

IDF WATCH

SUMMARIES

2011 UPDATE FROM DUBAI, UNITED ARAB EMIRATES

International Diabetes Federation Congress

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INTRODUCTION AND OVERVIEW

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In keeping with previous International Diabetes Federation congresses, the Dubai meeting presented an exciting and varied series of lectures and symposia. This paralleled the diverse and unique architecture of the city.

Preceding the official start of the congress was a Novo-Nordisk-sponsored programme titled *Advances in metabolic science and therapies*. It focused on the glucagon-like peptide-1 (GLP-1) agonists, liraglutide in particular, for the treatment of the obesity-pre-diabetes-diabetes continuum, as well as the potential future use of ultra-long-acting insulins such as insulin degludec (see Late-breaking clinical trials, page 4).

The congress began with a symposium dealing with reform in a post-United Nations diabetes world summit. Dr Richard Smith, former editor of the *British Medical Journal*, gave a thought-provoking review on new health strategies for dealing with diabetes. He stressed that we should concentrate on pre-diabetes, to prevent its progression to diabetes (his personal viewpoint). This should involve mainly lifestyle modification, with patients being encouraged to 'take charge' of their own medical problems.

Following this was a debate on best strategies to prevent diabetes in high-risk individuals. Dr Fronzo (USA) was of the opinion that early intervention must include drugs such as metformin, pioglitazone, acarbose and, for future use, exenatide and liraglutide. Dr Tuomiletho (Finland) however was against the use of drugs – but rather advocated lifestyle changes, including diet and exercise.

Diabetic neuropathy was the subject of a cutting-edge symposium in which the importance of early diagnosis was again emphasised. The usual clinical tests are too crude and techniques such as lower-limb skin biopsy and corneal confocal microscopy for detecting a fall-out in small nerve fibre

density were demonstrated. Gastroparesis is a frequently overlooked autonomic manifestation and is difficult to manage. Pyloric botox injections were even suggested.

A debate on whether blood pressure should be lowered as much as possible in diabetic patients aroused considerable interest. A blood pressure target of below 140/80 mmHg was generally regarded as reasonable, with the ideal hypotensive agents including ACE inhibitors, diuretics, calcium antagonists, and even the almost obsolete drug, reserpine.

The final topic attracting interest was the metabolic memory hypothesis. This hinges on the theory that alternative metabolic pathways of intracellular glucose metabolism remain dormant if tight glycaemic control is instituted and initiated in diabetic subjects, thereby reducing the risk of microvascular complications developing several years down the line, irrespective of later control. However, the reverse situation similarly applies.

Patients' bill of rights

The IDF traditionally focuses on the patient-caregiver interface and this year's meet-

ing in Dubai also raised the profile of the diabetic patients' bill of rights. Education for Society noted that the role of a young generation of patients is essential to the building of public awareness, according to Amir Karman Tayar, diabetologist and chair of the IDF for the Middle East and North Africa Region.

The contributions of Ibn Sina or Avicenna (980–1037), a Persian, born in Afshana near Bukhara in today's Uzbekistan, who described diabetes in his 14-volume *The Canon of Medicine*, was cited among the early contributions to today's understanding of diabetes from the Middle East region.

GETTING TO THE HEART OF DIABETIC CARDIOVASCULAR DISEASE

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This cardiovascular session, co-chaired by Profs A Chait and R Eckel (USA), took place in the Sheikh Maktoum A auditorium and included eight presentations, dominated by studies conducted in Asia, with a single African contribution.

TABLE OF CONTENTS

INTRODUCTION AND OVERVIEW	1	Vascular stiffening response in type 2 diabetes	3
Patients' bill of rights	1	ADVANCE model better predictor of cardiovascular risk in diabetes	3
GETTING TO THE HEART OF DIABETIC CARDIOVASCULAR DISEASE	1	Further results from global A,chieve™ study of insulin usage in type 2 diabetes	3
Relationship between adiponectin and carotid IMT	2	LATE-BREAKING CLINICAL TRIALS	
Oxidative stress and vascular complications of diabetes	2	Data show insulin degludec/insulin aspart combination significantly reduced hypoglycaemia in type 1 and 2 diabetes patients	4
Visceral fat and cardiovascular risk in a Chinese study	2	Pooled analysis: fewer major adverse cardiovascular events in type 2 diabetes patients treated with sitagliptin	4
Gastrectomy and atherosclerosis progression	2	Flat and stable blood glucose lowering shown with once-daily insulin degludec in both type 1 and 2 diabetes patients	4
Sagittal abdominal diameter a better predictor of arterial stiffening than waist circumference	2		
Raised adiponectin in orthostatic hypotension in diabetes	3		

Relationship between adiponectin and carotid IMT

Serum adiponectin, one of the most commonly occurring adipokines, has been shown to be associated with cardiovascular disease and related risk factors. In the first communication of this series, Dr Paul Lee, on behalf of his colleagues from the University of Hong Kong (China), presented the results of their study on the association of serum adiponectin with carotid intima-media thickness (IMT), a well-known surrogate marker of cardiovascular disease.

