Ten years of non-insulin-dependent diabetes (NIDDM): Review of two recent conferences on NIDDM*

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ABSTRACT

We present a review on two recent conferences on NIDDM held in Newcastle on Tyne, U.K., and Copenhagen, Denmark.

The review describes pathogenesis of NIDDM and its complications. Scope of monitoring control of NIDDM and various treatment strategies, including use of magnesium salts is discussed.

INTRODUCTION:

The National Diabetes Data Group (NDDG) of the National Institute of Health, NIH, Bethesda, USA, 1979 provided a classification of diabetes mellitus. Soon afterwards the World Health Organisation, WHO, Geneva, adopted this and published it in the Technical Report Series 646 (1980).

NIDDM refers to adult (maturity) onset diabetes; in most of the cases, the onset is after the age of 40 years. Environmental factors are superimposed on strong genetic susceptibility like familial aggregation with autosomal dominant transmission in Maturity-Onset Diabetes of Young (MODY). Amongst Non-insulin Dependent Diabetes of Young (NIDDY), 60-90 percent of subjects are obese, the remainder being non-obese. Such diabetics are neither insulin dependent nor ketosis-prone, though they may need insulin for the correction of symptomatic of persistent hyperglycemia.

Despite progress in scientific research, clinical experience and natural history pertaining to NIDDM, many questions still remain unresolved. These relate to pathogenesis, to interrelationship of glycaemic status with complications, or even the best mode of management. Basic issues relating to controversies are:

a) In the pathogenesis of beta cell dysfunction, is the primary event a cellular insulin receptor defect or a post-receptor defect?

b) What is the role of metabolic events such as hepatic glucose production or non-oxidative glucose utilization in pathogenesis of NIDDM?

c) Has hyperglycaemia in NIDDM any relationship with macro-or micro-vascular complications of diabetes?

d) In management strategy, what is the role of diet, exercise, oral hypoglycaemic agents or insulin, and what are the criteria for the use of one or the other mode of therapy?

In September 1990, the above mentioned symposia were held in Europe to take stock of the present knowledge of NIDDM. The following is a brief resume of these meetings.

PATHOGENESIS:

H. Keen (London) speaking on 'Focus on NIDDM' brought out the effect of age, body mass index (BMI), weight: height (W/H ratio) and race on glucose intolerance based on studies on various population groups amongst Asian Indians. Prevalence, hyperinsulinaemia, insulin resistance, hypertriglyceridaemia and centripetal fat distribution were more frequent in populations with higher prevalence of diabetes. Those with blood glucose in the 95th percent had twice the rate of coronary artery disease.

W.J. Malasisse (Belgium) summarized the effect of glucotoxicity on the beta cell function. The oxidative function of islet mitochondrial enzyme glycerophosphate dehydrogenase is impaired and there is a loss of glucose-stimulated insulin secretion. Thus, there is a loss of mitochondrial handling of stimuli.

E. Ferranini (Italy) brought out the fact that in NIDDM there is an excess of hepatic glucose output and gluconeogenesis is increased. Peripheral utilization of glucose in relation to insulin is reduced; the levels of counter-regulatory hormones are increased.

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O. Pederson (Denmark) discussed the role of glucose transporter (membrane transporters). GLUT 4 type plays the most important role in insulin-stimulated glucose uptake in fat and muscle cells. Defective functioning transporters would lead to adipose and muscle tissue resistance to insulin, and of glucose mediated insulin secretion at the beta cell level.

H. Beck-Nielsen (Denmark) referred to defect in glycogen synthetase in skeletal muscles of NIDDM subjects. This would reduce the non-oxidative glucose uptake and result in insulin resistance in NIDDM.

K.S. Polonsky (USA) had studied the profile of insulin secretion in normal control subjects and compared it with that observed in NIDDM. In normal individuals, there is pulsatile secretion of insulin at regular intervals (12-15 minute cycle). In NIDDM, there is loss of pulsatility, its rhythm is slower, irregular and pulse amplitude is smaller.

Amylin interferes with insulin secretion. This polypeptide also inhibits insulin-stimulated glucose transport in skeletal muscle.

G. M. Reaven (USA) referred to reduction in insulin stimulated glucose uptake in IGT and NIDDM and some normal individuals. This was related to the insulin response by beta cells; those exhibiting highest insulin levels having greatest degree of insulin resistance. In addition, insulin hypersecretors had high concentration of serum triglyceride, increased high-density lipoproteins and a high blood pressure. This complex situation becomes a major risk factor for cardiovascular disease which contributes maximally towards morbidity and mortality in NIDDM.

H.H. Parving (Denmark) referred to renal disease amongst diabetics. Based on renal biopsy studies he reported that in 25% of patients the renal lesions were due to non-diabetic causes.

