TREATMENT OF MALNUTRITION RELATED DIABETES-MELLITUS

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WELLCOME DIABETES STUDY

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- Introduction
- Treatment of Endocrine deficiency (Diabetes Mellitus)
- Treatment of Exocrine deficiency
- Treatment of associated disorders
- Treatment of diabetic complications
- Patient education and social rehabilitation.
- Future prospects (prevention & treatment)

Though peculiarities of diabetes in tropical and developing countries have been known for some time but it was the WHO Study Group (1985) that focussed attention on these as a clinically important entity.

Introduction:

Only recently has attention been focussed on varieties of diabetes occuring in tropical & developing countries, the so called Malnutrition Related Diabetes Mellitus (MRDM). The prevalence of MRDM is not fully known and acceptance of the terminology & classification into Protein-Deficient-Pancreatic-Diabetes (PDPD, recently changed to Protein-Deficient Diabetes Mellitus - PDDM) and Fibro-Calculous-Pancreatic-Diabetes (FCPD) is still controversial. Long standing 'malnutrition' coupled with dietary/environmental 'toxins' are supposed to play an important part in the genesis of these entities. Recent studies in tropical malnutrition (see chapter by Dr. M. Golden) and non-alcoholic chronic pancreatitis in U.K. (see chapter by Dr. J. Braganza) have raised interesting possibilities about aetiopathological role of micronutrient deficiencies (particularly selenium) and 'oxidant stress' in the genesis of tissue damage in these conditions. Application of these hypotheses as possible unifying aetiological mechanisms in the genesis of MRDM raises very interesting possibilities for future work, especially in prevention.Given the large population of the developing countries, MRDM poses a huge problem of management and intensive research is warranted into the aetiological factors if we are to prevent such varieties of diabetes posing an even greater threat to economy & medical services in future. Occurence of MRDM predominantly in poorer strata of society and limited economic and health resources in developing countries make management a difficult problem. Added to this are the barriers of poor

education of patients and social & communal beliefs which at times dictate the management of an individual patient over and above the accepted medical guidelines.

The type of MRDM prevalent in Pune and surrounding areas (Maharashtra, Central India) is the FCPD which is probably secondary to the so called Tropical Calcific Pancreatitis. Our comments on treatment are largely based on our experience of treating these FCPD subjects over last few years. Information obtained from other authorities in India (listed in acknowledgements) has helped me considerably in writing about the management of PDPD.

Some of the main features of MRDM in relation to treatment are - onset in youth, usually a moderate to severe hyperglycemia, exocrine pancreatic involvement (FCPD), associated malnutrition and other diseases, poor socio-economic background and low levels of education. Management of any individual has to take into account all these facts to set realistic targets for achievement.

TREATMENT OF DIABETES MELLITUS

It must be emphasised that hyperglycemia in FCPD appears to be due to islet dysfunction/destruction secondary to the pathological changes of 'chronic pancreatitis' in the exocrine pancreas. The total number of islets seems to be reduced but interestingly, many intact (some hypertrophied) islets with normal B and A cells are seen. It has been hypothesized that these islets cannot secrete their products into blood stream because of widespread fibrosis and vascular damage. Nesidioblastosis has been frequently described in this condition.

Arrested pathological changes in only some parts of pancreas have been described and raise interesting possibilities about the natural history of the condition.

On this background it is important to note that a full spectrum of glycemic status - normal, impaired glucose tolerance (IGT) and diabetes mellitus (DM) has been described in FCPD. Thus, 4 of our first 40 serial FCPDs were non-diabetic, 5 had IGT and 31 were diabetic. During our short period of follow up (less than 3 years) one girl became non-diabetic six months after abdominal surgery to remove pancreatic stones, at which time she had IGT. Similarly, a spectrum of B-cell function has been demonstrated in this group; and we have demonstrated improved B-cell function after a period of improved glycemic control with insulin treatment. Thus, FCPD bears a substantial resemblance to the pathophysiology of B cells in the two classical varieties of diabetes; and B-cell function and glycemic state appear to be much more dynamic than hitherto recognised.

