TREATMENT STRATEGIES
DIABETES

Volume 4 Issue 2

- Diabetes and the Brain
- Diabetes and Cancer
- Diabetic Foot Syndrome
- Diabetic Ketoacidosis
- Gynaecological Endocrinology
- Psychological Aspects of Diabetes
- Type 1 Diabetes

Articles include:

Discovering Buried Treasure: Ketone Testing Past and Present

Hyperglycaemia and Stroke – Implications for Prevention and Treatment

Recognising and Addressing Psychological Problems in People with Diabetes – The Relevance of Minor Depression and Diabetes-related Distress

The Diabetic Foot - An Approach to Pathophysiology, Diagnostics and Treatment

Cardiac Morphology and Function in Type 1 Diabetic Patients with Successful Pancreas Transplant Alone

EASD 2012 Berlin 1–5 October 2012

Includes a review of the 48th Annual Meeting of the EASD

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TREATMENT STRATEGIES DIABETES

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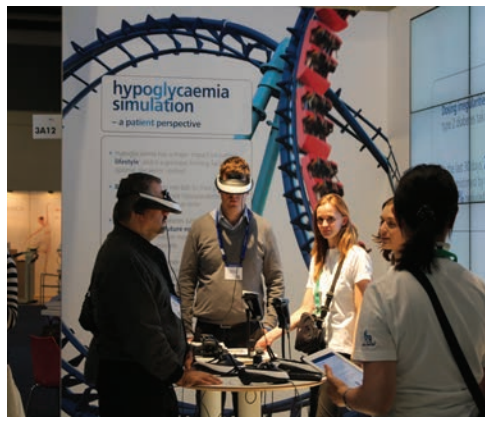
Welcome...



I am delighted to welcome you to the fourth volume of *Treatment Strategies – Diabetes*. This issue includes an independent review of the 48th Annual Meeting of the EASD. Following on from three successful years, I am excited to invite you back to the 2012 edition which will once again address the key topical areas in the field of diabetes and features an informative collection of articles from esteemed diabetologists.

Within this issue we aim to cover the key issues discussed at the 48th Annual Meeting of the EASD. This includes topics such as diabetes and the brain, diabetes and cancer, diabetic foot treatments, diabetic ketoacidosis, the psychological aspects of diabetes and type 1 diabetes.

With an attendance of over 17,000 delegates from over 127 different countries worldwide, the congress provided an educational epicentre, where attendees can witness the most cutting-edge research towards treating, preventing and curing diabetes. The EASD Annual Meeting has become an unmissable event for discovering the latest advances in the field of diabetes and we hope this comes across in our extensive review.

We hope that you find the information within *Treatment Strategies - Diabetes* beneficial and valuable. We aim to act as a forum in which to present the constantly evolving and developing findings from the field of diabetes. It would be most helpful if you would provide us with any feedback or comments you may have. By working with these opinions we will ensure that the *Treatment Strategies Series* will become one of the most useful publications in healthcare.

We are looking forward to meeting you next year in Barcelona 49th Annual Meeting of the EASD.

Nigel Lloyd, Editorial Director

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

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Foreword

Angus Forbes
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Diabetes is one of the most important global disease of the 21st century affecting over 300 million people globally. Diabetes is a complex metabolic disorder related to multiple end-organ damage, with associated complications such as blindeness, kidney failure, amputation, cardio vascular disease and stroke. Whilst there have been some significant advances in diabetes management over recent decades, there remains a number of important challenges that must be overcome, these include: how to address the preventable causes of diabetes; how to minimise patient risk in developing complications; and how to support patients in adjusting to diabetes and their adoption of protective self-management strategies. The papers presented within this edition of *Treatment Strategies* address many of these important challenges.

In examining the relationship between stroke and hyper glycaemia Dr. Mankovsky has illustrated that in preventing this important complication we need to look beyond tight glycaemic control. He has also highlighted that hyperglycaemia is important following the initial cerebral assault with increased 30 day mortality, extended hospitalisation and impact on the effect of anti-coagulation. In addition Dr. Mankovsky gives a very detailed overview of current research into glycaemic control post-stroke and highlights the importance of avoiding hypoglycaemia.

Patients with diabetes have a 17 fold increased risk of lower limb amputation compared to the general population, with a catastrophic affect on the patient's quality of life and well being. Drs Rathsman and Nyström provide a very comprehensive account of the pathlogogical pathway for foot complications, tackling the neurological and ischaemic components of the complication. They then apply this perspective to clinical assessment and management, emphasising the multiple pathways for therapeutic intervention and the importance of the multidisciplinary team.

In the paper of Dr Piaggesi we are presented with evidence to suggest that earlier revascularistion can help prevent further tissue damage in diabetic foot complications. This paper also shows the importance of integrating approaches both locally and systemically and through the application of surgical and medical management.

In a paper from Dr. Rosati and colleagues we have an interesting account of cardiomyopathy in T1DM and how this may contribute to increased mortality and morbidity in T1 population. They then present some emerging evidence from their own centre, to suggest that pancreatic transplantation may have a beneficial impact on ventricular cardiovascular health.

An often under managed area of diabetes is psychological well-being. Drs Pibernik-Okanovic and Ajdukovic demonstrate that sub-clinical depression and diabetes specific distress are both common and have a significant impact on self-management behaviour and metabolic outcomes. They go on to outline some of the treatment approaches to these problems and highlight that while there is limited evidence for treating depression with anti-depressants, psychological therapies, both individual and group based, show some promise in tackling these problems.

Diabetic ketoacidosis (DKA) is a common acute complication of diabetes. DKA carries an elevated mortality risk that requires rapid assessment and treatment. Dr. Foreback presents an overview of the mechanisms for ketosis and advocates the benefits of blood testing for a specific ketone body (3-β-Hydroxybutyrate).

Overall this collection of papers provides some informative perspectives on diabetes complications and their management. Common to all these papers is the need to understand, detect and treat diabetes complications effectively to protect patients from loss of function and both quality and quantity of life.

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EASD 2012 Annual Meeting Review

01 - 05 October 2012 - Berlin

48th Annual Meeting of the European Association for the Study of Diabetes

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Lauran Elsden, *Treatment Strategies*, takes a look over a number of key sessions, as well as spotlighting several stands and products being demonstrated at the exhibition. We then follow with papers and reviews which give a brief insight from a number of sessions highlighting findings that will have direct repercussions on clinical practise that are still very much being discussed.

The Annual Meeting of EASD has become the world's leading international forum for diabetes research, not only for individual scientists, but also for the pharmaceutical industry worldwide. The EASD Annual Meeting promises to offer exciting insights into the most recent research findings in all aspects of diabetology. After last year's Meeting in Lisbon, an event that saw over 17,000 attendees from 127 countries, this year's event proved to follow in a highly successful fashion.

The European Association for the Study of Diabetes' (EASD) 48th Annual Meeting, attracted a diverse audience of thousands of scientists, physicians, laboratory workers, nurses and students from around the world. The EASD, while inviting abstracts from members and non-members alike, utilises a strict selection process in which submissions are anonymously reviewed by the Programme Committee, to ensure that

***Introduction** continues on page 10*

EASD was hosted in Berlin Exhibition Grounds.

continued from page 9

year after year this congress is host to the highest quality science.

The Scientific Programme Committee this year selected 1,270 abstracts for presentation from a total of 2,307 that were submitted. The programme is made up of six parallel tracks which include inspiring symposia, keynote lectures and insightful debates, covering both basic and clinical science and providing an extensive scientific programme, which reflects the ongoing efforts to understand, cure and prevent diabetes.

The EASD Annual Meeting also affords a wonderful meeting place for the interchanging of thought and opinions. It is the forum for the promotion of diabetology. It is the perfect opportunity to impart news and views, to communicate information and to hear about colleagues' research work. Andrew J.M. Boulton welcomed delegates to the meeting stating "What better way to catch up with old friends, make new ones and go home with the feeling of having achieved something."

The chosen location of this year's EASD Meeting was Germany's capital city, Berlin.

Berlin, which is the seat of government in Germany, is located in the East of the country and is a world city of culture, politics, media and science.

After World War II Germany and also Berlin had been divided and still today you can find remains of the Berlin Wall kept as an international memorial for freedom – the East Side Gallery. Due to the history, the vibrant city of Berlin does not present a traditional city core, but various city centres within the different districts. That way the city emerged as a multicultural, always changing, exciting place to be.

" Through your participation, interest and commitment you can further the progress of diabetes research and contribute to the success of the 48th EASD Annual Meeting. "

Andrew J.M. Boulton, EASD Preseident

Berlin is one of the most popular cities worldwide and has many places of interest to offer: the Berlin Cathedral, the Television Tower, the Government District with the Reichstag (German Parliament Building) and a rich cultural program with plenty of theatres and museums, with the Museum Island as the highlight. The island is part of the world cultural heritage and one of Berlin's favourite places.

The 48th EASD Annual Meeting took place on the recently constructed southern section of the Berlin Exhibition Grounds, centrally located and very easily accessed in the western city quarter of Berlin. The German architect Oswald Mathias Ungers, winner of numerous honours and awards, was responsible for this trade fair and conference building complex.

Above all with his design of the impressive and transparent entrance structure covering 3,000 m^2 he left his mark in spectacular manner. Comprising a total of 20 halls of various sizes, with mobile partitioning and a modern technical infrastructure, the southern section of the Berlin Exhibition Grounds is a venue for all kinds of events.

The Berlin Messe has been organising large-scale, world-class congresses for more than 30 years, an achievement which in 2010 earned it the IAPCO EXCELLENCE AWARD.

The Annual Meeting proved to be rewarding with the opportunity to gain interesting contacts and a chance to visit (or revisit) a hospitable and attractive city.

JDRF Showcase Spectrum of Prominent Research at European Diabetes Conference

More than 30 abstracts of JDRF-funded research presented at the Annual International Meeting

JDRF, the world's leader in setting the agenda of type 1 diabetes (T1D) research, joined researchers from around the globe at the annual meeting of the European Association for the Study of Diabetes (EASD).

JDRF, which currently provides more than $100 million annually for research in as many as 18 different countries, is a key funder of more than 30 studies that were presented during the five-day event. The research covered topics including new tools for studying and treating T1D, prevention of the disease, and protecting and regenerating the insulin-producing beta cells in the pancreas.

"We're looking forward to joining leaders in diabetes research at this year's EASD," says JDRF's chief scientific officer, Dr. Richard Insel, who attended the meetings. "The JDRF-funded studies presented show the breadth of our work across the spectrum of type 1 diabetes research as we seek to cure, better treat, and prevent this disease."

Highlights of this year's conference include:

• **Beta cell imaging** - Two studies, performed by teams in Denmark and Sweden, looked at techniques for visualising the insulin-producing beta cells still in the body. Such capabilities, if perfected, would enable scientists to see and better understand how the cells are affected by the autoimmune response, contributing to efforts to halt their destruction and promote cell regeneration. The studies were led by researchers at Uppsala University in Sweden and The Bartholin Institute in Copenhagen.

• **Immune therapies** - Researchers representing multiple academic institutions will present their latest data on different therapeutic attempts to preserve the function of beta cells in people who have been recently diagnosed with T1D. Each of the three studies utilised different therapeutic agents, including the anti-CD3 agent teplizumab, developed by Macrogenics and tested by a team led by Dr. Kevan Herold of Yale University.

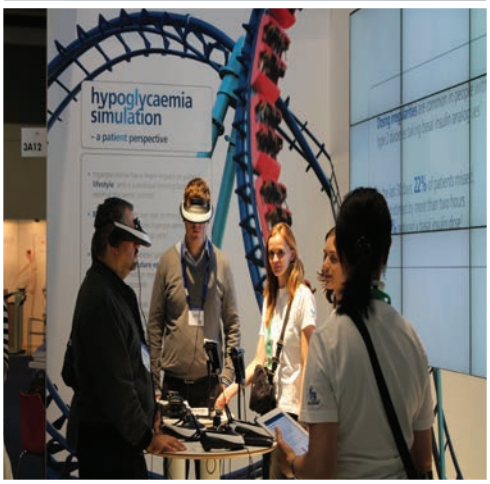
• **Biomarkers** - A team of JDRF-funded researchers from the Institute of Bioinformatics and Systems Biology in Munich, led by Dr. Gabi Kastenmuller, will present findings looking at metabolic signatures associated with autoantibodies in an attempt to determine whether the presence of the signatures could indicate an elevated risk for T1D. Accurate biomarkers would enable scientists to more precisely target patients for clinical trials as well as measure any potential therapeutic benefits.

In addition to the research presentations and two workshops being led by JDRF researchers, the organisation announced a partnership the with the Danish Diabetes Academy, a new program to develop the diabetes research infrastructure in Denmark that is supported by the Novo Nordisk Foundation.

For more information, please visit
www.jdrf.org

EASd saw showcased a variety of interactive presentations and events.

Study Shows EndoBarrier® Therapy Offers Improved and Sustained Glycaemic Control in People with Type 2 Diabetes Who Are Overweight



GI Dynamics announced data demonstrating that EndoBarrier® Therapy leads to improved glycaemic control in overweight and obese patients with type 2 diabetes due to improved insulin sensitivity observed early in the treatment period and sustained over one year. The study findings, which were presented by Dimitri Pournaras, of the Imperial Weight Centre, Imperial College London, during the 48th Annual Meeting of the European Association for the Study of Diabetes (EASD), provide further evidence of the impact EndoBarrier® Therapy may have on people living with type 2 diabetes who may be overweight, but not necessarily obese.

"These results further demonstrate the effects and improvements EndoBarrier® Therapy offers to patients with type 2 diabetes in gaining and maintaining glycaemic control," offered Ricardo Cohen, lead study investigator, Hospital Oswaldo Cruz, Sao Paulo, Brazil. "We found that EndoBarrier® Therapy improves HbA1c early in the treatment period. Our research also reinforced the effects of EndoBarrier® Therapy on insulin sensitivity and glucose metabolism, similar to that of gastric bypass, but without surgery or permanent alterations to the anatomy. These findings support EndoBarrier® Therapy as a viable treatment for overweight and obese patients with type 2 diabetes."

These data were discussed in an oral presentation titled, "Glycaemic control after endoscopically placed duodenal-jejunal bypass liner in patients with type 2 diabetes and body mass index between 23 and 36 kg/m^2." In this study, 16 patients with type 2 diabetes and a body mass index (BMI) < 35kg/m^2 (average=30.8 kg/m^2) were implanted with EndoBarrier® for one year to evaluate its effects on insulin sensitivity and glucose control. Key treatment results included:

- Significant improvement in insulin sensitivity from baseline ($p<0.001$)
- Significant reduction in HbA1c at one year; 8.6% at baseline to 7.5% ($p<0.001$)

"Clinical research and real-world experience demonstrate the benefits of EndoBarrier® Therapy as a successful treatment for people with type 2 diabetes who are overweight as well as those who are obese," stated Stuart A. Randle, president and chief executive officer of GI Dynamics. "EASD is the leading forum for the European diabetes community and we are very pleased to be able to share these data with endocrinologists from around the world. We look forward to continuing to educate and expand awareness about EndoBarrier® Therapy as an effective non-surgical, non-pharmaceutical treatment option for overweight and obese patients with type 2 diabetes."

In addition to the data being highlighted above, GI Dynamics had a booth in space # 4A13 and hosted an educational series there throughout the week featuring presentations on EndoBarrier® Therapy for the treatment of type 2 diabetes.

EndoBarrier® Therapy is currently available in select countries in Europe, including Germany, Austria, the United Kingdom and the Netherlands, as well as Australia and Chile. In August, GI Dynamics also received conditional approval from the U.S. Food and Drug Administration to commence a pivotal clinical trial of EndoBarrier® in the United States for the treatment of patients who have uncontrolled type 2 diabetes and are obese.

For more information, please visit www.endobarrier.com

Timesulin Celebrates One Year Since Launch

Timesulin is a brand of Patients Pending Ltd, established in 2010 to create solutions that will alleviate daily issues faced by people living with chronic conditions. Timesulin, the first product from Patients Pending LTD, was created in 2011 based on the need of one of the co-founders, John Sjölund, who has been living with Type 1 diabetes since one week before his fourth birthday.

"Due to the habitual nature of insulin administration, patients often forget whether they had injected their insulin dose or not. We regard this as a major challenge in managing diabetes and welcome the timely arrival of an innovative solution like Timesulin."

Åke Sjöholm,
Professor of Experimental Endocrinology

Operating on a global scale, Timesulin aims to help anyone living with insulin-dependent diabetes avoid low or high blood sugar symptoms and lead a better, safer and more balanced life. The Timesulin 'smart cap' fits onto all major insulin pen brands and has a built-in timer to show how long it has been since the user administered the last insulin injection. Timesulin is produced in Germany and was launched to consumers in 2011 through a network of independent distributors, pharmacies and direct via the company's own web shop.

→ Timesulin enhances safety

According to a recent study by Novo Nordisk, 30% of all people living with diabetes have missed injections or taken accidental double doses. Failure to administer injections as prescribed can lead to hyperglycaemia or hypoglycaemia - both with potentially serious consequences. Timesulin helps to avoid this risk and raises the standard of care for all living with diabetes. We also have the backing of some of the world's leading doctors and nurses who have verified the importance of a product like Timesulin.

→ Timesulin works with existing insulin pens

Timesulin is the only solution on the market that works with the insulin pens that people with diabetes are already using. When someone has been prescribed a certain type of insulin pen and are comfortable using it, switching pens can be a huge hassle, requiring an extra visit to the doctor's office and learning a new system. And many active people living with diabetes simply prefer the convenience of pre-filled insulin pens.

→Timesulin is easy to use

We designed Timesulin to be super simple to use. With no instruction manual, nothing to program and no buttons to push, customers need only replace the cap on their insulin pen with a Timesulin cap and they will always have a reference of when their last injection was taken. The benefits of Timesulin for the patient are simple, immediate and clear with absolutely no change in the user's routine.

For additional information, please visit the website at www.timesulin.com

One of the many oral presentations given at this year's EASD Meeting

Investigational Insulin Degludec Shows 43% Lower Rates of Night-time Hypoglycaemia than Insulin Glargine

New data presented today at the Annual Meeting of the European Association for the Study of Diabetes (EASD) showed that patients with type 2 diabetes starting insulin therapy had a 43% lower rate of night-time hypoglycaemia* when using insulin degludec compared with those using insulin glargine (0.27 [insulin degludec] versus 0.46 [insulin glargine] episodes per patient per year, p<0.001) with equivalent improvements in glucose control**.[1]

In this 2-year (1 year initial and 1 year extension) phase 3a study, comparing the efficacy and safety of once-daily insulin degludec versus once-daily insulin glargine (both in combination with OADs), the rates of overall hypoglycaemia were similar between the two groups (1.72 [insulin degludec] versus 2.05 [insulin glargine] episodes per patient per year, p=NS). Furthermore, while the rates of severe hypoglycaemia were infrequent, they were significantly lower with insulin degludec compared with insulin glargine (0.01 [insulin degludec] versus 0.02 [insulin glargine] episodes per patient per year, p=0.02). This randomised, open-label, treat-to-target study included 1,030 patients with type 2 diabetes not previously treated with insulin, of which 659 completed 2 years of treatment.[1]

"The reduction in rates of nocturnal hypoglycaemia with insulin degludec will hopefully allay some of this concern and encourage patients and physicians to aim for more ambitious glucose targets", said Dr Helena Rodbard, lead author and medical director, Endocrine and Metabolic Consultants, Rockville, Maryland.

Lower Rates of Night-time Hypoglycaemia with Insulin Degludec versus Insulin Glargine Confirmed in a Meta-analysis of Phase 3a Trials, Also Presented at EASD

In a separate, prospectively planned meta-analysis also presented at EASD, patient level data from 4,330 patients in seven randomised, open-label, treat-to-target phase 3a trials of 26 or 52 weeks showed that insulin degludec significantly reduced the rate of night-time hypoglycaemia in adults with type 1 and type 2 diabetes, while obtaining equivalent improvements in glucose control, when compared with insulin glargine.[2]

Patients with type 2 diabetes who had not previously been treated with insulin showed the greatest reductions in night-time hypoglycaemia when using insulin degludec compared with insulin glargine:

· 36% (p<0.05) reduction in night-time hypoglycaemia with insulin degludec compared with insulin glargine (0.3, 0.2 and 0.8 episodes per patient per year with IDeg versus 0.4, 0.3 and 1.2 episodes per patient per year with IGlar for the trials 3579, 3672 and 3586 respectively).[2]

· 17% (p<0.05) reduction in overall hypoglycaemia with insulin degludec compared with insulin glargine (1.5, 1.2 and 3.0 episodes per patient per year with IDeg versus 1.8, 1.4 and 3.7 episodes per patient per year with IGlar for the trials 3579, 3672 and 3586 respectively).[2]

> **"Hypoglycaemia, and particularly night-time hypoglycaemia, is a major concern for people living with diabetes and the principal limiting factor to effective glucose control, thereby increasing their risk of long-term complications."**
>
> Dr Helena Rodbard, lead author and medical director, Endocrine and Metabolic Consultants, Rockville, Maryland.

· 86% (p<0.05) reduction in the rates of severe hypoglycaemia with insulin degludec compared with insulin glargine (0.003, 0 and 0 episodes per patient per year with IDeg versus 0.02, 0 and 0.01 episodes per patient per year with IGlar for the trials 3579, 3672 and 3586 respectively).[2]

*Classified as low blood sugar occurring between 00:01 – 05:59 inclusive.

**Regulatory authorities require that studies of glucose-lowering agents be designed as treat-to-target trials. The use of treat-to-target trials, to treat the test and comparator groups to similar glucose goals, allows for comparison in frequency and severity of hypoglycaemia to inform risk-benefit assessments.[3]

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1. Rodbard HW et al. Reduced nocturnal hypoglycaemia with insulin degludec as compared to insulin glargine: results of a 2-year randomised trial in type 2 diabetes. Poster presented at the European Association of the Study of Diabetes (EASD) 48th Annual meeting, October 2012.

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3. U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER), February 2008: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm0.

European Project to Develop Artificial Pancreas for Diabetes Patients

A consortium of academic and industrial partners has announced a collaboration called AP@home that aims to develop an artificial pancreas (AP) that would allow automated glucose control for people with insulin treated diabetes.

Normally, insulin is given either by injections or via continuous infusion pumps. However, blood glucose (sugar) levels can be greatly affected by many factors such as diet, physical activity, illness and stress so that it is difficult for patients to judge how much insulin they need.

An advanced AP system that combines a Continuous Glucose Monitor (CGM), an insulin infusion pump, and a software algorithm that calculates how much insulin to deliver at any time in response to the blood glucose level could not only improve the quality of life for people with insulin treated diabetes but also reduce the escalating healthcare cost burden.

In the first phase of the AP@home project, the currently available AP algorithms will be tested with CGM systems and insulin pumps already on the market, using a "two-port" approach that requires two skin punctures to attach the glucose monitor and the insulin pump. In this stage, the aim will be to improve the accuracy of the glucose sensors and the safety and effectiveness of the algorithms that relate insulin delivery to blood glucose levels.

In parallel, innovative AP systems will be developed that combine an insulin pump and a CGM system into a single device that uses only one access point through the skin. In the final year of the 4-year project, the performance of the newly created AP system, including remote monitoring facilities, will be compared with standard intensive insulin therapy in daily life in a multinational controlled trial.

"The aim of this project is to let Europe lead in the development of AP systems", said project coordinator Lutz Heinemann of the Profil Institut für Stoffwechselforschung GmbH. "Simplified care and improved quality of life for patients with diabetes will diminish related complications and health costs in the long run", added Heinemann.

For more information, please visit www.apathome.eu

Phase IIb Data Showed Merck's Investigational Once-Weekly DPP-4 Inhibitor MK-3102 Significantly Lowered Blood Sugar in Patients with Type 2 Diabetes

Merck, known as MSD outside the United States and Canada, announced Phase IIb data for MK-3102, the company's investigational once-weekly DPP-4 inhibitor in development for the treatment of type 2 diabetes. MK-3102 significantly lowered blood sugar in this 12-week study compared with placebo, with an incidence of symptomatic hypoglycaemia that was similar to placebo, in patients with type 2 diabetes. These data were presented at the 48th Annual Meeting of the European Association for the Study of Diabetes (EASD) in Berlin.

"If approved, MK-3102 would provide a novel, once-weekly treatment option to help reduce blood sugar levels in patients with type 2 diabetes," said lead study author Ira Gantz, M.D., Clinical Research, Metabolism, Merck Research Laboratories.

Study Design

The findings reported today are from a multicentre, randomised, double-blind, placebo-controlled dose-ranging study designed to evaluate five doses of MK-3102 (0.25, 1, 3, 10 and 25 mg) in patients with type 2 diabetes who had inadequate glycaemic control on diet and exercise.

A total of 685 patients with a mean baseline HbA1c of approximately 8 percent were randomised: 571 patients received MK-3102 at one of the five once-weekly doses (0.25 mg, n=113; 1 mg, n=115; 3 mg, n=114; 10 mg, n=115; 25 mg, n=114) and 114 patients received placebo for 12 weeks. The primary endpoint was change in HbA1c from baseline at 12 weeks compared to placebo across doses. The secondary endpoints were 2-hour post-meal glucose and fasting plasma glucose.

Study Results

MK-3102 significantly reduced HbA1c compared to placebo ($p<0.001$) from a mean baseline of approximately 8 percent across all doses. In the full study population at 12 weeks, the placebo-adjusted reduction from baseline in HbA1c was 0.71 percent with MK-3102 25 mg; 0.67 percent with 10 mg; 0.49 percent with 3 mg; 0.50 percent with 1 mg; and 0.28 percent with 0.25 mg.

A statistically significant ($p<0.001$) trend was observed across doses studied for the secondary endpoints of 2-hour post-meal glucose (PMG) and fasting blood glucose (FPG). For 2-hour PMG placebo-adjusted reductions from baseline at week 12 were: MK-3102 25 mg=2.5 mmol/L; 10 mg=2.3 mmol/L; 3 mg=1.9 mmol/L; 1 mg=1.9 mmol/L; 0.25 mg=1.0 mmol/L. For FPG, placebo-adjusted reductions from baseline at week 12 were MK-3102 25 mg=1.2 mmol/L; 10 mg=0.7 mmol/L; 3 mg=0.8 mmol/L; 1 mg=1.1 mmol/L; 0.25 mg=0.1 mmol/L.

In the study, MK-3102 was generally well tolerated with a safety profile that was generally similar to placebo.

Diabetes is a chronic, progressive disease that affects 366 million people globally, including nearly 26 million people in the U.S., however, based on National Health and Nutrition Examination Survey (NHANES) data from 1999-2006, more than 40 percent of patients are not at the American Diabetes Association (ADA) goal of less than 7.0 percent for HbA1c.

> **"Since the discovery of the DPP-4 inhibitor class, Merck has been actively committed to advancing the science of how to treat type 2 diabetes. We are encouraged by these Phase IIb results in patients with type 2 diabetes, and we are initiating Phase III studies to move MK-3102 forward in the development process."**
>
> Nancy Thornberry,
> Senior Vice President and Franchise Head, Diabetes and Endocrinology, Merck Research Laboratories

For more information, please visit www.merck.com

Janssen and the European Foundation for the Study of Diabetes (EFSD) Announce Award Recipients

The European Foundation for the Study of Diabetes (EFSD) announced that Dr Ivonne Loeffler, University Hospital, Jena, Germany is the recipient of this year's award for the 'EFSD/Janssen Programme for the Study of the Role of the Kidney in Diabetes'. Dr Loeffler will be looking into the role of collagen type VIII in epithelial-mesenchymal transition in diabetic nephropathy, advancing knowledge in a therapy area which affects an estimated 329 million people worldwide.