Participants were 269 adults (132 men), all members of the Hong Kong Cardiovascular Risk Factors Prevalence Study 2 (CRISPS 2) cohort. CRISPS 2 was a community-based cohort study conducted from 2000 to 2004 as a follow up of a representative community-based survey (CRISPS 1) carried out from 1995 to 1996.

Serum adiponectin, IMT and cardiovascular risk factors were measured at baseline. Mean age of participants was 53 ± 12 years; 91 had hypertension and 33 had diabetes. Median (interquartile range) baseline adiponectin level was 5.28 mg/l (3.29–7.93). During the first five years of follow up, carotid IMT significantly increased from 0.62 mm (0.52–0.73) to 0.67 mm (0.57–0.78) ($p < 0.001$).

In linear regression analysis, after adjustment for several baseline covariates, the investigators found a modest association between low baseline adiponectin levels and IMT thickening ($\beta = -0.092$, $p = 0.039$).

The investigators concluded that measuring adiponectin level would improve cardiovascular disease risk stratification at the community level. The study was however based on a small sample size, and the investigators did not use measures of global performance to assess the contribution of adiponectin level to risk prediction.

Oxidative stress and vascular complications of diabetes

There is accumulating evidence on the important role of oxidative stress on vascular complications of diabetes mellitus. Dr Iso gave a talk on behalf of her colleagues from the School of Medicine, Toho University in Japan, on components of oxidative stress associated with carotid IMT in people with diabetes.

In all, they included 52 diabetic patients (17 women) with acceptable levels of control of blood glucose and blood pres-

sure on a cross-sectional basis. They were non-smokers and had non-ongoing acute or chronic inflammatory disease, kidney impairment or liver disease.

Urine levels of 8-hydroxydeoxyguanosine (8-OHdG, a marker of oxidative DNA damage) and 8-epiprostaglandin F2a (PGF2-a, a marker of lipid peroxidation), both makers of oxidative stress, were measured together with inflammatory markers [high-sensitivity C-reactive protein (hs-CRP)] and other clinical and biological parameters. Maximum IMT (max-IMT) was measured by ultrasonography. Mean age and duration of diabetes were 52 and five years, respectively.

In univariate linear regression analysis, age and PGF2-a were the main characteristics associated with max-IMT. These associations were borderline in multivariate analysis.

The authors concluded that in diabetic subjects with acceptable metabolic control, oxidative stress may be implicated in the progression of atherosclerosis in people with diabetes. This claim however was based on a small sample size and borderline association in a cross-sectional design.

Visceral fat and cardiovascular risk in a Chinese study

Body fat is a determinant of cardiovascular disease risk, and there are suggestions that the distribution of body fat may contribute differentially to this risk. This presentation from a group of researchers from Shanghai Jiao Tong University in China was delivered by Dr Ma on the contribution of visceral fat accumulation to carotid IMT in a group of 1 005 Chinese adults. Carotid IMT was quantified by ultrasonography, and visceral (VFA) and subcutaneous fat (SFA) were characterised through magnetic resonance imaging.

In multiple regression analysis, waist circumference (an indicator of body fat distribution) was associated with IMT while body mass index, a measure of the overall fat mass, was not. Similarly, VFA, a more accurate indicator of body fat distribution, was associated with IMT, while SFA was not.

The authors suggested that their findings were in agreement with reports from other studies in the USA and Korea, and concluded that VFA was effective in identifying atherosclerosis in both lean and obese individuals. Since other more reliable meth-

ods for quantifying atherosclerosis already exist, this study extends previous findings from other settings to China and confirms the thesis of differential contribution of body fat distribution to disease risk.

Gastrectomy and atherosclerosis progression

This presentation was from a group of investigators from the Centre for Diabetes and Endocrinology of Kitano Hospital in Osaka (Japan) and was delivered by Dr Wada. They investigated the effects of gastrectomy on progression of atherosclerosis in adults with diabetes.