Hyperglycemia and resultant symptoms and/or complications usually bring these subjects to medical attention. Hyperglycemia is usually moderate to severe, fasting blood glucoses ranging between 10 to 22 mmol/l and glycated haemoglobin (HbA1) from 1.5 to 3 times the upper range for normal. Non diabetic subjects with FCPD are usually treated by gastroenterologists or surgeons.

Classical symptoms of uncontrolled hyperglycemia - polyuria, polydypsia, polyphagia are usually present and weight loss is striking feature, mean body weight in our subjects was 36 kg (range 7.5 to 64 kg). Dietary prescription is based on the so

called 'High carbohydrate, high fibre, low fat' formula. Although the dietary principles are the same as for patients with other types of diabetes, the usual low BMI requires gradual buildup to a calorie intake in excess of energy expenditure, and emphasis on a balanced supply of essential amino-acids, especially those containing sulphur and labile methyl groups. The intake of fat will have been limited because of the diabetes but may need to be so even more rigorously if there is steatorrhoea. The general principles of an intake well distributed throughout the day whose calories come 30% or less from fat (with 8% of total calories from polyunsaturated fatty acids and not more than 10% from saturated fatty acids), 15 to 20% from protein and the rest from carbohydrate, together with 40 gm or more fibre daily, of which at least 10 gm should be of viscous type.

Caloric intake of upto 3000 kcal/dl or even more is not unusally achieved by these hungry, emaciated individuals. In some, pain of pancreatitis, associated infections (esp. Tuberculosis) produce anorexia or suppress the intake, making management much more difficult. Carbohydrates are made up of commonly eaten wholegrain cereal (wheat, jawar, bajra and rice), and cassava in some places. Green salads & vegetables provide the fibre. We routinely advise these individuals to increase their protein intake by mixture of different pulses, milk & eggs if available (to 2 gm/kg/day). Animal meat and fish are eaten depending upon availability (coastal areas) and economic strength. Economic restraints usually produce low fat intakes but we specially stress low fat intake (30 - 35 gm/day) for people with FCPD. Coconut oil with its high MCT contents may be

advisable.

Requirement and choice of anti-diabetic drugs could possibly be determined by residual B-cell function, but there are no systematic studies in this area. It's a common experience that 80% or more of these individuals will require insulin for satisfactory control of hyperglycemia and to ensure weight gain. An occasional patient can be managed on diet alone, either from diagnosis or after a variable period of control with insulin or oral hypoglycemic agents (OHA). Many of them will require insulin subsequently. Upto 25% of FCPD subjects reported from Diabetes Research Centre, Madras were treated with OHA, some more than ten years after diagnosis. Four of our subjects have been treated with OHAs from time to time, only two have received them for more than five years and both of these have recently been advised to change to insulin, because of unsatisfactory glucose control. Sulfonylureas are commonly used, occasionally biguanides have been added. Fibre supplementation with guar gum may be useful in some. Combination of OHAs and /or guar gum with insulin seems to work better in some and may reduce insulin requirements.

Majority of our subjects are intiated on insulin treatment in hospital. We have commonly used multiple dose regular insulin (usually 3 times) with or without intermediate insulin (lente) once or twice daily. During first few weeks after diagnosis it's a common experience that they will require large doses (in some cases upto 8 u/kg/day!). These high insulin requirements in early phases have to be interpreted in the

clinical setting of moderate to severe hyperglycemia in emaciated subjects (body weight usually 30 to 40 kgs.) who eat 2000 to 3000 calories/day in hospital compared to 1500 or less at home even when very symptomatic and glycosuric. They reach hospital after months of severe symptoms, ill health and weight loss. Hospital provides both food and insulin. They rapidly put on weight under medical care. These high insulin requirements tend to fall as weight stabilizes and blood glucose becomes more normal. Improvement in blood glucoses & symptoms usually takes a week or two to stabilize and increase in weight is especially rapid in first 3-4 weeks when gain of 3 to 5 kg is very common. Hypoglycemia is uncommon during this early period of treatment especially if advice about meal regularity is adhered to. Those with lesser hyperglycemia, minimal weight loss and symptoms may need only 0.5 to 1 u/kg/day and may do well on once daily injection of insulin.

