

Feature Article

Highlights of Advanced Course in Diabetes-March 12 to 16, 1984

Training potential of specialist care for diabetes received a great impetus at a recently conducted advanced course in Delhi. According to Director, Scientific Programme, it matched in standard any such educational programme conducted in a western country. The course was held under the auspices of National Academy of Medical Sciences of India, Research Society for Study of Diabetes in India and All India Institute of Medical Sciences, New Delhi, from March 12 to 16, 1984.

The course curriculum had 3 subsets :

1. Didactic lectures covering basic and clinical aspects of diabetes.
2. Specialist contributions as of ophthalmologists, anaesthetist, obstetrician and surgeon in the field of diabetes.
3. Practical patient problems and their solutions (CPC, therapeutic conference, radiology conference and nutritional planning exercises).

There was 25 member faculty drawn from all over the country and having experience of teaching this subject for many number of years.

There were 30 participants registered, 80% from medical colleges and associated with speciality poly-clinics, 10% practitioners. and 10% from neighbouring countries.

The highlights of the course are summarised as follows :

Glucose homeostasis

Various aspects of nutrient influx, absorption and utilisation were explained in relation to anabolic state, viz-a-viz catabolic state. The metabolism is adjusted based on fed or fasted status, insulin-glucagon ratio, modulation of enzyme content and their kinetics. Diabetes was compared to a state of accelerated starvation.

Gut Hormones

Enteroinsular axis was explained, and the intricate intercommunication channels, endocrine, paracrine, epicrine and tight junctions in pancreas were detailed. Of various gut hormones, role of GIP in insulin secretion was stated to be of definite physiological significance.

Receptors

Specific insulin receptors on adipose, liver, muscle and blood cell membrane were discussed. Monocyte/erythrocyte receptors are easier to secure and can be easily employed for replicate studies and provide same functional information and mirror events as their counterparts in liver and muscle. Following on internalization of insulin receptor complex, the action of second messenger (cAMP) on several metabolic events at post-receptor level

is initiated. Down regulation (insulin available in excess, obesity, high CH₂O diet) or up regulation (insulin level low; exercise, fasting) were explained.

Immunology in etiopathogenesis of type I was explained on basis of HLA. associations, T cell abnormalities and other autoimmune markers. Employing monoclonal antigen, it has been demonstrated that pancreatic islet cells have antigens of extremely heterogenous type and can react with neuroendocrine tissue, thymic epithelium, neurone, adrenal medulla, T-cells, thyroid, monocytes, fibroblasts, rim of nucleus or other cells of pancreas. Immune deficient animal model has been employed in study of surface antigens and variation of T-cell function. Again detection of ICA in relatives (identical twin studies) have opened possibilities for use of immunosuppression, steroids, or plasmapheresis as prophylatic measures prior to onset of diabetes, With Cyclosporin, more beneficial effect may be forthcoming.

Heterogeneity of diabetes mellitus

Genetic and immunological differences, variations in pathological lesions, different clinical presentations and the varied biochemical deviations in diabetes mellitus bring out the heterogeneity of this metabolic disorder. This was elaborated both in reference to Type I and Type II diabetes mellitus.

Pancreatic diabetes

Emphasis was placed on two varieties of diabetes observed in this country which are related to malnutrition. Pancreatic secondary diabetes in the young, calcification being sine qua. It is endemic in certain geographic areas such as Orissa and the southern states as Kerala. In the other varieties like Jtype diabetes calcification is absent, history of abdominal pain is lacking and steatorrhea is not a common feature. Clinical features in both are as of leanness, acute onset of symptoms and insulin requiring for control of blood glucose. Absence of ketosis even if insulin is not administered makes this type of diabetes distinctive.

Experimental diabetes

Account of various animal models indicating most commonly used Alloxan diabetic model (Korec's modification) was detailed and diabetic vascular complications were exemplified from various studies.

Diagnostic criteria

For uniformity in epidemiological assessment, blood glucose values as exemplified in the data of the NDDG were discussed. Variations as for children and pregnancy were stated. Reasons for the recent changes in criteria for diagnosis of diabetes were dealt with. In type II, need to recognise distinct lean type, and as well to incorporate previous abnormal GTT and potential AGT In IGT group was emphasised. Nutritional diabetes required further elaboration.

Monitoring schedules

HbA₁C determination correlated closely with long term control of diabetes. However, in a clinic setting where a fasting and/or post-prandial blood glucose and glycosylated hemoglobin were used to assess control of diabetes, glycosylated hemoglobin was at variance from the blood glucose interpretation regarding the degree of metabolic control in over half of the diabetics.