They recruited 157 patients with type 2 diabetes, among whom 20 had undergone a gastrectomy at least five years previously for cancer eradication. Carotid IMT and other clinical and biological parameters were assessed.

Participants with gastrectomy had higher systolic blood pressure, and lower HbA_{1c} and LDL cholesterol levels, compared to those without gastrectomy. Other clinical characteristics were similar between the two groups. Mean carotid IMT was significantly lower in the gastrectomised group than in those without gastrectomy ($p = 0.04$). This difference persisted in some subgroup analyses (smokers, patients with hypertension), but not in all. Subgroup analyses however, were based on small numbers.

The authors concluded that in addition to the known beneficial effects of gastrectomy on glucose tolerance, this procedure may also have a favourable effect on the progression of atherosclerosis. The study, as recognised by the investigators, was cross-sectional and based on a small sample size.

Sagittal abdominal diameter a better predictor of arterial stiffening than waist circumference

Ostgren and his collaborators from Linköping University in Sweden demonstrated a finding suggesting that sagittal abdominal diameter (SAD) was a better predictor of arterial stiffening than waist circumference (WC) in people with diabetes. This was based on 255 participants with type 2 diabetes, members of the CARDIPP cohort (Cardiovascular Risk factors in people with Diabetes – a Prospective study in Primary care).

Arterial stiffness was measured by pulse wave velocity (PWV) and participants were followed for four years between 2006 and 2010. They had acceptable metabolic control both at baseline and during follow up.

In multivariate linear regression analysis, they found that SAD, not WC or body mass index (BMI) was significantly associated with PWV at baseline. Likewise, during follow up, change in SAD and BMI, but not WC were associated with four-year change in PWV.

In general, SAD is much easier to measure than WC and may show less variability across populations than WC.

Raised adiponectin in orthostatic hypotension in diabetes

Orthostatic hypotension (OH), a frequent complication of diabetes mellitus, is associated with increased risk of mortality. Related mechanisms are still ill understood. This exploratory study was undertaken by Terasawa and co-workers from Dokkyo Medical University Koshigaya in Japan.

They hypothesised that serum high-molecular weight (HMW) adiponectin (the most commonly occurring adipokine, and a determinant of cardiovascular disease and mortality) might be elevated in patients with type 2 diabetes and orthostatic hypotension. They also investigated the associations of orthostatic hypotension with variables of coagulation/fibrinolysis and with arterial stiffness

They recruited a group of 105 type 2 diabetes patients (30 with OH), in whom the quantified HMW adiponectin level and many other clinical and biological parameters were assessed. Serum total and HMW adiponectin levels were higher in patients with OH than in those without. They also had worse renal function and a lower haematocrit, which may possibly be explained, at least in part, by the high levels of adiponectin.

In multivariate linear regression analysis, systolic blood pressure, HDL cholesterol, haematocrit, prothrombin and brachial pulse-wave velocity were the main determinants of HMW adiponectin. The study was cross-sectional and therefore precluded speculation about causal relationship. The authors however suggested that the presence of OH is probably an indicator of a clustering of cardiovascular risk factors including HMW adiponectin.

Vascular stiffening response in type 2 diabetes

This study by Penno and co-workers from Azienda Ospedaliero Universitaria Pisana in Italy focused on the single and joint effects of diabetes mellitus and hypertension on carotid and peripheral vascular stiffness. They recruited 114 subjects, including 14 normotensive non-diabetics, 37 hypertensive non-diabetics, 20 non-hypertensive diabetics and 39 hypertensive diabetics.

Pulse wave velocity (PWV) was measured by applanation tonometry, and carotid IMT and lumen diameter were assessed by ultrasonography. Peripheral PWV was similar between the four groups, while aortic PWV, carotid stiffness index, carotid IMT and lumen diameter differed and were higher in participants with diabetes or hypertension, compared with their non-diabetic or normotensive counterparts.

In mutually adjusted regression analysis, both hypertension and diabetes were associated with high aortic PWV. In addition, diabetes was associated with high IMT, while hypertension was associated with high carotid stiffness and diameter.

The authors concluded that type 2 diabetes and hypertension are characterised by discrete differences in the vasculature stiffening response. This, however, was based on a very small number in a cross-sectional analysis.

ADVANCE model better predictor of cardiovascular risk in diabetes

The use of global cardiovascular risk models is increasingly recommended as an appropriate basis for initiation and intensification of cardiovascular risk-reduction therapies in people with diabetes. However, those models specific to people with diabetes and developed only recently have not been extensively tested.