The award programme, initiated in 2010, is a joint partnership between EFSD and Janssen and offers joint funding of up to €300,000 per year. Within this up to €100,000 is available for basic research projects and €200,000 for clinical research projects, with a view to improving disease management.

Also announced, four leading young researchers have been awarded EFSD/Janssen Research Fellowships in conjunction with the European Association for the Study of Diabetes (EASD) Rising Star Symposium in recognition of their innovative work in diabetes research. Amélie Bonnefond, Lille Pasteur Institute, France; Josefine Beulens, Utrecht University, The Netherlands; Laura Herrero,

University of Barcelona, Spain and Henrike Sell, German Diabetes Center, Duesseldorf, Germany will present an overview of their past and current research activities at the EASD Rising Star Symposium and will each receive further funding of €30,000 to continue their work through the EFSD/Janssen Research Fellowships.

"Janssen is committed to working alongside the diabetes community and is proud to sponsor the EFSD/Janssen Programme for the Study of the Role of the Kidney in Diabetes and the EFSD/Janssen Research Fellowships during the Rising Stars Symposium at the EASD Annual Meeting. Programmes such as these stimulate and accelerate vital research that could contribute to improving management of the disease and patient care" commented Brian Woodfall, Vice President Janssen EMEA Medical Affairs.

"Diabetes is a global concern and the social and economic impact of this disease is increasing as the incidence and prevalence of diabetes continues to grow. Through our partnership with Janssen, we are pleased to support further research into the role of the kidney in diabetes and also to recognise and support the emerging researchers who have valuable contributions to make to expand our knowledge and understanding of diabetes."

Prof Andrew Boulton,
President EFSD

President of EASD Calls for Improved Device Registration and Monitoring in Europe

European diabetes device regulation is in need of "radical change," according to president of the European Association for the Study of Diabetes, professor Andrew Boulton, MD.

The approval process and regulation of diabetes devices has been an issue of debate in Europe due to a number of high-profile medical device failures that have occurred in recent years. And though an announcement on the subject was issued by the European Commission on Sept. 26, 2012, the EASD says the concerns were not addressed sufficiently, according to a press release.

"The general public, including diabetes patients, were rightly extremely concerned when the various medical device scandals came to light earlier this year," Boulton said during a press conference. "The European Commission appears to have missed its opportunity to tighten up these regulations. Without tougher rules, governing approval and surveillance for medical devices, how can we ensure the public has confidence in the system?"

In a letter published in the European diabetes journal Diabetologia, Boulton and Stefano Del Prato, MD, of the department of endocrinology and metabolism, Section of Diabetes and Metabolic Diseases in Pisa, Italy, addressed their concerns, citing multiple medical device failures, including the "spontaneous rupture" of silicone gel breast implants, "dangers of metal-on-metal hip implants and deaths caused by the likely failure of implantable cardioverter-defibrillator leads." Though such device failures have not, to date, been reported in the management of diabetes, the use of devices in diabetes treatment continues to grow and Boulton believes there is an "urgent need for reform of the entire [device registration and monitoring] process."

Device Approval Procedure

Currently, the process for approval of medical devices in Europe is less rigorous compared with that required for the approval of new drugs. Manufacturers must receive the Conformite Europeenne (CE) mark to obtain approval of new devices. The CE is awarded by a "Notified Body" (NB), usually an independent organisation supported partially by fees paid by the device manufacturing companies, according to Boulton.

Companies who wish to register a new continuous glucose monitor can choose any NB they want and pay them a fee to ensure their device meets specified requirements set by the European Union Council. A CE mark is then affixed to the device and the manufacturer can market their device throughout Europe, without the need for independent studies or trials. In addition, neither the national nor the European health authorities enforce any post-marketing vigilance system, Boulton wrote in his letter.

Increase in Diabetes Devices

The use of diabetes devices such as home blood glucose monitors, continuous subcutaneous insulin infusion and continuous glucose monitoring has increased rapidly worldwide. According to Boulton, the widespread use of such devices increases the risk for human error and device failure.

In 2005, literature published in Diabetologia demonstrated that a post-marketing reliability study of a non-invasive continuous glucose monitor found the device inaccurate. According to the study, there was a >50% mean absolute difference between the glucose readings on the device and those on the patients' home blood glucose monitor. Furthermore, >4% of the incorrect readings were potentially dangerous, Boulton wrote.

Call for 'Radical Change'

In their letter, Boulton and Del Prato endorse a proposal made by the European Society of Cardiology stating that, "similar to the EMA, which oversees medications, there should be a single, coordinated European system to oversee the evaluation, approval and post-marketing surveillance of medical devices; there could, for example, be a sub-division for device regulation within the EMA."

They have little belief, however, that the current revisions being made to the European Union directives on medical devices will result in the institution of a central European device registry, due to the current financial limits within Europe.

"The safety of our patients with diabetes who use devices in their day-to-day treatment and monitoring is of paramount importance: hence the EASD has organised a symposium on this topic at its 2012 meeting and has established working committees on devices in diabetes," they wrote.

The EASD plans to submit their solutions in 2013, but hope, in the meantime, that "the EU will reform the functioning of existing NBs and establish both surveillance and vigilance procedures for medical devices in Europe."

DiagnOptics present the AGE Reader and Diab-spot

DiagnOptics was the first to introduce a technology to noninvasively measure the tissue accumulation of AGEs by means of fluorescence techniques (AGE Reader). Diab-spot features the AGE measurement and combines this with a small number of patient characteristics to calculate the Diab-spot test result. These simple characteristics include questions about other well-known diabetes risk factors, which can be easily answered on the touch screen. Diab-spot yields an immediate screening result on the spot.

Diabetes Detection

Diabetes mellitus is now one of the most common diseases globally with an estimated 285 million affected persons worldwide and 344 million persons with pre-diabetes. Each year, another 7 million people develop diabetesl and 3.8 million deaths worldwide are linked directly to diabetes related causes. The estimate is that at least one third of the patients with diabetes is undiagnosed.

Diabetes complications are very common. A large proportion of diabetics (50% or more in some studies) have at least one complication present at the time of diagnosis. In order to reduce diabetes associated complications and mortality there is a great need for screening and monitoring methods to assess the risk of diabetes and diabetic complications. If (pre-)diabetes is detected early, with only lifestyle intervention, or with medication the development of diabetes and its complications can be postponed or even prevented.

Current Screening Methods

The current methods for diabetes screening are inadequate. Questionnaires are easy to use but score moderate as predictor of (pre-) diabetes and still need confirmation by blood testing as second step. Fasting and non-fasting plasma glucose, and also HbA1c are inconvenient for the patient, because they require a finger prick or blood draw. They also score moderate as predictors of (pre-)diabetes, and there is poor concordance between these different blood tests.

The gold standard for diagnosis of diabetes is an oral glucose tolerance test (OGTT). This OGTT is not feasible as a screening tool because it requires fasting, multiple blood samples and takes 2 hours per test. Currently there is no generally accepted alternative screening test, or stepwise procedure of tests, for early detection and diagnosis of diabetes.

DiagnOptics' Diab-spot

The AGE Reader provides an immediate cardiovascular risk prediction for major chronic diseases, such as diabetes, cardiovascular disease and renal failure. The AGE Reader yields a real time and non-invasive assessment of cardiovascular risk. The method is convenient, easy to use and validated. The AGE Reader measures tissue accumulation of Advanced Glycation Endproducts (AGEs) by means of fluorescence techniques (skin autofluorescence (skin AF)). AGEs play a key role in the pathogenesis of many age-related diseases, such as diabetes, cardiovascular disease and renal failure.


DiagnOptics' AGE Reader

Technology

The AGE Reader has a light source which illuminates the skin of the forearm. This light will excite fluorescent moieties in the tissue which will emit light of a different wavelength. In the used wavelength band the major contribution in fluorescence comes from fluorescent AGEs linked mostly to collagen, but also to other proteins and lipids. The emitted light is detected using a spectrometer.

By using specific technical adaptations including selection of specific wavelength, modulated or pulsed light sources, a more selective discrimination of specific AGEs is obtained.

Clinical Validation

The comfortable and safe AGE Reader measurement offers crucial clinical information to clinicians and researchers. The AGE Reader has been validated against the gold standard for measuring AGEs (skin biopsies). It was shown that skin AF is strongly correlated with AGEs.

The device has been clinically validated in multiple large-scale, clinical trials over the last few years involving tens of thousands of healthy controls, diabetics, cardiovascular and renal patients. The clinical studies demonstrate that skin autofluorescence is a strong and independent risk predictor for mortality and cardiovascular events. In particular, it can independently predict cardiovascular co-morbidity and mortality in diabetes, renal failure and dialysis patients.

For more information, please visit www.diagnoptics.com

Interactive stand at EASD

Lilly and Boehringer Ingelheim Present Health Outcomes Data for Investigational Novel Basal Insulin Analogue

Eli Lilly and Company and Boehringer Ingelheim announced patient-reported health outcomes data from a Phase II study of their investigational novel basal insulin analogue, LY2605541, in patients with type 2 diabetes. Study results showed that in addition to clinical results showing a statistically significant 48 percent baseline adjusted reduction in nocturnal hypoglycaemia compared with insulin glargine [0.25 vs. 0.39 events/ 30 days/patient, after adjusting for baseline hypoglycaemia events (p=0.020)],[1] patients treated with LY2605541* reported a statistically significant reduction in the anxiety and fear associated with experiencing a hypoglycaemic event based upon the Adult Low Blood Sugar Survey (ALBSS).[2]

Hypoglycaemia data were collected during a Phase II clinical study comparing LY2605541with insulin glargine in patients with type 2 diabetes. In addition to the reduction in nocturnal hypoglycaemia in LY2605541-treated patients, results showed the treatments had similar overall rates of hypoglycaemia (p=0.08, not statistically significant).[1]

The study used a validated patient-experience questionnaire called the Adult Low Blood Sugar Survey (ALBSS)3 to measure patients' fear of mild-to-moderate hypoglycaemia and associated behaviours during the previous four weeks. Hypoglycaemia was defined as low blood glucose levels that were less than or equal to 70 mg/dL. The ALBSS measures the worry or fear associated with the impact of the patients' experience with a hypoglycaemic event and subsequent behaviors that are associated with avoiding future events based upon a previous experience.

The results of this study found:

- Patients treated with LY2605541 had a lower average score on the fear subscale of the ALBSS at week 12 than those treated with insulin glargine (6.6 vs. 10.0; p=0.022).[2]
- LY2605541 and insulin glargine had similar effects on patient behavior at week 12 (p=NS).[2]

Examples of change in subsequent behaviours associated with avoiding future hypoglycaemic events included eating large snacks, keeping blood sugar levels higher in social situations, staying at home more than liked and limiting exercise/physical activity.

- LY2605541-treated patients had lower average total scores on the ALBSS compared with glargine-treated patients (13.0 vs. 16.5 in the glargine group; p=0.026).[2]

About the Phase II Study1 The Phase II, randomised, open-label, parallel study evaluated LY2605541 in lowering self-monitored fasting blood glucose levels compared to insulin glargine in adults with type 2 diabetes. Patients were converted to morning insulin administration during a four-week lead-in period and were randomised 2:1 to morning administration of LY2605541 (195 patients) or glargine (93 patients) for a total of 12 weeks.

"As we continue development of our investigational novel basal insulin, we wanted to understand both the impact of the fear of hypoglycaemia and the impact of hypoglycaemic events and the emotional toll for the person with diabetes. We look forward to further studying LY2605541 in a large Phase III program to better understand the clinical impact of these patient-reported health outcomes results."

David Kendall, M.D., Lilly Diabetes

The primary endpoint of the study showed that LY2605541 and glargine had similar effects on lowering average daily self-monitored fasting (before breakfast) glucose levels (p=0 .433) and HbA1c (p=0.279) over 12 weeks. Following treatment with LY2605541, blood tests on liver function (as measured by mean ALT and AST levels) statistically significantly increased from baseline and were higher than with insulin glargine. The mean levels of both liver enzymes remained within the normal range during the study for glargine and LY2605541-treated patients.

In the Phase II type 2 diabetes study, triglyceride levels in patients treated with LY2605541 were not significantly different from baseline (163 mg/dL to 172 mg/dL), but statistically higher compared to insulin glargine (160 mg/dL vs. 147 mg/dL). There was no signifcant difference in LDL-C or HDL-C in patients treated with LY2605541 from baseline or compared with insulin glargine.

Patients also completed the Adult Low Blood Sugar Survey (ALBSS), a 33-item questionnaire divided into two subscales that independently assess patients' behaviors related to preventing hypoglycaemia and its effects, and well as patients' fear (worry) about consequences of a hypoglycaemic episode. This was a prospective measure in the Phase II type 2 diabetes study for LY2605541.* For each item, patients reported how often the item was true using a 5-point Likert scale (0, never to 4, almost always). Patients completed the ALBSS at baseline, week 6 and week 12 of the study. The ALBSS yields an individual score for the behavior and fear subscales as well as a total score.[2]

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For information, please visit www.lilly.com or www.boehringer-ingelheim.com

Award Highlights from the 48th Annual Meeting of the EASD

The minkowski prize commemorates Oskaer Minkowski (1858-1931) who successfully performed the extirpation of the pancreas in dogs in 1189 and noticed that they developed diabetes.

The Minkowski prize is given by the EASD in recognition of research by scientists under the age of 45, normally residing in Europe, as manifested by publications which contribute to the advancement of knowledge about diabetes mellitus.

This year's recipient of the presitigious award was Timothy Frayling, Professor of Human Genetics at the Peninsula College of Medicine and Dentistry, University of Exeter, UK. He gave a lecture entitled *Human genetics and type 2 diabetes: behind the headlines*. Frayling looked behind the headlines of "personalised medicine", "fat genes" and "next generation sequencing", and argued that human genetic studies are, and will continue to be, a vital tool in our attempts to improve understanding of the complex disease of type 2 diabetes because it will reveal new biological pathways involved in the disease process. He outlined some of the progress made and how much has been discovered in the last 5 years. Later, examples of what has been learnt about the biology of diabetes were also explored. Any one genetic finding could lead to a cascade of new discoveries about diabetes pathophysiology.

The Camilo Golgi Prize is awarded for outstanding contributions in histopathology, pathogenesis, prevention and treatment of the complications of diabetes mellitus. The award honours Camilo Golgi (1843-1926) who was awarded the first Nobel Prize in 1906 for his research on the nervous system and kidney physiology. The 2012 recipient of the Camilo Golgi Prive was Giuseppe Pugliese, Associate Professor of Endocrinology and Metabolism, at the Department of Clinical and Molecular Medicine, University of Rome "La Sapienza", and Chief of the Diabetes Unit of Sant'Andrea Hospital in Rome. The aim of this award lecture by Pugliese is to review the evidence from the literature, in particular the work of his own group on galectin-3, to answer the question in the title: *Whether galectin-3 is only a stooge of RAGE or it is a leading actor too*.

The Claude Bernard Lecture and Award recognises an individual's innovative leadership and outstanding contributions in the field of diabetes mellitus, and is the highest scientific achievement award of the EASD. Dr. Daniel Drucker is the first and only Canadian to receive this honor and delivered the Claude Bernard lecture during the 48th EASD Annual Meeting in Berlin in September 2012. Dr. Drucker's research encompasses molecular biology, physiology, drug discovery, clinical investigation, and has led to development of new drugs, DPP-4 inhibitors and GLP-1R agonists, for the treatment of diabetes, as well as GLP-2R agonists, currently in late stage clinical trials for the treatment of short bowel syndrome and other intestinal disorders.

The Albert Renold Prize and Lecture is in memory of A. Renold (1923-1988). A. Renold, a distinguished diabetologist and researcher, was one of the founding fathers of the EASD where he served as Honorary Secretary from 1965-1969 and then President from 1974-1977. This award recognises an individual's outstanding contribution to the progress of knowledge in the islets of Langerhans.

At the 2012 Annual Meeting, the Albert Renold Prize was presented to Dr Decio L. Eizirik, Director at the University libre de Brussels (ULB).

Professor Eizirik and his colleagues at the Laboratory of Experimental Medicine at ULB have been investigating the molecular pathways involved in immune-induced beta cell impairment and apoptosis in type 1 diabetes (T1D). His research led to fundamental concepts such as the dialogue between the immune system and beta cells that trigger and amplify islet inflammation (insulitis) and progressive beta cell death by apoptosis.

EASD at a Glance...

The aims of the European Association for the Study of Diabetes are to encourage and support research in the field of diabetes, the rapid diffusion of acquired knowledge and to facilitate its application. This year's Meeting, like those before it, proved to be a resounding success. Not only were there a wealth of oral presentations, poster sessions aand symposiums, there was also the opportunity for delegates from around the globe to come together. Whether it was meeting old friends or making new acquaintances; all were joined by the universal goal of promoting and understanding diabetes research and looking at ways to cure and prevent in the future.

The Scientific Programme Committee this year selected 1270 abstracts for presentation from a total of 2307 that were submitted. The programme is made up of six parallel tracks which include inspiring symposia, keynote lectures and insightful debates, covering both basic and clinical science and providing an extensive scientific programme, which reflects the ongoing efforts to understand, cure and prevent diabetes.

Germany's capital didn't fail in being a worthy host, offering attendees of the EASD Meeting a variety of exciting options when not at the Berlin Messe.

The EASD Annual Meeting once again provided the best opportunity for efficient networking and the chance to enhance knowledge with the aim to advance high-quality care in diabetes. We are looking forward to attending this exciting event again in 2013.

Over 17,000 delegates attended the 2012 EASD Meeting.

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We look forward to meeting you next year in Barcelona for what promises to be yet another successful and exciting annual meeting!

For more information please visit
www.easd.org

Delivering Innovation in Type 2 Diabetes: Tailored Approaches with SGLT2 and Incretin-based Therapies

The Ongoing Challenge of Type 2 Diabetes: Why we Still Need New Approaches

Kamlesh Khunti
(Leicester, UK)

Diabetes is no longer just an epidemic but is considered a tsunami in medical terms, with significant increases in its prevalence in recent years. Current figures stand at around 530 million worldwide, with many of these patients not controlled in terms of their glycaemic targets.[1]

Classical studies have shown that diabetes is a progressive disease, even with conventional therapy.[2] This is largely because of continuing β cell failure and insulin resistance.

The management of diabetes should evolve over the duration of the disease.[3] Initially, patients should be advised on diet and lifestyle to manage HbA1c levels. This would then be followed by oral antidiabetic monotherapy, which is up-titrated as required. As the disease progresses, combination therapy should be utilised, with the eventual addition of basal insulin. In the latter stages of the disease, multiple daily insulin injections are often needed.[3] This is how diabetes should be managed in the ideal world. However, in the real world, this does not often happen for many patients, leading to the micro and macrovasculature damage frequently seen.

The barriers to effective treatment include many factors, such as poor adherence to therapy, fear of hypoglycaemia and physician behaviour.[4, 5, 6] The natural history of the disease, weight gain as a result of lifestyle or antidiabetic medication and the changing glucose targets set by various guidelines also play a role.[2, 6, 7]

The failure to advance therapy when required, often termed clinical inertia, was first described by Brown *et al*. in 2004.[8] This study found that therapy was advanced when HbA1c levels became >8% in around 67% of patients managed with diet only and in 35-45% of patients on antidiabetic monotherapy, but in only 19% of patients on combination therapy. Further to this, the study found that patients had an HbA1c >8% for more than 5 years and >7% for more than 10 years. These results show that clinical inertia becomes more prevalent as the disease becomes more advanced.

Many patients with diabetes do not adhere to their therapy. Retrospective analysis has shown that adherence rates are around 36-93% for oral agents and 62-64% for insulin.[9] In addition, therapy persistence has been shown to decrease with time, and with combination therapy vs. monotherapy.[10] The reason for this poor adherence is thought to be partly due to the fear of weight gain and occurrence of hypoglycaemia.[11] Hypoglycaemia is more frequent in patients on intensive vs. standard therapy.[12, 13, 14] The hypoglycaemic events also vary according to how quickly dose escalation occurs. More aggressive treatment has also been associated with greater weight gain, more so with insulin

Reducing the Risk of Stroke in Atrial Fibrillation: A Risk Benefit Approach
Bristol-Myers Squibb and AstraZeneca sponsored Satellite Symposium at the European Association for the Study of Diabetes (EASD) Meeting, Berlin, Germany, 1 October, 2012

Chairpersons: Andreas Pfeiffer, Charité Universitätsmedizin Berlin, Berlin, Germany and Jiten Vora, Spire Liverpool Hospital and Spire Murrayfield Hospital Wirral, Liverpool, United Kingdom

Lecture 1 - The Ongoing Challenge of Type 2 Diabetes: Why we Still Need New Approaches
Kamlesh Khunti, Leicester University, United Kingdom

Lecture 2 - A Novel way of Treating Type 2 Diabetes: Removing Excess Glucose through SGLT2 Inhibition
Paola Fioretto, University of Padova Medical School, Italy

Lecture 3 - SGLT2 Inhibition in Clinical Practice
Samy Hadjadj, University of Poitiers, France

Lecture 4 - Is SGLT2 Inhibition Safe for my Patients?
Andreas Pfeiffer, Charité Universitätsmedizin Berlin, Germany

Lecture 5 - What can we Learn from Retrospective Cardiovascular Outcome Studies?
Edoardo Mannucci, University of Florence, Italy

Lecture 6 - Cardio-protective Mechanisms of Incretin-based Therapies in Type 2 Diabetes
Laurie Baggio, University of Toronto, Canada

Lecture 7 - Introducing SAVOR, a Prospective Cardiovascular Outcomes Study
Petra-Maria Schumm-Draeger, Städtisches Klinikum München, Germany

Lecture 8 - The Clinical Profile of Incretin-based Therapies
Jiten Vora, Spire Liverpool Hospital and Spire Murrayfield Hospital, United Kingdom

treatment.[2, 15] Modifiable risk factors for cardiovascular disease in type 2 diabetes include dyslipidaemia, hypertension, cigarette smoking, hyperglycaemia and obesity.[16]

There is some controversy in terms of how tight the HbA1c targets should be. The UKPDS 10 year post trial follow up found that tighter control, earlier in the disease timeline and less tight control later on, was beneficial.[17]

The CODE-2 study has shown that 69% of patients fail to reach an HbA1c target of ≤6.5%.[18] This inability to reach targets in a significant proportion of patients has also been seen in the more recent European PANORAMA study, where 30-40% of patients did not reach the HbA1c target of ≤7.0%.[19]

Numerous guidelines have provided target HbA1c levels. However, the new ADA/EASD position statement recommends that therapy is individualised for each patient, dependant on patient attitude and expected treatment efforts, risk assessments, disease duration, life expectancy, comorbidities and established vascular complications, as well as the resources and support system that is available.[20] These guidelines recommend metformin as the initial monotherapy drug. After this, the choice of additional therapy will depend on the target to be achieved, e.g. dipeptidyl peptidase 4 (DPP-4) and glucagon-like peptide-1 (GLP-1) receptor agonists are recommended for patients who need to avoid weight gain. When the goal is to avoid hypoglycaemia, DPP-4, GLP-1 receptor agonists and thiazolidinediones (TZDs) should be considered. Cost is also a concern, and when this is a goal of treatment, sulphonylureas (SU) and insulin can be considered.

A Novel way of Treating Type 2 Diabetes: Removing Excess Glucose through SGLT2 Inhibition

Paola Fioretto

(Padova, Italy)

The kidney has been shown to play a very important role in glucose homeostasis by reabsorbing around 180 g of glucose per day.[21, 22] Under normal circumstances, around 90% of glucose is reabsorbed by the sodium-glucose transport (SGLT) proteins in the early part of the proximal tubule, with the remaining 10% is reabsorbed in the more distal end of the proximal tubule.[23, 24]

There are two main types of SGLT transporters.[22, 25] SGLT1 have a high affinity but low capacity to bind glucose. SGLT2 have a low affinity but high capacity to bind glucose. SGLT2 is predominantly expressed in the early part of the proximal tubule and SGLT1 is located more distally in the proximal tubule, as well as in the intestine where it is responsible for glucose and galactose re-absorption. As a consequence, inhibition of SGLT1 can result in malabsorption and diarrhoea.

The amount of glucose that is filtered is due to two factors, glomerular filtration rate (GFR) and plasma glucose levels.[26, 27] There is a linear correlation between plasma glucose and filtered glucose. If patients have a reduction in GFR, the filtered glucose will be lower. All filtered glucose is reabsorbed in a linear fashion until the transport maximum for glucose (TmG) is reached (~350 mg/min).

There is evidence that TmG is increased in type 2 diabetic patients, and therefore the absorption of glucose is increased, further contributing to systemic hyperglycaemia. An increase in SGLT2 and glucose transporter 2 (GLUT2) expression has also been shown in type 2 diabetes.[25] It is, therefore a rationale approach to block the reabsorption of glucose in order to increase renal glucose excretion resulting in reduced blood glucose levels.

Familial renal glycosuria is generally asymptomatic when occurring at <100 g/1.73 m^2/day. However, severe glycosuria (>100 g/1.73 m^2/day) can be associated with episodic dehydration and ketosis during pregnancy and starvation. The desired pharmacologic effect of SGLT2 inhibition is to induce a reversible state of increased renal glucose excretion (with minimal potential for hypoglycaemia) not exceeding 70 g/1.73 m^2/day.

A number of studies with SGLT2 inhibitors have been performed in animal models and healthy volunteers. This has been found to result in inhibition of renal glucose uptake,[28] a reduction in plasma glucose,[28] improved glucose tolerance[29] and a reduction in plasma insulin levels.[30]

A number of oral compounds are currently in development, including dapagliflozin, canagliflozin, empagliflozin, ipragliflozin and LX4211.

A number of clinical benefits are expected with these compounds. Their insulin independent mechanism, which induces osmotic diuresis would be expected to result in initial weight loss; the loss of excess calories in the urine would be expected to be associated with sustained weight loss; and the glucose lowering would be associated with a lower risk of hypoglycaemia.[31, 32, 33]

SGLT2 Inhibition in Clinical Practice

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The Phase III clinical development programme for dapagliflozin includes a number of placebo controlled studies. These include the investigation of naïve monotherapy, add-on combination therapy, comparator trials and studies in special populations, including patients with moderate renal impairment.

A consistent reduction in HbA1c levels (0.8-0.9%) was noted at 24 weeks across all studies, regardless of the baseline levels.[34] Most of these studies were extended to 1 or 2 years. The effect on HbA1c levels were found to be sustained over the period of the study, whether on monotherapy or as an add-on therapy.[35, 36, 37] In addition, when added to insulin therapy, the insulin dose was relatively unchanged over a 48

week period vs. an almost linear increase in insulin requirement in patients receiving placebo plus insulin.[37] Subgroup analysis have shown that the higher the initial HbA1c, the greater its reduction. In addition, due to the physiology of the drug, the better the renal function (eGFR), the better the improvement was in HbA1c.[38]

There is low intrinsic propensity for hypoglycaemia in patients treated with dapagliflozin.[38] When the combination of metformin and dapagliflozin was compared to metformin plus glipizide, a significantly lower incidence of hypoglycaemia was found at 52 weeks ($p<0.0001$).[39]

For patients with baseline body weight between 80-90 kg, there was a significant reduction in body weight across all studies with dapagliflozin at 24 weeks.[34] Dapagliflozin was also found to have additional benefits in sustaining weight loss over 2 years.[35] When metformin plus dapagliflozin was compared to metformin plus glipizide, a 5.1 kg weight difference was noted at 2 years.[39] In addition to the difference in body weight, a reduction in body fat mass was observed at Week 24.[40] When these combined therapies were compared for blood pressure differences, it was noted that there was a difference of 4.7 mmHg at 1 year and 3.9 mmHg at 2 years in favour of dapagliflozin.[41] Pooled analysis of all the different studies showed that, after 6 months of therapy, there was a rapid and sustained reduction in systolic and diastolic blood pressure up to 24 weeks.[38]

Is SGLT2 Inhibition Safe for my Patients?

