

IDF WATCH

SUMMARIES

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Spotlight on the developing world

Prof Jean Claude Mbanya from Cameroon is the new president of the International Diabetes Federation (IDF). After his introduction, Prof Mbanya gave an encouraging and motivating speech, where he clearly stated that if we want to address the global burden of diabetes, we must address it in all countries worldwide, including the third world. While we witness a diabetes epidemic in the westernised world with its abundance of medicines, we forget about the hardship of patients in third-world countries who don't have appropriate access to health-care, education and drugs. Patients die in a hyper- or hypoglycaemic condition because of lack of insulin or food. Prof Mbanya said that his aim while president is to start changing this. With this, he introduced a new area, which is to start raising awareness and improving cooperation worldwide to address the global burden of diabetes.

Glucose-lowering agents and risk of malignancy

An increased risk for the development of malignancy has emerged as yet another long-term complication of type 2 diabetes. Dr Edwin Gale reviewed this hitherto understudied and under-reported but real phenomenon. As emerging therapies for the management of type 2 diabetes bring new hope for longer survival and improved quality of life, the threat of increased risk of dying from a malignancy is becoming a new reality.

Cancer of the pancreas is the most commonly occurring malignancy in patients with diabetes, followed by cancer of the ovary, stomach, bladder, colon and endometrium, whereas the prevalence of prostate cancer in men with diabetes is decreasing. It is unclear whether the increased risk of malignancy is due to type 2 diabetes itself, the kind of therapy used, or the phenotype associated with type 2 diabetes. In this regard, obesity, insulin resistance, insulin, IGF-1, hyperglycaemia or other metabolic

abnormalities should all be considered in the pathogenesis of cancer in patients with type 2 diabetes. An association between diabetes and cancer does not equal causality, and confounding factors may also play a part.

It is also of note that the use of metformin is associated with a decreased risk of being diagnosed with malignancy. Clinical trials are currently underway to examine the efficacy of metformin as an anti-cancer agent. The statistical methods used in the German study that suggested an increased risk of malignancy with the use of insulin glargine were also critically evaluated. Dr Gerstein (USA) emphasised that the German database was an administrative database and that the results should be interpreted as hypothesis generating and not hypothesis testing.

All the speakers in this symposium concluded that much more research needs to be done in order to better explain the statistical association between diabetes and cancer.

Haemoglobin A_{1c} as a diagnostic test for diabetes?

The debate is no longer whether haemoglobin A_{1c} should replace the measurement of plasma glucose (fasting or two-hour post 75-g load) as the preferred diagnostic test for diabetes, but rather when. This is the opinion of Dr David Sachs, clinical chemist from the Brigham and Women's Hospital

and Harvard Medical School, Boston. Judging by the low mean of 6.0% of all HbA_{1c} tests requested in his hospital, doctors have already been doing so for some time, according to a recent survey (the diabetic patients in that hospital are apparently not that well controlled).

Since 2003, the considerable improvement in the accuracy of the HbA_{1c} assay has paved the way for a committee appointed by the American Diabetes Association to suggest that HbA_{1c} tests may now be a better means to diagnose diabetes than the measurement of plasma glucose levels. Apart from its accuracy, it is now also clear that HbA_{1c} levels correlate well with blood glucose concentrations. It must, however, be kept in mind that HbA_{1c} levels may be influenced by haemoglobin variants such as HbS, C and others.

The variability of HbA_{1c} values on repeated testing in the same individual is below 2%, which is similar to the inter-individual variation. Interestingly, in white subjects, the mean HbA_{1c} concentration is 0.4% lower than that in Afro-Americans, and it increases by 0.03% per year as a person ages. Variation in the lifespan of red blood cells, which is difficult to measure accurately, may also affect HbA_{1c} levels in normoglycaemic subjects. For example, the mean HbA_{1c} concentration in patients with haemolytic anaemia is much lower compared to that in normal individuals. A recent blood transfusion also renders the results of the HbA_{1c} assay inaccurate.

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The merits of replacing plasma glucose estimation with the measurement of HbA_{1c} levels to diagnose diabetes mellitus was also addressed by a World Health Organisation (WHO) committee tasked with revising its classification and diagnostic criteria. The recommendations of the committee are still being withheld by the WHO 'police'.

Prof Sir George Alberti briefly reviewed the pros and cons of switching the approach. The most important pros include the fact that HbA_{1c} is stable, it provides a time-average of blood glucose concentrations, patients do not have to prepare for the test, it is reproducible, and fasting is not required. The cons are: a standardised test is required, it is expensive, it is not freely available especially in developing countries, the test is not accurate in patients with anaemia or in the presence of a haemoglobinopathy, quality assurance schemes are lacking, few data are available, and the cut-off point is uncertain. Prof Alberti stressed that the WHO needs to be cognisant of the needs of all healthcare systems worldwide and hinted that the status quo may be maintained.