Colorimetric method had proved efficient and economical. Limitation of HbA₁C values especially by the column method were high values in instances with uraemia, in presence of fetal Hb, along with use of alcohol or aspirin, while low values in haemoglobinopathies, haemolysis or pregnancy.

High A₁C value in first trimester of pregnancy could warrant MTP due to high risk of congenital anomalies in the new born.

Glycosylation is increased in patients with IGT, indicating that these patients should be labelled diabetics and the term IGT may need to be abolished.

A live demonstration of use of dextrometer and various strip methods for home monitoring was provided.

Cardiovascular screening

Significant cardiovascular events in instances with IGT make the screening imperative as intervention therapy at this stage may provide reduction in morbidity and mortality. Data on follow up studies of Framingham, Bedford and ongoing study of ICMR were exemplified (hypertension in control 5%, IGT 50%, Diabetes 60%, ECG evidence of CAD in control 5%, IGT and Diabetes 20% each were exemplified).

Clinico-Pathological Conference

Case of 30 year old Keralite with calcific pancreatitis of 8 years duration was discussed. Present admission was due to acute vestibulitis while other parameters indicated unstable diabetes, hypertension, anaemia, uraemia, acidosis and albuminuria. He subsequently became oliguric and unconscious. The discussion was as regards the nature of underlying renal disease (acute or chronic nephritis with renal failure or diabetic nephropathy). Whether infection in the sinuses was related to opportunistic organisms or mycotic i.e. aspergillosis, mucormycosis especially rhinocerebral phycomycosis and whether nature of neurological deficit was solely due to uraemia, inadvertent hypoglycaemic or disseminated intravascular coagulation. Discussion was elaborated with differentiating clinical indicators.

Diabetic Ketoacidosis

Pathophysiology of metabolic events, wherein acidosis set in were outlined; dehydration and sequence of low volume perfusion, electrolyte imbalance, the usual magnitude of deficit being water deficit of 5-6 L, Na deficit of 300 mEq, K deficit of 300-1000 mEq. CI

deficit of 500 mEq. phosphate 50-100 mmol, base deficit 400 mEq. In the management, urgent fluid replacement by normal saline 1-2 L in ½ hour; 1 L in next hour then 1 L every

4 hour (approx. total 6 L). Plain insulin 80 units in 540 ml. administered intravenously as 1 ml (15 drops)/min. provides about 6 units per hour and obviates need for insulin pump. K 20-30 mEq/L is provided based on ECG review, electrolyte analysis and ensuring adequate urine output. Bicarbonate is not favoured unless blood pH is lower than 7.1 Role of other supportive measures was discussed.

Cardiovascular complexities in Diabetes

Non-coronary events were attributed to cardiomyopathy which was combination of specific angiopathy, metabolic changes or collagenous early degeneration. Obstructive lesions of coronary vessels were not the features in such instances. Autonomic involvement could be evaluated by RR interval. Valsalva maneuver, epinephrine, atropine infusion test-heart behaving as a denervated organ. Autonomic neuropathy provides background for increased anaesthetic mortality and sudden death amongst diabetics. Therapeutically, use of nitrates, beta blockers, thiazides or hypotensive agents pose subtle, real and practical problems in Diabetes.

Lipids and lipoprotein profile

Various classifications and their bases were presented, and WHO (1977) recommendation on categorisation as I chylomicron, II LDL (a) beta and (b) beta and pre-beta, III IDL (broad beta), IV VLDL (pre-beta) and V. mixed were exemplified. Diabetes was common in type I (IDL remnants) and V (Chylomicron + VLDL) types. In IDDM, after treatment, VLDL, cholesterol, triglyceride, apoprotein normalise significantly than the other lipid parameters. Low HDL cholesterol more closely relates to rate of development of atherosclerotic process, while earlier notion was type II (a) and (b) being associated with increased risk of CAD.

Complications of various modes of therapy in diabetes

These were discussed under the headings of those due to insulin, oral drugs, diet or as a result of drug interaction. Protean modes of onset of hypoglycaemia, its varied symptoms in different situations were illustrated.

Relation of insulin antibodies to species source, purity, pharmaceutical form, irregular administration and genetic factors was brought out. Significant side effects of sulphonylurea and biguanides were summarised. Evidence for oral hypoglycaemic agents to promote cardio-vascular morbidity was found lacking. Important drug interactions were outlined.

Practical aspects of treatment of diabetes

This emphasised time relationship of antidiabetic therapeutic agent, diet intake undue physical activity, and intercurrent problems (commonest being infection, incipient renal

failure on a metabolic disorder.) Irregularities in therapy or continuing without appropriate check were other causes for failure of therapy.