COMPLICATIONS

D.R. Owens (UK) highlighted the major differences in complications of IDDM and NIDDM. These are tabulated as follows:

	IDDM	NIDDM
1) Micro-vascular		
a) Retinopathy	Never before 2 years of onset of diabetes, and threatens vision after 10 years.	May be present even at time of diagnosis
	After 20 years, 70-80% will have retinopathy.	After 20 years, 30-40% will have retinopathy.
	Relates to insulin dependence; Being lean and hypertensive (diastolic) increases risk.	Relates to degree of control, hypertension and smoking.
b) Nephropathy	Clinically overt nephropathy is observed in 35-40%.	Progression to clinical nephropathy less often than in NIDDM.
	Albuminuria rate is related to duration of diabetes.	Microproteinuria in 20-25%.
	End stage renal disease (ESRD) occurs in 15-16%.	ESRD occurs in 5-10%.
2) Macro-vascular	Not before age of 30 years regardless age of onset of IDDM.	It is not duration-related. It relates to hypertension.
	Cardio-vascular disease frequent. Concomitant proteinuria is more likely. It is the cause of death in 35% of subjects.	It also relates to changes in HDL-C and Apo-B. (cardio vascular disease is cause of death in 59.4% of subjects.

J. Ward (UK) referred to arterio-venous shunting in the prepheral limb vessels resulting in a reduction of blood flow. This coupled with neuropathic changes (loss of sub-cutaneous tissue and dryness of skin) would cause the non-healing foot ulceration.

Tomlinson (Manchester, UK) in an analysis of 1652 diabetics including Caucasians (50%), Asian (16%) and Afro-Caribbeans (15%) found no ethnic variations as regards the magnitude of different complications. There was no correlation of complications in Type II diabetes with the glycaemic control. The micro-vascular complications correlated largely with diagnosed hypertension; the duration of the macro-vascular events was related to smoking, age, weight for height and lipids (triglycerides and HDL-C).

MONITORING

Tattersall (UK) indicated scope of monitoring (self-monitoring of blood glucose at home) in type II diabetes. (i) NIDDM, newly diagnosed and requiring insulin therapy, (ii) NIDDM with pregnancy, (iii) NIDDM with abnormal renal threshold and (iv) NIDDM suffering from hypoglycaemia unawareness.

R.C. Turner (UK) provided an overview of UK study of treatment of NIDDM (5000 patients for glucose study, and 1000 patients with hypertension by 1991). On recruitment, 50% had evidence of end-organ damage. It is aimed to determine whether improved glycaemic control reduces morbidity and mortality amongst diabetics and what is the effect of the type of treatment (insulin or sulfonylureas)

TREATMENT

The European Association for Study of Diabetes (EASD) has evolved a consensus on the algorithm for the management of NIDDM (Gries F. A., Germany). This is a step-wise approach, initiating therapy with diet, addition of sulfonylurea if diet is not able to control blood glucose, and institution of insulin therapy if there is continued poor control and patient is severely symptomatic. Targets for control, fasting and post-pran-dial blood glucose, hemoglobin A_{1c} urinary glucose, HDL-cholesterol, triglycerides, BMI and blood pressure values are defined. Time involved between trial of dietary therapy and initiation of OHA is not stated. Frequent monitoring (1-2 days week) in stable or well-controlled NIDDM may not be acceptable to many.

Treatment advised seemed bereft of individual grade of glycaemic, associated cardiovascular disease, age profile or possible drug interactions.

P. Lefervre (Belgium) covered the use of fish oils (omega-3 fatty acids) in NIDDM. Though there was a reduction of serum triglycerides and lowering of blood pressure, there was increase in cholesterol, LDL and HDL-C. A decrease in insulin sensitivity or worsening of glucose intolerance was also observed. An increase in bleeding tendencies with use of fish oils is also reported.

There was an emerging view on keeping fat content of diabetic diets around 40% and a move to replace the saturated fats by poly or mono-unsaturated fats.

Use of magnesium salts in NIDDM:

Reports from Europe have documented a reduction in plasma and erythrocyte magnesium (Mg) in NIDDM. Administration of Mg salt, 2 g twice a day restores this and improves beta cell response and insulin sensitivity.

R. J. Heine (Netherlands) highlighted the role of central obesity, waist-to-hip ratio and its relationship with insulin resistance, dyslipproproteinaemia and cardiovascular disease.

Role of environmental factors, behaviour, metabolic factors and heredity was outlined in obesity. Thus obesity is arising not only from gluttony but was described to be multifactorial. Results of very low calorie diet (600 Kcl/d), exercise and cognitive behaviour therapy were discussed.

Indications for insulin therapy in NIDDM were discussed by M. R. Taskinen (Finland). Secondary failure to sulfonylureas, those with poor glycaemic control or with complications and some newly diagnosed NIDDM were being advised insulin therapy. Various regimens including intermediate acting insulin at night or two injections of mixed insulin or multiple injections were described, though none of these were found suitable in all the subjects.

A. Dejgaard (Denmark) referred to new insulins. Insulin analogues are now being developed with an aim to improve their kinetic properties, bioavailability and ease of administration. There are 10% of sulfonylurea failures each year and such subjects require insulin therapy. Use of Novopen II was described because of ease and flexibility in the use of insulin that it provides for the NIDDM diabetics.