Complications of Diabetes

Q. Do repeated hypoglycemic episodes effect congnitive function?

A. It is recognized that there are certain electrophysiogical changes as studied by EEG, P300 and Somatosensory evoked potential during hypoglycemia. Glucose threshold for an individual to register this is variable and a degree of adaptation is there. These changes are marked in the anterior areas (frontal lobes) in the diabetic patients and related to cognitive dysfunction. Hypoglycaemia has to be severe and of a longer duration as to bring about this alteration (More than 3 episodes a year, severe enough to require hospitalization an I.V. glucose drip for recovery)/ [S.S]

Q. It is now recognized that hyperinsulinaemia leads to atherogenesis. Is it then safe to administer insulin in NIDDM?

A. There is sufficient data in animal experiments to indicate that insulin is atherogenic. The mechanism involved is proliferation of arterial muscle cell which then migrates towards intima and leads to atheromatous process.

Insulin application locally to the arterial wall is lipogenic and increases lipid synthesis. Insulin also inhibits regression of diet induced experimental atherosclerosis. The main issue is whether administration of insulin is physiological (to replace lack of endogenous insulin) or pharmacological (in excess dosage to meet insulin resistance)

There is evidence that hyperinsulinaemia is closely associated with a cluster of cardiovascular risk factors. I.e., hypertriglyceridemia, low HDL level, hypertension, hyperglycaemia, central obesity. Hperinsulinemia relates to actual state of insulin resistance at tissue level, reduction in glucose oxidation at peripheral level, increase in FFA leading to increased triglyceride synthesis (dysliporoteinaemia). Insulin also causes increase in sympathetic activity, increase in renal sodium retention, hypertension and thus induction of atherosclerosis.

Such data cannot be extrapolated to exogenous insulin which is being administered for therapeutic purposes. In this situation, by bringing about a eumetabolic or normoglycaemic status, insulin is protective against cardiovascular disease. [M.M.S.A.]

Q. Which lipoprotein abnormalities occur with diabetes and what is the line of approach?

A. Altered lipid metabolism is common in diabetes mellitus. As emerging evidence serves to confirm the pivotal role of blood cholesterol and particularly LDL cholesterol in the development of atherosclerosis related diseases, it is timely to consider the importance of lipid and lipoprotein disorders in diabetes. In an individual patient, lipid and lipoprotein levels will depend on the extent of insulin deficiency or insulin resistance, hyperglycemia, obesity, diet and presence of concomitant primary and other secondary causes of hyperlipidemia.

In addition to absolute levels of lipids and lipoprotein, the composition of lipoprotein may be changed by diabetic state. Most common lipid abnormalities include alteration in LDL, VLDL, or HDLC.

LDL is the most atherogenic type of lipoprotein. Although no specific defects in the production or removal of LDL has been identified, diabetics have high LDL levels than normal people and non-insulin dependent diabetics have LDL levels higher than insulin dependent diabetics.

Insulin increases LDL receptors(Mazzone et al, 1984). Chronic insulin deficiency might be associated with delayed clearance of LDL. Also, uncontrolled diabetes can bring in changes in cell membrance thus affecting LDL receptor function. Thirdly glycosylation of LDL apoprotein B may occur secondary to hyperglycemia.

VLDL - In IDDM patients the clearance of VLDL may be decreased as the enzyme lipoprotein lipase depends on insulin for its full activity.

HDL-C- has protective role against atherosclerosis as it extracts cholesterol from the arterial wall. Serum HDL-C values may be low, normal or high in diabetic patients. HDL-C values are inversely related to serum triglyceride values since TG displaces cholesterol from the lipoprotein. Because hypertriglyceridemia is fairly common among diabetics, it may contribute to reduction in serum HDL cholesterol.