The classification of diabetes on the other hand may have to change to accommodate the growing prevalence of type 2 diabetes in children and adolescents, as well as the fast-growing list of genetic mutations associated with diabetes. The unfortunate category 'pre-diabetes' (formerly including impaired glucose tolerance and impaired fasting glucose) is expected to be renamed 'intermediate hyperglycaemia' according to Prof Alberti.

The role of beta-cell mass and function in the pathogenesis of type 2 diabetes

Dr Peter Butler challenged the view that type 2 diabetes is the end result of long-standing insulin resistance. In the majority of insulin-resistant individuals, islet beta-cells successfully respond by increasing insulin secretion – the so-called appropriate response. In a minority of subjects, the response is inappropriate, resulting in type 2 diabetes. The mechanism behind this inappropriate response is possibly due to a loss of beta-cell mass due to accumulation of insulin amyloid polypeptide (IAPP). Animal data show that dysglycaemia develops when approximately 50% of beta-cell mass has been lost. The critical loss of beta-cells is accompanied by a decrease in hepatic insulin clearance, which buffers the

decrease in insulin secretion.

The loss in beta-cell function is most likely due to the production of toxic IAPP oligomeric precursors disrupting mitochondrial function, resulting in apoptosis of the beta-cells. Dr Butler presented evidence that beta-cells can regenerate but the net effect is a decrease in beta-cell mass due to a mismatch between apoptosis and regeneration. He also showed data that the regeneration of beta-cells is accompanied by an increase in the replication of pancreatic ductal cells, which may possibly explain the increased incidence of chronic pancreatitis and carcinoma of the pancreas in obese patients and in patients with type 2 diabetes. It is a matter of concern that GLP-1-based therapy is also associated with chronic pancreatitis and ductal hyperplasia. The opposite has been noted in metformin-treated subjects.

Where are we regarding the PPAR-agonists 10 years on?

'We are only at the beginning' responded Dr B Staels from the Institut de Lille, France. Because of their wide range of actions on glucose homeostasis, lipid metabolism and vascular inflammation, the peroxisome proliferator-activated receptors (PPARs) remain ideal targets for the development of new drugs. Despite the initial promise, there is little outcome data demonstrating a cardiovascular benefit of thiazolidinedione (TZD) use.

The increase in cardiac ischaemic events associated with the use of rosiglitazone, as revealed by the meta-analysis reported by Nissen and Wolski, could not be confirmed by longer-term studies, explained Dr Leiter from Toronto. A closer look at the results of the RECORD study showed that the predictors of heart failure associated with the use of rosiglitazone include age over 60 years, a waist circumference above 104 cm and an increased urinary albumin:creatinine ratio. Rosiglitazone should not be used in patients with symptoms of or who have developed heart failure, said Prof Beck-Nielsen from Odense, Denmark.

The observation in the RECORD study that after 5.5 years of use of rosiglitazone, an increase in fracture rates became apparent came as no surprise to Prof Ian Reid, osteoporosis expert from Australia. Evidence was produced in 2002 that PPAR gamma agonists in *in vitro* studies promoted adipogenesis, whereas osteoblastogenesis was inhibited. Prof Reid cal-

culated from published study results that the number needed to harm (fracture risk) ranged from 21 to 55 patients. An increased fracture risk is therefore an issue with the use of thiazolidinediones. Prof Reid recommended that fracture risk should be thoroughly assessed in patients where TZD treatment is contemplated. Should fracture risk be increased, another agent should be selected or measures should be taken to protect the bone.

Progress in foot care

A history of foot ulceration is a marker of increased risk of mortality among persons with diabetes, was the finding of Dr M Iverson and colleagues from Norway. Their study included 1 339 patients with diabetes without a history of foot ulcers, 155 subjects with a history of foot ulceration, and 63 632 non-diabetic persons, followed for 10 years. During this period, 49% of patients with diabetes and a history of foot ulceration died, compared to 35% with diabetes and without a history of foot ulceration, and 11% of the control group without diabetes. The adjusted hazard risk (HR) for mortality in diabetics with a history of foot ulceration was more than double that of non-diabetic subjects (HR = 2.29) while a HR of 1.38 was found for diabetics without a history of foot ulceration. The authors concluded that their study underlined the importance of organising future healthcare services with follow-up routines that allow for optimal patient care and monitoring of persons with diabetic foot ulceration.

The use of autologous platelet gel as an adjunct to good standards of care enhances wound healing in diabetic patients suffering from deep chronic foot ulcers, said Dr S Clavel from Le Creusot, France. Good standards of wound care include surgical debridement where indicated, infection control, medical management of co-morbidities and off-loading measures. Wounds must be free of infection, and bone sequestrants must be removed if present. This group reported complete wound healing in 77 of the 91 patients after only one application, and in almost all patients after several applications. Proper wound care and patience were key to their success.