Therapeutic Conference

3 clinical case histories were presented, including situations of side effects of antidiabetic drugs or the related drug interactions. Some examples were neurological symptoms induced by INH, Propranolol or hypoglycaemia, abdominal pain due to diabetic ketosis or drug induced pancreatitis and aggravation of insulin induced hypoglycaemia by phenyl butazone.

Neurological manifestation

Classification was based on polyneuropathy, mononeuropathy, radiculopathy or autonomic neuropathy. The two present etiological concepts were in relation to myoinositol or sorbitol pathway causing Schwannopathy or segmental degeneration. Myelopathy was in fact femoral mononeuritis. Nihilism of the available therapeutic measures in relieving symptoms of peripheral neuropathy was highlighted.

Exercise and diabetes mellitus

Metabolic events at muscle and liver inducing accelerated rate of utilization more than rate of production, with exercise were presented. Role of insulin in intermediary metabolites was brought out. Increase in blood flow, changes in intracellular calcium and increased receptor sensitivity are factors which assist in glucose utilisation. With severe lack of insulin in the body as in IDDM and excess of counter regulatory hormones, there is inherent risk of augmenting hyperglycaemia and ketogenesis. Exercise in NIDDM improves glucose tolerance and as well promotes cardiorespiratory efficiency and brings psychological uplift. This would also induce weight reduction.

Ocular complications

Almost all structures of eye become involved in diabetes though most significant are retinal lesions. For diagnosis, treatment and prognosis of retinopathy, fluorescein-angiography is most useful. Classification is based now on criteria of Eva Kohner (i) simple or background, (ii) proliferative (iii) exudative maculopathy. With photocoagulation according to multicentre study of DRRG, parameters such as visual acuity showed significant improvement and vasoproliferative process was halted.

Dermatological complications

Analysis of 140 cases in AIIMS Dermatology Clinic showed presence of a dermatological lesion in 55.7% instances, pyoderma being commonest (18%). next being moniliasis or pruritis. Dermal angiopathy, Xanthelasma and gangrene were of rare occurrence (2% or less each).

Renal complications

After manifest diabetic renal disease, survival was 3-5 years only. Analysis of causes of chronic renal failure reveals that 12.5% of these were due to diabetes in our country.

Besides glomerular damage, there is as well significant involvement of tubules and the interstitium. Role of coagulation factors in pathogenesis was under study. There was also

need to recognise the syndrome of low aldosterone secretion in some diabetic instances. Clinically variations in grades of diabetic nephropathy are wide, i.e. from asymptomatic proteinuria to renal failure, Nephrotic syndrome is present in about 20% instances. Scope of dialysis and transplantation were briefed.

Immune complex related glomerulonephritis in diabetics is characterised by macromolecular involvement of mesangium, which spill over and damage the capillary wall. The quality of basement membrane was altered and this led to entrapment of complexes. Most of such cases show low C3 and positive ANF.

Anaesthesia in Diabetes

Necessity of pre-operative complete assessment of metabolic and vascular status (including test for autonomic dysfunction) was emphasised. Choice of anaesthetic agent was important, use of ether or chloroform in a diabetic was prohibited. Management was based on schedules, designated as NTR (non-tight rigid control) or TR (tight rigid control)). A film on resuscitation was also shown.

Surgery in Diabetes

A pre-operative evaluation risk score was presented. Errors of management included hypo or hypertension, volume depletion or expansion, electrolyte imbalance as hypokalaemia or azotemia. Steps in management ensuing appropriate insulin through drip to maintain euglycaemia during surgery was suggested.

Radiology conference

New techniques in imaging, subtraction radiology, angiography ultrasonography or Doppler's method have opened new vistas in diagnosis. Some techniques as angioplasty are used in management of vascular lesions of diabetes mellitus. Non-invasive methods have now provided better appreciation of extent of end-organ damage in diabetes than possible before. Findings in imaging were profusely illustrated.

Diabetes and Pregnancy

In our country at present prenatal mortality in diabetes has been reduced from 90% to 16-25%. As pregnancy advances maternal-fetal metabolic homeostasis is adjusted, insulin needs gradually increase. Monitoring includes estriol determination, ultrasound, CPD measurements, amniotic fluid examination for L/S ratio and CST/or DCT. Complications included increased risk of congenital anomalies, macrosomia; respiratory distress syndrome and neonatal hypoglycaemia. A team work approach is most called for in the management of pregnant diabetic.

Diet modulations in Diabetes

Acceptance of higher content of carbohydrates (complex), increase in fibre content and realization of variable composition of vegetable oils regarding polyunsaturated/saturated ratio were highlighted as the new vistas for this decade. Choice of appropriate items in

food groups could substantially assist in bringing an optimal control of glycaemia with or without other antidiabetic therapeutic measures.