Insulin resistance is a frequently stressed feature of MRDM but 'true clinical' insulin resistance (daily requirement > 200 u/day is relatively rare except in some during initial hospital days. Most of the studies have reported average daily requirements of 40-50 u/day in FCPD and 70-80 u/day in PDPD on long term basis. Less than 20% are thought to require >2 u/kg/day by most of the authorities.

One of the reasons for the fall in insulin requirements with time is the improvement in B-cell function with improved glycemic-metabolic status. Thus in 2 serial OGTTs (2 months to 18 months apart) in 11 FCPD subjects we demonstrated improved

fasting and peak C-peptide concentrations. There was significant improvement in body weight, fasting glucose and HbA1 at the time of second OGTT. Rise in C-peptide was proportional to the fall in fasting glucose. Such improvement in B-cell function in FCPD has not been documented before. C-peptide concentrations at presentation were no different than age, body weight and diabetes duration matched IDDMs. Subsequent improvement in C-peptides was associated with substantial reduction of insulin dose in many, and stoppage in 2 individuals who experienced repeated hypoglycemia even on <10 u/day. This is reminiscent of the 'honeymoon phase' in IDDM and the so called 'phasic insulin dependence' in Jamaican patients, which could be a very long period of 'remission'. This residual B-cell function is thought to be mainly responsible for ketosis-resistance of these individuals. We have demonstrated lower concentrations of NEFA, glycerol and 3-hydroxy butyrate (3-HB) in these FCPDs compared to matched IDDMs (see above) who had comparable B-cell function, raising the possibility that FCPDs might actually be more insulin-sensitive than IDDMs. Most of the reports of insulin 'resistance' in FCPD are based on anecdotal case reports in subjects treated with 'impure' insulins for a long period, with a possible contribution from insulin antibodies.

It's our practice to teach patients reuse of plastic 'disposable' syringes without sterilization and insist on them giving their own injections. Any dependence on medical practitioner for daily injection will disrupt life style and make more than one injection a day impossible.We routinely advise

twice daily (Regular + Lente) mixture. Home monitoring even of glycosuria is rarely done and we call patients once a month or as indicated for blood glucose testing, clinical follow up and treatment advice. Reuse of plastic syringes and insistence on self injection has improved compliance considerably. The fineness of the needle in plastic syringes and freedom from the hastle of boiling the syringe has made it possible to convince many of the patients to take two injections a day, a rarity in the olden days of glass syringes!

Role of the medical social workers in education and follow up cannot be over emphasised. A substantial number would stop insulin injections after a time, either because of poverty, lack of appreciation of the need and importance of regular insulin treatment, or influence of social customs. Ketosis has not occurred in our patients even after stoppage of insulin for weeks to months and we have seen significant ketonuria only ocassionaly. Hyperosmolar coma has never been reported in such individuals even when glucoses were very high. Superimposition of infection, however, is likely to lead to disaster. This resistance to ketosis might be due to residual B-cell function, better insulin sensitivity, concomitant A cell damage and therefore diminished glucagon effect, decreased hepatic carnitine levels due to malnutrition, or a severe reduction in adipose tissue mass and consequently the supply of NEFAs. This relative immunity from serious, life threatening metabolic complication of diabetic ketoacidosis adds to the difficulty of convincing these mostly uneducated subjects about importance of regular insulin

treatment.

TREATMENT OF EXOCRINE PANCREATIC PROBLEM:

Exocrine pancreatic damage distinguishes FCPD from PDPD, though admittedly there is a lot of confusion in literature about exocrine pancreatic involvement in the so called PDPD. It is interesting to note that the latter is now rechristened PDDM (Protein Deficient Diabetes Mellitus) possibly to stress this difference from the former group.

