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Diabetes Mellitus, 1987

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In this presentation, endeavour is made to provide an up dated information on the scientific achievements in the field of diabetes mellitus. The areas covered relate to etiogenesis, pathogenesis of complications and new modes in management with some reference to intervention surgical procedures now being followed.

Molecular Genetics in Diabetes, markers for NIDDM

Molecular genetics in diabetes mellitus are being studied employing the restriction fragment length polymorphism (RFLP). The DNA prepared from the nuclei of peripheral leucocytes is digested with restriction endonuclease. The digested DNA is electrophoresed on agarose gel and transferred to nitrocellulose filters. At this stage hybridization is carried out using 9zP-labelled human insulin probe. The resulting hybrids are then visualized by autoradiography, and the poly-morphism studied. The RFLP have been studied both for the insulin gene on the short arm of chromosome 11, and the insulin receptor gene on chromosome 19.

A polymorphic region of heterogeneous length occurs about 350 base pairs (bp) at the 5' coding portion of insulin gene, and this length of heterogeneity has been categorized into:

Class I alleles of about 570 bp, class 2 alleles of about 1320 bp (1.3 kb) and the class 3 alleles of about 2470 bp (2.4 kb) in size. The human insulin receptor gene has shown polymorphism with a band at 6.7 kb (kilobase), 6.2 kb or 3.6 kb.

An association between RFLP of the insulin gene and the susceptibility to diabetes mellitus has been claimed in certain reports while others found such association lacking. There are ethnic variations in the RFLP. Thus when studying the insulin gene the insertion frequency of class 3 allele was only 0.014 in the Japanese non-obese healthy individuals compared to Caucasians, American blacks and other races. However, the class 3 allele insertion frequency was higher in type 2 diabetic individuals than controls (Nomura et al, 1986).

An association has been claimed between DNA sequences flanking the insulin gene and atherosclerosis (Owerback et al, 1982).

Ethnic variations in RFLP of insulin receptor gene have also been shown. In the Japanese 6.7 kb frequency was shown to be less than that of Caucasians, and 15% lacked 3.6 kb band which is commonly found in Caucasians (Takeda et al, 1986).

Receptors are recognized far modulating the insulin action. The insulin receptor gene has been localized to chromosome 19 but its organisation has not been elucidated yet. The insulin receptor has intrinsic tyrosine specific protein kinase activity, and the autophosphorylation of this tyrosine is proposed to play a key role in the effects of insulin at the cellular level.

Modes of management, insulin

The diabetes control and complication trial (DCCT) was conceived by the National Institute of Arthritis, Diabetes & Digestive and Kidney diseases (NIADDK). The main objective has been to determine whether a statistically significant and clinically meaningful difference in the level of glycaemic control can be achieved between randomly assigned experimental and standard therapy groups while maintaining glucose levels in both groups in clinically accepted ranges (capillary blood glucose and Hb A_1C). The clinical events related to hyperglycaemia (DKA) and hypoglycaemia, body weight changes were to be recorded. 21 centres in U.S.A. and Canada are collaborating, cohort of 1400 subjects is envisaged in a follow up study of 5-10 yrs.

Standard treatment aims to achieve freedom from symptoms and rnaintenance of ideal body weight. Two injections of insulin (any mixture) per day are followed. Clinic visits are every 3 months. In the experimental group, insulin is administered by continuous subcutaneous infusion (regular purified pork insulin) or multiple daily injection using combination of insulins with different duration of action.

Blood glucose is to be maintained fasting $\leq$ 120 mg and post-prandial $\leq$ 180 mg and Hb $A_1C \leq 6.05\%$. Clinic visit is every week till blood glucose control is achieved and then onwards every month (DCCT Research Group, 1986). Only preliminary results have become available so far and are summarized as follows : (Table I)

Schedule for insulin administration seems to have gone through a full circle realizing that any technique employed should ensure optimum glucose level provided allowances are made for the meal and consequent glycaemia. The various regimes could be categorized as follows :

(a) Conventional split mixed (combination of regular (Plain) and intermediate acting (NPN) in 1 : 2 ratio, 2/3rd being administered in the morning, and 1/3rd in the evening.

Table 1

DCCT Trial in 278 Subjects-MBG mg/dl/HbA_1C

Group	(n)	0 m	3 m	6 m	12 m
Experimental (adults)	100	237/9.2	153/7.3	135/6.9	133/6.7
Standard (adults)	90	228/9.0	211/8.7	213i8.5	219;8.6
Experimental (adolescence)	45	279/10	183/8.4	169/8.0	162/7.7
Standard (adolescence)	42	263/9.8	270/9.8	247/9.3	261/9.6
			Other parameters		
			Experimental	Standard	
Weight gain (Kg.)			5.2	2.4	
Hypoglycaemia %			26	9.8	
Ketoacidosis %			2.7	2.3	

(b) Intensified split mixed (as above with the exception, that at night regular insulin is administered pre-dinner while intermediate acting insulin is given at bed time).

(c) Ultra-lente basal and regular premeal (3 times regular insulin is administered preceding meals, while ultralente is administered in the evening that provides 24 hour coverage to sustain basal level).

(d) NPH may replace ultra-lente in the same dose adjustment.