Principles of diet therapy in Diabetes

The cornerstone of dietary therapy in diabetes was optimization of body weight. Variations in age, sex, activity, cultural factors or nature of disease, ketosis proneness, insulin dependence or status of blood glucose control provided the background for working up caloric needs and respective adjustments.

Concept of exchange in food groups was highlighted and alternatives that promote weight reduction were e; amplified.

Nutritional Planning

Three case histories were outlined exemplifying cases of obesity with cardiovascular and renal disease, pancreatic diabetes with steatorrhae, and of pregnancy with renal glycosuria. Clinical details were presented with relevant biochemical data. Participants offered solutions in diet planning for each problem case. Role of nutritional counselling in alleviating such additional complications was brought home by discussing diet management for such problem cases. Improvement in the clinical state was related to dietary adjustment.

Newer insulins and delivery systems

Newer insulins in context of species source, purity, neutral pH and dispensing strength (U 100) were discussed.

Pure pork insulin (Monocomponent) or human insulin offered advantages of improved biological effectiveness and absence of immunogenicity but cost was exorbitant. Delivery systems, close loop and open loop, were exemplified and practical experience of various infusion pumps in India was presented. Intensive conventional therapy matched the open loop methods in achieving good control of diabetes.

Second generation sulphonylurea

Glibenclamide, Glibornuride, Gliclazide, Glipizide and Gliquidon, as second generation sulphonylureas have same core structure, with difference in the side chains. Their potency is 100-200 times increased. These drugs were metabolized by liver so the accumulative effect as hypoglycaemia was less frequent.

In clinical practise, no greater advantage was forthcoming, and in a trial lasting for 4 months effects on lipid were not significantly different. There were fewer effects of this therapy.

CRITERIA OF CHOICE of particular methods of treatment employed were discussed by a panel, and upto date information with policy of investigators was elaborated. While insulin was always indicated in ketosis diabetic children, those with pregnancy, those

undergoing surgery and during complications. (Its usage in those with significant weight loss or secondary failure to sulphonylurea seemed optional. Single or multiple dose administration seemed to be guided by virtue of status of blood glucose control. Pure insulins become indicated in those with brittle control, significant antibody titre, those showing allergy to conventional insulin, in state of lipoatrophy and situations requiring short term or intermittent usage of insulin.

Insulin through pump was recommended for those with unstable control, macular oedema, painful) neuropathy or reversible state of nephropathy.

In India, for ketoacidosis, insulin dosage schedule was initial bolus of 0.3 U/kg b.w. and then 0.15 u/Kg b.w. every hour IV or IM. If there was no response by fall of blood glucose in 2 hours, dose of insulin was to be doubled.

Sulphonylurea seemed indicated in type II diabetes (NIDDM) wherein diet therapy had not been able to normalize glycaemia. In other diabetics with non-ketotic characteristics, it is unlikely to bring about adequate control of blood glucose.

For the individual group, chlorpropamide should be avoided in elderly or lean diabetics, those who consume alcohol and those with renal or hepatic dysfunction.

Similarly risk of hypoglycaemia was more imminent if glybenclamide was employed than tolbutamide in type II lean diabetics.

Although combination of biguanide with sulphonylureas in fixed dosage was deprecated, in case of inadequate control with sulphonylurea, combination with varying dose of biguanide could improve control. Metformin has lesser possibility to induce lactic acidosis.

In instances of NIDDM with myocardial infarction and compromised renal failure, evaluation of overall status and extent of actual organ damage would guide to indicate if oral drugs could be continued.

Similarly insulin and oral drug combinations may provide means for control in rare cases of NIDDM where insulin dosage was too high and no further stepwise fall in blood glucose was being achieved.

When the diabetic state is properly regulated, risk of cardiovascular morbidity because of sulphonylurea had not been substantiated.

Patient education and compliance

The life long problems of disease, with many and varied psychological repercussions of inadequacy of treatment and inevitable long term complications were elaborated. The solution through education of the patient by individual or group discussion or sources of

media or created literature was being sought. This would improve compliance. And wherein element of self-care is inbuilt, control of diabetes also improved.

Illiteracy, lack of resources and cultural beliefs added a further challenge in our setting and await a solution from political determinations, scientists participation and. media involvement.

Towards the completion of course, assessment by the participants through an objective proforma was sought. This included comments on course contents, faculty composition, relevance of course to practical needs, educational techniques employed, learning facilities, restraining factors and other amenities provided. Significant comments were that participants graded course adequately structured and were complimentary for the efforts of the faculty drawn from different subsets for one subject (Diabetes) discussions. They expressed that more clinical bias be introduced, and. live patient contact introduced at some phase of course.