Line of approach to overcome the lipid abnormality in diabetics will be as follows :-

1. To attain improved glycemic control.
2. Adjust caloric intake to achieve or maintain ideal body weight.
3. To consume low fat, high complex carbohydrate, 40-50 g fibre diet.
4. To follow dietary principles to lower cholesterol intake.

i) Total intake of fat should be <25% of total caloric intake

ii) Substitute whole milk and its products with skimmed milk.

iii) Replace organ meat and red meat with fish and chicken

iv) Avoid use of egg yolk

v) Replace use of butter, pure ghee and dalda with refined oils

vi) Opt for coarse cereal grain, husked pulses, fruits and vegetables instead of refined foods.

vii) Avoid rich salad dressing like salad oils and mayonnaise.

viii) Include plenty of onion and garlic in the diet.

5. Intake of adequate amounts of natural antioxidants in a diet (Vitamin C,B Carotene and Vitamin E)
6. To include natural sources of N-3 fatty acids in diet.
7. To practice regular exercises.
8. To avoid use of alcohol

Adherance to these principles will keep serum triglycerides also under control. [I.K.]

Q. A diabetic has severe gram negative septicaemia. What is the risk involved and how does its management differ from that of a nondiabetic patient?

A. A diabetic has abnormal white blood cell function and the potential for immune response to infection is reduced especially during the period blood glucose is not under control. Infection acquired by diabetics may be polymicrobial or involve ubiquitous commensal or fungi.

Septicaemia may be secondary to some localized infection which may be over or occult (deep tissues as perinephric or deep pelvic). Fever, chills may not be so obvious in a diabetic. Profound hypotension or loss of urine out-out signifies a septic shock. There is a high fatality rate amongst this category. Management has to be wide and may include cloxacillin, gentamycin and metroniadazole parenteral in full dosage. If source of infection is known and with prior antibiotic use, one should select a third generation cephlosporin i.e. cefotaxime or a quinolone like ciprofloxacin. Fluid therapy should include Ringer lactate, and patient may require plasma if volume depletion is associated with low osmality. (CVP monitoring may be required). Dopamine is the next consideration; 2-10 ug/kg/min will assist in raising blood pressure and improving cardiac output. In gram negative septicaemia, anti-endotoxin immunoglobulin is worthy or addition if available [N.P.S.V.]

Q. A diabetic has acute appendicitis with impending peritonitis, a blood glucose value>350 mg/dl and urine ketone moderately positive. What would be your approach ?

A. This needs a team work, as there is dual risk to life. On one hand there is acute abnominal emergency and on the other there is a metabolic crisis.

Initial correction of fluid, electrolyte deficit is the prime step. Simultaneously there is need to initiate regular insulin 8-10 u IV bolus per hour (0.1 u/kg body wt). Hourly blood glucose should be done and simultaneously the patient is prepared for surgery. As soon as acidosis is reversed and blood glucose value shows some reduction surgeon can go ahead. In such situation one need not wait till blood glucose is quite normal or ketones fully disappear from urine. [N.P.S.V.]

Q. A diabetic has developed gas gangrene in a foot, what are the indications for amputation ?

A. One should ensure complete evaluation as regards to the etiological agent (aerobic/anaerobic) and the extent of ischaemia, X-ray of the limb may show subcutaneous gas but this could be due to organisms other than Closteridia.

As regards surgical intervention, if there is only digital involvement and sepsis is controlled, and arterial reconstruction is not feasible it is best not to amputate the digit but to continue conservative treatment with regular review. Only debridement of local necrotic tissue should be undertaken. The necrotic digit will probably fall off later on. Indications for below knee amputation include extensive gangrene or more limited gangrene in the presence of gross sepsis.

Intractable pain which can not be relieved by other measures is occasionally an indication for

amputation even if the lesions themselves are relatively minor. Operative surgical risk is not high if diabetes is controlled. Patients find great relief especially if there has been sepsis. [N.P.S.V.]

Q. Plan strategy for management of diabetes with hypertensive heart failure and incipient renal failure.

A. The objectives of therapy in such instances will be

a) Adequate control of blood pressure.
b) Use of certain diuretics that would relieve heart failure and not aggravate renal decompensation.
c) Choice of cardiac drugs as not to jeopardize control of blood glucose.