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For any new therapy, safety is always a key consideration. With regard to SGLT2 inhibitors, risk of malignancy, volume depletion/hypotension, increase in urinary tract infections (UTIs), genital infections and cardiovascular disease are frequently asked questions.

In the clinical trial programme for dapagliflozin, an overall favourable safety profile, which was comparable to placebo, was reported.[42]

Pre-clinical studies in animal models detected no off target pharmacology with dapagliflozin. In addition, there were no reactive metabolites, no genotoxicity or liver toxicity and no SGLT2 target expression in the bladder or breast tissue. In addition, no signal for bladder, breast or other tumours, or hyperplasia was found.

In human studies, the overall incidence of cancers was balanced between active treatment and control.[42]

Liver function, as measured by alanine transaminase (ALT) elevation was again comparable between active treatment and control, with around 1.4-1.6% of patients with ALT elevation 3x upper limit of normal (ULN). Total bilirubin elevations and combined aspartate transaminase (AST)/ALT >3xULN and bilirubin >2xULN within 14 days were also comparable.[38]

Diuresis as a result of the glucose excretion did not adversely affect renal function. Pooled data from the 12 randomised controlled trials (RCTs) showed that eGFR levels were comparable between dapagliflozin and placebo.[42] There was an initial small drop in eGFR at the start of treatment with dapagliflozin, after which mean eGFR levels were comparable to placebo over 96 weeks.[38]

Pooled 24 week data also showed that the number of patients with hypotension, syncope, dehydration and decreased urine flow were low (<0.5% for all) and comparable between dapagliflozin and placebo.[42] There were also no electrolyte imbalances. A slight decrease in uric acid and a slight increase in haematocrit were observed.[34]

Pooled analysis showed that UTIs occurred in 4.3% vs. 3.7% of patients at 24 weeks and 7.7% vs. 6.3% at 102 weeks for dapagliflozin and placebo, respectively.[43] All events were mild to moderate in intensity and most responded to an initial course of standard treatment. UTIs rarely lead to treatment discontinuation (0.3%), and most patients who had an event, had only one event in 102 weeks. Upper UTIs were rare and balanced between the treatment groups (0.1% vs. 0.2% for dapagliflozin and placebo, respectively). Most UTIs occurred in the first 6 months of treatment.[38]

A difference in the rate of genital infections was observed between dapagliflozin and placebo in the pooled analysis at 24 and 102 weeks. A total of 4.8% vs. 0.9% and 8.2% vs. 1.3% of patients had a genital infection at Week 24 and Week 102 in the dapagliflozin and placebo groups, respectively. All events were mild to moderate in intensity and, again, most responded to a standard course of treatment and rarely led to treatment discontinuation (0.2%). As with UTIs, most genital infections occurred in the first 6 months, and most patients who had an event, had only one event over 102 weeks.[44]

Cardiovascular safety of dapagliflozin was also investigated in the pooled analysis. The percentage of patients with a prior history of cardiovascular disease (42.3% vs. 33.2%) and hypertension (74.0% vs. 67.6%) was comparable between the dapagliflozin and placebo groups, respectively.[42] The event rate (patients with events/1,000 patient years) for a major adverse cardiovascular event was 16.4 and 19.9 for dapagliflozin and placebo, respectively, indicating that dapagliflozin may have a favourable effect.[42] However, longer term data is needed to confirm this observation.

What can we Learn from Retrospective Cardiovascular Outcome Studies?

Edoardo Mannucci

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A key question is whether it is possible to reduce cardiovascular risk simply by lowering blood glucose. Meta-analysis of available RCTs has

shown that it can lead to a significant reduction in the incidence of myocardial infarction, but it does not affect the incidence of stroke and cardiovascular mortality, and that it could even be associated with increased cardiovascular mortality.[45] A determinant for the increased risk of cardiovascular mortality is body mass index (BMI).[45] Trials that enrolled patients with a higher BMI have shown an increase in cardiovascular mortality.[45] Duration of disease also has an impact.[45]

Aggressive glycaemic control in patients with more advanced disease is associated with a higher rate of mortality than that seen in patients with early stage disease.[45] Another important determinant is hypoglycaemia. When glycaemic control was attained with treatment with a relatively low risk of hypoglycaemia, there was an associated lower risk of cardiovascular mortality.[45] This meta-analysis has shown that the interpretation of clinical trials for cardiovascular risk is complex.[45] The same intervention can produce opposing effects on different cardiovascular outcomes. In addition, some side effects of treatment (e.g. hypoglycaemia) are detrimental for the cardiovascular system. The analysis is also confounded by heterogeneity across different trials. Additionally, individual drugs, or combinations of drugs, could have beneficial or harmful effects on cardiovascular risk independent of blood glucose.[45]

Metformin has been suggested to have associated cardiovascular morbidity and mortality benefits. This has certainly been seen in trials comparing metformin to placebo.[46] However, in comparator trials with other HbA1c lowering treatments, no additional benefit was seen.[46]

The PROACTIVE study showed marginally significant benefits for the TZD pioglitazone vs. placebo.[47] This again, could be due to a difference in metabolic control and not just as a result of drug treatment.

SUs have been shown to have no effect on cardiovascular outcomes compared to insulin or metformin.[48] Additionally, results from the RECORD trial have shown that patients on background metformin randomised to the TZD rosiglitazone or SU had similar cardiovascular outcomes.[49] As we all know, rosiglitazone has since been withdrawn from the market in Europe due to the associated increased rate of cardiovascular events.

The effects of basal insulin on cardiovascular outcomes has been investigated in the ORIGIN trial.[50] It was shown to have a neutral effect on cardiovascular events, with similar levels of myocardial infarction, stroke or cardiovascular death to that seen with standard care.

For more recent drugs, such as DPP-4, there are no large scale studies to investigate cardiovascular risk. Pooled analysis of Phase II and Phase III studies designed for metabolic endpoints, show a trend towards decreased cardiovascular risk, which is significant for saxagliptin and linagliptin.[51, 52, 53, 54] A meta-analysis of the RCTs for the DPP-4 class of drugs has shown a reduction in the incidence of major cardiovascular events of around 30% vs. comparators.[55] A recent update of this analysis, which is a meta-analysis of all available RCTs with a duration ≥24 weeks (70 trials including 41,959 patients with type 2 diabetes), has confirmed earlier observations, with a significant reduction of cardiovascular events again around 30%.[56] Of particular interest in this analysis was the observation that all cause mortality was reduced by around 40%.

Cardio-protective Mechanisms of Incretin-based Therapies in Type 2 Diabetes

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GLP-1, an incretin hormone that enhances glucose-stimulated insulin secretion, exerts direct and indirect actions on the cardiovascular system.[57] GLP-1 and its related incretin hormone, glucose dependent insulinotropic polypeptide (GIP), are rapidly inactivated by the enzyme DPP-4, a key determinant of incretin bioactivity. Both GLP-1 receptor activation and DPP-4 inhibition exert multiple cardioprotective actions in preclinical models of cardiovascular dysfunction, and short term studies in human subjects appear to demonstrate modest yet beneficial effects on cardiac function in subjects with ischaemic heart disease.

The augmentation of GLP-1 by inhibition of DPP-4 has been shown to improve global and regional left ventricular performance in response to stress and mitigates post-ischaemic stunning in humans with coronary artery disease.[58] In addition, genetic disruption or chemical inhibition of DPP-4 does not impair cardiovascular function in the normoglycaemic or diabetic mouse heart.[59] In mice animal models, pre-treatment with a DPP-4 inhibitor has been shown to reduce myocardial infarct size[60] and inhibits atherosclerosis.[61]

Recent studies indicate that type 2 diabetes is associated with an increased secretion of both hepatic and intestinal lipoproteins, leading to the accumulation of atherogenic triglyceride (TG)-rich lipoproteins. DPP-4 inhibition in patients with type 2 diabetes has been shown to have a beneficial effect on postprandial lipid (intestinal and hepatic) and incretin hormone levels as well as glucose homeostasis.[62] It is thought to mediate this effect by increasing incretin hormone levels, reducing circulating plasma free fatty acid concentrations and improving insulin sensitivity and β cell function.

Endothelial cell dysfunction contributes to insulin resistance in diabetes and is characterised by reduced nitric oxide (NO) release, increased nitroxidative stress and enhanced inflammation. Enhanced glycaemic control with DPP-4 inhibition has been shown to improve NO release and reduced inflammation in a manner not predicted by fasting glucose changes alone.[63] The improved NO production was seen prior to any observed changes

in fasting glucose levels.

Endothelium and cardiac and vascular myocytes have been shown in a mice model to express a functional GLP-1 receptor.[64] However, data from this and other studies suggest that the protection against ischaemia-reperfusion injury seen, occurs through both GLP-1 receptor dependent and independent pathways.[64, 65] Although endogenous GLP-1 receptor signalling is essential for the control of intestinal lipoprotein biosynthesis and secretion,[66] the effect of DPP-4 inhibition on lipid metabolism has been shown to be modulated via both incretin-dependent and independent pathways.[67]

There appears, therefore, to be both direct and indirect mechanisms of cardioprotection induced by DPP-4 inhibition.

A synergy between DPP-4 inhibition and granulocyte colony-stimulating factor has been shown to improve cardiac function after acute myocardial infarction.[68] The cardioprotective effect of DPP-4 inhibition appears to be partially due to the preserved activity of SDF-1 α, a major chemokine that attracts stem cells to the heart. DPP-4 inhibition has also been shown to potentiate the positive inotropic effect of exogenous brain natriuretic peptide in pigs after pacing-induced heart failure.[69]

Introducing SAVOR, a Prospective Cardiovascular Outcomes Study

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SAVOR is an ongoing long term, multicentre, randomised, double blind, placebo controlled, multinational Phase IV trial designed to study both the efficacy and safety of the DPP-4 inhibitor saxagliptin in the treatment of type 2 diabetes patients at high risk for cardiovascular complications.[71, 72]

The trial is being conducted at 532 sites in 25 countries and will include approximately 16,500 patients with HbA1c ≥6.5% and ≤12.0%, with an average follow up of 3 years.

Eligible patients who are either treatment naïve or on any background antidiabetic treatment (except incretin therapy) with a history of established cardiovascular disease or multiple risk factors have been randomised 1:1 to saxagliptin 5 mg once daily (2.5 mg in subjects with moderate/severe renal impairment) or matching placebo, stratified by qualifying disease state.

Patients with moderate or severe renal impairment are being included in the trial to assess safety in patients with renal dysfunction.

Patients with non cardiovascular comorbidities that may cause the patient to drop out of the study have been excluded, as have patients on chronic dialysis and/or who have had a renal transplant and/or a serum creatinine >530 µmol/L. Additionally, patients with uncontrolled cardiovascular or metabolic risk factors have been excluded.

The primary study endpoint is a composite of cardiovascular death, nonfatal MI or nonfatal ischaemic stroke. The secondary endpoints are the primary composite endpoint together with hospitalisation for heart failure, coronary revascularisation or unstable angina. Other safety assessments will include adverse events, hypoglycaemic events and malignancies.

Enrolment for this trial is now complete and results are expected in 2014.

The Clinical Profile of Incretin-based Therapies

Jiten Vor
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As we have seen, incretin based therapies can be divided into two broad categories: DPP-4 inhibitors and GLP-1 receptor agonists. The latter includes exendine based therapies and human GLP-1 analogues.

There are a number of key characteristics that distinguish DPP-4 inhibitors from GLP-1 analogues.[72] DPP-4 inhibitors result in a reduction in HbA1c of 0.5-1.0%; are weight neutral; can be administered orally; have no significant gastrointestinal (GI) side effects; result in improved meal-related insulin secretion and reduce glucagon release; are associated with low rates of hypoglycaemia and their dose can be maintained or reduced in patients with renal impairment. GLP-1 analogues result in an HbA1c reduction of 0.6-1.5%; result in weight loss; are an injected therapy; can be associated with some GI side effects, such as nausea and diarrhoea, particularly on initiation; have a multiple mechanism of action and are associated with low rates of hypoglycaemia.[72]

A recent meta-analysis has shown that incretin based therapies are associated with significant reductions in HbA1c levels from baseline.[73]

Various studies have shown that saxagliptin, when added to metformin, SU or TZD results in significant improvements in HbA1c levels from baseline after 24 weeks of therapy.[74, 75, 76]

Saxagliptin in combination with insulin resulted in significantly greater reductions in mean HbA1c (difference: -0.41%, $p < 0.0001$) versus insulin alone.[77]

In patients with renal impairment, saxagliptin has been shown to significantly reduce HbA1c levels vs. placebo at 52 weeks (difference: -0.73, $p<0.001$).[78, 79] Saxagliptin exposure is increased by renal impairment.[80] Consequently, in patients with moderate (CrCL ≥30 to ≤50 ml/min) and severe (CrCl <30 ml/min) renal impairment, the dose should be reduced from 5 mg/day to 2.5 mg/day.[81]

With regard to side effects associated with saxagliptin, pooled data

show that hypoglycaemia levels are similar to placebo.[82] It is not associated with changes in lipid parameters, blood pressure or heart rate. There are no hepatic, skeletal myopathy or renal safety signs, no evidence of clinically meaningful effects on haematological or blood chemistry parameters and no increased cardiovascular risk.[53]

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Hyperglycaemia and Stroke – Implications for Prevention and Treatment

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Introduction

Many epidemiological studies have convincingly shown that diabetes mellitus is one of the leading risk factors for stroke, especially ischaemic stroke. Several large prospective studies report a population risk of stroke which is attributable to diabetes, (a proportion of cases which potentially could be prevented by eliminating this disease) ranging from 2 to 42%, depending on the race-ethnicity of the population studied, type of stroke suffered, and gender.[1-4] Fifteen percent of total costs of cerebrovascular disease are related to diabetes.[5] Moreover, the association between diabetes mellitus and stroke is on the rise - from 1996/1997 to 2005/2006 the numbers of admissions with diabetes and stroke recorded rose almost 2-fold - from 6.2% to 11.3% for stroke.[6] In the recent study in England it was shown that despite the decrease of admission for myocardial infarction amongst patients with diabetes for the period from 2004-2005 till 2009-2010 there was no decrease for hospital admissions due to acute stroke in diabetic patients.[7]

Diabetes is an independent risk factor of death from stroke.[8-11] Tuomilehto *et al.*[9] calculated that 16% of all stroke mortality in men and 33% in women could be directly attributed to diabetes. Patients with diabetes have higher hospital and long-term stroke mortality, more pronounced residual neurological deficits, and more severe disability and prolonged hospital stay after acute cerebrovascular accidents.[12-15]

The importance of hyperglycaemia as the risk factor for stroke, its impact on the stroke outcome and the results of the clinical trials addressing the possibility to decrease risk of stroke or improve its outcome by correction of hyperglycaemia are discussed.

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The Role of Hyperglycaemia as the Risk Factor for Stroke

As hyperglycaemia is the typical metabolic abnormality in patients with diabetes mellitus it is important to address the association between the elevated glucose levels and the risk of stroke in diabetic patients. A casual and linear relationship between hyperglycaemia and the risk of microvascular complications of diabetes has been proven beyond doubts by many epidemiological and interventional studies. In contrast, for macrovascular complications the relation with high glucose levels remains controversial. Hyperglycaemia was shown to be a significant predictor of the risk of fatal or non-fatal stroke in subjects with diabetes in a substantial number of studies.[16-22] Some studies suggest that this relation may be more evident in type 2 than type 1 diabetes mellitus.[10] Recently, in the observational prospective study of 43,933 symptom-free men it was found that each 10-unit increment of fasting plasma glucose above normal values was associated with a 6% higher risk of total stroke events.[23]

Data from the Northern Manhattan Study suggested that inappropriate glycaemic control rather that the presence of diabetes mellitus itself was associated with an increased risk of stroke. It was shown that diabetic subjects with elevated fasting blood glucose were at increased risk of stroke with the hazard ration 2.7, but those with target fasting glucose levels were not.[24] In the same study it was revealed that an association between risk of stroke and fasting glycaemia exists in African-Americans only while being non-significant in subjects of other ethnic origin.[25]

Age seems to modify the role of hyperglycaemia as a stroke risk factor. A linear increase in stroke morbidity and mortality for each 1% increment of HbA1c was found in older diabetic patients with onset of disease at an age older than 30 years, while there was no such association in younger subjects.[26, 27]

The landmark UKPDS study showed that the odds of stroke being

fatal was 1.37 per 1% HbA1c,[28] but did not confirm the importance of hyperglycaemia in stroke incidence.[29] The estimated decrease in risk of stroke for a 1% reduction in HbA1c was 4% (p=0.44).[30]

The controversy on the relation between blood glucose levels and the risk of stroke extends beyond studies in individuals with diabetes mellitus. While several studies report relations between different indices of glucose metabolism and the risk of stroke in non-diabetic individuals,[31-33] other studies do not confirm such associations.[34-36]

In a meta-analysis of 3 studies addressing the relationship between HbA1c levels and the risk of cardiovascular disease in type 2 diabetic patients the pooled relative risk for stroke was 1.17 for each 1-percentage point increase in HbA1c level.[37] In the another recent meta-analysis of 26 prospective studies it was shown each 1% increase in glycosylated haemoglobin level among patients with type 2 diabetes was associated with 11% increased risk of stroke.[38] In the analysis of the large database of National Diabetes Registry in Sweden which includes 22,135 patients with type 2 diabetes mellitus followed for 5 years 15% increased risk of stroke per 1 SD increase in updated mean HbA1c was found.[39]

We may summarise that the relationship between hyperglycaemia and stroke remains subject to debate. In this respect, the association between hyperglycaemia and cerebrovascular disease is established less strongly than the association between hyperglycaemia and coronary heart disease. Nevertheless, better understanding of the impact of hyperglycaemia on increased stroke risk is important to establish effective guidelines for stroke prevention. The results of clinical trials addressing the possibility of decreasing the risk of macrovascular complications by achieving normoglycaemia could provide the deeper insight into the role of hyperglycaemia as the stroke risk factor in diabetic patients.

Correction of Hyperglycaemia as the Tool for Prevention of Stroke

The data from large clinical trials addressing the possibility to prevent diabetic complications including stroke by achieving good metabolic control became available in the recent years.

In the long-term 17 years follow-up of type 1 diabetic patients who received intensive or standard insulin treatment in the Diabetes Control and Complications Trial (DCCT) the combined risk of stroke, myocardial infarction and cardiovascular death was 57% lower in those treated intensively, but the data did not allow to draw conclusions regarding the long-term treatment effect on stroke as a single end-point.[40] It is interesting to note that the difference in the risk of cardiovascular disease between the two treatment arms appeared long after the end of the randomised treatment period which suggest the presence of the "metabolic memory" and emphasise the need of active treatment from the early stages of the disease.

In contrast, the results of UKPDS trial did not support the hypothesis that control of glycaemia could prevent stroke in type 2 diabetic patients. Conversely, an 11% statistically non-significant increase in stroke incidence was found in the intensively treated compared to the conventionally treated diabetic patients.[41] Recently the results of three large clinical trials (ADVANCE, ACCORD, VADT) that aimed to prevent cardiovascular disease in patients with diabetes mellitus through strict glycaemic control have been presented. None of them were able to demonstrate a significant reduction of the risk of cardiovascular disease in patients intensively treated to achieve good glycaemic control.[42, 43] Furthermore, in ACCORD trial in the group of intensively treated subjects who achieved mean HbA1c levels 6.4% a significant increase of cardiovascular mortality compared to standard treated group was observed while the rate of non-fatal stroke was similar between the groups.[43]

During the last few years the several meta-analysis of the large clinical trials aiming at the achieving of normoglycaemia in patients with type 2 diabetes mellitus were published. In the large meta-analysis of 5 trials enrolled 33,040 patients with type 2 diabetes mellitus it was shown that intensive antihyperglycaemic treatment resulting in the mean reduction of HbA1c of 0.9% had no significant effect on the stroke risk.[44] In another meta-analysis based on the results of 4 landmark trials – ACCORD, ADVANCE, VADT and UKPDS it was shown that average reduction of glycated haemoglobin by 0.88% was associated with non-significant reduction of stroke risk with the HR=0.96 (0.83-1.10).[45] No reduction of the risk of non-fatal stroke was reported in another large recent meta-analysis of 6 trials enrolling 27,654 patients with type 2 diabetes mellitus with relative risk of stroke being 1.02 in the intensively treated patients.[46]

The influence of the mode of antihyperglycaemic treatment on the risk of stroke is uncertain. Mortality from cerebrovascular disease was increased to a similar extent in patients treated by oral hypoglycaemic medications or insulin compared to those on diet only.[47] Although the incidence of stroke was higher in diabetic subjects treated with insulin than in those receiving oral medications or diet this difference disappeared after adjustment for other confounding factors.[48] Stroke incidence did not differ in patients treated with chlorpromamide, glibenclamide, or insulin in the UKPDS. However, in overweight diabetic patients intensive therapy with metformin was more effective in preventing stroke compared to other intensive treatment modalities achieving a stroke reduction by 42% compared to the conventionally treated group.[49] Although in the UKPDS an early addition of metformin in sulphonylurea-treated patients did not lead to an increased stroke incidence,[49] another study showed a 2.3-fold increased mortality from stroke in patients treated with both medications compared to those treated with sulphonylurea alone.[50] However, it is not known whether such a harmful effect of this combined treatment reflects

adverse interactions of both medications or more severe diabetes course requiring the prescription of both drugs to achieve optimal metabolic control.

The PROACTIVE trial showed that pioglitazone was able to decrease the risk of recurrent stroke in patients with diabetes by 47%, while there was no effect on the prevention of a first stroke.[51] One of the possible underlying mechanisms of such protective action could be the slowing of the progression of carotid artery intima-media thickness shown for pioglitazone compared to glimepiride in CHICAGO trial.[52] In the comparison of the outcomes in patients treated with pioglitazone and rosiglitazone based on the analysis of the charts of 28,361 patients with diabetes there was no difference in the stroke rate while it was an increased mortality in those treated with rosiglitazone.[53] In the data from the large cohort of 227,571 patients covered by Medicare in the USA a significantly increased risk of stroke by 27% was shown in patients with diabetes treated with rosiglitazone compared to those on pioglitazone.[54] However, in the large RECORD trial which enrolled 4,447 patients with type 2 diabetes mellitus followed up for 5.5 years it was the statistically non-significant trend toward the decrease of the stroke risk in the group of patients treated with rosiglitazone (HR - 0.72 (0.49-1.06).[55]

However, the risks associated with the use of medications of this class (thiazolidinediones) such as increased risk of heart failure, myocardial infarction, oedema, bone fractures and weight gain probably do not allow recommending their wide use for stroke prevention.

Earlier it was suggested that oral sulfonylurea medications could adversely influence the outcome of ischaemic events. However, sulfonylurea medications were not independent predictors for increased mortality, deterioration of stroke, or stroke severity and even could have beneficial effect of the outcome of nonlacunar stroke in diabetic subjects.[56, 57]

In summary, despite control of hyperglycaemia is well proven approach to significantly decrease the risk of microvascular complications of diabetes there is no strong data supporting the possibility to halt the stroke risk in subjects with diabetes by achieving normoglycaemia.

The Role of Hyperglycaemia in Stroke Outcome

The independent impact of hyperglycaemia on the course and outcome of stroke either in diabetic or non-diabetic subjects remains subject of intense debate. Hyperglycaemia in people with stroke could result from previously known or newly manifesting diabetes or could be "transitory" in subjects with otherwise preserved glucose tolerance ("stress hyperglycaemia"). Alternatively, hyperglycaemia may independently affect and worsen the outcome of stroke or merely reflect the severity, type, site, and size of stroke being an epiphenomenon not influencing course of stroke itself. Pathogenetic mechanisms underlying the effect of hyperglycaemia on cerebral tissue could be the following: tissue acidosis, free radical formation, blood-brain barrier disruption, augmentation of cerebral oedema formation.[58, 59]

Hyperglycaemia is highly prevalent in stroke patients but the rates range from 5.6% to 40%.[60-64] This variability in estimating the prevalence of hyperglycaemia in patients with acute stroke could be attributed to differences in the time of glucose measurement and inclusion/exclusion criteria of diabetic patients.

Hyperglycaemia at admission represents a significant predictive factor of worse outcome of stroke.[65-67] In some studies the worse outcome of stroke in patients with transitory hyperglycaemia compared to those with diabetes or normoglycaemia was found.[60-62] Capes *et al.*[68] in a meta-analysis of 26 clinical studies estimated that the pooled relative risk of in-hospital or 30-day stroke mortality associated with hyperglycaemia was 3.07 (95% CI - 2.50-3.79) for non-diabetic subjects, 1.30 (95% CI - 0.49-3.43) in patients with known diabetes, and 1.93 (95% CI - 1.15-3.24) in combined cohorts of diabetic and non-diabetic cohorts. In the same meta-analysis the pooled relative risk for poor functional recovery after stroke associated with hyperglycaemia was 1.41 (95% CI – 1.16-1.73) in non-diabetic population and 1.07 (95% CI – 0.39-2.95) for diabetic and non-diabetic patients combined.[68]

The impact of hypergycaemia on the course of stroke is different in patients with and without diabetes. A strong association between hyperglycaemia and stroke mortality was noted only in non-diabetic subjects, while this was not the case in those with diabetes.[69, 70] However, in another study an increase of plasma glucose by 1 mmol/L was associated with increased stroke mortality by 1.13 only in patients with previously known diabetes but not in non-diabetic subjects.[71] Recently, in the cohort of almost 2,500 stroke patients it was confirmed that even mild elevation of admission glucose levels is an independent predictor of 30-day case fatality and hyperglycaemia represents stronger prognostic factors for patients without diabetes compared to those with diabetes.[72]

The observed worse stroke outcome in patients with transitory hyperglycaemia could be explained by a high percentage of hemorrhagic strokes among them (up to 29%). Patients with hemorrhagic stroke and hyperglycaemia had more severe stroke, lower level of consciousness on admission, higher incidence of intraventricular rupture, and worse 1-month outcome of stroke.[73] However, in the meta-analysis of Capes *et al.*[68] higher admission glucose levels were associated with an increased risk of in-hospital or 30-days mortality in non-diabetic patients suffering from ischaemic stroke while there was no such an association in case of hemorrhagic stroke either in diabetic or non-diabetic patients.