Pancreatitis precedes diabetes in most of the FCPDs. Recurrent episodes of childhood abdominal pain suggest the chronic relapsing nature of pancreatitis. By the time permanent hyperglycemia occurs, exocrine pancreatic damage is fairly advanced and the usual tests of pancreatic function (Lundh or secretin-pancreozymin test, serum amylase, serum immunoreactive trypsin- IRT, stool chymotrypsin, NBT-PABA etc.) show severely diminished exocrine reserve. Tube tests of pancreatic function are understandably very unpopular with patients and search is still on for a sensitive as well as specific, non-invasive test. No such test is currently available but NBT-PABA test with correction (PAS modification) has generated a lot of interest. The main drawback of this test is its cost (>£ 10.0 per test). We have demonstrated severely reduced serum IRT and stool chymotrypsin in the majority of our FCPDs but about 20% seem to have some reserve. This is borne out by morphological studies (ultrasonography as well as CT-scans) showing partial preservation of pancreatic tissue in some. CT-scan has

demonstrated a full spectrum of pancreatic changes; swollen and large pancreas due to active pancreatitis in some, severely shrunken, fibrosed and fat-infiltrated in others, and various intermediate appearances. As yet there are no studies comparing either exocrine or endocrine function with morphological appearances but we have demonstrated a direct relationship between serum IRT and C-peptide, indicating a parallel damage in exocrine and endocrine pancreas.

Exocrine dysfunction adds substantially to the 'malnutrition' in these subjects and is responsible (along with severe endocrine dysfunction) for severe weight loss seen in some subjects. Thus, digestion and absorption of the three major food components (carbohydrates, proteins and fats) as well as fat soluble vitamins (vit A, D and E) will be affected.

Approximately 25-30% of subjects in different series are reported to have steatorrhoea on their normal diet. Figures are low, possibly because of low dietery fat in poor people. Fat loading tests have demonstrated steatorrhoea in over 90% of subjects.

Pancreatic enzymes are very useful in cases with frank steatorrhoea and also in those who fail to gain weight despite good glucose control and adequate dietary intake. Economic restraints prevent recommendation of full doses and most have to be treated intermittently. Pancreatic enzymes are said to improve glycemic control by improving B-cell function through stimulation of entero-insular axis (GIP) and this may reduce insulin requirements. There are as yet no formal trials of such treatment in FCPD but it would be interesting so to assess any protective

effect of such treatment.

Chronic recurrent abdominal pain is the hallmark of FCPD. Its severity is usually diminished in many by the time diabetes is diagnosed but this is possibly a reflection of reduced pancreatic function. Some however, continue to get pain due to pancreatitis -visible on ultrasonography or CT-scan. Others suffer pain of ductal obstruction due to stones. Pain usually responds to anticholinergics and diet modification. Pancreatic enzymes may help some. From time to time severe episodes of pain occur necesitating hospital admission, IV fluids, nasogastric suction and narcotic analgesics. Ultrasonography might reveal a pancreatic or pseudopancreatic cyst in these severe cases and occasionally a large growth, hitherto unsuspected.

Surgery is frequently performed for severe and intractable pain in FCPD subjects. Various techniques have been employed. Modified Peustow procedure seems to be the most popular amongst surgeons. Pancreatic duct is opened in part or full length, stones and debris removed, and the duct is anastomosed side to side with a length of jejunum. Sometimes a partial pancreatectomy has to be combined and occasionally Whipple's operation may have to be undertaken. A large dilated duct with large intraductal stones and preferably some residual pancreatic tissue are usual pre-requisites for Peustow procedure. Undilated duct with 'peripheral' or 'intra'pancreatic stones make the procedure technically difficult and pancreatectomy may be the only choice left. Size and distribution of stones on an abdominal X-ray are usually a reliable guide in this matter, but now

ultrasound and CT-scan offer more sophisticated means of directly visualizing the pancreatic morphology.