It needs to be kept in mind that most of the drugs commonly available for this purpose have side effects, e.g. thiazide worsen hyperglycaemia and induce hypokalaemia, loop diuretics will worsen hyperlipidaemia. Similarly with presence of heart failure, beta-blockers will not be advisable and along with diabetes, hypoglycaemic symptoms may not remain discernible with the use of beta blockers.

Again in the presence of incipient renal failure, angiotnsin converting enzyme inhibitors may worsen proteinurea and induce hyperkalaemia.

Thus with this restricted choice, calcium channel blocker may be found useful. Of the diuretics, amiloride may be of benefit in achieving adequate response without much metabolic disturbances. [M.M.S.A]

Q. A patient has CRF and "burnt out diabetes" : Discuss management approach.

A. The management strategies for managing a subject with chronic renal failure and "burnt out diabetes" consist of :

Optimized insulin treatment:

Though the importance of ideal diabetic control in the early stages with hyper-filtration/ microproteinuria is clear, it is not so in CRF, when no dramatic effect has been demonstrated on optimized insulin therapy. On the other hand subjects in CRF are unduly sensitive to insulin and oral hypoglycemic agents as 25% of insulin is catabolized by kidneys, prolonging its half life and duration of action. With the long duration of diabetes associated with CRF, levels of the associated antiinsulin hormones like glucagons are low. This makes the occurrence of hypoglycemia more common, and also more severe and prolonged. Deaths associated with hypoglycemia usually occur with associated significant nephropathy. Moreover, as discussed elsewhere, with long duration of diabetes and associated elsewhere, with long duration of diabetes and associated autonomic neuropathy, hypoglycemia unawareness may also be commoner.

Thus the optimal control targets may be relaxed to:

Blood glucose (fasting): 100-600 mg/dl
Blood glucose(post-prandial): 100-180 mg/dl
HbA_1 : 8.5-9.5%

Low protein diet : With the earlier stress on restriction of carbohydrates, and then on restriction of fats over the past few decades, excessive protein intake became a routine. Excessive protein has meanwhile been shown to be nephrotoxic, both in incipient diabetic nephropathy and frank, clinical proteinuria. Both the urinary albumin excretion (UAE) rates (or rates of increase of UAE) and glomerular filtration rate (or rate of fall of GFR) have been demonstrated to improve with protein restriction. Moreover, there are indications that vegetable protein , may be less damaging to kidneys than animal protein. Based on current knowledge (though sketchy, from preliminary studies), it would seem advisable to recommend a protein intake (preferably vegetarian protein) of 0.6 g/kg body weight in diabetic nephropathy.

Control of hypertension: After several revision, targets for blood pressure in diabetic nephropathy have come down to "borderline hypertension as defined by WHO i.e. 135/85 mm Hg. With reduction in BP the progressive rate of fall of GFR is reduced. In an advanced case of nephropathy this may require more than 1-2 drugs. Angiotens in converting enzyme inhibitors (captopril, enalapril etc.) should be given (unless contraindicated due to presence of hyporeninemic hypoaldosteronism), along with loop diuretics, and if needed, vasodilators. Loop diuretics are the first line of therapy in the presence of significant edema.

Ancillary measures:

1) Protection of kidney against iatrogenic insult:
   (a) Use of nephrotoxic drugs like contrast media, which can precipiate acute or chronic renal failure in diabetic nephropathy, should be avoided
   (b) Urinary infection should be prevented (least uro-genital intervention) and treated promptly.
2) Protection of large vessels:
   (a) Monitoring of lipid status and intervention if dyslipidemia develops (often associated with diabetic nephropathy).
   (b) Salt restriction (2-5 g/day) unless salt losing state
   (c) Regular checking and appropriate intervention for coronary involvement
   (d) Treatment of anemia
3) Protection of bones:
   (a) Phosphorus restriction and extra calcium intake
   (b) Vitamin D (preferably, 1-alpha hydroxylated vitamin D)
4) Investigations and intervention for other diabetic microangiopathy (including retinopathy, diabetic foot)
5) Regular monitoring and follow-up for renal failure:
   (a) urinary albumin excretion, serum creatinine, GFR
   (b) consideration for continuous ambulatory peritoneal dialysis/ hemodialysis/renal transplant as indicated. [I.V.]