Insulin Pump Therapy (open loop) provides basal insulin requirement at 0.8 u/hr and in addition premeal bolus is provided, approximately 1/2 basal +1/2 premeal total. Patient monitors the blood glucose (atleast 4 times a day) and maintains blood glucose 100-160 mg/dl. At present usage of pump is being indicated in the following conditions :

(a) Wide fluctuations in blood glucose in a day despite optimal insulin therapy and diet control.

(b) Requirement of immediate control of blood glucose in a diabetic awaiting urgent surgical intervention or a pregnancy with complications.

(c) In delineating type of insulin resistance and its management.

Review of complications of pump therapy in 3500 users brings out that besides local problems i.e. infection or catheter plugging, connection dysfunction and run off, severe hypoglycaemia has followed in 9.3% and ketoacidosis in 4.4%. Out of 35 deaths reported only 2 were pump related, the remaining being accounted for by ketoacidosis 7, atherosclerotic vascular disease 7, end-stage renal disease 5, sudden death 3, accidents 3, status epilepticus l, and unknown causes (7) (Teutsch et al. 1984).

(ii) Second Generation Sulphonylureas

Second generation sulphonylureas have now wider clinical usage. Of these glibenclamide and glipizide are now available in India. The main advantages are smaller dosage required, sustained effectiveness inspite of short halflife and significant effect on insulin receptors helping to decrease the insulin resistance in some instances, Again, there seem to be less number of secondary failures with second generation sulphynylurea though earlier claim for less hypoglycaemic episodes (as side effect) is not borne out in Indian experience.

(iii) Starch blockers

Alpha glucosidase inhibitors (Acarbose) belong to a group of new complex oligosaccharides of microbial origin that block starch digestion, which inhibits gastrointestinal absorption of carbohydrates. Hypoglycaemic response is not too marked and so this is being employed in combination with sulphonylureas or insulin and many clinical trials support its usefulness.

(iv) Management of complications-Aldose reductase inhibitors

Aldose reductase inhibitors have been gaining ground in management of complications of diabetes. Tissues that do not require insulin for the uptake of glucose, possess polyol pathway wherein glucose gets converted to sorbital under the influence of aldose reductase, and again sorbital dehydrogenase converts sorbitol to fructose. The accumulation of sorbitol and fructose impairs the nerve conduction. Additionally they reduce the uptake of myoinositol by the peripheral nerves, and the decrease in myoinositol content has been linked to improved nerve conduction.

In literature there are scores of studies, clinical and experimental, that have cited beneficial effects of sorbinil (aldose reductase inhibitor). These are summarized as follow:

(i) Improvement in nerve conduction velocity and axonal transport.

(ii) Restoration of lost C wave in etectro-retinogram.

(iii) Prevention of basement membrane thickening (so reversal of overt proteinurea).

(iv) Prevention of inceased vascular permeability (reduction of leakage as observed by vitreous flourophotometry).

(v) Restoration of decreased red cell deformability. Consensus at present is that earlier institution of sorbinil therapy may prevent microangiopathic complications in diabetes.

Surgical Intervention Procedures

Pancreas transplantation has gone through many modifications. Presently the Minnesota group is practising segmental graft (50% of the organ - body and tail) from a living related donor. This is anastomosed to iliac vessels in the pelvis, while the duct is either occluded with synthetic polymer or drainage established in bladder (urinary amylase remains a guide on viability of the graft).

Scope of pancreatic transplant is being viewed independent of the renal transplant with end-stage renal disease. Non-uraemic diabetics who have microangiopathic complications and deteriorating rapidly are being accepted.

Indications for coronary bypass surgery in a diabetic could be summarised as follows : Patients with unstable angina should undergo angiographic studies. Instances that show (i) angiographically greater than 70% reduction in lumen diameter of a major proximal coronary artery, (ii) a patent coronary artery distal to the obstruction with a diameter greater than 1.5 mm and (iii) acceptable left ventricular performance (ejection fraction greater than 30%, left ventricular end-diastolic volume less than 125 ml/m^2).

The coronary bypass surgery has twice the peri-operative mortality in diabetics when compared to non-diabetics. High blood pressure, ventricular hypertrophy and diffuse disease amongst diabetics are contributory factors for this enhanced mortality and also proportionately reduce ten year survival (Solomon et al., 1983).

Photocoagulation is fairly widely practised now and diabetic patients wherein severe visual loss of 25% in 2 years or those with visual acuity of <20/20 or vision has become cloudy are offered photocoagulation. Laser technique is preferred and either pan-retinal or peripheral field coverage is done.

The following high risk instances are indications for photocoagulation.

1. Moderate to severe new vessel formation elsewhere than disc (NVE) with vitreous or pre-retinal haemorrhage or both.
2. Mild new vessel formation on disc (NVD) with vitreous or pre-retinal haemorrhage or both.
3. Moderate or severe new vessel formation or disc NVD with or without vitreous or pre-retinal haemorrhage.

4. Macular oedema.

Patient Education Programmes

Patient Education for Self Care has now been professionalised. The teaching contents are standardized, and skills to be practised defined. The nurse assistant or paraprofessional is specifically trained in imparting the curriculum and teaching the skills. The interaction is informative, practical and personalized so that individual patient feels involved and receives the necessary support required. In certain diabetes teaching units, a team approach is employed and in a 5 day programme the patient is provided with all health care measures that a diabetic needs to follow. Using such educative innovations, compliance to therapy is improved and this greatly reduces the risk of various complications and of hospital admissions. The patient education programmes have set points and are being objectively assessed.

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