hypoglycaemia,[51] but in general, insulin therapy carries a risk of hypoglycaemia in type 2 diabetes. It has, for example, been shown that 7% of insulin treated patients require emergency treatment due to severe hypoglycaemia every year[52] and that 15% of insulin-treated patients with type 2 diabetes experienced severe hypoglycaemia every year.[53] The UK Hypoglycaemia Study Group study showed that the annual incidence of hypoglycaemia was 51% in patients who had been treated with insulin less than 2 years and 64% in patients who had been treated with insulin for more than 5 years.[1] It should be emphasised, however, that long-acting insulin analogues have a lower risk for hypoglycaemia than medium-acting NPH insulin.[54]

Conclusions

Hypoglycaemia is common in type 2 diabetes. It has negative consequences for both the daily life and the well-being of the patients, for the glycaemic control of diabetes and for long-term risk of complications. It also carries a high cost for the patient, the healthcare system and the society at large. Strategies to mitigate hypoglycaemia involve increased awareness of hypoglycaemia, education of patients, relatives and healthcare providers, and consider relative risk of hypoglycaemia for different glucose-lowering medication when selecting the glucose-lowering therapy for the individual patient.

Disclosure

The author has received honoraria for lecturing and membership in advisory board for Astra Zeneca, Bristol Myers Squibb, GSK, Lilly, Novartis, Novo Nordisk, Merck, and Sanofi, which all are companies producing GLP-1 receptor agonists or DPP-4 inhibitors.

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Further Reading

Please see the abstracts below for further reading on diabetes management and patient empowerment. These articles plus others are available in previous editions of *Treatment Strategies - Diabetes*. Please see our website for more articles on diabetes management and patient empowerment and a range of other topics within diabetes.

Incretins in the Management of Diabetes

Santosh H Shankarnarayan and **Jiten P Vora**
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Recent evidence from large, long-term, multicentric trials has provoked a considerable debate regarding how intensively one should treat hyperglycaemia. The addition of newer agents to the armoury of anti diabetic agents has provided more options to achieve the intended glycaemic goals. The data from prospective epidemiologic studies have shown that the incidence of many of the micro and macrovascular complications are directly associated with the degree of hyperglycaemia. An increase in the HbA1c by 1% is associated with an 18% increase in the risk of cardiovascular events, (1) an increase of 12 -14% in the risk of death and an increase of 37% in the risk of retinopathy or renal failure, (2) (3) demonstrating that the glycaemic control is fundamental to the management of diabetes. The DCCT-EDIC and the follow up of the UKPDS cohort have shown that early intensive glycaemic control has beneficial effects, even when the glycaemic separation between the intensive and standard cohorts are lost during the follow up period, referred to as the glycaemic memory or the legacy effect. This article explores the use of incretins in the management of diabetes and the way in which they work in great depth.

Patient Empowerment in Diabetes: Time for Returning Back to Basics?

Koula Asimakopoulou, Sasha Scambler and Dave Gilbert
Senior Lecturer in Health Psychology, King's College London, Dental Institute, Oral Health Services Research and Dental Public Health

Patient empowerment is currently a very popular concept, both in the clinic and in research. An electronic search that we carried out, in July, 2010, on Scopus (the online register of published research), yielded 17,102 published papers which included the term 'empowerment' in the title, abstract or keywords. Of these, at least 353 publications were about empowerment in diabetes and included the terms 'diabetes' and 'empowerment' in their title, abstract or keywords. What is more, one frequently hears healthcare professionals (HCPs) talk anecdotally about 'being empowering', 'empowering their patients', or following empowerment-inspired ideas and practice. There can be no doubt, then, that empowerment is a 'hot' topic in research, but for that research to be goal-directed and well co-ordinated, there should be a widespread concordance about what the term means and encompasses. As we shall outline in this article, that might not presently be the case. We takes a look at the concept of patient empowerment, and how this translates into clinical practice.