The changes of glucose levels within the first hours after stroke onset could influence stroke outcome. An increase in blood glucose levels

within 12 hours after stroke onset was shown to be related to stroke severity.[74] There was a significant correlation between blood glucose levels, outcome of stroke, and plasma cortisol levels suggesting a role of hyperglycaemia as response to stress.[75-77] Stroke patients with hyperglycaemia developed more pronounced cerebral oedema than those with normoglycaemia.[78] Transitory hyperglycaemia was associated with the severity of hemiparesis, more severe neurological deficit on admission and 24 hours later, and worse stroke outcome.[60, 79, 80] Risk for poor outcome of stroke was 1.2 for each 1.0 mmol/L increment of plasma glucose.[81] Bruno *et al.*[82] reported that in patients with acute stroke odds ratio for neurologic improvement decreased with an increase in admission glucose (OR was 0.76 per each 100 mg/dL elevation of glycaemia) and arterial hypertension exaggerates this association.[82] Hyperglycaemia at admission is associated with longer in-hospital stay of patients with stroke and higher inpatient hospital charges compared to those with normoglycaemia.[83]

There are contradictory data regarding an impact of transitory hyperglycaemia on stroke mortality for longer periods of follow-up. At day 90 after stroke onset mortality rate became almost equal between those with transitory hyperglycaemia and diabetes and did not differ either after 180 or 365 days. Furthermore, transient hyperglycaemia upon admission was not an independent risk factor for 1-year mortality after stroke.[60] However, in another study hyperglycaemia at admission independently increased the risk of death either at 30 days, 1 year, or 6 years after stroke onset.[83]

When hyperglycaemia was recorded across the range of clinical stroke subtypes, it was significantly more common and the mean admission plasma glucose was higher in subjects with total anterior circulation syndrome.[63]

However, not all studies support the idea that hyperglycaemia simply reflects the severity and type of stroke. Hyperglycaemia was significantly associated with worse stroke outcome but no such an association was seen with stroke severity, and there was no correlation between plasma norepinephrine, epinephrine and glucose levels.[84] The association of stroke mortality and hyperglycaemia independent of type, severity of stroke was found in other studies.[69, 85] The impact of hyperglycaemia on stroke outcome was estimated to be equal to adding more than 20 years to patient's age.[85]

Hyperglycaemia may have a different impact on stroke outcome in patients with different pathogenetic types of stroke depending on the integrity of collateral circulation in the damaged area. Higher admission glucose levels were significantly associated with worse stroke outcome at 3 months in subjects with nonlacunar stroke while in patients with lacunar infarction hyperglycaemia was even associated with a better outcome. Moreover, in patients with lacunar stroke and hyperglycaemia improvement of circulation with low-molecular weight heparinoids reduced the chance for a favourable outcome.[86] However, in another study the impact of hyperglycaemia on stroke mortality was more pronounced in those with lacunar infarction compared to subjects with total, partial anterior or posterior circulation syndrome.[85] The importance of preserved circulation for harmful effect of hyperglycaemia could be confirmed by the data which showed that admission blood glucose correlated negatively with the degree of neurological improvement at 24 hours after stroke onset only in reperfused but not in not-reperfused treated patients.[87]

Hyperglycaemia modifies the effect of thrombolytic treatment of patients with acute stroke leading to a higher risk of intracranial haemorrhage.[88, 89] Admission glucose levels more than 140 mg/dl were the only independent predictor for poor outcome in stroke patients treated with tissue plasminogen activator reperfusion.[87] However, in another study admission glucose level was not associated with altered effectiveness of tissue plasminogen activator.[82]

We may conclude that hyperglycaemia is associated with worse course and outcome of stroke, however, its causative role remains not proven.

Correction of Hyperglycaemia and Course of Stroke

A better understanding of the impact of hyperglycaemia on stroke course and outcome could be obtained from interventional trials aimed at achieving and maintaining normoglycaemia early after stroke onset. The largest trial addressing this issue is Glucose Insulin in Stroke Trial (GIST-UK) which enrolled 933 patients with acute stroke and hyperglycaemia. The study investigated the influence of correction of acute hyperglycaemia on stroke outcome by intravenous administration of glucose, potassium and insulin (GKI) for 24 hours to maintain capillary blood glucose within 4-7 mmol/L compared to administration of saline. The results of the trial showed that despite the overall mean plasma glucose (by 0.57 mmol/L) and mean systolic blood pressure (by 9.03 mm Hg) were significantly lower in the GKI group, treatment with GKI did not significantly reduce mortality in 90 days (30.0 vs 27.3%) and there were no significant differences for secondary outcomes.[90] There are suggestions by the authors that the study was underpowered to reveal the real advantage of correction of hyperglycaemia due to the slow speed of recruitment and smaller than expected number of subjects enrolled. However, it is quite alarming that in *post-hoc* analysis of the trial it was observed that patients receiving GKI with a 2-mmol/L or more decrease in blood glucose between baseline and 24 hours had a higher mortality at 24 hours (34%) when compared to patients with a glucose reduction of less than 2 mmol/L over the same period (22%; P=0.009).

Another smaller trial (Treatment of Hyperglycaemia in Ischaemic Stroke (THIS) addressed the same issue and enrolled patients with cerebral infarction within 12 hours after onset and a baseline glucose value 8.3 mmol/L or higher (>150 mg/dL). Forty-six patients were randomised 2:1 to aggressive treatment with continuous intravenous insulin or subcutaneous insulin injections as needed (usual care). Target glucose levels were less than 7.2 mMol/L (<130 mg/dL) in the aggressive-

treatment group and less than 11.1 mMol/L (<200 mg/dL) in the usual-care group. Glucose was monitored every 1 to 2 hours, and the protocol treatments continued for up to 72 hours. Final clinical outcomes were assessed at 3 months. Glucose levels were significantly lower in the aggressive-treatment group throughout protocol treatment (7.4 vs 10.5 mmol/L, P<0.001). However, the final clinical outcomes were non-significantly better in the aggressive-treatment group.[91]

Recently the results of the INSULINFARCT study which compared cerebral infarct growth in patients with hyperacute stroke and poststroke hyperglycaemia receiving intensive insulin therapy or usual care were published. One hundred eighty patients with MRI-proven ischaemic stroke and with National Institutes of Health Stroke Scale from 5 to 25 at admission were randomised to receive intensive insulin treatment or usual subcutaneous insulin for 24 hours regardless of admission hyperglycaemia. As expected the number of patients who reached the target capillary blood glucose less than 7 mMol/L was higher in intensively treated group but the 3-month functional outcome, mortality and serious adverse events were similar in the subcutaneous insulin and intensively treated group. Moreover, intensive insulin therapy was associated with larger infarct growths.[92] These data are in line with the results of earlier study of 40 patients with acute stroke and hyperglycaemia which found that glucose-potassium-insulin infusion did not affect cerebral infarct growth despite lowering of glucose levels and attenuating the rise of brain lactate concentration. Moreover, insulin infusion was associated with greater infarct growth in patients with persistent arterial occlusion and with high incidence of asymptomatic hypoglycaemia.[93]

It is important to note that both hyperglycaemia and hypoglycaemia can be harmful in patients with acute stroke. In the analysis of 1,446 stroke patients J-shaped association between glucose levels and functional outcome at 24 hours and 12 months was shown and the most favorable outcome was observed at those patients with glucose levels within 3.7 and 7.3 mMol/L.[94]

Quite disappointing data were presented in the recent Cochrane analysis which included seven trials involving 1,296 participants (639 participants in the intervention group and 657 in the control group). The patients with acute stroke in the treatment group had glucose levels within 4-7.5 mMol/L at the first 24 hours after acute ischaemic stroke onset. However, there was no difference between treatment and control groups in the outcome of death or disability and dependence or final neurological deficit and there was significantly increased risk of hypoglycaemia in those treated intensively.[95]

The results of the large trial – SHINE (Stroke Hyperglycaemia Insulin Network Effort) in this area are highly anticipated. SHINE is a multicentre, randomised, controlled clinical trial of 1400 patients to be conducted at 56 centres in the USA. The objective of this trial is to determine the efficacy of tight glucose control (target glucose of 80-130 mg/dL) with IV insulin infusion using a validated computerised decision support tool in hyperglycaemic ischaemic stroke patients within 12 hours of symptom onset. The outcome is measured by a validated functional outcome scale at 90 days post stroke. Also, the patients with stroke are stratified by the treatment with intravenous thrombolysis to assess the connection between glycaemic control and outcome of thrombolysis.[96]

The current guidelines of the management of patients with acute stroke based on the results of studies available today suggest that the goal for antihyperglycaemic treatment in patients with acute stroke should be to maintain glycaemia in the range between 140 mg/dl (7.8 mmol/L) and 180 mg/dl (10 mmol/L) by the following means: Critically ill patients should receive intravenous insulin infusion and all non-critically ill patients with hyperglycaemia should be managed using a subcutaneous insulin algorithm with basal, nutritional, and correctional dose components.[97, 98]

The new hypoglycaemic medications could be promising in the correction of hyperglycaemia at the setting of acute stroke without causing hypoglycaemia. Recently it was shown that glucagon-like peptide-1 receptor activation reduces ischaemic brain damage in the rats with type 2 diabetes and experimental acute stroke.[99]

The future research has to provide answers to the questions regarding the glycaemic goal in patients with acute stroke, type and rate, duration of insulin infusion in these patients, efficacy and safety of other glucose lowering medications, importance of glucose monitoring. These data will allow to improve the management of patients with acute stroke and diabetes mellitus and/or hyperglycaemia and better understand the pathogenetic significance of hyperglycaemia in the course and outcome of stroke.

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Interrelation between Prevalence Rates of Diabetes and of Malignant Neoplasms Evaluated by Crossing Different Databases: A Retrospective Study

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Introduction

Many evidences have been accrued during the last years, pointing to a significantly raised risk of cancer in diabetic patients. According to several meta-analyses the risk increases are between 20% for breast cancer, to about 200% for pancreas and liver cancer, the figures for kidney, colon-rectum, endometrium, bladder cancer and non-Hodgkin-lymphomas are somewhere between the two previous figures.[1] The unique exception to this rule is prostate cancer, where diabetes seems to be 'protective' with a relative associative risk of 0.81 (95% CI: 0.71-0.92).[2] Both type 1 and type 2 diabetes share a similar increase in risk of cancer even if type 2 diabetes has a more elevated risk, accordingly to a wide Swedish population based cohort-study.[3] However, due to the fact that over 90% of diabetic patients are affected by type 2 diabetes, all conclusions about the association between diabetes and cancer are applicable, almost totally to type 2 diabetes.

These epidemiological observations have prompted many lines of enquiry to better understand why diabetes and cancer are two ominous 'bad companions', there is in advance to say that the biological mechanisms underlying this association are unclear. Regarding this latter aspect, many factors which are traditionally linked with the pathogenesis of diabetes, seem to have a role in the link with cancer: hyperglycaemia, insulin resistance/hyperinsulinaemia, presence of overweight or obesity, either clustering or not with all clinical correlations of the metabolic syndrome. It is however outside of the aims of this review detailing the reasons as well as the basic or clinical evidences which mutually link any of these pathogenetic factors with the increment in cancer risk.

A further intriguing aspect of this 'affair', is the relation between anti-hyperglycaemic therapy and incidence of neoplastic diseases. Insulin therapy is an often investigated 'defendant' due to its known mitogenic growth, promoting properties related to the intracellular signalling cascade RAF-1-MEK-ERK, possibly triggered by exogenous insulin. Regarding this latter point it is vital to stress that endogenous hyperinsulinaemia associated with insulin resistance is the cornerstone of the hypothesis relating insulin with risk of cancer. However, we can only conclude that the possible link between insulin therapy and raised risk of cancer is really elusive. In recent years a raging controversy has upset the world of diabetes, regarding any possible relationship between chronic therapy with the long-acting insulin analogue glargine and the augmented risk of cancer.[4] Even if the most recent evidences exclude any real increment in neoplastic risk with glargine therapy,[5] the issue is far from being definitively solved, also in relation to the difficulties in excluding potential confounding variables that occur when one takes into account retrospective epidemiological studies.[6] A possible solution could be the design of prospective studies aimed at evaluating the risk of cancer in relation with use of insulin or its analogues even if it appears to be practically impossible.

All the issues concerning the relationship between diabetic therapy and risk of cancer are in addition made more complicated, considering the possible effect exerted by oral antidiabetic drugs, and especially by the possible protective role against carcinogenesis exerted by metformin.[7]

In conclusion, however, the link between cancer and diabetes has been well known and documented for a long time; this relationship is made all the more worrying by the increasing incidence and prevelance of both diseases within our population.

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His professional education includes: degree in Medicine, at the University of Florence School of Medicine; Specialty Board Certification in Clinical Pharmacology, Gastroenterology, Internal Medicine and Endocrinology at the University of Florence and Pisa, all of which he acheived *cum laude*. He has published over 100 original papers in the field of diabetes, metabolism and hypertension, and also many reviews and textbook chapters. He is a member of several scientific societies which include ESCI, ADA, EASD, and has been the Assistant Editor of the official Journal of EASD (*Diabetologia*, 1995-1997).Current research areas include: insulin resistance and atherosclerosis; gestational diabetes; obesity; hypertension; taurine; macro and microvascular complication of diabetes.

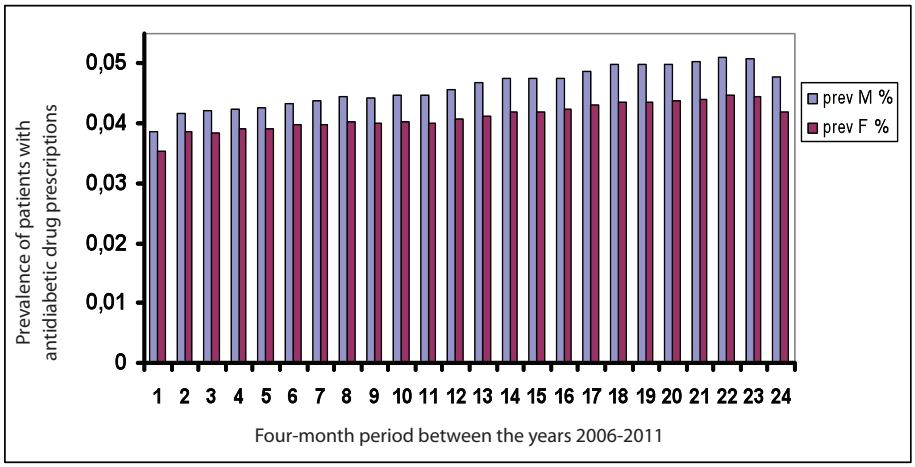


Figure. 1. Prevalence of patients with antidiabetic drug prescriptions over a four-month period between the years 2006-2011, stratified for sex (M=males; F=females) in the whole Local Health Unit of Pistoia, Italy.

Materials and Methods

With the purpose of obtaining indirect information about the relationship between malignant neoplasms and diabetes in our population during last six years we have utilised a database of the pharmaceutical service, as well as the database of exemptions from payment for services linked to the presence of cancer in our local health area which covers a population of about 280,000 inhabitants. In our Region (Tuscany, Italy), in fact, all health services linked with the presence of neoplastic diseases are exempt from payment of prescriptions, and all pharmaceutical prescriptions concerning the use of antidiabetic drugs are likewise exempt from payment and are completely reimbursed by the Regional Health Service. We had, therefore, the opportunity of crossing all database records of the pharmaceutical registry containing all patients who received prescriptions for antidiabetic drugs (oral and/or insulin), with the records of those who have obtained exemption from payment of prescriptions for diagnostic or therapeutic procedures related to malignant neoplasms. This survey covers retrospectively the period between 2006-2011. Doing so we have used, an 'index period' of the last three months of each year, because by choosing this 'period window' we had the opportunity to monitor the situation more accurately. Each prevalence rate was corrected for the total population's figure, or for the number of diabetic patients, as appropriate. Statistical analysis was performed by means of the SAS® software for Windows, ver. 8.2., USA.

Results

In our area the total population changed between 2006 and 2011 from 279,061 (134,340M/144,721F) to 293,061 inhabitants (140,626M/152,435F), and diabetes prevalence presented a similar upward trend, with the number of people who were given prescriptions of antidiabetic drugs, (expressed as a percentage rate of the total population), rose from 4.06% to 4.47% (from 4.23% to 4.48% amongst males and from 3.90% to 4.80% amongst females; figure1).

In the group of diabetic people, we noticed, over this same time, a stepwise upward increase in prevalence of patients with exemption from payment of health services for presence of neoplastic disease from 574 (5.06%) to 868 (6.62%; figure 2A).

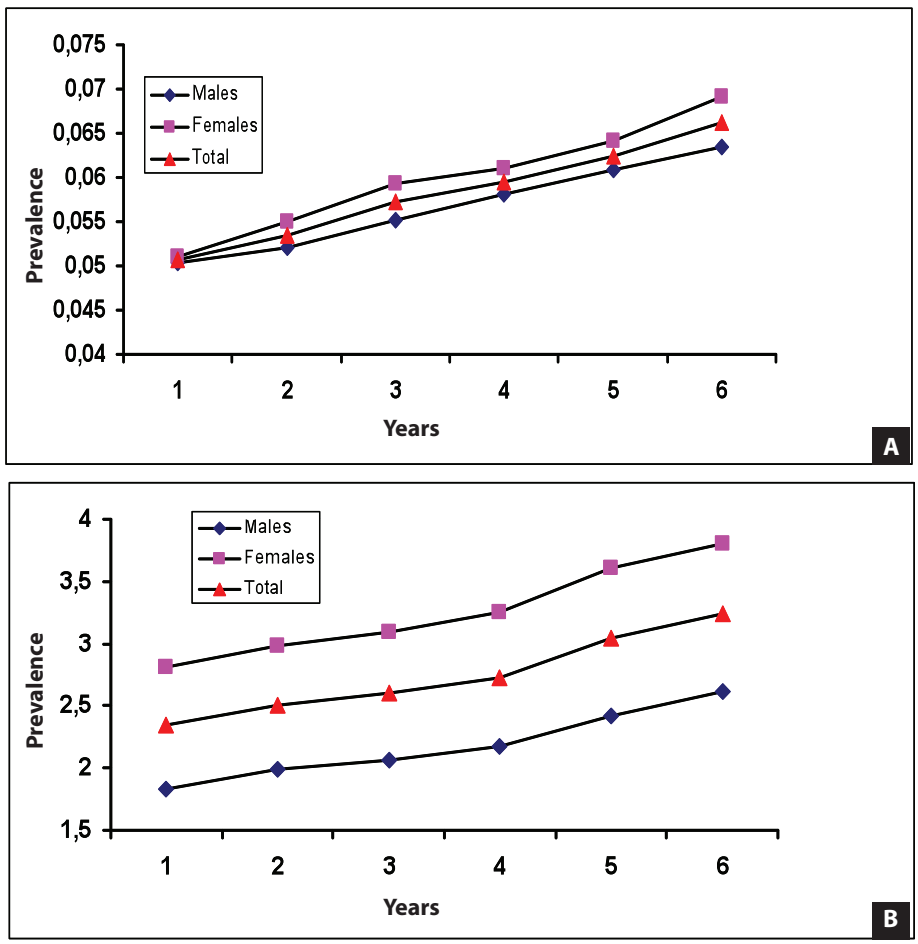
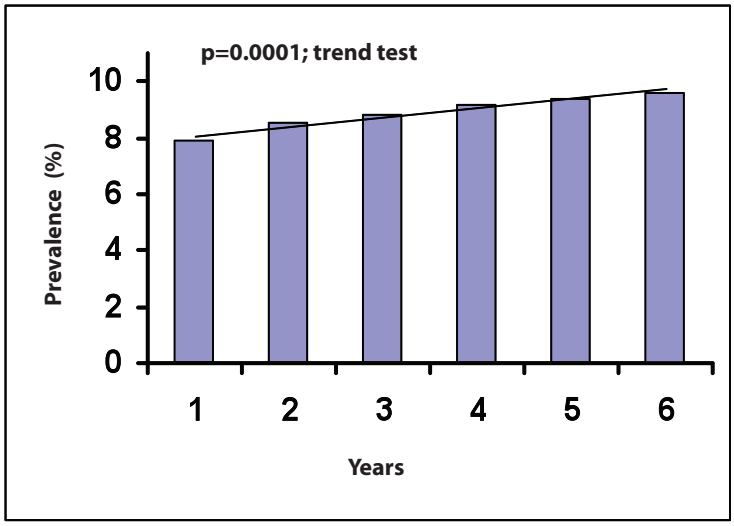


Figure. 2. Prevalence of patients with exemption from payment of prerscriptions for both diagnostic and therapeutic health services due to presence of neoplastic diseases in the last three months of years from 2006 to 2011 in diabetic **(A)** or non diabetic patients **(B)**.



Year	2006	2011
	OR (95% CI)	
	2.23 (1.13-2.89)	2.06 (1.14-2.92)

Figure. 3. Prevalence of diabetes among those who were exempted from payment for health service due to neoplastic pathology in periods covering last three months of each observation year from 2006 to 2011 in Local Health Unit of Pistoia, Italy (above). Relative risks (OR; 95%CI) of co-presence of diabetes and neoplasms in year 2006 and 2011 (below).

Among 'non diabetic' individuals there was a progressive rise of those with exemption for neoplastic pathology, from 6,267 (2.34%) to 9,057 (3.23%; figure 2B).

Specularly we observed an upward trend in the prevalence of diabetic individuals in the group of neoplastic patients (7.9% in 2006, 8.5% in 2007, 8.8% in 2008, 9.2% in 2009, 9.4% in 2010 and 9.6% in 2011; p=0.0001 for trend test). However relative risk (95% CI) of co-presence of diabetes and malignant neoplasms remained similar in 2006 and in 2011: (2.23 (1.13-2.89) in 2006 and 2.06 (1.14-2.92) in 2011), even after adjusting for age (figure. 3).

In the whole diabetic population the Males/Females (M/F) ratio was constantly >1 and, in the subgroup of diabetic patients with co-presence of exemption for neoplastic pathology, the M/F ratio was persistently < 1, ranging between 0.96 and 0.99 (figure. 4). Among non-diabetic individuals the prevalence rate of females with exemption for neoplastic pathology was persistently higher as compared with male population, and in this case the M/F ratio resulted much lower than among diabetic subjects, ranging between 0.60 and 0.62 (figure 4).

Conclusions

The hypothesis of this study was to demonstrate that it is possible to cross different databases utilising data that are routinely used for administrative purposes, with the aim of monitoring parallel epidemiological events such as the time course trend for prevalence of diabetes and of neoplasms in a population.

In summary, this preliminary study suggests three conclusions. The first is that in our population both prevalence of neoplastic diseases in diabetic patients and prevalence of diabetes in neoplastic patients are progressively growing with time, as widely expected by the temporal trends observed in most of western populations.

The second conclusion is that, in spite of increasing rates of treated diabetes, and of patients exempted from payment of prescriptions because they are affected with malignant neoplasms, the relative risk of co-presence of both pathologies remains constant with time.

And finally, the third conclusion is that diabetes prevalence is constantly higher among men than women; whilst women seem to be more exposed to 'neoplastic pathology', even if to a greater extent amongst 'non diabetic' subjects than amongst those labelled as 'diabetics' i.e. with prescription of antidiabetic medications. In other words, the risk of being affected with neoplastic diseases is more related to the male gender in diabetic patients, whilst it is more related to females in non diabetic people. Whether this is the consequence of the co-presence of other possible confounding variables (age, type of neoplasm, smoking, comorbidities, co-medication, discharges from hospital wards etc...) can not be deduced by our data.

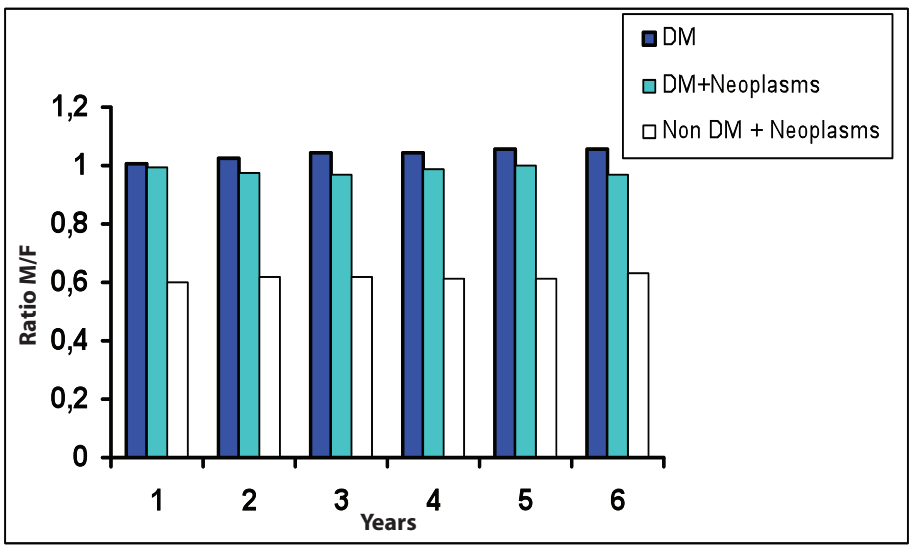


Figure. 4. Ratio of males to females (M/F) in diabetic as well as in non diabetic individuals with exemption for neoplastic pathology, stratified for each three month period over the time 2006-2011 in the population of Local Health Unit of Pistoia, Italy.

The main weakness of this study is that the database we have utilised does not contain some important information that would allow a more exact characterisation of the results. However, our main purpose was to introduce a method of investigation, and, finally, our data is preliminary. Further steps will be use this method to answer the following questions:

1. What is the relation of any single drug to any specific type of cancer? In particular, are different insulin analogues a risk factor for cancer promotion or progression and, on the other side of the coin, is metformin protective, independently of any possible confounder?

2. Is there any difference in the temporal trend of association between a particular neoplasm and diabetes?

3. Does gender difference play a real role in modulating the risk between diabetes and cancer?

Using the cross-referencing of more databases, even if some of these are mainly designed for administrative purposes, will be able to obtain reliable answers to all these questions, and, in addition, to monitor these events during the time.

Acknowledgments

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The Treatment of the Complicated Diabetic Foot

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Introduction

The complications of diabetes of the lower limbs, commonly known as diabetic foot (DF), still represent the most prevalent cause of lower extremity amputation (LEA) , it has been estimated that a limb is lost every 30 seconds worldwide, because of diabetes.[1]

This figure is bound to increase up to fourfold in the next 20 years because of the sharp increase of the incidence of diabetes and its complications.[2]

Although DF recognises a multifactorial pathogenesis in which both neuropathy, immunopathy and peripheral arterial disease (PAD) play a role, determining a cluster of contributing factors that, over a long time of exposition, lead to progressive foot pathology, it has been demostrated how PAD is the major risk factor for LEA in diabetic patients, both alone or in association with infection.[3, 4]

A recent multicentre study involving more than 1200 patients from 10 different european countries demonstrated how the presence of PAD increases significantly the risk of LEA in DF, to such an extent that the authors suggest to consider DF with PAD a different and more serious pathology compared to DF without PAD.[5]

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Beyond the risk of LEA, the ischaemic DF has been asociated with a higher cardiovascular morbidity and mortality, such that it has been indicated as a marker of severity in diabetic patients, because of the high prevalence of co-morbidity.[6]

Far from being a local problem identifyiable with a foot ulceration, the ischaemic DF is a complex and evolutive pathology in which both local and systemic aspects contribute to determine a critical condition in a fragile patient which deserves an integrated therapeutic strategy to avoid LEAs and increase the life expectancy of patients.

Until recently, the prognosis of ischaemic DF patients was depressingly bad, with a relative risk of LEA 20 times higher than in non-diabetic population, but the pioneering work that opened the way to distal surgical by-passes, and more recently the introduction of endovascular re-vascularisation and conservative surgical techniques for foot salvaging, dramatically improved the prognosis of our patients.[7, 8]

This review will focus on the management of the critical ischaemic DF patients with a modern approach which takes into account the new re-vascularisation options, as well as the local surgical management and the systemic aspects of this complex condition.