In the last presentation in this series, Dr Kengne, on behalf of the ADVANCE investigators, shared their validation studies of the ADVANCE risk model. ADVANCE is the largest global trial of cardiovascular prevention in people with diabetes. Dr Kengne and his colleagues used the four to five years' follow-up data of the trial to develop a model for predicting major cardiovascular disease based on 10 predictors.

They subsequently applied their model to participants from the DIABHYCAR study, a trial of ramipril for the prevention of kidney disease in people with diabetes,

conducted in 16 countries around the Mediterranean. The model had an acceptable performance with a c-statistic of 0.69, equivalent to what was obtained when the model was tested on the ADVANCE cohort (internal validation).

The ADVANCE model also largely did better than two popular Framingham equations. Based on a four-year risk threshold of $\geq 8\%$ (equivalent to a 10-year risk of 20%), the ADVANCE model identified the 39% of the DIABHYCAR participants in whom 66% cardiovascular disease events were recorded.

Based on this performance, the investigators concluded that the ADVANCE risk model is appropriate for cardiovascular risk stratification in contemporary populations with diabetes who are already receiving many risk-reducing therapies. It would be interesting if this acceptable performance was demonstrated in other validation studies, and that the uptake of the model be shown to improve decision making and the outcomes of care.

Further results from global A₁chieve™ study of insulin usage in type 2 diabetes

J Aalbers, Special Assignments Editor

The A₁chieve™ study was the largest-ever observational study on the use of insulin therapy in patients with type 2 diabetes. The baseline data involving almost 70 000 patients were presented for the first time at the 2011 American Diabetes Association (ADA) meeting in June last year.

The study was a non-interventional 24-week observational study of type 2 diabetes patients, including both insulin users and non-insulin users, who were started on insulin detemir (Levemir®), insulin aspart (NovoRapid®) or biphasic insulin aspart 30 (NovoMix 30®) in 28 countries across four continents.

Of importance to our region is that the study concentrated on less well-resourced and newly developed countries. It could well be the pivotal study of insulin management in type 2 diabetes, providing unique data that are more applicable to Africa than that from other studies such as the UKPDS.

The highlights of data presented at the IDF is summarised in this report and will be extensively covered in future issues of the *South African Journal of Diabetes and Vascular Disease*.

- In an evaluation of the factors influencing early insulin initiation, a deterioration of HbA_{1c} levels of 1% increased the probability of early insulin use by 6%. Higher baseline postprandial glucose (PPG) levels also predicted earlier insulin use, but higher baseline fasting plasma glucose (FPG) levels had the opposite effect.
- Interestingly and perhaps a reflection of inappropriate care, the presence of micro- or macrovascular complications did not favour the introduction of insulin.
- The negative association with higher FPG levels and positive association with raised BMIs require further explanation.
- Optimisation of insulin therapy in patients on basal insulin was, for the most part, with premix insulin, rather than switching to a multiple-injection regimen.
- In the real-life clinical setting, switching from biphasic human insulin (BHI) to biphasic insulin aspart 30 (BIAsp 30) allowed patients to significantly lower their HbA_{1c} levels and enabled more patients to achieve HbA_{1c} values less than 7% without increasing the risk of hypoglycaemia.
- Adding mealtime insulin (insulin aspart) is usually an opportunity for markedly improving the health of people with type 2 diabetes who are already on basal insulin.
- Results in this real-life clinical situation suggest that when transferring from insulin glargine with or without oral glucose-lowering agents, use of insulin detemir may offer the opportunity to improve glucose control with fewer major, minor and nocturnal hypoglycaemic events.

LATE-BREAKING CLINICAL TRIALS

Data show insulin degludec/insulin aspart combination significantly reduced hypoglycaemia in type 1 and 2 diabetes patients

A soluble co-formulation of insulin degludec and insulin aspart (IDegAsp) was associated with a 58% lower rate of confirmed hypoglycaemic episodes in people with type 2 diabetes compared to biphasic insulin aspart 30 (BIAsp 30), when dosed twice daily.¹ The unique way in which insulin degludec/insulin aspart

works, with the basal insulin component providing an ultra-long and steady action profile, plus a bolus boost of insulin aspart, provides a simple way to introduce mealtime dosing at any meal.