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Upcoming Congresses and Meetings

World Diabetes Congress

02 - 06 December 2013

Melbourne, Australia

The International Diabetes Federation is the global voice for people with diabetes, as well as those that are at risk of the disease. Today, more than a third of all people with diabetes are found in the Western Pacific Region, which is why the Congress has returned to the area via Melbourne. This congress provides the opportunity to network with over 400 speakers, 12,000 delegates and more than 200 IDF Member Associations from over 160 countries. Attendees will have the choice over 1000 posters and over 275 hours of scientific sessions, and will be able to follow 7 distinctive programme streams. These include brand new sessions on 'Diabetes Research in the 20th Century' and 'Diabetes Research in Indigenous People'.

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

05 - 08 February 2014

Vienna, Austria

Filling a unique niche, this conference attracts an international audience made up of researchers, clinicians and developers from the medical technology industry. ATTD 2014 will build upon the successes of previous years and will preset the latest technological advances in the treatment of diabetes and its related conditions. Valuable networking opportunities stand alongside unparalleled access to unique scientific knowledge, making it one of the most exciting events in the calendar.

Diabetes UK Professional Conference

05 - 07 March 2014

Liverpool, UK

The Diabetes UK Professional Conference is the only event of its kind in the UK run exclusively for healthcare professionals and scientists working in the field of diabetes. It is one of the largest healthcare conferences in the UK, and provides delegates with the opportunity to discover more about the latest research, hear from a range of inspiring, renowned speakers and share best practice. The theme for the 2014 conference is 'Cell Science to Self Care: Getting it Right', and the programme will feature plenary sessions on the diabetic heart, a full-day paediatrics track, sessions on multi-organ transplantation as well as symposia and oral sessions.

16th World Congress of Gynecological Endocrinology

05 - 08 March 2014

Florence, Italy

The 16th World Congress Gynecological Endocrinology (ISGE) is the main meeting of the members and friends of the ISGE. Throughout the years it has evolved into an event of unrivalled scientific relevance. The congress will offer an unprecedented number of chances for scientific and professional advancement for participants. The traditional International Faculty will be embodied by the top leaders in the area of gynaecological and reproductive endocrinology and will provide that unique flair of science and practice that is the trademark of this congress.

12th International Congress on Obesity (ICO)

17 - 20 March 2014

Kuala Lumpur, Malaysia

The 12th ICO Congress is being jointly held by the International Association for the Study of Obesity (IASO) and the Malaysian Association for the Study of Obesity (MASO), and is open to all healthcare professionals working in the field of obesity and related disorders. The eight track scientific programme will provide delegates with the unique opportunity to share their experiences and expertise, enhance their knowledge and discover practical solutions which can then be used in real life situations.

Society for Endocrinology BES 2014 Meeting

24 - 27 March 2014

Liverpool, UK

The Society for Endocrinology BES 2014 Meeting is an established event within the field of endocrinology, and 2014's programme features 9 plenary lectures and 12 symposia, at which leading international experts will impart their knowledge and expertise. These sessions will cover a number of translational topics, and will be focussed towards both clinicians and basic scientists. Other sessions will include workshops, oral and poster sessions and meet-the-expert sessions. Two key sessions will also be held for nurses, while both young endocrinologists and senior endocrinologists will each benefit from dedicated symposia.

16th European Congress of Endocrinology

03 - 07 May 2014

Wrocław, Poland

The European Society of Endocrinology promotes research, education and clinical practice in endocrinology through the

organisation of conferences and training courses. This prestigious congress will offer attendees an insight into the latest advances in endocrinology through participation in lectures and workshops, which will be presented by a group of distinguished, international speakers. The congress also offers delegates the opportunity to meet and network with professionals from across the globe. Topical and relevant issues will be heavily featured, making it a valuable congress for endocrinologists.