The Peculiararity of Peripheral Vascular Involvement in Diabetes

The involvement of the peripheral vascular system in the evolution of diabetes is early and frequent. More than 20% of type 2 diabetic patients show signs of PAD at diagnosis, while more than half of the patients aged more than 60 years present PAD among the features of their clinical manifestations of the diabetic syndrome.[9, 10]

In addition and independently of atherosclerotic changes, the popliteal and BK arteries of diabetic patients are characterised by increased amount of connective tissue, such as fibronectin, collagen, and glycoproteins, as well as increased amount of calcium in the medial layer named Monckeberg's sclerosis, a constellation named

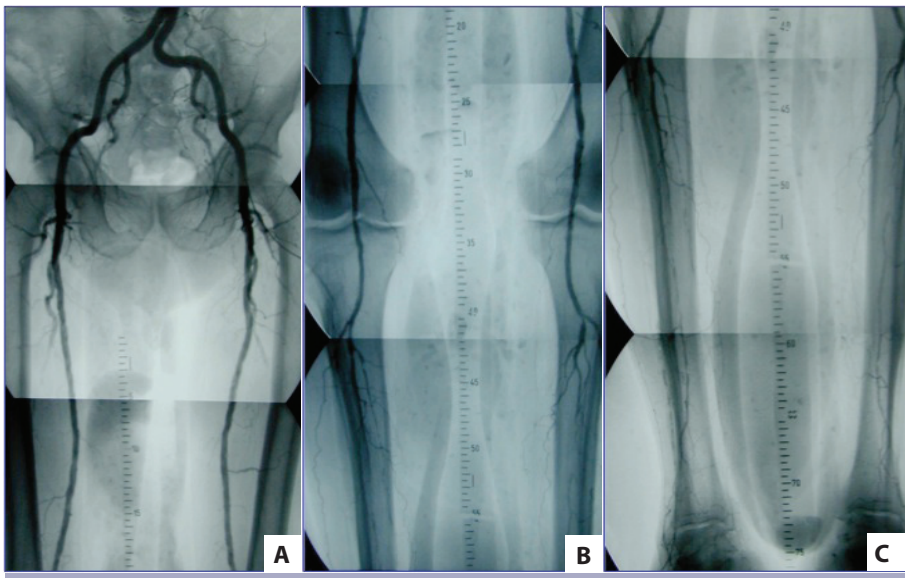

Figure 1. The characteristic angiographic presentation of peripheral diabetic macroangiopathy (DMA): Compared to a substantially preserved circulation both in the femoral (A) and popliteal (B) districts, there is a bilateral involvement of all the three vessels in the infra-popliteal district (C).

diabetic macroangiopathy (DMA). Monckeberg's medial calcification, a condition which is characterised by the absence of macrophages and lipid, is common in diabetics and occurs independently from atherosclerosis, implying different etiological mechanisms.[11]

The presence of neuropathy in the lower limb, in the same district to where the peripheral vascular involvement occurs, seems to play an important role in determining many of the differences observed in diabetic subjects: the denervation of the medium layer of the artery wall, and the consequent muscular hypotrophy, drives the diffuse deposition of calcium observed in the Monkeberg syndrome, while the reduced neurotrophic activity may explain the reduced capacity of forming collaterals.[12]

In diabetic subjects with critical limb ischaemia (CLI), collaterals contribution is typically poor due to the depression of arteriogenic and collateral growth process in response to ischaemia, particularly in BTK arteries.[13]

Particularly chronic hyperglycaemia negatively affects the different phases of arteriogenesis: impaired shear induced vasodilatation, impaired outward collateral growth, reflected in the number of collaterals and blood volume index and inhibition of monocyte chemotaxis.[12]

Moreover, the early and generalised emodynamic modifications due to the fixed neuropathic vasodilation could justify the multidistrictual involvement of the infrapopliteal arteries in DM, like can be seen in figure. 1.[14]

In a recent study, out of 2893 arterial lesions in 417 ulcerated DM patients with CLI only 1% were in the ilac arteries, while 74% were in the infrapopliteal arteries. Among these, 66% were occlusions and 50% were occlusions longer than 10 cm.[15]

Multilevel involvement was the most common condition, whereas an exclusive infrapopliteal involvement was found in only 25% of all cases.

The clnical translation of this complex and multifactorial extensive vasculopathy is a diffuse disease that affects patients 10 years earlier, without sex differences, and with a higher tendency of evolution towards severe forms, compared to the PAD occurring in non diabetic patients (Table. 1).[8]

Other characteristics of DMA are the reduced symptoms secondary to the sensitive component of neuropathy, which delay the clinical manifestation and contribute to the underestimation of the severity of the pathology at a point that trophic lesions and necrosis are common onset features of DMA.[5]

Intermittent claudication, the pathognomonic feature of PAD, is unfrequent in DMA, and, when present, indicates a clinical situation far worse than what could be expected; the same can be said about rest pain, which is uncommon but, when present, should be considered as a indicator of extreme severity.[16]

Ischaemic lesions and necrosis are common features of DMA: they localise predominantly in the margins of the foot, distally to the dorsal pedis and plantar arches, where even in presence of a large

Feature	DMA	PAD
Age at presentation (yrs)	40 -50	50 - 60
Sex	No sex prevalence	Male prevalence
Localisation	Infra-popliteal	Femoro-popliteal
Involvement	Multi-vessel/Bilateral	Single-vessel/Monolateral
Collateral circulation	Scarce	Frequent
Evolution	Critical Limb Ischaemia	Chronic Ischaemia
Clinical Symptoms	Reduced/Absent	Claudicatio/Rest pain
Trophic lesions/necosis	Frequent	Exceptional

Table 1. Differences in presentation and clinical manifestations between diabetic macro-angopathy (DMA) and peripheral arterial disease (PAD).

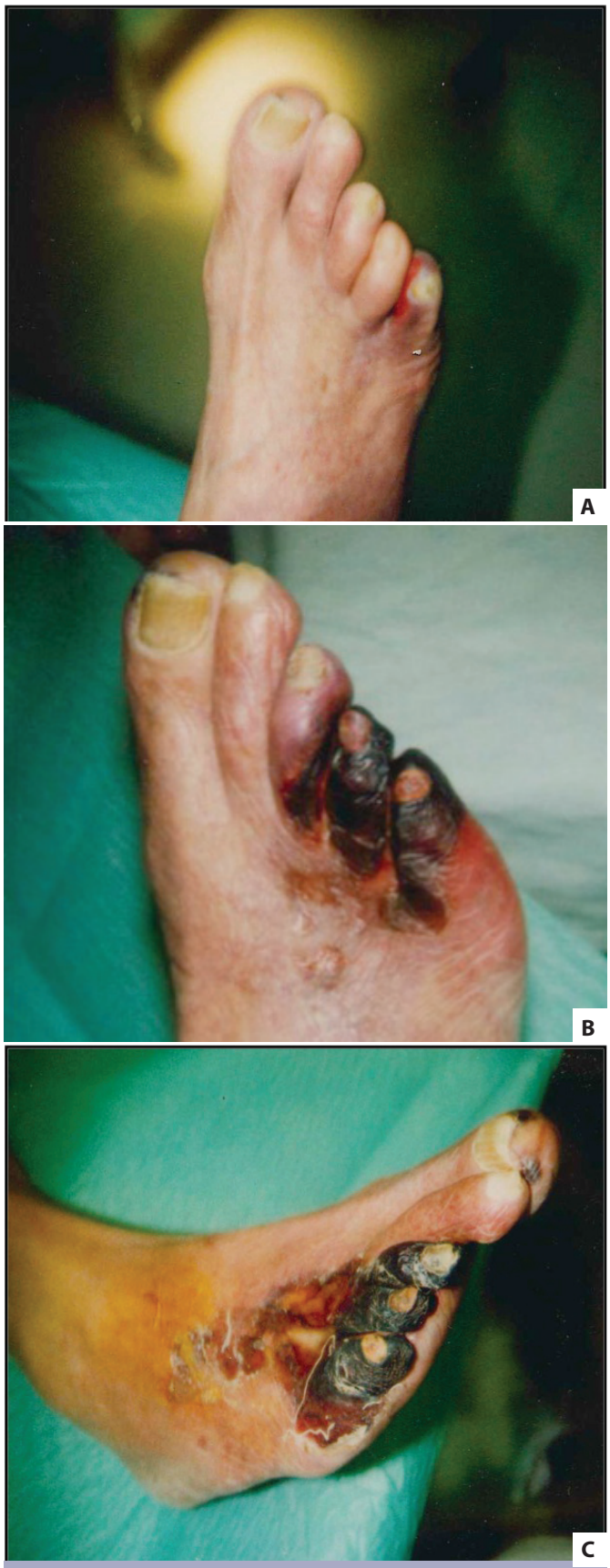

Figure 2. Typical presentation of critical limb ischaemia in the neuro-ischaemicic foot: (A) The acrocyanosis is accompanied by an intial necriosis of the 5th toe. (B) Despite the prompt endovascular revascularisation, performed in few hours from admission, the necrosis interests the 5th, the 4th, and partially the third toe. (C) 48 hours later, the gangrene extended to all the three toes, and there are initial signs of initial necrosis on the first toe. The territory of distribution of the distal artery (angiosome) is clearly identifiable.

natural anastomosis like the plantar arch, occlusion of distal arteries cannot rely on the possibility of collateral compensation. Pale skin, cyanosis, skin oedema and nail hypotrophy, associated with reduction in skin temperature, are frequent signs of DMA and should be searched any time the condition is suspected, as well as the absence of peripheral arterial pulses at the ankle.[10]
Whenever, despite the absence of rest pain, skin lesions or necrosis are present together with a measured significant reduction of blood pressure at the ankle (<50 mmHg) or at the first toe (<30 mmHg), critical limb ischaemia (CLI) should be suspected in diabetic patients.[17]

In figure. 2, a typical case of CLI due to DMA is reported: the rapid evolution of the local conditions, despite the prompt endovascular revascularisation led to the gangrene of the forefoot in less than 48 hrs. Noticeable was the absence of pain, common in DF patients, which delayed the referral from the GP to our observation. At the admission the ankle pressure was 40 mmHg and TcPO2 was 9 mmHg.

Indications to Revascularisation

The possibility of restoring the peripheral direct blood supply to the foot with surgical and endovascular techniques changed the prognosis of the DMA and contributed to significantly reducing the rate of lower limb amputations in our patients.[18, 19]

What was considered an unavoidably worsening condition has gradually turned in a treatable disease, at least in a majority of cases, thanks to a process similar to that which, thirty years ago changed the clinical course of myocardial ischaemia.

The progress in the operative techniques, as well as the impressive technological upgrade, rapidly extended the indications to revascularisation for DMA, from a limb-salvage procedure strictly reserved for extremely severe cases, to a more suitable option to address a wider range of patients, depending on the degree of severity of local and systemic conditions, as part of an integrated therapeutic strategy.[20]

CLI still remains the clinical indication for revascularisation, as indicated by all clinical guidelines, but its definition has been adapted in many experienced centres of excellence, to the peculiar features of DMA.[21 - 24]

In particular, the systemic clinical evaluation of the cases acquired more relevance compared to a rigid interpretation of the signs and symptoms, because of the frequent co-morbidity of these patients, which influences the decision making process about the therapeutic strategy.

Thus, the same local condition may lead to different therapeutic options depending on the general condition of the patients, especially when renal and cardiac insufficiency complicate, as frequently happens, the scenario.[25]

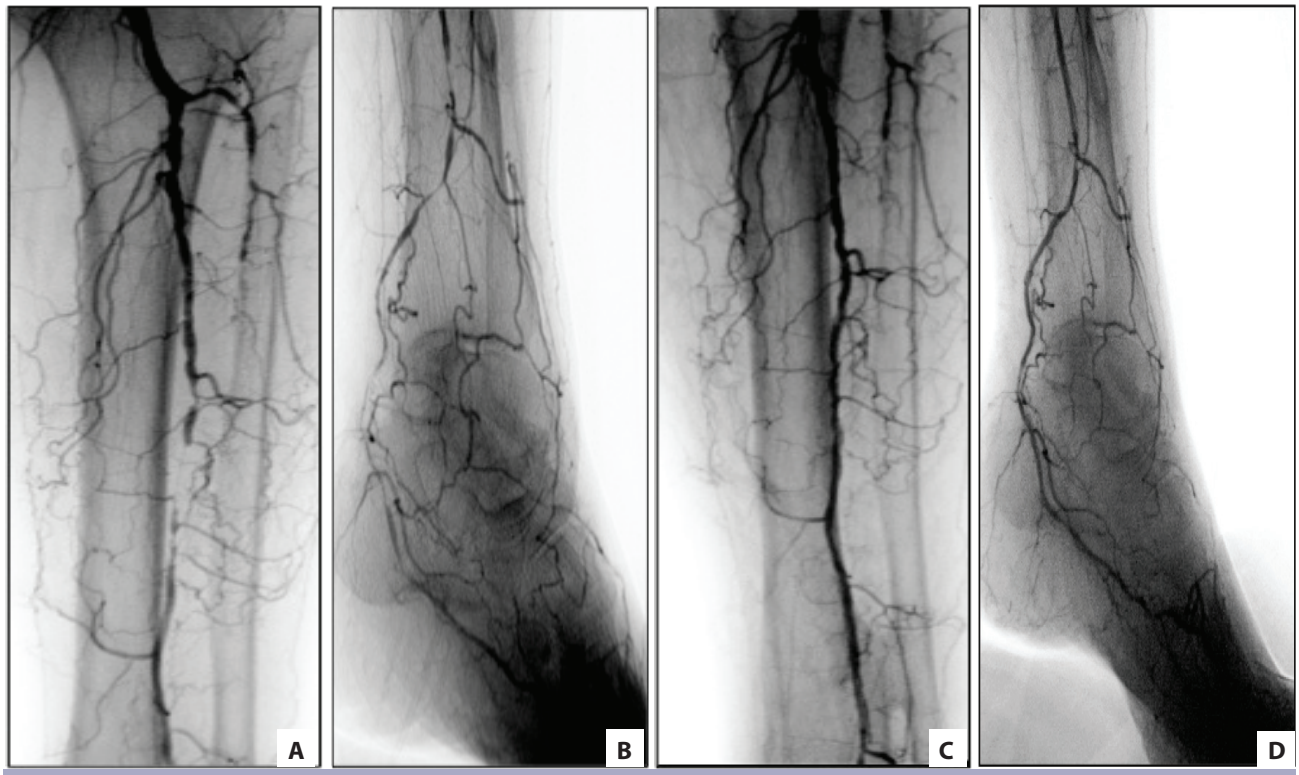

Figure 3. (A) Occlusion of peroneal artery at the lower leg. This artery is actually the only one recognisable in the leg, since both posterior and anterior tibial arteries are occluded at the origin. (B) Distally, the peroneal artery, after a critical stenosis, through a comunicant recanalises the plantar arch, which is visible, although with multiple stenosis up to the forefoot. With multple angioplasties, in the same session, both the peroneal in the leg (C), and the plantar arch in the foot (D) are successfully recanalised, bringing direct blood flow to the forefoot.

The wider diffusion of the use of contrast medium, both for coronary and peripheral revascularisation increased the number of cases of contrast medium induced nephropathy (CMIN), which has been estimated to be among the most frequent causes of acute renal failures in admitted patients.[26, 27]

The strategies which have been demonstrated to be effective in preventing and eventually treating CMIN include the hydration of patients with saline, the use of bicarbonate and acetyl-cisteine as detoxificant and, eventually, emofiltration.[28, 29]

Thanks to these preventive measures, and to the adoption of advanced technical solution, like low-osmolarity contrast media, the dilution of contrast media with saline and the limitation of the number of diagnostic procedures in favour of the "one-step approach" permitted the extension of the revascularisation procedures also to patients with an impaired renal function.[25, 30, 31]

Another important aspect is the one related to the risk/benefit ratio of the revascularisation procedures, and to the quality of life of the patients.

Though the risks related to the interventions have been significantly reduced in the last few years, both surgical and endovascular procedures still maintain a risk profile which should be proportionated to the characteristics of the single patients: a bedridden patient with lower limb anchilosis and CLI is not a candidate for a potentially risky revascularising procedure but would eventually profit of a major amputation, the same consideration could be applied to patients with a short life expectancy.[32]

On the other side, the psychological refusal for amputation may constitute, in some patients, an additional indication for a revascularisation attempt.

In any case, a major amputation should never be performed without an in-deep accurate evaluation of the lower limb circulation aimed to explore the possibility of a revascularisation, performed by a multidisciplinary team involving the diabetologist, the vascular surgeon and the endovascular specialist.[33]

Endovascular, Surgical and Combined Approaches

The first reports of peripheral revascularisation in diabetic patients date back to the early eighties and are the results of the work carried on at the Vascular Surgery Department of the Deaconess Hospital in Boston which, for the first time, demonstrated that giving direct flow to a foot artery with a pedal surgical bypass was not only feasible in diabetic patients, but that it also was able to stop the progression of CLI, and to produce durable results, changing the fate of a large number of patients otherwise candidated to amputation.[34, 35]

For a long period the surgical approach, with pedal by-pass approach, was considered the standard for the treatment of DMA, mainly because

of the multidistrictual infrapopliteal localisation of the lesions, while the endovascular approach was limited to the femoro-popliteal disease, which characterises PAD.

This philosophy was captured and encrypted in the guidelines produced both by the intersociety consensus for the management of peripheral arterial disease (TASC II) and by the American Heart Association and American College of Cardiology Association (AHA/ACA) Guidelines which *de facto* contraindicated the endovascular approach for long, multiple and infrapopliteal lesions, the typical pattern of DMA.[17, 36]

In the late nineties, thanks to the pioneering experience maturated from the collaboration between diabetologists and endovascular interventionists in Italy, the endovascular approach was proposed as a valid alternative to the traditional surgical techniques; Faglia *et al.* demonstrated, in a seminal multicentre prospective trial, how endovascular procedures reduced dramatically the rate of amputations in a large cohort of patients followed up to five years after the procedure.[18]

The study had a wide resonance - though it elicited some criticism for its design, and more recently other authors reported similar results, like DeRubertis *et al*., who, in a cohort of 1000 patients undergoing to percutaneous endovascular revascularisation at the lower limb, reported a 2-year secondary patency of 80%, concluding that PTA "should be considered first-line therapy in patients with chronic lower extremity ischaemia".[38]

The application of endovascular techniques extended the possibilities of intervention both transversally, because, due to its lower risk profile, more patients with more severe systemic conditions could access the revascularisation, and longitudinally, because due its reproducibility, the single patient could repeat the procedure in case of recurrences.

As a result of this approach, new indications emerged, for example the dyalised patients, and the geriatric ones, who could profit from the benefits of a very effective intervention without running the risk of a major surgical procedure.[32, 33]

A multicentre prospective trial comparing surgical and endovascular strategies in patients who were suitable for both the indications, demonstrated a substantial equivalence of the procedures in terms of efficacy, with a better safety profile for endovascular compared to surgery, and a containment of costs as well.[39]

An intention-to-treat analysis of the results of the trial after a five-year follow-up confirmed the previous results for the whole cohort of patients both for amputation-free (AFS) and overall survival (OS), but showed a significant improvement in OS in the cohort of patients who survived more than 2 years from the revascularisation when treated with by-pass compared to the ones treated with angioplasty.[40]

Another aspect of the diffusion of the endovascular procedure is related to the evolution of the techniques and materials, that produce a significant increase of the technical possibilities for many different options in such a complex field as DMA; from subintimal revascularisation to the angioplasty of collaterals to the application of drug-eluting stents to cryoplasty, the clinical experiences in the field multiplicated, though a lack of specific solid evidence characterises most of them.[41, 42]

In figure. 3, a typical distal PTA in DMA is shown, recanalising posterior tibial artery at the ankle level and restoring plantar arch in a CLI patient, with extensive lesions in the forefoot.

Vascular surgery has changed in recent years, increasing the indications and therapeutic options for patients with DMA. Vascular surgeons are becoming more and more convinced by the usefulness of the endovascular approach and insert this option amongst the range of their interventional choices.[43, 44]

A promising option could be the possibility of integrating endovascular and traditional surgical techniques in a way that also addresses DMA, since now those who are unsuitable for endovascular or tradtionalsurgical tenchinques may effectively be treated by a combination of both; a femoropopliteal by-pass may be integrated with an angioplasty of the tibial and peroneal arteries via femoral approach or a surgically exposed popliteal artery, to ensure both direct blood flow to the foot and to substantially increase the run-off and to increase the durability of the by-pass.[45]

Another aspect that emerged in recent years was the possibility of repeating a revascularising procedure in a patient in which a previous one had failed or, as very frequently happens in DMA, a restenosis occurs after a period of patency, re-creating a context of CLI.[46]

In many specialised centres there are diabetic patients who underwent more than one endovascular procedure in the same district, eventually with different technical solutions, each time with the indication of limb salvage.

The Role of Medical Therapy

Although to a lesser extent than in the past; thanks to improvement in techniques and to the extention of the indications for revascularisation, there still remains a number of DMA patients for which revascularisation, endovascular or surgical, is not indicated or not feasible. The contraindications come from the general conditions of the patients; those who may be simply too ill to sustain any invasive procedure, or those who have a short life expectancy, or from the local vascular conditions , which may be too compromised to allow an intervention.

While in the first case the evaluation is only related to the actual conditions of the patient, in the second case it is also related to the expertise of the centre which manages the case: depending on their expertise, different specialists would make different decisions in the same situation.

Since the experience plays a crucial role from this point of view, it would be advisable that any case in which revascularisation has been judged not feasible would be submitted to a second opinion in centre with documented activity in the specialistic field of lower limb revascularisation in DMA.[34]

In cases where the impossibility of performing a revascularisation is documented, there are options that can be evaluated as alternatives to a major amputation.

Iloprost proved to reduce the rate of amputation and to extend the survival of limbs in DMA patients with CLI, both as an alternative to revascularsation and as an adjunct to it.[47, 48]

Melillo *et al*. in a cohort of patients with DM not suitable for vascular reconstruction, demonstrated how repeated cycles of ilorprost infusion were able to improve TcPO2 and save the limb of a significant number patients, reducing rest pain as well.[49] Iloprost infusion still has been confirmed as a suitable option in case of impossible re-vascularisation also in the TASC II guidelines.[17]

A very important issue is represented by the antithrombotic therapy in patients with DMA, both as an adjuvant to revascularissations and as a medical chronic therapy *per se*.

Despite its relevance, no definitive evidence is available in diabetic patients with peripheral arterial disease, although a variety of therapeutic regimens have been proposed.[50-52]

Antiplatelet therapy has been proven to be effective in reducing acute cardiovascular events in diabetic patients with multidistrictual macroangiopathy, and to extend the duration of revascularisations in a significant number of trials, and their chronic administration in these patients is recommended by diabetologic societies' guidelines.[17, 37, 53]

Nevetheless, there is not yet a definitive agreement as far as agents, doses or associations of drugs are concerned, although the majority of the authors are favourable to the use of more than one agent in diabetic patients with DMA.[54-56]

Anticoagulants have a limited role in patients with multiple involvement of both the peripheral and cartoid district, to prevent stroke, expecially when chronic myocardial ischaemia is present.[57-58] Low molecular weight heparins have been proposed as a possible alternative to revascularisation when ischaemic pain is present and the quality of patients is impaired,[58] and a multicentre prospective trial is ongoing to challenge this hypothesis.

Hyperbaric Oxygen (HBO) therapy was proposed as a etiologic treatment for CLI before endovascular revascularisation became available for the majority of cases; though its still diffuse application in these indications, the evidence behind it has been evaluate too scarce to confirm its use as a first line treatment in CLI. Rather, a complementary application, to maximise the effect of revascularisation have been proposed in DMA patients with CLI.[59-61]

Local and Systemic Management of the Ischaemic Diabetes Foot Patient

As the EURODIALE study recently confirmed, peripheral ischaemia is frequently associated with infection in diabetic patients and the consequences of this pernicious association will most likely lead patients to a major amputation, while the frequent association of systemic co-morbidities exposes them to a higher risk of mortality.[5, 6]

Thus, any realistic treatment strategy for these patients has to encompass either the management of the local aspects of the pathology at the level of the foot and the systemic aspects of the multi-systemic evolutive disease.

At the level of the foot the ischaemic pathology determines not only a higher prevalence of infections, which range from superficial soft tissue to deep fascial infection, from abscesses to osteomyelitis, but also the ischaemic necrosis of segments of the foot; the contemporary presence of necrosis and infection determinates the gangrene.

All of these conditions deserve a surgical approach, aimed in draining and debriding incase of infection, and in eliminating the necrosis in case of necrosis or gangrene.[62]

Thus surgery plays a crucial role in the treatment of the ischaemic diabetic foot, alongside and in conjunction with revascularisation: its application should be finalised to restore the function of the revascularised foot, eliminating the part of it which are no longer viable, and reconstructing an organ which is efficient from a biomechanical point of view.[63] In figure. 4, a clinical case is reported as an example.