In this phase 2 study, the overall occurrence of confirmed hypoglycaemia was lower with IDegAsp than with BIAsp 30 during the day as well as at night (nocturnal events, occurring between midnight and 06:00). Improvements in FPG were also seen, with levels significantly lower in the IDegAsp group than the BIAsp 30 group (6.4 vs 7.5 mmol/l). The study also found that IDegAsp was well tolerated and provided comparable overall glycaemic control to BIAsp 30 (mean HbA_{1c} at week 16: 6.7 vs 6.7%).¹

'The unique way in which IDegAsp works, with the basal insulin component providing an ultra-long and steady action profile, plus a bolus boost of insulin aspart, provides a simple way to introduce mealtime dosing at any meal', said Dr Alan Moses, corporate vice president and chief medical officer of Novo Nordisk. 'These benefits, along with the lower risk of hypoglycaemia and improved FPG shown in these studies, are very promising for people living with type 2 diabetes.'

In addition, a phase 3 study, also presented, showed that rates of hypoglycaemia at night were lowered by 37% in people with type 1 diabetes using once-daily IDegAsp at any meal (with additional insulin aspart doses for the remaining meals), compared to those using insulin detemir once daily plus insulin aspart at all main meals.²

IDegAsp, in development by Novo Nordisk, will, pending approval, be the only soluble insulin combination of ultra-long-acting basal insulin degludec and rapid-acting insulin, insulin aspart. Clinical studies have shown it provides an optimal glycaemic control with significantly less nocturnal hypoglycaemia compared to premix insulin.³

Insulin degludec has a unique, slow rate of absorption which provides a flat and stable action profile.^{4,5} In several clinical trials, insulin degludec has demonstrated effective glycaemic control and improvements in both HbA_{1c} and FPG levels.⁶⁻⁹ It has also demonstrated a significantly lower rate of nocturnal hypoglycaemia when compared to insulin glargine.^{6,8}

Both insulin degludec and insulin degludec/insulin aspart were submitted to the European Medicines Agency (EMA) and the

US Food and Drug Administration (FDA) earlier this year for regulatory review.

Pooled analysis: fewer major adverse cardiovascular events in type 2 diabetes patients treated with sitagliptin

In a pooled analysis also presented at the IDF congress, a lower incidence of reported major cardiovascular events (MACE) was observed in patients with type 2 diabetes treated with sitagliptin compared to those treated with a sulphonylurea (SU).

In this analysis of cardiovascular (CV) safety data from three previously published, randomised, blinded clinical studies, which included patients with type 2 diabetes who had been randomised to either sitagliptin 100 mg/day ($n = 1\ 226$) or an SU (glipizide or glimepiride, $n = 1\ 225$) as monotherapy or add-on to metformin, there were no reports of a major adverse CV event (ischaemic events and CV deaths) in the sitagliptin group, whereas 11 patients in the SU group were reported to have experienced at least one major adverse CV event.

'Although a retrospective, pooled analysis with distinct limitations, this analysis shows that patients with type 2 diabetes treated with sitagliptin had fewer major adverse cardiovascular events compared to patients treated with sulphonylureas', said Barry J Goldstein, MD, PhD, vice president, Diabetes and Endocrinology, Merck. 'These data are important, but prospective studies are needed. Results of a previously published pooled analysis of 19 clinical trials to evaluate the safety and tolerability of sitagliptin did not show an increased risk of CV events with sitagliptin 100 mg/day compared to placebo or other medicines.'

Flat and stable blood glucose lowering shown with once-daily insulin degludec in both type 1 and 2 diabetes patients

A double-blind, cross-over trial in type 2 diabetes patients has shown that once-daily insulin degludec has a flat and stable blood glucose-lowering effect over 24 hours. Dosages of 0.4, 0.6 and 0.8 U/kg were evaluated at steady state in 49 type 2 diabetes patients.

For all dose levels, mean 24-hour glucose infusion rate (GIR) profiles were flat and stable, while on ending therapy, con-

trol was retained for a terminal half-life of 25 hours. Insulin degludec was well tolerated and there were no safety concerns.

A second study was presented at the IDF following the earlier published observation that insulin degludec has less within-subject variability than insulin glargine in treating type 1 diabetes patients. This study evaluated whether this reduced variability was constant over the 24-hour period at steady state.

Using euglycaemic glucose clamps on the sixth, ninth and twelfth days of treatment, area-under-the-curve (AUC) evaluations of glucose infusions over 24 hours showed less variability with insulin degludec than with insulin glargine, perhaps due to the slow release of IDeg monomers from the soluble multi-hexamers that form after subcutaneous injection.^{10,11}

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