13th International Primary Care Diabetes Europe Conference

23 - 24 May 2014

Barcelona, Spain

Primary Care Diabetes Europe (PCDE) aims to promote high standards of care for people living with diabetes throughout Europe, with emphasis placed upon incorporating evidence-based medicine into daily practice as well as the promotion of diabetes education and research in primary care. The theme of the conference is 'Diabetes Education in Multi-morbidity and Hypoglycaemic Management', and will feature a broad range of topics within this area which will be relevant for all healthcare practitioners. The scientific programme will feature keynote lectures, state of the art sessions and workshops from international experts addressing topics such as drugs and hypoglycaemia, self-monitoring blood glucose, communications skills, the influence of E-media and social networks as well as multifaceted management. Additionally, in a special "rising star session" a young promising researcher will have the opportunity to present his work, while the 5th "Paul Cromme lecture" will honour a European primary care celebrity, active in the diabetes field.

ICE/ENDO 2014

21 - 24 June 2014

Chicago, USA

ICE/ENDO 2014 is the joint meeting of the International Society of Endocrinology and The Endocrine Society. The world's largest endocrinology meeting, ICE/ENDO 2014 will feature a programme which will benefit both the clinician and the researcher. This will include pre-meeting workshops, plenary sessions, meet-the-professor sessions and oral and poster abstracts. Awards will also be given in science, leadership, teaching and service.

AADE14

06 - 09 August 2014

Orlando, Florida

The AAD Annual Meeting and Exhibition is a fantastic event which delivers all of the tools, resources and connections that attendees will need to help their patients. The meeting provides attendees with comprehensive updates in the latest treatment strategies for diabetes management through a series of keynote addresses and sessions, workshops and special courses. Delegates will also be able to learn about many new and innovative products in around 300 exhibits and company stands, and there will be many opportunities to network and make new contacts from around the globe.

Join us for:

World Diabetes Day:
Wednesday 13 November

Breakfast Debate: Access to Medicines and Medical Devices for diabetes care in Europe

08.15 to 9.15, Members' Salon, EP, Brussels - RSVP to Lala@idf-europe.org by 4 November 2013

Award ceremony of the 2013 IDF Europe Prizes in Diabetes & Cocktail

Join us for the award ceremony of the IDF Europe Prizes in Diabetes and enjoy refreshing fruit and vegetable cocktails at our stand.

15.00 to 16.30, ASP 0 Zone D-E (Escalator Area)

All day - Blood Glucose Testing

ASP 0 Zone D-E (Escalator Area)

All week:
Monday 11 to Friday 15 November

World Diabetes Week Lunch

Choose our vitality dish on offer all week at the canteen of the European Parliament in Brussels and Luxembourg. Our vitality dishes will also be on offer at the canteen of the European Parliament in Strasbourg from 18 to 22 November.

Get active with our special sports sessions at the European Parliament Sports Centre

Get active with free trial cards and special sports session at the EP Sports Centre in Brussels. For more information and to register, contact the Sports Centre at 02/284.10.85 or epsportscentre@ext.europarl.europa.eu

Diabetes Exhibition

Learn about diabetes and the importance of a healthy diet and physical activity for diabetes management and prevention.

ASP 0 Zone D-E (Escalator Area)

FEND 2014

12 - 13 September 2014

Vienna, Austria

The Foundation of European Nurses in Diabetes (FEND) is an organisation which provides a unique voice for nurses working in the field of diabetes care, research and education in Europe. FEND is also a founding member of the European Coalition in Diabetes (ECD). This two day annual conference takes place before the EASD conference every year, and attracts both nurses and other healthcare professionals. Leading European diabetes experts will deliver informative keynote lectures, which will be accompanied by oral presentations, symposia and masterclasses.

50th EASD Annual Meeting

15 - 19 September 2014

Vienna, Austria

The European Association for the Study of Diabetes (EASD) is one of the leading European conferences on diabetes, which brings together physicians, scientists, nurses, laboratory workers and students involved in fighting the diabetes epidemic. The meeting is dedicated to the exploration of diabetes and metabolism issues, and will offer a number of exciting insights into the most cutting-edge and innovative developments in the field.