Also the coordination of the surgical management of the foot with the revascularisation procedures is important; while in case of necrosis the surgical intervention is usually performed after the revascularisation, to profit of the restored vascular conditions, in case of acute infection or gangrene surgery should be performed as soon as possible, to avoid the local diffusion of the pathology and the systemic consequences. Faglia *et al.* demonstrated how, in a cohort of patients with infection or gangrene, those who received a surgical

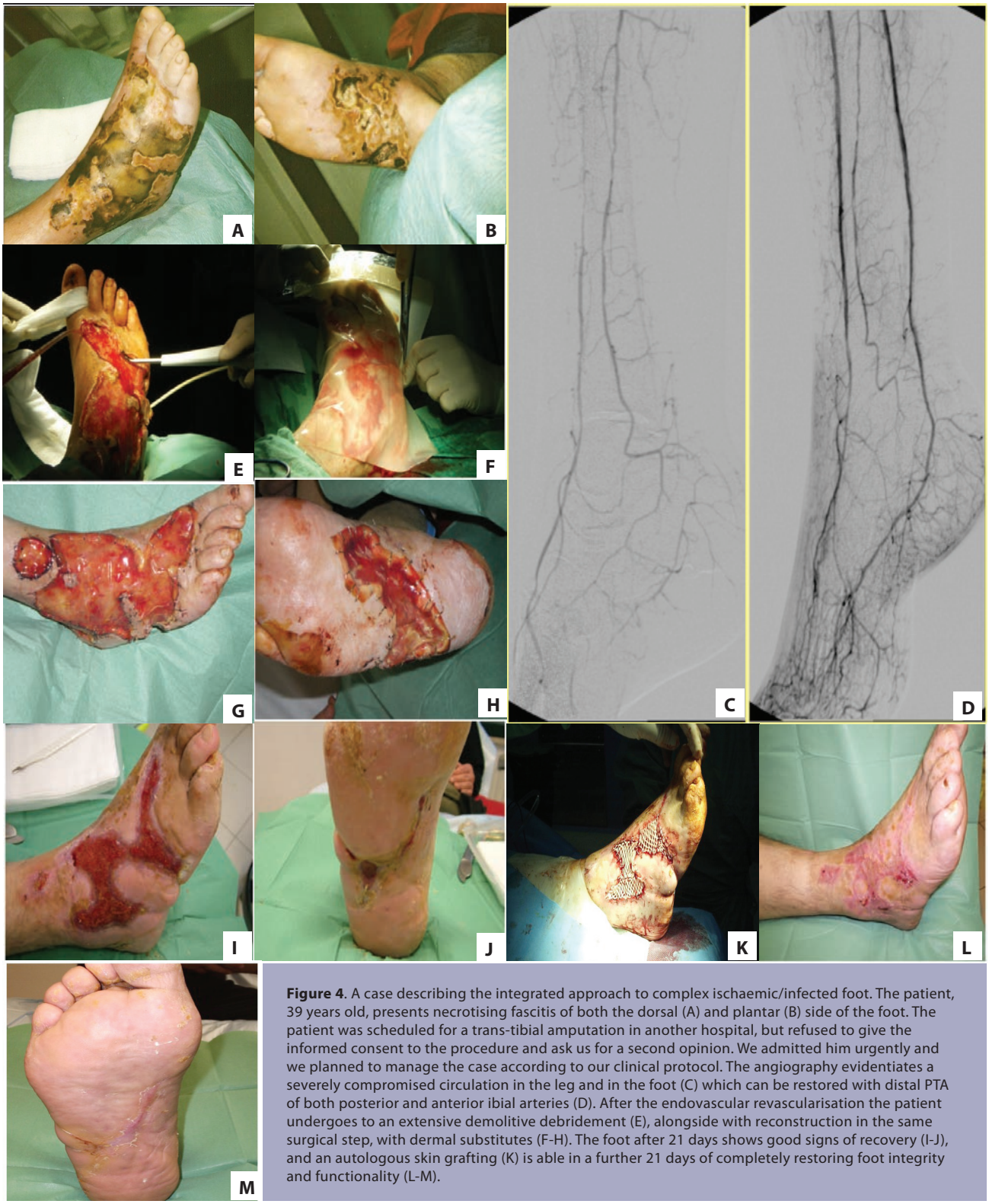

Figure 4. A case describing the integrated approach to complex ischaemic/infected foot. The patient, 39 years old, presents necrotising fascitis of both the dorsal (A) and plantar (B) side of the foot. The patient was scheduled for a trans-tibial amputation in another hospital, but refused to give the informed consent to the procedure and ask us for a second opinion. We admitted him urgently and we planned to manage the case according to our clinical protocol. The angiography evidentiates a severely compromised circulation in the leg and in the foot (C) which can be restored with distal PTA of both posterior and anterior ibial arteries (D). After the endovascular revascularisation the patient undergoes to an extensive demolitive debridement (E), alongside with reconstruction in the same surgical step, with dermal substitutes (F-H). The foot after 21 days shows good signs of recovery (I-J), and an autologous skin grafting (K) is able in a further 21 days of completely restoring foot integrity and functionality (L-M).

intervention within 24 hrs from diagnosis ended with a more favourable outcome than those in which the intervention was delayed for different reasons.[64]

The management of the systemic aspects of the pathology play a crucial role, not only in ensuring the success of the actual condition of the patients, but also in improving their prognosis, since it has been noted how the mortality rate of patients is higher than that of many forms of cancer.[65]

Evaluating cardiovascular, renal and general metabolic condition of patients at admission, stabilising and monitoring them throughout the clinical management of the case is mandatory, expecially when renal or left ventricular insufficiency is present. This, in the view not only of the high mortality rate, but also of the low prevalence of symptoms due to the presence of peripheral neuropathy, is a warranty for the patient.[66, 67]

Our experience in the integrated management of the ischaemic DF,

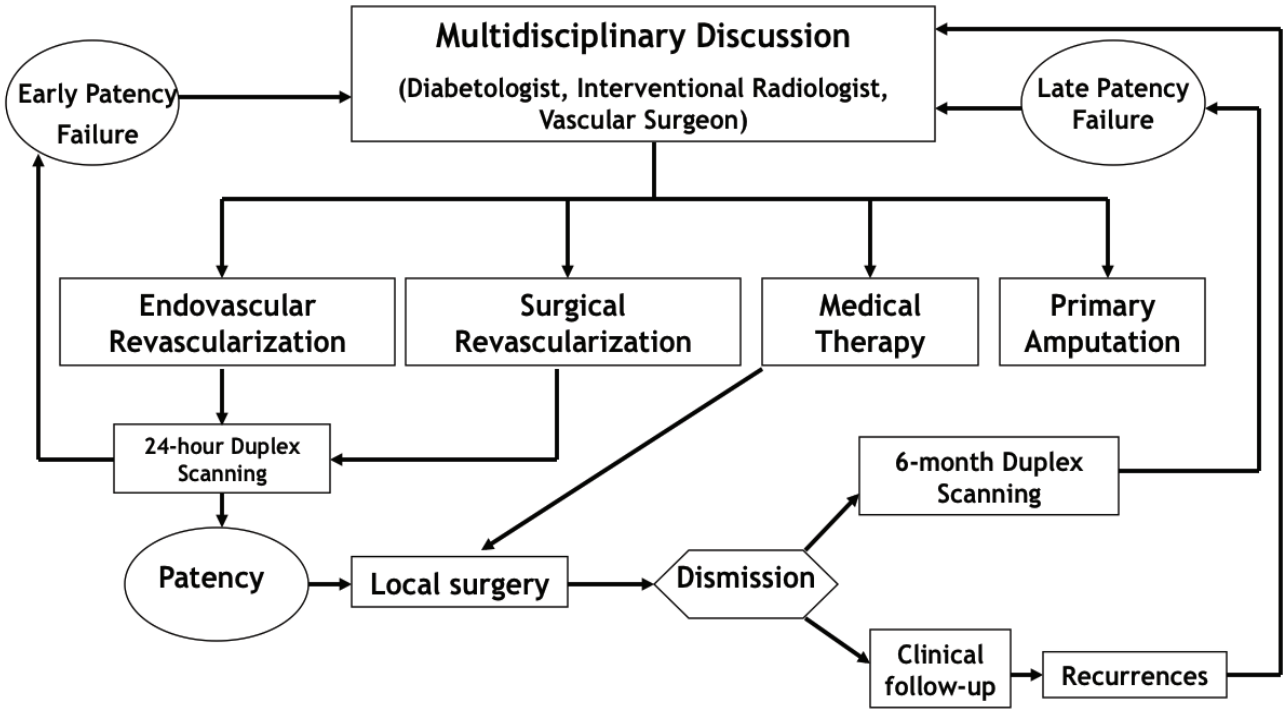

Figure 5. The algorythm for the integrated management of the patients with CLI and acute DF in the DF Section of the Unversity Hospital of Pisa. Modified from.[68]

lasting more that 20 years, confirmed the efficacy of this approach. A recently published retrospective analysis of three years of consecutive patients with CLI managed according to the algorythm described in figure. 5 demonstrated how more than 95% could be effectively revascularised, and how more than 90% could save the limb at the three-year follow up .[68]

Evaluation of Outcomes

From a patient's perspective, amputation-free survival, healing of the ulceration, relief of pain and prevention of recurrences have to be considered the most important marker of success of a revascularisation of lower limbs, although they are poorly quantifiable and need to be integrated by quantitative measures.

In recent times, guidelines still reflect this opinion, the success of revascularising interventions was measured by the patency of the vessels treated, irrespectively of the actual clinical outcomes.[69]

This way of looking at things, beyond being reductive, since it does not take into account the reason why the procedure has been performed, is particularly difficult to apply to DMA, a multi-level vascular condition, in which the choice of treating one vessel instead of another one depends on the local conditions, by the expertise of the operator and by the vascular anatomy, where the artery feeding the lesion is to be preferred.[46]

In more recent times, due to the clinical experiences of a large cohort of patients, a new and more rational approach to the evaluation of revascularisation has been developed, which takes into account the clinical conditions and the functional parameters besides the technical outcomes.[70]

The Ankle-Brachial Pressure Index (ABPI) has, for a long time, been indicated as the parameter of reference when assessing the vascular conditions of the limb; unfortunately some 20–25 % of DMA patients have vascular calcifications that interfere with pressure determination at the ankle, making ABPI not adequate.[71]

Trans-cutaneous oxygen tension (TcPO2) measured at the dorsum of the foot replaced ABPI in diabetic patients as a trustable indicator of local vascular conditions; it is a non-invasive measurement that measure the O2 concentration in tissues, as a variable dependent from local vascular supply. When accurately performed it has been demonstrated to correlate with clinical outcomes and limb salvage.[72]

Also skin temperature, monitored with a infra-red thermometer is a reliable indicator of blood supply, although less precise than TcPO2, and an be considered as a integrated measure to determine when evaluating the results of revascularisation.[73]

The local condition of the lesions are important to evaluate the success of a revascularision procedure: Sheehan *et al.* demonstrated how the reduction of the ulcers' area in the first weeks after the intervention can be a reliable predictor of outcome in diabetic patients.[74]

Area, depth, and local conditions of the lesions, as well as the eventual persistence of pain, are part of the clinical evaluation of the procedures

Feature	Successful	Consider a re-PTA	Consider amputation
ΔTcPO2	>30 mmHg	30 - 10 mmHg	<10 mmHg
Wound area	Reduced	Unchanged	Increased
Δ skin temperature	>3° C	3° C - 1° C	<1° C
Cyanosis[1]	Absent	Present	Increased
Necrosis[1]	Absent	Present	Increased
Pain[1]	Absent	Present	Increased
[1]If present at baseline			

Table 2. Decision grid in the clinical evaluation of a revascularisation procedure - Modified from.[74]

and can all be integrated in a decisional grid which may help in the strict follow-up that such patients deserve , as reported in Table. 2.[75] The longitudinal observation of the features of the lesions, and their stratification according to the Texas University Score System (TUSS) is another important point to take into account, since the changing in the TUSS can be considered as an index of improvement, or deterioration, of local perfusion.[76]

TUSS actually identifies four worsening types of lesions, from 0 (no open lesion) to 3 (lesion penetrating to the joint or bone), further characterised by a letter from A (no ischaemia, no infection), to B (infection), C (ischaemia) and D (ischaemia and infection), which takes into account the presence of these conditions that may complicate the evolution of the ulceation at any level of tissue involvement. The TUSS has been validated in a large DF population and has confirmed its reliability in identifying and stratifying the DF patients according to their amputative risk.[76]

Recently, data coming from many countries reported a consitent reduction of major amputation in DF patients; although it would be difficult to evaluate all the possible contributors to these important results, at least in one case the parallel increase of revascularisation procedures at lower limbs has been correlated to the significant reduction of lower extremity amputation over a five-year duration of follow-up.[7, 77]

Conclusions

Revascularisation represents the etiologic therapy for the critically ischaemic diabetic foot, and its implementation in the integrated managment of this pathology favourably changed the prognosis of our patients.

Endovascular procedures in our opinion should be considered as a first choice in DMA patients because of their wider indication profile, for the repeatability and safety, but also surgical and combined approaches should be evaluated by a multi-disciplinary team when CLI is present.

The indications for the revascularisation and the evaluation of results should take into account the actual clinical conditions of the patients and not rely only on the vascular pattern as described by angiography.

Due to the coexisting co-morbidities, revascularisation, local surgery and systemic management of the patients should be considered as integral parts of the therapeutic approach and critical patients should, preferably, be referred to specialised centres with a documented expertise in the field to be managed according to the best clinical practice guidelines, before considering a major amputation.

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The Diabetic Foot - An Approach to Pathophysiology, Diagnostics and Treatment

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Introduction

Diabetes mellitus is associated with accelerated atherosclerosis with an increased risk of micro and macrovascular complications.[1-4] Foot ulcers in patients with diabetes are common with serious implications, including leg amputations.[5] The majority of leg amputations are caused by peripheral arterial disease (PAD) often superimposed by deep skin infection. Endothelial dysfunction and neuropathy are early disturbances in the atherosclerotic process and contribute to microvascular dysfunction and precede the development of foot ulcers.[6, 7] The diabetic PAD has a more distal distribution engaging the profunda femoris and infrapopliteal segments more often when compared to non-diabetics,[8] suggesting this is due to the multifactorial disturbances such as hyperglycaemia, hypertension and dyslipidaemia, often seen in these patients. A multidisciplinary approach to diabetic foot complications reduces amputation rates considerably, which was recently published by the *International Working Group* on the Diabetic Foot (IWGDF).[9] This review will briefly discuss the molecular disturbances and the management of the diabetic foot ulcer.

Pathophysiology

Peripheral Neuropathy

Peripheral neuropathy is an important contributor to the development of foot ulcers in patients with diabetes. Sensorial neuropathy leads to an inability to feel appropriate protective pain including pressure and temperature sensations, as well as proprioception, thus leaving the foot vulnerable to minor injuries. Motor neuropathy, is closed associated with microvascular dysfunction and may further, in conjunction with deteriorating proprioception, cause foot deformities with limited joint mobility, callus formation, subcutaneous haemorrhage and ulcerations.[10-12]

Peripheral Vascular Dysfunction

Microvascular Dysfunction

Endothelial dysfunction, often refered to as an imbalance in the production of vasodilator factors e.g. nitric oxide (NO), on one hand, and vasoconstricting factors e.g. endothelin-1 (ET-1), on the other hand, is an early disturbance in the atherosclerotic process contributing to the deteriorating function in the skin circulation. Microvascular dysfunction is considered be caused by a combination of factors, such as precapillary sphincter dysfunction e.g. loss of sympathetic vasomotor autoregulation, and arteriovenous shunting which pooling the blood to the venules bypassing the capillary circulation.[13] Moreover, disruption of the endothelial balance exposes the vasculature to prothrombotic and proatherogenic conditions, which may ultimately result in vasoconstriction, adherence of leukocytes, activation of platelets, impaired coagulation, vascular inflammation, atherosclerosis and thrombosis.

One unifying hypothesis, explaining the crucial role of hyperglycaemia and endothelial dysfunction, is that increases in glycolysis and flux, through the tricarboxylic acid cycle, generate a high potential across the inner mitochondrial membrane and thus prolong the half-life of reduced coenzyme Q, which mediates a pronounced elevation in the production of superoxide by endothelial cells and oxidative stress.[14] This excess superoxide production inhibits the glycolytic enzyme glycerylaldehyde-3-phosphate dehydrogenase, resulting in accumulation of upstream glycolytic metabolites.[15] Subsequently, accumulation of glycerol-3-phosphate induces *de novo* synthesis of diacylglycerol which, in turn, activates protein kinases C (PKC) -β and –γ, important contributors to the cardiovascular complications of diabetes.[16] Activation of PKC by hyperglycaemia is known to up-regulate expression of ET-1 and angiotensin-II in endothelial cells cultures.[17] Furthermore, inhibition of PKC-β prevents the endothelial dysfunction induced by acute hyperglycaemia in healthy individuals.[18] Incubation of endothelial cells in the presence of high concentrations of glucose causes reactive oxygen species (ROS) mediated activation of the hexosamine pathway, which promotes O-linked glycosylation of endothelial nitric oxide synthase (eNOS) and subsequent inhibition via posttranslational modification by phosphatidylinositol kinase (PI-3K)/Akt.[19, 20] Impairment in these pathways may contribute to a diminished vasodilator response in the diabetic state.[21, 22] Other factors considered to contribute to impaired perfusion are reduction in neurogenic inflammation[23] and hypercoagulability changes with increased plasma fibrinogen activity.[24]

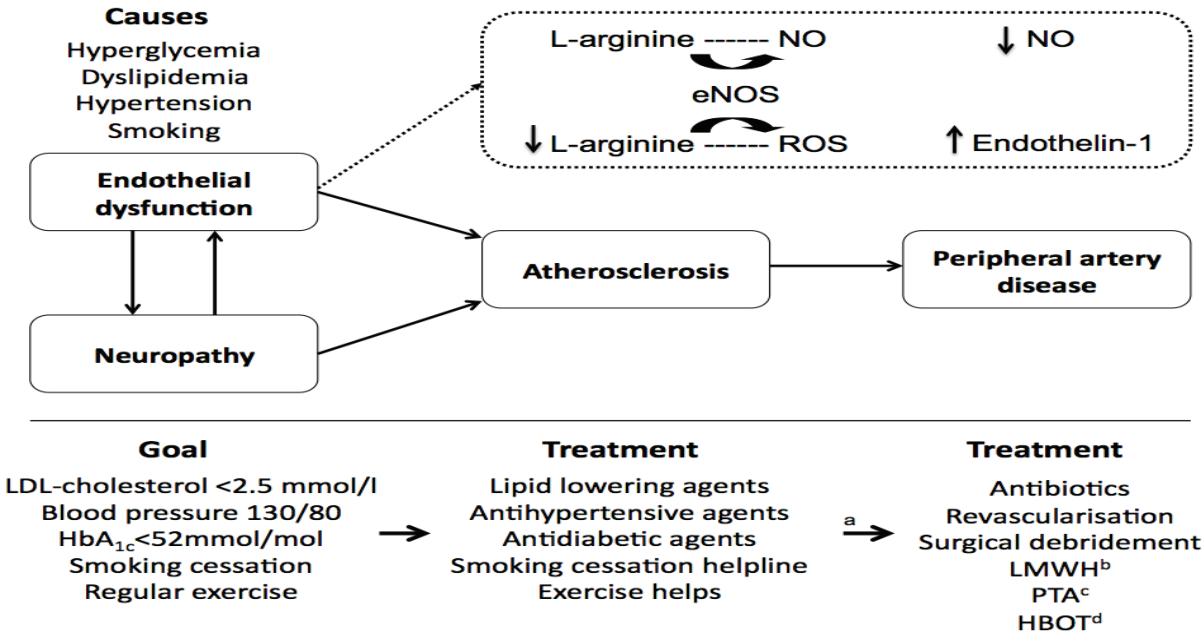

Figure 1. Endothelial dysfunction and neuropathy are early contributors in the development of foot ulcers in patients with diabetes. This simplified scheme depicts a unifying hypothesis, explaining the crucial role of contributing cardiovascular risk factors in diabetes i.e. hyperglycaemia, dyslipidaemia and hypertension, towards endothelial dysfunction. In the presence of suboptimal concentration of co-factors, or the substrate L-arginine, for the synthesis of nitric oxide (NO) enzyme endothelial NO synthase (eNOS) may become uncoupled. This results in the production of reactive oxygen species (ROS) decreasing the bioavailability of NO and may ultimately lead to endothelial dysfunction. In that condition an imbalance between vasoconstrictors such as endothelin-1 (ET-1) and vasodilators e.g. NO, might further take part, affecting endothelial function towards a proatherogenic milieu. The development of a diabetic foot ulcer is an ongoing process. Therefore it is of great importance to examine the foot regularly and proactively aim for the treatment goals that were recently suggested by the International Working Group on the Diabetic Foot (IWGDF) (see ref 9). Hyperglycaemia, dyslipidaemia and hypertension have to be treated aggressively. Helps with smoking cessation and exercise are of great importance. A multidisciplinary approach consisting of a diabetologist, podiatric, infectious disease, orthopedic and surgeon physician, to diabetic foot complications reduces amputation rates considerably. [a]Pharmacological treatment has to be continued. [b]Low-molecular weight heparin, [c]Percutaneous-transluminal angioplasty, [d]Hyperbaric oxygen therapy.

Macrovascular Dysfunction

Diabetic patients have a 2-4 fold increased risk of PAD,[25] and commonly more infra-popliteal arterial occlusive disease and vascular calcification, than non-diabetic patients.[8, 26] Atherosclerotic changes in the large infra-popliteal arteries may cause limb threatening reduction in blood flow and perfusion pressure eventually leading to foot ulcers, tissue necrosis and gangrene.[27] As a consequence of the combination of peripheral vascular disease and sensory neuropathy many patients with diabetes have limb ischaemia in the absence of rest pain and leg claudicatio. Importantly, this might happen in conjunction with a falsely high ankle blood pressure due to calcification of the vasculature and reduced inflammatory response to injury, which may lead to a delayed treatment.[28, 29]

Clinical Evaluation

A multidisciplinary team consisting of a diabetologist, podiatric, infectious disease, orthopedic, and surgeon physician, having a multifactorial intervention approach (including polypharmacy) has been shown to improve the outcome of foot ulcer and decreasing leg amputation rates.[30-32] Considerations have to be made to treat systemic factors hampering heeling. Prevailing cardiovascular risk factors should be highlighted. Treatment of hypertension, dyslipidaemia, hyperglycaemia and treatment with low-dose aspirin need to be initiated.[33] Smoking cessation and exercise is most important (Figure. 1). Intensified insulin treatment has been shown to retard the development of microvascular and neurological complications in type 1[2, 3] and type 2 diabetes.[34] Normoglycaemia, reflected by lowering HbA_{1c}, has long-term beneficial effect in both preserving microvascular function in the foot[35] and in preventing leg amputations.[36] Recently, IWGDF published practical guidelines to the approach of the diabetic foot.[9] The guidelines emphasise the need for regular inspection and examination of the diabetic foot to identify neuropathy and deformities increasing the risk for ulcer development. It is also essential to educate patients, families and health care provider's how to prevent problems by foot care and appropriate footwear choice. Identifying the at-risk foot treatment of callus, nail and skin pathologies may be initialised before ulcers appear.

Clinical Examination

Observing pallor of the foot in an elevated position above the heart may indicate ischaemia. Pulse palpation is vital and gives a good measure of the vascular status. Absent pedal pulses can indicate the presence of PAD, but the reproducibility might be low.[37, 38] A combination of hands-on diagnostics and objective measurements as ankle bracial index (ABI), ankle pressure, toe pressure and/or transcutaneous oxygen pressure (tcpO2) can help decision-making.[39]

TcpO2 is a non-invasive technique measuring local arterial blood flow and tissue oxygenation. It may be helpful in predicting the chance of ulcer and infection healing and has been used in the decision-making

regarding amputation level selection.[29, 40, 41] The American College of Foot and Ankle Surgeons recommend indications for vascular consultation to include ABI <0.7 and toe blood pressure <40 mmHg or TcPO2 level under 30 mmHg. ABI <0.40-0.45, absolute systolic ankle pressure <0.55 mmHg and toe pressure <30 mmHg indicate a need for revascularisation.[10, 40, 42, 43] It has been stressed that the use of ABI and ankle pressure might underestimate the prevalence of PAD due to arterial calcification and non-compressibility. The atherosclerosis is often more distal in diabetes but usually not affecting digital arteries. Therefore measuring systolic toe pressure might give additional information to assess the skin microcirculation.[44] A systolic toe pressure <30-50 mmHg is associated with a high risk of development of gangrene and dramatically increases the need for leg amputation.[29] If clinical examination indicates PAD, Colour Doppler ultrasound can provide a non-invasive image of blood flow and vascular anatomy, providing images of plaques and stenosis. The sensitivity and specificity is fairly good but requires a skilled operator[45] and when revascularisation is considered contrast angiography is the golden standard.[46] Alternative methods are computer tomography (CT) or magnetic resonance imaging (MRI) angiographies presenting high-resolution images of the vessels. Limitations are the use of nephrotoxic contrast agents and to artefacts because of calcification or previous stent implants.[47, 48]

Treatment and Interventions

Ulcer Treatment

Foot ulcers in patients with diabetes can be divided into neuropathic, ischaemic and neuro-ischaemic, whereas the two latter, contributing with as much as 50-60% of all diabetic foot ulcers.[49, 50] Neuropathic ulcers are often seen on the plantar surface of the foot or over bony deformities. On the other hand, ischaemic or neuro-ischaemic ulcers are more often located on the tips of the toes or the lateral border of the foot. The foot ulcer need to be relieved from pressure for example by off loading it by change of footwear or applying insoles, the use of different castings and/or the use of crutches or limiting standing and walking.

Management of Foot Infections

Usually foot infections are not the cause of foot ulcers, but rather a secondary complication. However, deep skin infection considerably increases the risk for leg amputations. The clinical signs of infection are often less pronounced because of the co-existing neuropathy, also because of leukocyte dysfunction and the absence of fever.[51] To avoid treatment delay (doctor's delay) this has to be considered when evaluating blood tests for erythrocyte sedimentation rate, C-reactive protein concentration and white blood cell count. It is recommended to evaluate the extent of infection, especially signs and symptoms of deep foot infection, e.g. ostemyelitis. Thus, bone scan radiography, MRI, CT, scintigraphy and bone biopsy can all be useful tools to aid the clinical decision-making. Furthermore, often debridement of callus and necrotic tissue is needed to give a clear picture of the extent and depth.[52] Superficial infections are often caused by aerobic Gram-positive cocci such as Staphylococcus aureus and deeper or chronic infections are often polymicrobial origin with aerobic Gram-negative rods and anaerobes. Ones should always obtain culture specimen for microbiological diagnosis prior to treatment and therapy may thereafter be aimed at gram positive cocci in superficial infections. In case of severe infections a broad spectrum antibiotic therapy should be considered.[53] Importantly, foot infections with abscess, necrotising fasciitis, necrosis or gangrene or extensive bone or joint involvement often need surgical intervention promptly. Drainage of an abscess and radical debridement of infected, non-viable tissue should be considered urgently to avoid limb-threatening and septic infection. Subsequently revascularisation may be needed to aid infection and ulcer healing.[54, 55]

Revascularisation

Critical limb ischaemia (CLI) may occur when the PAD is advanced and there´s a risk for limb-threatening ischaemia e.g., ischaemic pain, ulcers and gangrene. Percutaneous-transluminal angioplasty (PTA) is increasingly becoming the method of choice for CLI. If one or more of the crural arteries are revascularised the chance of saving the limb and improve ulcer healing is greatly increased.[56, 57] Bypass surgery or sub-intimal recanalisation may be alternative methods for revascularisation or chosen when PTA is not possible or not successful. Open bypass surgery vs. PTA has not yet been compared in randomised trials, although in a systematic review the major outcome seems similar.[58]

Pharmacological Treatment and Non-invasive Wound Therapy

Intensified pharmacological treatment of systemic factors such as hypertension, dyslipidaemia and hyperglycaemia should always be considered, factors that are components of insulin resistance. The dysregulation of carbohydrate and lipid metabolism caused by insulin resistance further induce endothelial dysfunction, perhaps due to an increase in ROS production downregulating eNOS activity and subsequently NO suppression. Insulin does not only lowering blood glucose levels it is also an anti-lipolytic hormone and when the normal suppression of the release of free fatty acids (FFAs) from adipose tissue is impaired by insulin resistance, characteristic diabetic dyslipidaemia occurs, involving hypertriglyceridaemia, low serum levels of HDL cholesterol and an elevation in circulating FFAs, occurs. Elevated circulating levels of FFAs and transient hypertriglyceridaemia induce endothelial dysfunction in healthy subjects.[59] Moreover, such dysfunction has also been observed in patients with hypertension.[60] Anti-hypertensive agents are also of great importance since arterial hypertension is a major risk for PAD. Current goals of anti-hypertensive treatment are arterial blood pressure of 140/90 mmHg and should be 130/80 mmHg if patients have diabetes or renal insufficiency. Increased total cholesterol and low-density lipoprotein (LDL) cholesterol are independent risk factors for PAD. Current recommendations for the management of dyslipidaemia in patients with PAD is to achive a LDL-cholesterol level of <2.5 mmol/l,[61] whereas statins often are used

for that goal. Interestingly, some small experimental studies suggest that statins, beyond lipid lowering action, improve endothelial dysfunction[62] by upregulating eNOS.[63] Also, there are some small experimental studies demonstrating improvement of foot ulcer outcome in patients with diabetes treated with low-fraction heparin,[64] suggested to be due to an improvement in the skin microcirculation.[65] The interest in the oxidative stress hypothesis raises the possibility that the cofactors for eNOS and L-arginine might be present at inadequate levels. Small experimental studies, using drugs that block vasoconstriction or induce vasodilatation, have recently been published. Improvement in peripheral perfusion during ET-1 blockade has been demonstrated in humans.[66] In addition, administration of L-arginine during acute hyperglycaemia reverses haemodynamic changes associated with this condition, providing another indication that the availability of NO may be insufficient.[67]

Negative pressure wound therapy might improve wound healing in diabetic patients with foot ulcers. This technique applies negative pressure across the wound surface increasing local blood flow, which may reduce oedema and promoting granulation tissue. The effectiveness of the method is still under investigation and should be used primarily in patients with adequate skin perfusion.[68] Hyperbaric oxygen therapy (HBOT) has been tested in some randomised clinical trials indicating improvement of wound healing and reduction of leg amputations. HBOT can enhance mobilisation of endothelial progenitor cells (EPC) in the bone marrow.[69] The deficiency of EPC mobilisation is presumable due to impairment of eNOS activity in bone marrow. The clinical use of this therapy is still controversial, but might prove useful for some patients.[70]

Summary

Management of the diabetic foot is a multidisciplinary task. Taking into account the complexity of the problem one should emphasise optimising metabolic control such as blood pressure, lipids and hyperglycaemia. It is also important to take care of callus development and deformities and educate the patient in ulcer prevention. It is essential to regularly examine neurologic and vascular function and when clinical symptoms indicate PAD further diagnostics should be initiated to consider the need for revascularisation. Ulcer infections should promptly be evaluated and especially in combination with limb threatening ischaemia should call for antibiotic treatment, surgical debridement and subsequent revascularisation. Doing this might minimise the risk of limb-threatening infection and the need for amputation. Finally, studies by using agents targeting endothelial dysfunction are very much needed since foot ulcer is a matter of vascular disease.