Q. In a diabetic foot, would doppler study provide better information than angiography?

A. A "diabetic foot" is a result of peripheral vascular disease (PVD) combined with neuropathy. Evaluation besides history and physical examination include not only Doppler and angiography , but also pulse volume recording (PVR), transcutaneous oximetry, laser Doppler, and pedography. Which test is better, and in which situation?

But first, why is PVD so important in the diabetic? As compared to nondiabetics, it occurs earlier and more frequently, progresses faster, is often present even at diagnosis (in non-insulin dependent diabetics), and is almost as frequent in diabetic women as men. Typically, the smaller arteries (below the knee:tibials an peroneals) and their arterioles and collaterals are involved, in both lower limbs, with occlusions at multiple sites. The spectrum of clinical presentation ranges from peripheral arterial calcification, absence of peripheral pulses, or claudication, to ulcers and gangrene. Amptutation is indicated more often, high, and may be needed on the contralateral side after a few years; hospital mortality is high; and associated problems (cardiac, renal etc). compromise the outcome. Thus the diabetic has a more severe form of the disease in every way; he/she is also at increased risk for coronary artery and cerebrovascular disease. Uncontrolled hyperglycemia and associated smoking, hyopertension, hypercholesterolemia, an dhypertriglycerdemia, all worsen the condition.

Doppler is used to measure and compare blood pressure (e.g. ankle to brachial systolic pressure ratio), evaluate flow patterns and detect areas of stenosis. However, if vessels are incompressible due to clacifications, Doppler pressures will be falsely high. PVR, using a sensitive segmentsal plethysmograph, measures pressures in the presence of calcification and also digital pressures. PVR is therefore preferred in diabetics with marked vessel calcification or involvement of smaller vessels. Normal resting pressure measurements may need to be repeated after exercise or reactive hyperemia; vascular disease results in significant fall in pressures, which take longer to return to normal.

Newer techniques being developed include regional trascutaneous oximetry (measured oxygen tension) or helium-neon laser Doppler (measures skin blood flow velocity). They assess local perfusion to indicate level of amputation and predict successful healing of ulcers or amputation sites. Using Doppler, predicting ulcer healing is correct only in 50-65% of patients, while with laser Doppler it is correct in over 85% patients, and with transcutaneous oximetry in 95% patients.

Angiography carries significant risks in the diabetic, especially in the presence of nephropathy, and should be performed only if vascular surgery is planned, never for routine evaluation of PVD. Apart from local comoplications (hematomas, bleeding), the major risks are of thrombus formation and renal shutdown (sometimes irreversible), due to injection of the radiocontrast dye.

These tests therefore are not better or worse than each other, but complimentary to each other. Doppler is simple and non-invasive, useful for routine study of the entire vascular system, and can be repeated as often as necessary, but is often unreliable in diabetics. Arteriography is more

definitive, but also far more risky, and indicated only as a preoperative procedure. Transcutaneous oximetry is more useful for evaluating ulcer and amputation site healing. Each procedure should be done only when necessary, and in the light of clinical judgment. [I.V.]

Q. A diabetic is suffering from insomnia due to painful neuropathy. Out-line management for this condition.

A. Diabetic Neuropathy-where are we now? Can we do anything about it or joust document it? This was the title of an editorial in the Lancet in 1983. This title is very appropriate because treatment of diabetic neuropathy can be a very frustrating experience. There exists a large number of modalities of treatment which illustrate that none of them is universally effective and that we have to titrate the various modes of therapy to find out which would suit a particular patient. The first step is to do a proper examination and rule out other neurological conditions which may mimick diabetic neuropathy. There are disc-prolapse, arthritic spurs and vasculitis which cause radiculopathy. The disorders which cause mononeuropathy are compression, trauma and vascular involvement of lumbar and brachial plexuses by haemorrhage or neoplasm. Diabetic polyneuropathy has to be differentiated from those caused by heavy metals, drugs and cauda equina tumors.