53rd Annual ESPE Meeting

18 - 20 September 2014

Dublin, Ireland

The theme of the 53rd Annual ESPE Meeting is "Prevention and Therapeutic Innovations in Paediatric Endocrinology' and the meeting will focus on creating an interactive environment in which high quality clinical information and basic science will be explored. Delegetes will be treated to a number of plenary sessions, symposia, meet-the-experts, free communications and poster sessions, hosted by international experts. The European Society for Paediatric Endocrinology is an international organisation which aims to promote the highest levels of knowledge, research, education and clinical practice and indeed, the meeting is the perfect way in which to achieve this.

42nd Meeting of the British Society for Paediatric Endocrinology and Diabetes

12 - 14 November 2014

Winchester, UK

The British Society for Paediatric Endocrinology and Diabetes (BSPED) aims to improve the care of young people with endocrine disorders and diabetes mellitus by bringing together professionals from a range of disciplines including tertiary paediatric endocrinologists and diabetologists, general paediatricians and researchers amongst others. The society promotes research and training by encouraging collaboration and open dialogue. The meeting of the BSPED is one of the UK's most anticipated events, and will feature a range of sessions including symposia events, poster sessions, and oral communication sessions, as well as many social events and opportunities to network with other healthcare professionals. The 42nd meeting of BSPED is not to be missed.

Further Reading

Please see the abstracts below for further reading on treatment and therapeutic strategies. These articles plus others are available in previous editions of *Treatment Strategies - Diabetes*. Please see our website for more articles on treatment and therapeutic strategies and a range of other topics within diabetes.

Future Treatments for Type 2 Diabetes

Andrew J. Krentz and **Marcus Hompesch**
Profil Institue for Clinical Research, California

The rapidly rising numbers of people with obesity-associated Type 2 diabetes presents major challenges to public health authorities and clinicians. The limited range of pharmacological interventions hampers the management of Type 2 diabetes, a highly complex and heterogeneous metabolic disorder. While recent insights into the pathophysiology of the disorder have led to the development of novel pharmacologic approaches the goal of safe restoration of normal metabolism remains elusive. The need for new agents that maximise metabolic benefits while minimising unwanted effects has led to an explosion of scientific activity. This raises the prospect of greater individualisation of therapy, an important tenet in modern diabetes care.

By definition, therapies for diabetes must lower blood glucose effectively. Non-glucose actions of certain drugs, such as metformin, are well documented. The impact of new drugs on other aspects of metabolism and on vascular function has become an issue of great interest. However, it has become abundantly clear that beneficial metabolic effects do not invariably guarantee improved clinical outcomes. In this article, the authors review the main classes of glucose-lowering drugs in development for Type 2 diabetes.

Incretin Therapies in Type 2 Diabetes: The Liver Takes a Bow

Susan L. Samson
Diabetes and Endocrinology Research Center, Baylor College of Medicine, St. Luke's Episcopal Hospital and Ben Taub General Hospital, Houston

The incretin hormones, Glucagon-like peptide-1 (GLP-1) and Glucose-dependent insulinotropic polypeptide (GIP), are secreted from specialised intestinal cells in response to a meal. Both contribute to the historical observation of the "incretin effect", whereby insulin secretion is stimulated to higher levels with oral glucose compared to parenteral delivery when equivalent serum glucose levels are achieved. This ability to augment insulin secretion from the pancreatic β-cell in a glucose-dependent manner has led to great efforts to develop incretin-based therapies for Type 2 diabetes. The β-cell response to GIP is disappointingly dampened in patients with Type 2 diabetes, but pharmacologic levels of GLP-1 can improve defects in first phase and late phase insulin release from the islet 3-5. As a bonus, other well known effects of GLP-1 are slowed gastric emptying and appetite reduction, which is desirable in a patient population that usually is overweight or obese. Therefore, much attention has been focused on harnessing the actions of GLP-1 for treatment of Type 2 diabetes while avoiding the rapid degradation which occurs within minutes of secretion by the ubiquitous dipeptidyl peptidase IV (DPPIV). This article takes an in-depth look at incretin therapies in Type 2 diabetes.