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The Diabetic Foot: What's New? Highlights from EASD 2012

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Introduction

Every thirty seconds somewhere in the world, a lower limb is lost due to diabetes. Foot ulceration affects up to 15% of patients with diabetes at some point in their life and is the most common triggering event for infection and gangrene that ultimately lead to limb loss.

EASD 2012 hosted three exciting diabetic foot sessions: Diabetic foot – risk factors (poster session, Tuesday, chaired by Vilma Urbancic), foot ulceration and amputation – treatment outcomes (poster session, Thursday, chaired by Fran Game), and foot ulceration – can we do better? (oral session, Friday, chaired by Fran Game and Edward Jude).

The major risk factors for diabetic foot ulceration and gangrene are neuropathy, impaired blood supply, trauma and infection. Other contributing factors include history of previous foot ulcer, improper footwear, low-quality chiropody service, poor metabolic control, psychological factors, tobacco smoking, old age and low social status. Foot complications usually develop due to an interplay of several component causes and so far only severe ischaemia has been identified as a single cause for amputation.[1] The cornerstones of foot ulcer management include wound debridement, off-loading, infection control and treatment of peripheral arterial obliterative disease.

Despite appropriate management, the prognosis diabetic patients with foot ulcer remains poor and it is not surprising that diabetic foot ulcer has been called "the cancer of diabetes" – the five-year survival rate of diabetic neuropathic foot ulcer patients and diabetic amputees is comparable to those with colon cancer, while the prognosis of the patients with ischaemic foot ulcers is even worse, comparable to lung cancer patients.[2]

As demonstrated by Jeffcoate *et al.* in 2006,[3] ulcer-related outcomes may underestimate the true morbidity and mortality associated with diabetic foot disease and greater emphasis should be placed on patient-related outcome measures. The results of his eight-year observational study of patients with diabetes newly diagnosed with osteomyelitis of the foot, which were presented at the poster session during EASD 2012, have confirmed that the long term outcome for patients newly diagnosed with osteomyelitis of the foot in diabetes is poor with an ipsilateral minor amputation rate of 28.9%, a contralateral minor amputation rate of 13% and a 17.7% major amputation rate. 61.9% of the cohort had died by 8 years, those with major amputation within 31 (range 1-78) months post amputation.

The clinical outcomes of diabetic foot ulceration, ulcer-related and patient-related – healing vs non-healing, amputation and mortality reflect the influence of various factors, the most significant being the adequacy of arterial blood supply, infection and baseline ulcer area.[4] Diabetic ulcer is an expression of a complex systemic disease and requires multidisciplinary treatment by both medical and paramedical personnel.[5] As demonstrated by A. Nielsen and A. Rasmussen *et al.* from Steno Diabetes centre, Denmark, and the two groups from Italy (S.Acquati from Forli and R.Anichini from Pistoia), comprehensive care offered by a multidisciplinary foot team, preferably as an integrated part of the public health care system, can significantly reduce foot ulcer incidence, decrease ulcer healing time and lead to significant reduction of major amputation rate, possibly through improved diagnostic and therapeutic workup of peripheral arterial obliterative disease.

Adequate offloading of areas with high pressure remains a challenge not only in foot ulcer patients but also in those with healed ulceration – failure to off-load the high pressure areas inevitably leads to ulcer recurrence. A novel approach to this problem was presented by Z. Pataky *et al.* from Geneva, Switzerland. The authors evaluated the impact of a new walking strategy learned by biofeedback on plantar pressure distribution under both feet in patients with diabetic peripheral neuropathy. The biofeedback technique was based on a subjective estimation of performance and objective visual feedback following walking sequences. The peak plantar pressures were evaluated at baseline, directly after learning and 10-days after. The foot off-loading by biofeedback led to a safe and regular plantar pressure distribution without inducing any new "at-risk" area under both feet. In the second poster session, G. HaVan presented the results of therapeutic footwear on the

recurrence of foot ulceration in the patients with Charcot foot. Corrective surgery has been avoided in 91% of patients with healed foot ulceration by wearing therapeutic footwear.

Peripheral arterial obliterative disease is one of the most important predictors of ulcer outcome. As demonstrated by Jacqueminet *et al.*[6] primary PTA in diabetic patients with severe ischaemic foot ulcers provides similar outcomes to usual results obtained in severe ischaemia in absence of diabetes. With non-feasible revascularisation, the risk of amputation and mortality rates are significantly higher than in case of succesful endovascular or surgical revascularisation.[7] It has to be kept in mind however that the distribution of atherosclerotic changes is different in the patient with diabetes. As demonstrated by E. Lacopi *et al.* from Pisa, Italy, who presented the comparison of angiographic and clinical results of percutaneous recanalisation in diabetic patients with critical limb ischaemia according to three different classification systems (the Trans Atlantic Society Consensus II -TASC II, the Joint Vascular Society Council - JVSC, and the morphological classification), TASC II is inadequate to describe vascular involvement in the of diabetic patients with critical limb ischaemia. While both the other classifications are effective in describing both basal and post-PTA conditions of DMA, only JVSC is a reliable predictor of outcome in DF patients with critical limb ischaemia.

The need of a holistic approach to diabetic foot ulcer patient and the significance of concomittant ilnesses have been increasingly recognised during the last two decades. The implementation of the philosophy summarised in the simple sentence "Treat the whole patient and not just the hole in the patient", begins with good glycaemic regulation. The beneficial effect of improved glycaemic regulation, achieved by basal/bolus insulin regimen, on foot microcirculation in a long time perspective has been demonstrated by B. Ratsman from Karolinska Institutet, Stockholm, Sweden.

Reduced level of physical activity or even bed rest is often advised for foot ulcer patients in order to achieve sufficient off-loading of the wound. Unfortunately, this may lead to steady and significant increase in BMI which can contribute to increased cardiovascular morbidity and mortality rates, in spite of appropriate management of other risk factors – hyperglycaemia, dislipidaemia and arterial hypertension, as shown by T. Tay *et al.* from Singapore. The authors therefore suggest early mobilisation of foot ulcer patients, and weight-neutral treatment such as GLP-1 agonists for maintaining glycaemic control as well as BMI.

As stated in the Editorial by Robert G. Luke in *The New England Journal of Medicine* from 1998,[8] chronic renal failure is a vasculopathic state and recent commencement of renal dialysis is a risk factor for lower extremity amputation in a high risk diabetic population.[9] In Eurodiale study,[10] the probability of non-healing and amputation was highest in the subgroup of foot ulcer patients with ischaemia and infection. Besides, congestive heart failure and renal impairment have been demonstrated to be indepent predictors of non-healing. Similarly, Apelqvist *et al.*[11] have demonstrated that probability of ulcer healing is strongly related to comorbidity, extent of tissue involvement, and severity of PVD in patients with diabetes with severe PVD, with serum creatinine below 130 µmol/L and absence of congestive heart failure being factors significantly related to wound healing.

As suggested by the results of the pilot study of Hinchliffe *et al.*, dialysis-associated limb hypoxia could be the possible explanation for the increased incidence of critical ischaemia in haemodialysis patients since a trend towards a fall in lower limb TcpO2 after haemodialysis has been demonstrated.[12] Based on these results, therapeutic measures which might help offset any tendency for tissue oxygen to fall should be adopted, such as more widespread use of lipid-lowering agents and earlier vascular reconstruction. A very disappointing fact however is that despite the well known high mortality rates of diabetic patients with foot ulceration and proven efficacy of aggressive cardiovascular treatment, more than 35% of these patients receive no ACE inhibitors, anti-platelet treatment and statins.[13]

That kidney disease not only has a significant impact on the prognosis of the diabetic lower limb but could also facilitate the identification of at-risk patients earlier in the disease process has been demonstrated by L. Hurley *et al.* from Ireland who presented the data from 12 general practices and confirmed the relationship between the extent of sensory dysfunction and vascular impairment on one side and renal impeirment on the other.

In 2007, Khalida Ismail *et al.* published the results of an 18-month prospective study demonstrating that minor and major depressive disorders were associated with an approximately 3-fold hazard risk for mortality compared with no depression.[14] This trend was confirmed in a follow-up study by Winkley *et al*.[15] where depression was associated with a persistent 2-fold increased risk of mortality in people with their first diabetic foot ulceration at 5 years. In 2010, Vedhara *et al.*[14] demostrated that confrontation coping and depression predict ulcer healing and suggested that cortisol and precursor MMP2 might be the potential biological mechanisms that underlie these relationships.

Potential psychological stress-induced biomarkers linking stress to DFU chronicity have been explored by L. Vileikyte *et al.* The preliminary results of the study show the association of multiple measures of increased generalised and diabetic foot ulcer-specific emotional distress with decreased local IL-1beta at baseline, decreased MMP-9 and increased MMP-2. Greater than 80% DFU area reduction at 6 weeks were found to be associated with higher baseline levels of systemic IL-6 and local MMP-2.

The research in the recent years has focused on better understanding of the molecular mechanisms of wound healing, alternative possibilities for treating critical limb ischaemia and more efficient

approaches to treat infections.

An interesting study on necrobiosis lipoidica was presented by D. Semenova *et al.* The authors demonstrated that the evaluation of the expression of Toll-like receptor type 2 on monocytes and Toll-like receptor type 3 on neutrophils can be used for nerobiosis lipoidica risk stratification, predicting disease severity and improving management strategy in patients with diabetes mellitus type1.

L. Moura from Coimra, Portugal presented the results of the use of neurotensin and collagen dressings in an animal model. Wound dressing with appropriate biomaterials should potentially protect the wound and avoid contaminations and enhance the wound healing process through sustained and effective release of bioactive substances. The authors demostrated that collagen alone or in combination with neurotensin potentially decrease the inflammatory conditions in the wound, making it a potentially advantageous wound dressing for the treatment of diabetic foot ulcers.

Besides inadequate off-loading and compromised arterial blood suopply, uncontrolled infection is the third most important cause of non-healing in diabetic foot ulcers. Diabetic foot infections in the developing countries cause substantial morbidity and mortality and are associated with prolonged hospital stays and high costs. Because of these costs and limiteds inpatient services and available hospital beds, a program for instituting out-patient intravenous antimicrobial therapy was instituted in Tanzania by Z.G. Abbas *et al.* 909 patients were included, complete ulcer healing was achieved in 760. Independent factors associated with poor ulcer healing included macrovascular disease, hypertension and concomitant administration of amoxicillin/clavulanic acid or quinolones in addition to third generation cephalosporins. Independent factors associated with complete ulcer healing included palpable peripheral foot pulses, ulcers of area <1,000 mm^2, or concomitant receipt of an anti-anaerobic agent. No deaths or side effects were documented. The authors conclude that outpatient IV antimicrobial therapy is efficient and affordable in the management of infected diabetic foot ulcers in Tanzania.

The results of DANTE study were presented by M. Monami and co-workers from Pistoia, Italy. A photosenzitizer compound RLP068/Cl has shown pharmacological activity in reducing the bacterial load *in vitro* and *in vivo* models. The substance was tested in 62 diabetic patients with infected foot ulcers. The results of the study showed that RLP068/Cl is able to reduce the bacterial load in infected diabetic foot ulcers. This effect, demonstrated for the first time in patients, strongly confirms the pre-clinical data and supports the development of RLP068/Cl as an innovative treatment for infected diabetic foot ulcer.

A.O'Loughlin *et al.* from Galway, Ireland, presented the results of topical allogeneic mesenchymal stem cell therapy for diabetic ulceration. Mesenchymal stem cells are known to promote angiogenesis. A topical cell based therapy was developed by seeding allogeneic non-diabetic bone-marrow derived MSCs in a type 1 collagen scaffold. The cells were delivered to a full thickness cutaneous wound in the alloxan-induced diabetic rabbit ear ulcer model at increasing doses. The therapy led to augmented wound healing with increased angiogenesis, which is a central pathological feature in the non-healing diabetic foot ulcer.

On Friday oral session, W.N.Nowak from Poland spoke about the possible association between diabetic foot syndrom pathogenesis and alterations in stem and progenitor cell mobilisation as well as with growth factor levels. The study demonstrated that patients with T2DM and different forms of DFS have a decreased number of circulating pro-angiogenic progenitor cells. In addition, T2DM may be associated with a changed serum growth factor profile. Altogether, some of these factors can contribute to the pathogenesis of T2DM complications such as different forms of DFS.

M. Dubsky *et al.* from Czech Republic explored the relation between angiogenic cytokines and clinical effect of stem cell therapy in diabetic patients with no-option critical limb ischaemia. The levels of angiogenic cytokines and their relation to clinical effect evaluated by changes of transcutaneous oxygen tension (TcPO2) were assessed. Systemic angiogenesis was evaluated by serum levels of VEGF, b-FGF, Ang-1, Endostatin, PDGF-AA and PDGF-BB after 1, 6 and 30 days from treatment and visualisation was assessed by eye fundus examination before and 6 months after therapy. Clinical effect was evaluated by changes of TcPO2 after 6 months. The study showed no relation between serum levels of angiogenic cytokines and clinical effect of stem cell therapy measured by TcPO2, but the effectiveness of this procedure was confirmed by significant increase of TcPO2 in patients with NO-CLI. No increase of serum levels of pro-angiogenic cytokines during first month and no changes on eye fundus after 6 months may indicate safety of autologous stem cell treatment in terms of systemic angiogenesis.

The Friday session ended with the presentation of Robert Bem from Prague, Czech Republic who presented the results of the study comparing antimicrobial effects of negative wound pressure therapy, maggots, ozone and standard local therapy in patients with infected diabetic foot ulceration. The study demonstrated that both ozone therapy or MDT and NWPT added to standard treatment may help influence polymicrobial infection in the DFU in comparison with standard local therapy. NWPT was slightly less effective than both maggot and ozone therapy.

The three diabetic foot sessions of the EASD 2012 provided interesting data on epidemiology, aetiology and treatment of diabetic foot ulcers. The research in the recent years has focused more and more on understanding the diabetic footwounds on a molecular basis. Still the most important message for the clinician remains that holistic approach to the foot ulcer patient is essential and that we should treat the whole patient, not only the hole in the patient.

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Discovering Buried Treasure: Ketone Testing Past and Present

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Introduction

It is often the case that the solution to a problem already exists. It is just a matter of knowing where to look. The diagnosis and monitoring of ketosis is a good example. Since 1949 the determination of urine ketones using Ketostix® or Acetest® has been standard practice for the diagnosis and monitoring of ketosis. Here we review alternative ways to diagnose and monitor ketoacidosis using assays for the major ketone body, 3-β-Hydroxybutyrate, which have been available on automated analysers since 1987.

The onset of ketosis requires changes in both adipose tissue metabolism and liver function. The primary substrates for ketone body formation are fatty acids from adipose stores. Ketone bodies are produced by the liver and used peripherally as an energy source when glucose is not readily available. Acetoacetate (AcAc) and 3-β-Hydroxybutyrate (βHB) are the two main ketone bodies; acetone is the third and least abundant. Strictly speaking βHB is not chemically a ketone since it does not possess a keto structure.

Ketone bodies are always present in the blood and their levels increase during fasting and prolonged exercise. Diabetes is the most common pathological cause of elevated ketones. In diabetic ketoacidosis (DKA), which occurs in poorly controlled diabetes, low insulin concentrations and high levels of counter regulatory hormones initiate a cascade of events that results in increased lipolysis and decreased re-esterification, thereby increasing plasma fatty acids (see figure 1). In addition, the increased glucagon:insulin ratio enhances fatty acid oxidation in the liver. Increased counter regulatory hormones also increase lipolysis and ketogenesis in fat and liver respectively. The combination of increased hepatic ketone synthesis and decreased peripheral tissue metabolism leads to acetoacetate accumulation in the blood. A small fraction undergoes spontaneous decarboxylation to form acetone but the majority is converted to βHB. In acute DKA the ketone body ratio (βHB:AcAc) rises from normal (1:1) to as high as 10:1. In ketoacidosis βHB levels are typically 78-80% of total ketone bodies.

The classic method for the detection and determination of ketones utilises nitroprusside. The nitroprusside test is 10 times more sensitive to acetoacetic acid than to acetone and gives no reaction at all with βHB because βHB lacks a ketone ring. The fact that most of the commonly used methods for the determination of ketones measure only acetoacetate can produce a paradoxical situation. In a patient initially presenting in ketoacidosis the ketones, as measured by nitroprusside reaction, may be only weakly positive, whereas they are in fact high. This occurs because after initial treatment βHB is converted to acetoacetate which indicates a worsening condition.

Clinical Significance

Excessive formation of ketone bodies results in increased blood ketone concentrations (ketonaemia) and increased excretion of ketones in urine (ketonuria). This process is observed in conditions associated with decreased availability of carbohydrates such as starvation, frequent vomiting, diabetes mellitus, glycogen storage disease or alkalosis. High fat, low carbohydrate diets are ketogenic and increase ketone bodies in circulation. Ketogenic diets and prolonged exercise are also associated with physiological ketosis. Ketogenic diets, which are used in certain weight-reduction programs and which have been used to treat patients with refractory epilepsy, contain at least 50% of their calories as fat. This degree of fat content is nearly twice as high as that found in the typical diet of individuals in developed nations.

Prolonged exercise is also associated with mild hyperketonaemia, with ketone body levels not uncommonly rising to the range of 1-2 mmol/L. Diabetes mellitus and alcohol consumption are the most common causes of ketoacidosis in adults. Diabetic ketoacidosis (DKA) and the hyperglycemic hyperosmolar non-ketotic state (HHNS) are two serious, acute metabolic complications of diabetes. Ketoacidosis can also be precipitated following binge drinking and withdrawal in chronic alcoholics. Ketosis can also occur following ingestion of isopropyl alcohol and salicylates. After DKA, alcoholic ketoacidosis is the most common cause of ketoacidosis in adults. It is a relatively common syndrome in chronic alcohol abusers and binge drinkers. Alcoholic ketoacidosis (AKA) is generally associated with a period of excessive alcohol consumption, followed by withdrawal and minimal food intake.

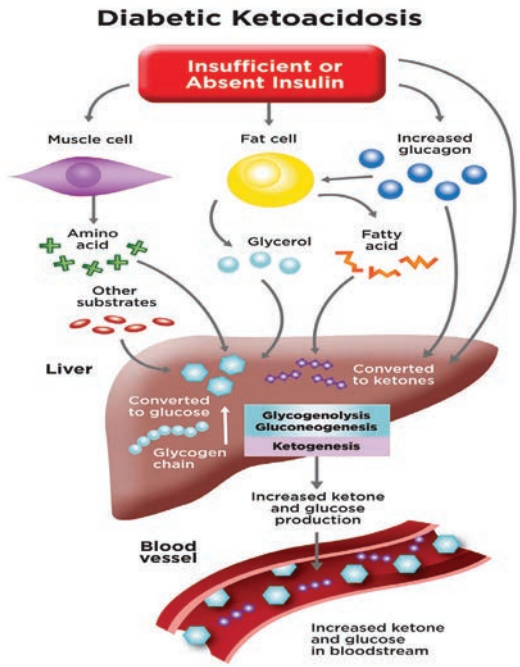

Figure 1. Schematic of pathways involved in diabetic ketoacidosis.

Urine ketone tests are positive in approximately 30% of first morning specimens from pregnant women. During periods of glucose deficiency ketone bodies play a key role in sparing glucose utilisation and reducing proteolysis. Unlike most other tissues the brain cannot utilise fatty acids for energy when blood glucose levels become compromised. In this case ketone bodies provide the brain with an alternative source of energy, amounting to nearly two thirds of the brain's energy requirements during prolonged fasting and starvation.[1] Ketone bodies stimulate insulin release *in vitro*, generate oxygen radicals and cause lipid peroxidation. Lipid peroxidation and the generation of oxygen radicals may play a role in vascular disease in diabetes.

Determination of Ketone Bodies in Body Fluids

The nitroprusside test in the form of the semi-quantitative Acetest® and Ketostix® is commonly used to determine ketones in urine but is insensitive to βHB. It is important therefore to remember that a negative nitroprusside test does not rule out ketoacidosis. The semi-quantitative determination of ketone bodies in blood is more sensitive but still does not detect βHB. The reaction is shown here:

Determination of Ketone Bodies in Serum or Urine

Na-nitroprusside + acetoacetic acid or acetone

(glycine, Na_2HPO_4, lactose) ⟶ Purple complex

Serum or plasma samples should only be analysed with the Acetest® tablets. When a positive is initially detected samples should be serially diluted until a negative is obtained. The Ketostix® test gives a positive reaction within 15 seconds with a specimen containing at least 50 mg of acetoacetic acid. A colour chart is used for reading the ketone concentrations.[2]

Quantitative enzymatic assays for the determination of βHB have been available for many years. A report from the University of Wisconsin Hospital and Clinics, Madison, WI, describes the development of an optimised method for the determination of serum βHB for use on a Cobas FARA.[3] Umpierrez[4] reported on the clinical utility determined by a reflectance meter in the management of diabetic ketoacidosis in 1995. The instrument was developed commercially as a bench top analyser (Ketosite; GDS technologies, Elkhart, IN). The test uses a simple slide and requires 20 µl of serum. The reaction is shown here:

Determination of βHB

$$\beta HB + NAD \longrightarrow \text{Acetoacetic acid} + NAHD + H^+$$

$$NADH + NBT\ (\text{colourless}) \longrightarrow NBT\ (\text{reduced -blue}) + H^+$$

The comparison of the determination of βHB vs. Nitroprusside (Acetest® or Ketostix®) is shown below:

βHB

- Quantitative
- Measures largest component of ketones
- Best and earliest indicator of ketosis
- Best predictor of resolution of ketoacidosis

Acetest

- Only measures acetoacetic acid and acetone (weakly)
- Qualitative assay often requiring multiple manual dilutions
- Increase lags behind symptoms of ketosis
- Decrease begins 2-4 hours after resolution of ketoacidosis

Several reports conclude that the use of Acetest® may be misleading and should be avoided because the fall of acetoacetate lags behind the resolution of ketoacidosis. βHB levels correlate better with acid-base changes during the course of treatment for DKA than changes in acetoacetate concentrations. The study by Umpierrez[4] highlights that all patients with βHB levels of 1.1 mmol/L or less had resolved their ketosis. In contrast 8 out of 15 patients in whom ketosis had been resolved as demonstrated by blood gas and acid-base parameters still had positive Acetest® results for up to 24 hours after resolution. Studies at Henry Ford Hospital[5] demonstrated that at βHB levels of 1.0-1.5 mmol/L and resolution of ketoacidosis, the Acetest® procedure still gave positive results. Furthermore, in the same study, βHB levels were just as sensitive as blood pH for demonstrating resolution of ketoacidosis.

Rapid determinations of βHB levels were useful in establishing the diagnosis of DKA and in the management of patients with prolonged metabolic acidosis, combined diabetic and lactic acidosis and other mixed acid–base disorders. Direct measurement of βHB in serum

improved laboratory turnaround time and replaced a subjective, qualitative result with a method that is quantitative and less subject to observer bias.[6] In addition the nitroprusside method has demonstrated susceptibility to false positive results from drugs containing free – sulfhydryl groups and false negative results from reagent deterioration.[7, 8] Blood testing for ketones is superior to urine testing because fluid intake can affect concentration rendering urine testing unreliable.[9] Improved clinical outcomes and enhanced cost efficiency have been attributed to blood testing of βHB.[5] Improvements were seen in the following areas:

- Earlier detection of clinically significant ketosis
- Improved turnaround times
- Significant reduction in laboratory testing
- Faster resolution of ketoacidosis with significant reduction in the patients' length of stay in the clinical decision unit

Alternatives are now available for βHB testing on multichannel chemistry analysers and several point-of-care devices. A recent web search found a number of companies that manufacture or distribute kits for the determination of βHB.

Summary

As discussed in this paper, assays for βHB in blood are superior to Acetest® or Ketostix® in a number of respects. Physicians and medical facilities should no longer be performing nitroprusside-based testing to diagnose or monitor ketoacidosis. Numerous assays for small point-of-care devices and liquid reagents for automated analysers are highly reliable and have been in use for two decades. For example, the University of Wisconsin has used an automated enzymatic assay for βHB since 1988. Healthcare organisations need to rediscover and implement the diagnostic treasures available to them.

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Recognising and Addressing Psychological Problems in People with Diabetes – The Relevance of Minor Depression and Diabetes-related Distress

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Introduction

Since the early study results by Davis *et al*.[1] have demonstrated psychosocial factors to be one of the five predictors of mortality in patients with type 2 diabetes, and a better predictor than many physiological variables, emotional problems have been increasingly recognised as relevant to diabetes care. Extensive research data have demonstrated that diabetic patients are at increased risk for emotional problems that adversely affect their well-being and self-management of diabetes.[2, 3] Recognising and addressing them by diabetes care providers is considered necessary to improve provider-patient relationship, patients' well-being, and diabetes prognosis.[4]

The present review focuses on research examining the interactions between subthreshold depression and emotional distress with diabetes-related outcomes, and reports the results of recent interventional studies proven to be efficient in treating these conditions.