The non-specific treatment for diabetic neuropathy consists of relative rest during acute painful phase of mononuropathy and amyotrophy, a cradle over legs to protect legs from weight of bed clothes, graduated passive and active exercises. Supportive braces are necessary for foot drop. Adequate foot care has to be taken to prevent foot from trauma, baro or thermal.

For mild to moderate pain analgesics and NSAID's suffice. They have to be given in a carefully timed regular basis throughout the day rather than waiting for the pain to increase.

For severe pain amitriptyline , cholropromazine, carbamazepline, clonidine an xylocaine are the drugs used. Out of these amitriptyline cholropromazine combination is the most useful. Clonidine and Xylocaine is used as an IV infusion.

The specific treatment of painful diabetic neuropathy consists of good glycemic control, aldose-reductase inhibitors and myionositol. The DCCT trial and long term trials with intensive insulin therapy with pumps and multiple subcutaneous injection regimens have demonstrated increase in nerve conduction and velocity and decrease in plan.

The increased conversion of glucose to sorbitol that occurs through the polyol pathway in the hyperglycemic state has been suggested to play an important role in the pathogenesis of diabetic neuropathy. Aldose reductase inhibitors stop production of excess sorbitol.
The aldose reductase inhibitors are Alerstatin, Sorbinil, Tolrestat ONO 2235 and Statil. They were very popular until last 5 years ago but the enthusiasm for them is fast fading because they are expensive and results have not been statistically significant.

The treatment of painful diabetic neuropathy just consist of good glycemic control, relative rest, analgesics, anti-depressants, active and passive exercises and psychotherapy. [C.M.B]

Q. A diabetic has autonomic neuropathy with bladder involvement and impotence. Discuss on management of this patient.

A. The clinical presentations of a diabetic neurogenic bladder are straining and hesitation, weakness of stream, sensation of incomplete bladder emptying, overflow incontinence and f urinary frequency.

The investigations that are done for this condition are ultrasound bladder to rule out obstruction, cystometry. EMG of perineal muscles and profilometry.

The treatment for a neurogenic bladder is to encourage to void every 3-4 hours, drugs, Bethnecol, self catheterization and finally bladder neck resection if everything else fails.

Impotence is a common problem in diabetic men. The factors responsible for it are psychogenic, autonomic neuropathy, motor neuropathy (peripheral muscle involvement), macro and microvascular abnormalities , hormonal dysfunction, drugs and medications. The main points that have to be elicited in the history are drugs which the patient is taking, out of which anti-hypertensives and anti-depressants are the most important. The time sequence of the impotence whether he can still masturbate, erection during slip and history of systemic disease are important points to be elicited. The

treatment options available for diabetic impotence include improvement of glycemic control, discontinuation of medication like ganglion blockers, beta blockers and reserpine. Discontinuation of alcohol and antidepressants will also help.

The surgical options are non-inflatable prosthesis, inflatable prosthesis and revascularization surgery.

The pharmacological options is injection of papaverine into the corpora cavernosa. This is done in graduated doses, with a 25 mg per cc. Solution starting with 0.25 ml and going upto 1 ml. When the dose has been titrated, the patient can be taught the technique and can inject it himself. The technique uses an insulin syringe with 30 guage needle. There are also suction devices available which produce vasodilation by producing a vacuum and thereby promoting blood flow into penis. Once the penis is erect, the turgidity can be maintained by using rubber bands.[C.M.B.]