Beneficial effects of surgery include relief of pain and improvement in quality of life in most of the individuals, at least for some time. Many surgeons have claimed better glucose control, reduced insulin requirements, improved exocrine function and appetite after surgery. Anecdotal reports of hypoglycemia in immediate post operative period have been quoted as a proof of improved B-cell function. We have observed reduced insulin requirements for 2-3 weeks after surgery but this is on the background of grossly reduced food intake and perioperative weight loss. Subsequent improvement in dietary intake and weight gain usually are associated with increased insulin requirements. Measurements of C-peptide before and after surgery did indeed show some improvement but this was possibly due to better metabolic control in perioperative period because it occurred in subjects similarly controlled in wards who had not undergone surgery. It's quite possible that removal of an impacted stone will improve exocrine (and possibly endocrine) pancreatic function by relieving the backpressure and may even reduce the rate of pancreatic degeneration in subsequent years. Clearly, controlled trials of surgical intervention (? 'secondary prevention')are needed to answer these very important questions.

TREATMENT OF ASSOCIATED DISORDERS

Malnutrition (especially low body weight) is a striking accompainment of MRDM. However, there is no definite proof that

malnutrition is the causal factor. Malnutrition could be entirely secondary to poor endocrine and/or exocrine pancreatic function in these individuals. Most of the subjects improve satisfactorily when provided with adequate doses of insulin and usual ward diet. We attempt to increase the protein content of the diet to at least 1.5-2 gm/kg/day and prevent excessive fat losses by reducing fat intake. Final weights achieved are still lower than average in most cases but quite representative of the social class. Vitamin B complex deficiencies are found in varying number of cases and need appropriate supplements. However, it is not our practice to prescribe B complex routinely, espcially at home. If total intake is adequate,then it usually provides adequate vitamins also. There is no good data available on the Vit A and D status of these individuals. Vit A is usually prescribed if clinical signs of deficiency are present but this may represent only the tip of the iceberg. We have never seen symptomatic Vit D deficiency, and X-rays of wrist in these individuals have not shown any evidence of past or present rickets.

There is as yet no data on the status of trace element nutrition in this group of subjects. Zinc and chromium deficiencies are traditionally linked with diabetes. Selenium deficiency has recently generated a lot of interest as a possible factor in promoting tissue damage in tropical malnutrition and in chronic pancreatitis. Clearly there is a scope for testing these hypotheses in MRDM. Equally, role of nutritional deficiencies of 'anti-oxidants' e.g. vit C, vit E, glutathione etc. needs looking into.

ASSOCIATED DISEASES

Tuberculosis is the commonest lethal accompaniment in MRDM. Drug treatment is like other cases of TB. Crucial point is the high index of suspicion and early detection. Unexplained anorexia, failure to gain weight, unexplained low grade fever should raise suspicion of pulmonary or other tuberculosis. X-ray chest is usually diagnostic. Diagnostic confusion arises in abdominal tuberculosis because pain might be mistakenly ascribed to pancreatitis. Laparoscopy has facilitated diagnosis of abdominal TB.

Urinary infections are said to be common in MRDM. We have observed it only infrequently, and these patients had associated polycystic kidneys. Treatment is along standard guidelines but may be difficult due to uncontrolled hyperglycemia & glycosuria.

Amenorrhoea and infertility are major problems in young women with MRDM. Treatment is primarily directed to control of diabetes and improvement in general health. Gonadotropin levels are usually low indicating a hypothalamic-pituitary failure. Delayed puberty is equally common in males due to similar factors.

Liver cirrhosis was a common accompaniment of FCPD in the original series of patients described from South India, but seems to be on decline.

TREATMENT OF DIABETIC COMPLICATIONS

Contrary to earlier assertions it's now well established that MRDMs suffer from similar long term diabetic tissue damage as other varieties. Thus, they suffer from microangiopathy - retinopathy, nephropathy and neuropathy in due course of time. Macroangiopathic complications e.g. coronary artery disease, cerebrovascular disease, peripheral vascular disease are relatively rare, possibly due to young age, lack of obesity, lower cholesterol and shorter life expectancy.