Minor Depression in Diabetes is as Harmful as a More Severe One

Research data suggest that subsyndromal depression, defined as the presence of depressive symptoms that fall short of full diagnostic criteria for major depression or dysthymia, has a profound influence on the affected patients' quality of life.[5] Data from the general population have shown that minor depression in older adults is at least 2-3 times more prevalent than major depression,[6] with spontaneous remission rates being very low.[7] Subsyndromal depression was found to increase the risk for subsequent major depression – approximately 8-10% of older persons with subthreshold depression develop major depression per year.[8] Recent studies have uncovered predictors of conversion from minor depression into its more severe clinical forms, with chronic illness, female gender, functional disability and poor social support being among them.[6] A recent study examining the course of subsyndromal depression in patients with diabetes demonstrated that the two-year incidence of major depression was 42% in individuals who had subthreshold depression at baseline. Higher baseline levels of depression and anxiety appeared to be related to incident major depression after two years.[9]

Like clinical forms of depression, subsyndromal depression is associated with poor self-management of diabetes.[10] Beverly *et al*. have demonstrated that patients with elevated depressive symptoms are reluctant to discuss self-management issues with their health care providers, thus hindering benefits which can be expected from effective physician-patient communication.[11] Findings on the association between depressive symptoms and glycaemic control are not quite consistent, with some studies confirming an adverse interaction and other failing to confirm it.[10] A recent study by Nefs *et al*.[12] suggests that specific depressive symptoms, in particular anhedonia, rather than depressive symptoms in general, are associated with poor glycaemic control in type 2 diabetic patients. In both patients with type 1 and type 2 patients, the association between depressive symptoms and glycaemic control was shown to be mediated by diabetes-related distress.[13, 14] These findings imply that patients suffering both depressive symptoms and diabetes-related distress are at the greatest risk of deteriorating glycaemic control.

Subthreshold depression affects long-term diabetes outcomes as well. Relative risks (RR) for developing diabetes complications are

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greater in patients with any depressive symptoms compared to those with diabetes alone – RR for macrovascular complications, microvascular complications and disability were shown to be 2.4, 8.6 and 6.9 respectively.[15] Mortality rates, proven to be increased in patients with diabetes and clinical depression, are increased in subthreshold depression as well.[15, 16] In a longitudinal study examining mortality in patients with myocardial infarction, a 47% mortality rate was found at 6-year follow-up in patients with diabetes and depressive symptoms versus 22% in those with diabetes only, and 14% in patients without diabetes and depression.[17]

Diabetes-related Distress Makes Self-managing Diabetes Difficult, Requiring Support by Diabetes Care Providers

Diabetes-related distress is a condition that is related to diabetes outcomes and distinct from depression. Patients reporting depressive symptoms frequently report emotional problems related to diabetes as well.[18-21] Moreover, research findings suggest that diabetes-related distress or significant emotional reactions to burdensome aspects of diabetes, such as fear of hypoglycaemia or threat of late complications, are more common than depressive difficulties and more closely related to diabetes self-care and glycaemic control.[22, 23] Relative effects of depressive symptoms and diabetes distress on glycaemic control were analysed in 234 patients with type 2 diabetes during a self management educational intervention and six months later.[24] Change in diabetes distress, and not change in depressive symptoms, was associated with both short- and long-term change in glycaemic control.

Both objective indicators of disease severity and subjective ratings of its burden contribute to emotional distress in the affected individuals. A recent study by Due-Christensen *et al*. has demonstrated that not only patients with poor glycaemic control but also those who are well controlled may benefit from support groups to improve their psychosocial functioning. Reduced psychological and diabetes-related distress was reported at the end of the course and after one year in both groups, regardless of the HbA1C levels.[25] These results suggest that not only poorly controlled individuals but also those in good glycaemic control might experience psychosocial burden of living with diabetes.

Diabetes-related distress has been shown to persist over time, especially in younger diabetic individuals, women, and those with complications and/or co-morbidities.[20] Some other risk factors for developing and maintaining diabetes distress were highlighted in the longitudinal study by Fisher *et al*.[26] Patients who had previously experienced depressive disorders, reported more chronic stress, and had poor diet and low exercise, were more prone to become distressed over time. The authors suggest that both current life stressors and disease-related stressors should be regularly appraised in clinical care. Also, perceived changes in disease intrusiveness over time may increase emotional distress, thus making the depressive symptoms in the affected individuals more severe.[27]

Diabetes-related emotional problems are frequently overlooked in clinical practice. For example, diabetes nurse specialists recognised and reported anxiety, depression or diabetes-specific emotional distress in only 20-28% patients with high scores on the corresponding questionnaires.[28] Low recognition rates are considered the main barrier to successful management of diabetes-related distress. Therefore, addressing patients' experience of living with diabetes, supporting them, and providing them with self-management education that would meet their specific needs, is likely to be helpful. Diabetes-related distress should be considered a common part of living with diabetes, rather than a disturbance which would require referral to mental health services.[29]

How can Subthreshold Depression and Diabetes-related Distress be Approached in Diabetes Care?

Treating emotional problems at their early stages may be assumed beneficial for improving the affected patients' mood and their self-management of diabetes. However, in mild to moderate depressive symptoms, evidence suggests that a benefit of pharmacological approach is minimal or nonexistent.[30] A small randomised placebo-controlled pilot study of pharmacological treatment in 15 mildly depressed women with type 2 diabetes[31] has indicated beneficial effects of treatment on insulin sensitivity. However, a later study by the same authors[32] did not confirm the preliminary findings, concluding that any possible benefit from administration of paroxetine in diabetic patients with sub-threshold depression is likely to be modest and of short duration. A recent meta-analysis comprising six RCTs also did not provide evidence for the efficacy of anti-depressants in patients with minor depression.[33] Instead of pharmacological treatment, unspecific monitoring and guided self-help activities are recommended as reasonable treatment options.

Non-pharmacological studies exploring the effects of treating mild to moderate depression, and those targeting diabetes-related distress, are still rare. In general, studies carried out in this field can be classified as relying on a) psychological approach, most frequently using cognitive-behavioural based psychoeducation or psychotherapy, and b) self-management education and life style interventions.

a) Psychological approach

A small non-randomised study exploring the effects of a psycho-educational intervention on mood and glycaemic control in adults with diabetes and visual impairment[34] has shown positive effects on diabetes-related distress, as measured by the Problem Areas in Diabetes scale, and on glycaemic control. A significant positive relationship was found between glycaemic control and improvement in depression. The effects of a minimal psychological intervention based on cognitive-behavioural principles were tested in depressed elderly persons with diabetes and COPD within a randomised trial. Small to medium effect sizes of the intervention were obtained, indicating improvements in

anxiety, self-efficacy and social participation.[35]

A telephone-based counselling and walking intervention was used to reduce depressive symptoms in type 2 diabetic patients.[36] The results of this randomised controlled trial have demonstrated an improvement in depressive symptoms, number of steps walked, systolic blood pressure and health-related quality of life in the intervention versus the control group after 12 months. Another recent study has reported preliminary results of a combination of cognitive behavioural therapy and aerobic activity delivered to patients with type 2 diabetes and depressive symptoms.[37] Participants experienced significant improvements in depression and glycaemic control which were sustained during a three-month follow-up period.

A psycho-educational intervention for women with mild depression[38] compared with treatment as usual has shown positive effects on depressive symptoms, anxiety and anger expression while glycaemic control did not differ between the groups neither after the intervention nor after six month follow-up. A randomised controlled trial comparing psycho-educational and physical activity interventions with a control group receiving a short re-education on diabetes self-management is currently being carried out. Preliminary results have suggested that both the psycho-educational course and re-education about diabetes have beneficial effects in reducing depressive symptoms.[39]

In general, psychological treatments were shown to be effective in alleviating a burden of minor depression. Whether improved depressive symptoms lead to improved glycaemic control remains to be clarified. The studies carried out so far have indicated that treatment effects on glycaemic control are generally smaller than the effects on mental health outcomes.[40] However, collaborative care based on team approach and proactive follow-up of both depression and diabetes seem to be optimal to achieve improvements in depressive symptoms, self-management of diabetes and diabetes-related outcomes.[41, 42]

b) Educational and lifestyle interventions

Described educational and lifestyle interventions including assessment of depressive symptoms have not specifically dealt with treating them but rather with exploring how diabetes-related education may affect depressive symptoms and diabetes-related distress. The recent study by Ruusunen *et al*.[43] aimed to assess the effects of individualised counselling on reducing weight vs. placebo group during a 36-month clinical trial. Participation in the study lowered depressive symptoms regardless on the group assignment. Successful reduction of body weight was associated with greater reduction of depressive symptoms suggesting that gaining mastery over health related issues may affect patients' mood positively. The impact of blood glucose monitoring on depression and diabetes-related distress was studied by Fisher *et al*[44] showing that collaborative, structured self-monitoring blood glucose (SMBG) course leads to reductions in depressive symptoms and diabetes distress over time for a large number of moderately depressed and distressed patients. Changes in affective status were shown to be independent of improvement in glycaemic control and changes in SMBG frequency for these patients.

Based on the described studies, structured education on diabetes self-management has a potential to favourably affect both depressive symptoms and diabetes-related distress.

In general, the presented studies have indicated that minor depression and diabetes specific emotional distress, common in diabetic patients, can be successfully treated. However, more randomised controlled trials are needed to increase evidence-based data, and to test stepped care approaches that would best meet patients' needs for treatments.

Points to be stressed:

- Depressive symptoms and diabetes-related distress are common in diabetes affecting patients well-being, self-management of diabetes and diabetes outcomes
- Not only severe depressive symptoms but also their subclinical forms, and emotional distress caused by diabetes, interact adversely with diabetes outcomes
- Non-pharmacological studies to treat minor depression and diabetes distress have indicated that short psychological treatments based on cognitive behavioural principles, physical exercise and diabetes self-management education have a potential to improve psychological symptoms
- Patient-centred care including recognising and addressing emotional problems, providing ongoing support, and integrating psychological care with diabetes care is considered crucial for optimising outcomes.

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Cardiac Morphology and Function in Type 1 Diabetic Patients with Successful Pancreas Transplant Alone

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Introduction

A tight glycaemic control has beneficial effects on chronic complications of diabetes, including cardiovascular disease (CVD).[1, 2] However, an intensive insulin regimen increases the incidence of hypoglycaemic events and some patients experience recurrent severe acute complications on medical therapy. Pancreas transplantation (PT) restores pancreatic endocrine function and represents a valuable therapeutic venue for selected type 1 diabetic patients and even for a small minority of type 2 diabetic patients.[3-5] Growing evidence is accumulating on the beneficial effects of PT on secondary complications of diabetes.[6, 7]

Cardiac Dysfunction in Patients with Type 1 Diabetes

Diabetic patients suffer an increased overall mortality in comparison to the general population. For individuals born in the United States in 2000 the estimated average lifetime risk of developing diabetes is about 33% for males and 38% for females. If an individual is diagnosed at age 40 years, men will lose 11.6 life-years and 18.6 quality-adjusted life-years (QALYs) and women will lose 14.3 life-years and 22.0 QALYs.[8] The main cause of mortality in diabetic patients is represented by cardiovascular disease (CVD). In comparison to type 2 diabetes, type 1 diabetes (T1D) is less prevalent and is usually diagnosed at a younger age. However, taking into consideration age and other classical cardiovascular risk factors (such as hypertension, dyslipidemia, obesity, and smoking), the adjusted relative risk for CVD in T1D far exceeds that of type 2 diabetes,[9-14] and it displays a higher dependency on metabolic control.[15, 16]

The relative risk of mortality from ischaemic heart disease is exceptionally high in young adult women with T1D (10- to 15-fold higher than nondiabetic women), in comparison to T1D men (who have a 4- to 6-fold higher relative risk than nondiabetic men), being no gender difference in absolute mortality for CVD in T1D patients.[10-14]

T1D children and adolescents suffer from early-onset subclinical atherosclerosis and CVD.[17-19] Among children diagnosed as having diabetes at age 10 years, on average boys will lose 18.7 life-years and 31.0 QALYs and girls will lose 19.0 life-years and 32.8 QALYs.[8]

T1DM is associated with cardiac dysfunction out of proportion to what would be predictable by traditional cardiovascular risk factor alone (e.g. hypertension, dyslipidemia, obesity, and smoking), which certainly play a role in the development of cardiovascular complications in this patient population. Although the pathophysiology of cardiac dysfunction in T1D has not been fully elucidated,[20] current thinking supports a model in which many different factors (such as glucotoxicity, inflammation,[21-23] fibrosis, a peculiar phenotype of insulin resistance,[24-26] mitochondrial dysfunction,[27, 28] and high-density lipoprotein dysfunction[29, 30]) lead to pathologic alterations that affect coronary vessels (endothelial dysfunction, increased arterial stiffness, coronary artery calcification, accelerated atherosclerosis),[31] autonomic nerves,[32, 33] (reduced heart rate variability,[34] increased resting heart rate, impaired coronary vasomotor capacity, arrhythmia), and cardiac muscle itself.[14] In this regard, ventricular dysfunction in the absence of coronary atherosclerosis and hypertension has long been described in T1D patients and termed diabetic cardiomyopathy.[35-37] Cardiac dysfunction is often detectable even in paediatric T1D patients,[38-40] even if in this patient population the incidence of cardiovascular events is low in the first years after diagnosis.

The natural history of diabetic cardiomyopathy has been usually described as a progression from preclinical ventricular diastolic

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(impaired relaxation, increased ventricular stiffness),[41-46] and then systolic dysfunction,[43] to overt echocardiographic evidence of ventricular hypertrophy and dysfunction and left atrial dilatation, and finally to symptomatic heart failure.[20]

We previously reported our echocardiographic findings in 78 diabetic patients on the waiting list for solitary pancreas or pancreas-kidney transplantation.[47] While hypertensive patients showed an increased left ventricular mass and abnormal diastolic function, normotensive patients had normal left ventricular structure and function, notwithstanding a long duration of T1D, severity of disease (they were listed for solitary pancreas transplantation) and, for 13 out of 24 normotensive patients, associated retinopathy. A possible limitation of our study, however, could have been represented by the lack of structural myocardial analysis (such as backscatter,[48] tissue Doppler imaging,[40] speckle tracking,[45, 46] or strain rate imaging).[49]

Pre-transplant Evaluation and Cardiac Risk Assesment

A thorough pretransplant patient evaluation is mandatory and serves three main purposes:[50] verification of the presence of appropriate indications for PT, exclusion of contraindications, and adequate patient preparation in order to minimise peri- and post-operative risks. Cardiovascular events represent a primary cause of morbidity and mortality after PT,[51] both in the immediate post-operative period[52] and in the long-term.[53] Severe preoperative cardiovascular disease may represent a contraindication to PT. However, since diabetic transplant candidates may have significant cardiovascular disease even in the absence of overt clinical signs and symptoms,[54] a careful preoperative cardiac risk assessment is mandatory, not only to identify patients whose cardiovascular risk would be too high, but also to adequately manage those who may benefit from pretransplant cardiovascular intervention, such as coronary revascularisation.[55-57]

Coronary angiography represents the gold standard for the diagnosis of coronary artery disease and allows for concurrent therapeutic intervention. It is therefore valuable in this patient population. However, due to its invasiveness and potential side effects (e.g. nephrotoxicity due to the contrast medium), it should ideally be reserved for high risk patients. The University of Minnesota developed and validated a clinical algorithm (sensitivity 97%, negative predictive value 96%) for type I diabetic candidates for kidney transplantation, according to which coronary angiography should be recommended, in the case of asymptomatic patients with no past medical history of CVD, in the presence of either age over 45 years, a smoking history, ST-T wave changes on EKG, or diabetes duration longer than 25 years.[58]

Pharmacologic stress thallium scintigraphy and exercise radionuclide ventriculography have been proposed, but proved to be suboptimal screening tests for coronary artery disease in diabetic patients awaiting kidney and/or pancreas transplantation.[59] Dobutamine stress echocardiography could be a useful screening test,[60] but is not sufficiently accurate.[61]

Of interest, Ruparelia *et al.* recently proposed myocardial perfusion scintigraphy as a useful first-line screening tool.[62]

At the University of Pisa, in accordance with the algorithm validated by the University of Minnesota,[58] coronary angiography is performed in PT candidates which at least one of the following feature: previous cardiac events, cardiovascular symptoms, long-standing diabetes (disease duration longer than 25 years), and/or age over 45 years; in adjunct, every patient is evaluated by a careful history and physical examination, EKG and a basal transthoracic echocardiography.[48, 63]

Effects of Pancreas Transplantation on Cardiac Morphology and Function

Regarding the impact on macrovascular complications of diabetes,[64] for diabetic patients with end stage renal disease, simultaneous pancreas and kidney transplantation (SPK) is superior to kidney transplantation alone (KTA),[65, 66] with better outcomes in term of longer patient survival and reduced cardiovascular death rate.

A sufficiently long follow up is however necessary to properly assess the impact of PT on macrovascular complications of DM. While Biesenbach *et al*. (mean follow up: 70 months)[67] and Knight *et al.* (median follow up: 45 months)[68] reported no differences between SPK and KTA in their impact on macrovascular disease, and Morrissey *et al*. (mean follow up: 4 years)[69] reported even worse vascular outcomes for SPK vs. KTA patients, Biesenbach *et al.*[70] in a following publication found that while for the first 5 years after transplantation the progression of macroangiopathy (coronary artery disease, cerebrovascular disease, and peripheral arterial disease[71-73]) in patients with SPK and KTA was not significantly different, after a mean 10-year observation period the progression of macrovascular diseases was significantly lower in recipients with a functioning SPK compared to patients who had undergone a KTA.[70]

The beneficial effects of SPK over KTA on coronary atherosclerosis (as assessed during an observational angiographic study[74]) are dependent upon pancreas graft function. Moreover, the superiority of SPK over KTA has been reported regarding left ventricular function (assessed by radionuclide ventriculography)[75, 76] and on left ventricular energy metabolism (evaluated by phosphorous-31 magnetic resonance spectroscopy).[77]

The effects of pancreas transplantation alone (PTA) on cardiac function are more controversial. We previously reported our findings on 13 T1D patients who received a PTA at the University of Pisa and 11 matched control patients who were under evaluation to enter the waiting list for PTA or were already on the waiting list.[78]

In the 13 patients who underwent PTA, insulin independence was

promptly achieved and then maintained; at a 6 months follow up, total and low-density lipoprotein cholesterol levels were significantly lower, whereas high-density lipoprotein cholesterol and triglyceride concentrations did not change; likewise, both systolic and diastolic blood pressure values and fibrinogen levels improved significantly. In addition, PTA determined a significant amelioration of several morphologic and functional cardiac indices, as assessed by Doppler echocardiograohy (Table 2). On the contrary, none of the measured parameters changed in the control patients. We reported a significant reduction in left ventricular mass index and posterior wall telediastolic diameter after PTA.

We recently reported our updated single-centre experience: 71 patients who underwent PTA at the University of Pisa with a 5-year follow-up.[79, 80] Patient and pancreas survivals at 5 years were 98.6% and 73.2%, respectively. One patient died 5 months after transplant due to disseminated CMV disease. No cardiac events were observed. After a five year follow-up period there was a significant reduction in serum total and low-density lipoprotein-cholesterol levels with no change in high-density lipoprotein-cholesterol and triglyceride levels, despite similar use of statins, and improved systolic and diastolic blood pressure control, without relevant differences in the use of antihypertensive medications.

Cardiac morphology and function was assessed through echocardiography. Diastolic function, in particular, had been investigated through conventional two-dimensional Doppler echocardiography and Tissue Doppler Imaging.[47] Cardiac parameters assessed pretransplant resulted within the normal range as reported for a local control population. At the end of posttransplant follow-up, left ventricular ejection fraction increased slightly, but significantly, from 54.4±4.3 to 58.1±2.0% (P<0.01), and the E/A velocity ratio (a diastolic parameter obtained by Doppler mitral flow) also improved (from 1.18±0.33 to 1.39±0.49 cm/sec), although not significantly. The other indexes remained stable.

There are currently no other reported experiences on the improvement of ventricular systolic function after PTA. No definite mechanism has been identified to explain this beneficial effect of PTA; however it is tempting to assume that the resumed normoglycemic status, together with the other metabolic changes, may interrupt the process of progressive fibrosis and accumulation of glycated derivatives of extracellular matrix components in the context of the myocardium, which have been described both in animal models of T1DM and in human patients, and which concur to determine the alterations of diastolic function and the increase in left ventricular mass that are observed early after onset of the disease, even in the absence of arterial hypertension.

Conclusion

T1D patients suffer from early-onset cardiac dysfunction. While the superiority of SPK over KTA as far as cardiovascular disease is concerned is widely appreciated, the impact of PTA on cardiac morphology and function remains to be fully elucidated. However, growing evidence, including our single-center experience, suggests that PTA may have a favourable effect on ventricular hypertrophy and both diastolic and systolic cardiac function. Further data and longer follow up are needed to thoroughly assess this interesting and important topic.

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Upcoming Congresses and Meetings

Excellence in Diabetes Conference

6 - 9 Feb 2013

Istanbul, Turkey

The theme this year is "Interdisciplinary approaches: from prevention to cure" and we will be exploring the impact of diabetes on the health and wellbeing of the individual, and the community at large. There will be tracks dedicated to discussing the latest innovations in therapeutics, prevention and new insights into effective global diabetes management. We have an outstanding faculty who has already agreed to participate. Colleagues from developing countries are particularly welcome. There is a Community Interventions for Health Summit embedded within the programme which explicitly addresses health promotion in lower and middle income countries.

5th International Conference on Advanced Technologies and Treatments for Diabetes (ATDD)

27 Feb - 2 March 2013

Paris, France

ATTD 2013 is an innovative conference that will bring together the world's leading researchers and clinicians for a lively exchange of ideas and information related to the treatment and prevention of diabetes and related illnesses. Over the last five years, 'ATTD' has become synonymous with top calibre scientific programs that have provided participants with cutting edge research and analysis into the latest developments in diabetes-related technology.

Diabetes UK Annual Professional Conference (APC)

13 - 15 March 2013

Manchester, UK

The Diabetes UK Annual Professional Conference is one of the largest healthcare conferences in the UK attracting over 3,000 attendees. The event provides delegates with the opportunity to hear from a wide range of innovative speakers, share best practice and network with diabetes specialists from across the globe. This year's conference is in the exciting city of Manchester.

The Society for Endocrinology BES Conference

18 - 21 March 2013

Harrogate, UK

This annual meeting brings together the best of basic science, translational research, clinical investigation and clinical practice. It encompasses a number of plenary lectures, including the Society's medal lectures, symposia including the Young Endocrinologists' symposium, Clinical Management Workshops, Meet the Expert sessions, Nurse sessions and a Clinical Debate. The meeting features both oral communications and poster presentations with many prizes available for high scoring presentations by Young Endocrinologists.

5th International COngress on Prediabetes & Metabolic Syndrome

18 - 20 April 2013

Vienna, Austria

The markedly increased risk of diabetes and cardiovascular disease (CVD) underlines the importance of this metabolic syndrome congress. Discover pioneering research and explore the latest issues from gut hormones in obesity; GLP-1 mimetics and DPP-4 inhibitors in early diabetes and the metabolic syndrome; the role of the GLP-1 axis in prevention, cardiovascular health and cognition; and lessons from bariatric surgery and interventional diabetology. Learn from world leaders, network with fellow specialist, and enjoy the beautiful, historic setting of Vienna.

5th European Congress of Endocrinology (ECE)

27 April – 1 May 2013

Copenhagen, Denmark

Next year's congress in Copenhagen promises to be challenging and stimulating as we consider key topics of interest and concern. Lectures and workshops will be presented by a group of distinguished international speakers who will cover a range of topical and relevant issues which affect us all from the laboratory to the clinic.

20th European Congress on Obesity (ECO)

12 - 15th May 2013

Liverpool, UK

The programme aims to place obesity research at the centre of national and European policy agendas for the next decade. The scientific committee has constructed a programme more inclusive than ever before, bringing together basic science with clinical management, and behavioural and nutritional expertise with policy and intervention. Utilising cross-cutting themes, the congress will appeal to a wider possible audience than previous years, including researchers, policy makers and clinicians caring for people with obesity and related conditions. This will encourage active discussion and debate both within and across the traditional scientific, clinical

and public health disciplines represented in the meeting.

40th AADE13 Annual Meeting and Exhibition

07-10 Aug 2013

Philadelphia, Pennsylvania

AADE is a multidisciplinary association of healthcare professionals dedicated to integrating self-management as a key outcome in the care of people with diabetes and related chronic conditions. AADE are constantly working towards a vision of optimal health and wellness for all people with diabetes and related chronic conditions. To help reach this vision, they have created a dynamic organisational structure and a strong mission and values. This can be seen during their annual meeting, which is this year in Indianapolis.

9th Joint Meeting of Paediatric Endocrinology

19 - 22 Sept 2013

Milan, Italy

This prestigious occasion will reunite the European Society for Paediatric Endocrinology (ESPE) with the Pediatric Endocrine Society (PES), Australasian Paediatric Endocrine Group (APEG), Asia Pacific Paediatric Endocrine Society (APPES), Japanese Society for Pediatric Endocrinology (JSPE), and the Sociedade Latino-Americana de Endocrinologia Pediátrica (SLEP).

18th Foundation of European Nurses in Diabetes (FEND) Annual Conference

20-21 Sept 2013

Barcelona, Spain

FEND has established a unique voice for nurses working in the field of diabetes care, research and education in Europe. FEND's two day Annual Conference precedes the EASD conference each year. Attendances at our conferences grows year on year and attracts not only nurses but other relevant health care professions in diabetes. The next conference will take place in Barcelona, Spain.

49th Annual European Association for the Study of Diabetes (EASD) Meeting

23 - 27 Sept 2013

Barcelona, Spain

The EASD is one of the leading European conferences on diabetes, bringing together physicians, scientists, nurses, laboratory workers and students involved in fighting the diabetes epidemic. The 2013 EASD Annual Meeting promises to offer exciting insights into the most cutting-edge developments in all aspects of diabetology and will take place at the Fira de Barcelona's Gran Via exhibition centre. The conference is dedicated to diabetes and metabolism issues, covering topics such as genetics of diabetes, prediction and prevention of diabetes, diabetes and immunology, insulin issues, lipid metabolism, diabetes in childhood and diabetes complications.

41st Meeting of the British Society for Paediatric Endocrinology and Diabetes

13–15 Nov 2013

Brighton, UK

This year the 41st Annual BSPED meeting will be held in Brighton. Against this background, the committee hope to offer a world class educational meeting with a number of outstanding national and international speakers. The BSPRED aim to support children with endocrinological disorders and diabetes mellitus. this year's event promises to be an exciting and stimulating scientific and social programme.

World Diabetes Congress

2 - 6 Dec 2013

Melbourne, Australia

The International Diabetes Federation aims to consolidate the direction of previous congresses and push boundaries to enhance the lives of people with diabetes. They hope to create a platform that allows key players to take up the challenge of giving a voice to the millions living with diabetes. The Programme Committee aspires to create a wide-ranging programme covering all aspects of the diabetes field.

16th World Congress of Gynecological Endocrinology

5 - 8 March 2014

Florence, Italy

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

12th International Congress on Obesity (ICO)

17-20 March 2014

Kuala Lumpur, Malaysia

The International Congress on Obesity (ICO) is the official Congress of IASO and is held every four years. The International Congress on Obesity (ICO) provides the opportunity to hear and discuss the latest research on all aspects of obesity, new innovative preventive and treatment strategies, global alliances to reduce the prevalence of obesity and its associated burden of diseases and offer an insight from the world's leading obesity specialists.

International Congress of Endocrinology

21 - 24 June 2014

Chicago, Illinois

The International Society of Endocrinology (ISE) was established in 1960 to advance the profession and to improve the efficiency and effectiveness of endocrinology information exchange at international level. Its worldwide membership comprises national endocrine societies from over 70 countries. The ISE aims to become the premier international organisation for endocrinologists and associated scientific professionals in all settings including universities, industry, government agencies, health care facilities, and not-for-profit organisations.

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