The IDF's Step-by-Step foot-care programme is gaining popularity in many resource-poor settings. Dr Z Abbas and colleagues have introduced this training programme, with success in 14 health

districts in Tanzania. The main objectives of the programme are to train healthcare professionals in diabetic foot management, reduce rates of foot complications by education and the early detection and prompt and appropriate treatment, and develop an infrastructure for support and service development. Also inherent in this programme is data collection to monitor secular trends in amputation rates. The annual amputation rate among referrals was 18% before the introduction of the programme. Dr Abbas showed that the upward trend in the amputation rate was reversed following the introduction of the training programme. Their data suggested improved foot ulcer management at a regional level.

The Step-by-Step foot programme is also systematically being introduced into the Western Pacific region as well as the Caribbean. Dr S Kono from Hanoi, Vietnam presented data from seven Asian countries comprising 309 patients hospitalised with a new foot ulcer. Risk factors for foot ulceration as well as clinical characteristics of patients differed widely across the region. Some of the common features included relatively young age and short duration of diabetes, late presentation, trauma, and a high amputation rate, ranging from 17 to 61%.

Dr Kono emphasised that increased awareness of diabetic foot problems, reduction in tobacco use, screening for high-risk patients, improved skills in the management of diabetic foot ulcers and the implementation of clinical guidelines were all essential steps to prevent diabetic foot ulcers and to reduce the amputation rate. Dr K Bakker from the Netherlands who spearheaded the introduction of the Step-by-Step programme in five Caribbean islands explained the logistics involved in the process, as well as funding issues. One of the difficulties is to get local health authorities involved.

New IDF study reveals that people in developing countries pay more for diabetes care and have poorer health results

Type 2 diabetes is often seen as a condi-

tion affecting older, unproductive adults in wealthy countries. However, the reality is that 70% of people with diabetes now live in low- and middle-income countries, and the economic impact of diabetes is much greater in poorer countries. Yet the majority of the spending, 90% of all medical expenditures for diabetes care, is made in the United States, Canada, the countries of Western Europe, and other wealthy countries. This is the conclusion of the most comprehensive investigation on the economic impact of diabetes ever to be conducted in low- and middle-income countries.

The new data from the IDF came from researchers in five African countries (South Africa, Cameroon, Kenya, Mali and Tanzania) who interviewed 2 300 men and women with type 2 diabetes and an additional 2 300 of their neighbours who did not have diabetes. The studies revealed that people with diabetes have roughly three times the rates of heart disease, stroke, kidney disease and heart failure as their otherwise similar neighbours. People with diabetes also have more tuberculosis, HIV/AIDS and malaria.

All these diseases lead to very high out-of-pocket medical expenses and lost income due to complications such as blindness, paralysis, amputation, pain, cognitive deficits, and other disabling problems. One out of six of the people interviewed said that they could not work at all because of their health, one of three said they could not work as much they wanted to, and 3% said that they had to work more than they wanted to, to cover their medical expenses. One of five reported that they were not able to buy much-needed food because of medical expenses, and more than half said they could not buy all the medicines they needed.

Perhaps the most surprising findings were that 15% of the family members had quit work to care for a family member with diabetes, 20% had to cut back on work and 15% had to work more to contribute to the cost of medicines and care for a family member with diabetes. The result of this, according to Jonathan Betz Brown, PhD, chairman of the IDF Task Force on Health

Economics and of the Kaiser Permanente Center for Health Research, the global study leader, is that 'children are kept out of school and deprived of food, families lose farms and businesses, and women and girls are forced to stay home and care for parents. In the end, these family tragedies add up to a less-educated and smaller workforce, greater social disorganisation and slower economic growth'.

'You might think that the best way to help children in Africa would be to ignore chronic illnesses such as diabetes', said the African study leader and IDF vice president, Dr Kaushik Ramaiya, of Shree Hindu Mandal Hospital in Dar es Salaam, Tanzania, 'but in developing countries, children's lives and prospects depend on the survival and strength of their parents and grandparents. When a father is fired because of a stroke, or a mother cannot raise crops and animals, or cook because of blindness or an amputation, the entire family can find themselves homeless and pulled into dire poverty.'

Findings from the African study show that people with diabetes on the continent have many more medical problems than healthy people of comparable age and gender, are much less able to function physically and work, are more frequent and more intensive users of medical care and drain precious economic resources from their family and society.

The lead investigators in each study were recruited locally and all enjoy international reputations for their research. IDF President Prof Jean Claude Mbanya led the study in Cameroon, Dr Eva Njenga in Kenya, Mr Stephane Besançon in Mali, Dr Paul Rheeder in South Africa and Dr Kaushik Ramaiya in Tanzania. Other studies are underway in 17 cities in China, in Kazakhstan and in three countries in Central America. These are preliminary results and the data continue to be analysed. Final results will be published at a later stage.

This report was compiled by WF Mollentze, consulting editor of the *South African Journal of Diabetes & Vascular Disease* and Julia Aalbers, assistant editor.