Q. A young IDDM has acute macular oedema with severe hyperglycemia. Discuss ophthalmic management.

A. Diabetic mascular oedema is defined as the presence of retinal thickening and/or hard exudates within one disc diameter of the center of macula. Macular oedema may be classified as focal where leaking capillaries and microaneurysm are relatively discrete, diffuse where the leakage is extensive ,ill defined and accompanied by cystoid change and ischaemic, in which odema is associated with extensive areas of capillary non-perfusion. This can be best identified by flourorescein angiography. This definition is independent of visual acuity. Usually visual actuity tends to be good _ 6/6-6/12) if the leakage is focal and the hard exudates is not deposited in the fovea. Acuity is moderately reduced (6/12to 6/24) if leakage is diffused and the fovea is oedematous and poor (6/24 to 6/60) if the macula is ischaemic with enlargemet of the normal avascular zone at the fovea. Clinically, significant macular oedema is that which threatens the fovea and central vision and is present as any of the following features:

(a) Thickening of the retina at or within 500 mm of the center of macula.

(b) Hard exudates at or within 500 m m of the center of the macula, only if associated with thickening of adjacent retina.

(c) A zone or zones of retinal thickening one disc area or larger in size, any part of which falls within one disc diameter of the center of macula.

Here also definition is purely anatomical and takes no account of visual acuity. Patients enrolled in Early Treatment Diabetic Retinopathy Study (ETDRS) had vision renging from 6/4 to 6/60. Treatment of macular oedema-

(a) Photocoagulation – is the treatment of choice for clinically significant macular oedema. In this procedure focal treatment is given for discrete lesion and diffuse ‘grid, treatment is given for wide-spread capillary leakage and nonperfusion. In ETDRS 3928 patients were recruited till 1985 and the results indicate that over all risk of severe visual control eyes.

(b) The retinal blood flow is increased in untreated or poorly controlled diabetes with macular oedema. This may damage endothelial cells. Retinal blood flow is reduced by correcting hyoperglycaemia. Therefore in such patient, blood sugar should be lowered slowly since an acute and profound glycaemic fall may cause retinal ischaemia and deterioration in retinopathy. [J.S.S]

Q. A middle age diabetic has chronic active hepatitis. Are there special measures in management?

Discuss treatment issues relating to

(a) over sensitivity to insulin

(b) Resistance to insulin

(c) Desirable dose change, species source or route of administration of insulin.

A. The normal liver has the capacity to increase its glucose production several-fold. Hence, to produce hypoglycaemia extensive liver disease is required specially in absence of markedly accelerated glucose utilization. Therefore, hepatogenous hypoglycaemia is most common when hepatic destruction is both rapid and massive . It is rare in common form of cirrhosis and hepatitis although glucose metabolism is demonstrably altered with diminished glycemic response to glucagons, reduced hepatic glycogen and delayed post absorptive glucose concentration.

Depending upon hepatic destruction in CAH there may be associated abnormality of many glycoregulatory hormones like glucagons, growth hormone and cortisol. This may lead to increased insulin sensitivity in some patients where hypoglycaemia with appropriate low level of insulin has been seen.

On the other hand hyperinsulinaemia due to impaired degradation and/or shunting of portal blood into systemic circulation has been implicated for disturbance in glucose metabolism in chronic liver disorder. Absence of fasting ghypoglycaemia in presence of hyperinsulinaemia suggesting insulin resistance state has also been documented. Hypersomatotropism among cirrhotics is an other important cause for glucose metabolic disturbances. Associated therapy of primary disease (chronic active hepatitis) with steroids may also add to insulin antagonism in such complex disturbances of glucose metabolism, worsen glucose control or even lead to ketoacidosis. Immunosupperssion or interferon therapy will also modify glucose value and require corresponding adjustment in insulin dosage.

Treatment of diabetic state with oral hypoglycaemic agents in presence of chronic liver disease is not recommended since inactivation of various OHA is reduced thereby prolonging, their half life. Thus insulin therapy remains modality of choice for controlling diabetic state in such situation. Human and purified insulins are preferred since risk of autoantibody formation is far less. Thus requirement of insulin in patient of chronic active hepatitis will from patient to patient depending upon insulin sensitivity/resistance state.[J.S.S]

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