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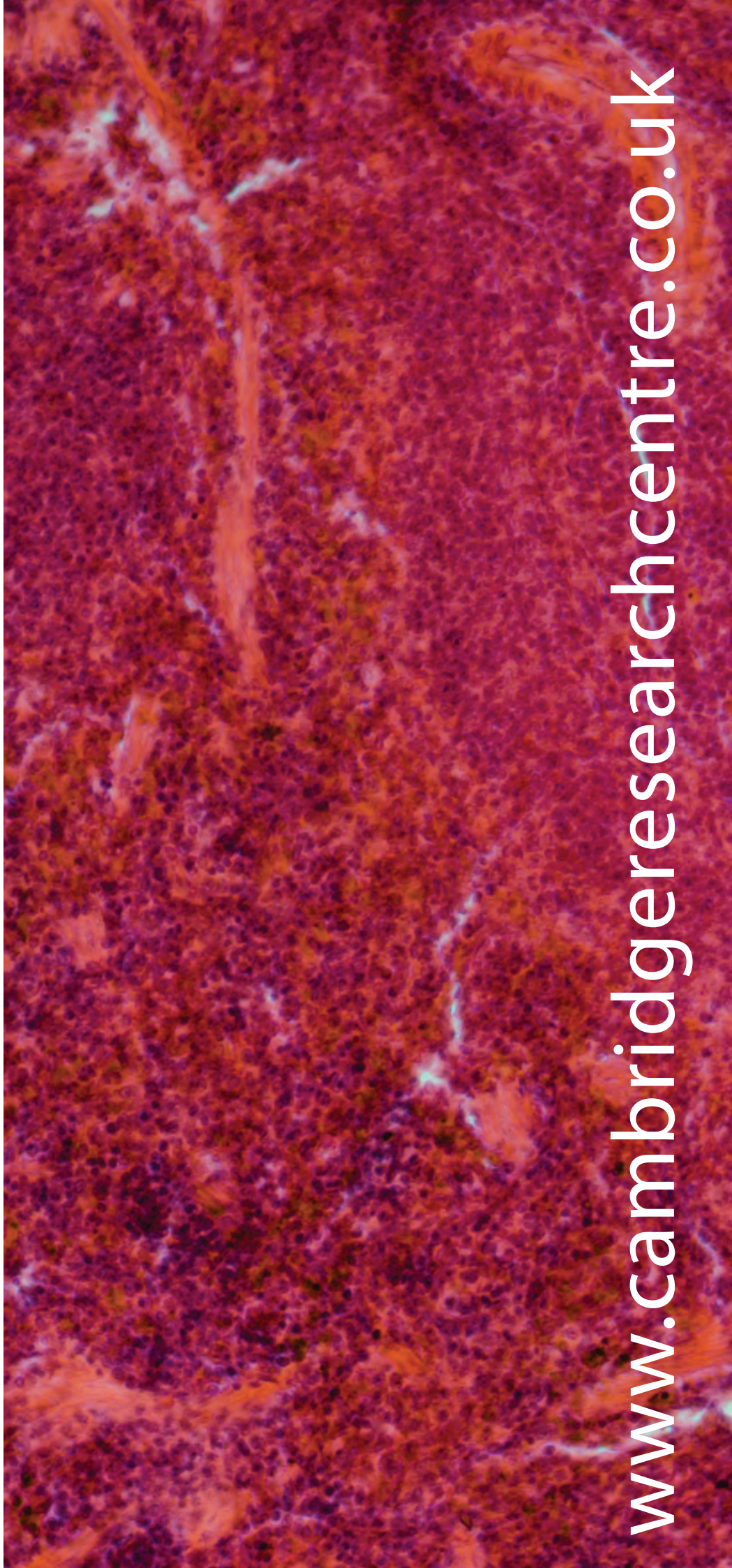

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