Microvascular disease especially retionopathy seems to occur early because of long duration of symptomatic diabetes before these individuals receive medical care. Treatment is similar to that in other varieties of diabetes. Nephropathy seems relatively uncommon either because patients die early or due to protection from low protein diets, lower blood pressure or other unknown factors. Economic considerations severely restrict therapeutic interventions (laser photocoagulation, dialysis, transplant etc.) in these individuals.

One complication commonly encountered, is a severely painful neuropathy in early stages after initiation of insulin treatment. Presumably this has 'metabolic basis'. Symptomatic relief with amitryptiline or similar drugs and persistence in glycemic control usually help.

PATIENT EDUCATION AND SOCIAL REHABILITATION

Poor socioeconomic background and lack of education are prominent features of MRDM in a majority of patients. This fact

alone makes their management a challenging problem. It's very difficult to convince many patients of even the necessity of treatment, regularity of follow up and blood testing. Many lives have been lost for want of this appreciation. Social beliefs and alternative treatments make their contribution to the disasters. Role of a well trained, sympathetic medical social worker in patient and family education cannot be overemphasised.

Poverty contributes to irregularity in treatment and many cannot afford even small doses of insulin. It's only after providing free insulin and syringes that we have been able to achieve a moderate glycemic control and a somewhat regular follow up.

Occupational rehabilitation of undernourished individuals is another major problem. Even after reasonable glycemic control these individuals tend to remain underweight and therefore, physically handicapped to carry out labourer's jobs. Lack of education makes rehabilitation even more difficult.

FUTURE PROSPECTS : PREVENTION AND TREATMENT

A lot of research needs to be done in the areas of aetiopathogenesis, natural history, metabolic-endocrine aspects and treatment of MRDM. Urgent need is to define the groups properly and standardise research protocols to obtain uniform information. If malnutrition is causally important, reduction in MRDM will be intimately linked to improvement in general nutrition and health of the population in developing countries. The major feature, of at least one type of MRDM (FCPD) is chronic pancreatitis. We have no clue to the aetiopathogenesis of this

condition. An easy marker to identify early stages of this disease will be a great help in this direction. Recent hypotheses linking oxidant stress to tissue damage in malnutrition as well as chronic pancreatitis raise very interesting possibilities for future research and possible prevention. Role and mechanism of action of cyanogenic alkaloids from various foodstuffs needs to be more clearly defined. If they are causally important, development of less toxic varieties may have a high priority. Role of pancreatic stones in the initiation and/or perpetuation of pancreatic damage needs to be elucidated so that it may define clearer guidelines for stone-oriented interventions.

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References:

1. Tripathy BB, Kar BC. Observations on clinical patterns of diabetes mellitus in India. Diabetes 14:404- ; 1965.

2. Ahuja MMS, Talwar GP, Varma VM, et al. Diabetes Mellitus in young Indians. Ind J Med Res 54:1138- : 1965.

3. Geeverghese PJ. Pancreatic Diabetes, Popular Prakashan, Bombay; 1968.

4. Viswanathan M. Pancreatic Diabetes in India : An overview. In: Secondary Diabetes : The spectrum of the diabetic syndromes. Podolsky S, Viswanathan M (Eds), Raven Press, New York; p105- ; 1980.

5. Pitchumoni CS. Special problems of Tropical Pancreatitis. Clin Gastroentero. 13:941- ; 1985.

6. Mohan V, Mohan R, Susheela L et al. Tropical Pancreatic Diabetes in S India : Heterogeneity in clinical and biochemical profiles. Diabetologia 28: 229- ; 1985.

7. Yajnik CS, Katrak A, Kanitkar SV et al. Serum immunoreactive trypsin in Tropical Pancreatic Diabetes Syndrome. Ann Clin Biochem (in press) 1988.

8. Chronic pancreatitis in India. Balakrishnan V (Ed), Indian Society of Pancreatology, Trivandrum, 1987.

9. Creutzfeldt W, Ebert R. Release of gastric inhibitory polypeptide (GIP) to a test meal under normal and pathologic

conditions in man. Diabetes, Bajaj JS (Ed), Excerpta Medica, Amsterdam, pp 63-75, 1977.