

Review

REFLECTIONS ON MRDM : FCPD AND MMDM

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INTRODUCTION

The complicity of over-nutrition and obesity with diabetes mellitus is age old as Sushrutua (~600 BC) described diabetes in the obese and the indolent. The concept was revived by Bose in 1985 (1) and taken up vigorously by Joslin in early decades of the twentieth century.

On the reverse, the association of malnutrition with diabetes was possibly first elucidated by Zuidema (1959) (2) from Indonesia who found pancreatic calcification and diabetes in patients majority of whom suffered from clinically evident protein malnutrition. Shaper (1969) (3) reported similar association from Uganda.

Hugh Jones in 1955 (4) reviewed 215 patients, attending University College Hospital in Jamaica, thirteen of whom could not be classified to either type 1 or type 2. These patients were thin, young, severely hyperglycemic, but in contrast to IDDM did not have ketonuria and required high doses of insulin for control (J-type). Implication of malnutrition as a possible factor in the genesis and atypical features of this form of diabetes was first envisaged by Kar and Tripathy (1963) (5) from Cuttack, Orissa, India. Clinical observation of patients with these features have been described from different parts of India and several other tropical and developing countries (5). An international conference held at Bombay in 1966 and the IX IDF meet at New Delhi 1976 aroused the interest of diabetologists round the world on this atypical form of diabetes encountered in good numbers in several developing tropical countries.

RECOGNITION

Global acceptance of the association of malnutrition with diabetes was first expressed by the National Diabetes Data Group (1979) (6) and subsequently corroborated by WHO Expert Committee (1980) (7). Describing "Special types" of diabetes, the technical report acknowledged two with background of malnutrition viz.

1) Malnutrition related syndrome of severe non-ketosis diabetes in children in tropics: 'J-type'.

2) Diabetes with fibrosis and calcification of the pancreas and a history of severe childhood malnutrition. Also excessive consumption of cyanide especially from casava.

These "special classes" were described under other types of clinical diabetes - subhead miscellaneous (7). In the final classification by WHO Study Group (1985) (8) the position was altered. Next to the well recognized classes (1) IDDM and (2) NIDDM, Malnutrition-related Diabetes Mellitus (MRDM) was placed at No. 3 in the classification table.

MRDM was further subtyped as (a) Protein-Deficient Pancreatic Diabetes (PDPD) and (b) Fibrocalculous Pancreatic Diabetes (FCPD).

PROBLEMS

We at Cuttack, Orissa have the opportunity to observe good number of patients of both these categories. The recognition of our reports and views were very much welcome. Yet there were misgivings from two angles.

First the term Protein-Deficient PANCREATIC Diabetes was inappropriate, as by the 'Experts' own statement "pancreatic calcification and fibrosis are absent" as also "absence of radiographic of other evidences of intraductal pancreatic calcification or dilatation of the ducts" as well as absence of "demonstrable malabsorption of nutrients caused by exocrine pancreatic insufficiency". The issue was discussed at the VI National Conference on Diabetes held at Cuttack in 1987 and by consensus the name was changed to Protein-Deficient Diabetes Mellitus (PDDM) which was subsequently ratified at the 13th IDF Congress, Sydney (1988).

Secondly although the term FCPD was considered to be appropriate, its placement in the classification table did not appear to be so. Several groups including our own observed FCPD to occur in individuals in the absence of alcohol intake, gall bladder disease or hyperparathyroid states where malnutrition could be ruled out. Further, as in FCPD diabetes occurs in association with florid exocrine pancreatic disorder, to classify it along with primary

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forms such as IDDM, NIDDM and PDDM was felt to be inappropriate.

MRDM: CLINICAL FEATURES

By and large, patients are below 30 years of age at onset of symptoms. Typically, they are lean even before onset of symptoms and appear poorly nourished. Onset is insidious but may be relatively rapid. Polyuria, polydipsia, asthenia, weakness and cramps often lead to prostration in course of time (months). Hyperglycemia is often moderately severe but urine tests negative for ketones. Oral hypoglycemic agents are ineffective. Insulin in relatively high doses is required for control.

Some such patients may give history of abdominal pain. This is much more often seen in Kerala than elsewhere in India or Bangladesh. X-ray and ultrasonography of abdomen in these patients and some others (without history of distinctive abdominal pain) reveal pancreatic calculi and other features of pancreatic disease.

CONFUSION

FCPD, known in gastroenterology circles as Tropical Calcific Pancreatitis has a clear marker, easily brought out by imaging procedures. When onset is at younger age, with little likelihood of alcoholism and gall bladder disease, there can be little doubt about its diagnosis. PDDM on other hand has to be diagnosed on clinical basis alone. Patients of this type are encountered mainly in charitable general hospitals or in remote rural practice. At many places there is failure to take note of the atypical features and tendency to overlook or ignore the same. At places where these are noticed, in the absence of a consensus, terms such as ketosis resistant diabetes in young (KRYD) insulin requiring diabetes mellitus (IRDM), J-type or M (malnutrition) type have been applied. During the 60's to 80's of the last century, distinction between the two types of so called MRDM was blurred particularly in places where both types were not seen in fair numbers. This was the case at Delhi where KRYD was seen almost exclusively and in Madras where FCPD was much more common. Investigators at both places considered J-type as early, precalcific stage of FCPD.

Controversies continued beyond 1987 as Madras workers suggested that we should agree to differ. It was in the next year (9) that Mohan came out with clear cut criteria required for the diagnosis of FCPD (Table 1), thus squashing the speculations on pancreatic involvement in PDDM. Further, reports

on pancreatic function tests from Cuttack, Delhi, Lucknow, Chennai and Dhaka clearly established pancreatic acinar dysfunction in FCPD in contrast to near normal values in case of PDDM. CT scan, ECRP and autopsy studies also established the distinction between the two. Moreover, a follow up of several patients diagnosed J-type over 10 years before at Cuttack, established that they remained free from pancreatic exocrine disorder and in contrast to IDDM retained β -cell function over the long period of time (5).

Table 1: Diagnostic Criteria for FCPD

- Occurrence in a tropical country
 - Diabetes by WHO Study Group criteria
 - Evidence of chronic pancreatic disease - pancreatic calculi on X-ray or any three of the following:
 - (a) Abnormal pancreatic morphology with ductal dilatation detected by sonography, CT scan or ERCP;
 - (b) Abnormal exocrine pancreatic function tests
 - (c) Chronic recurrent abdominal pain since childhood;
 - (d) Steatorrhoea.
- Absence of other causes of chronic pancreatitis i.e. alcoholism, hepatobiliary disorder or hyperparathyroidism etc.

PDDM (PDPD, MMDM)

Cardinal features of PDDM are presented in table 2.

Table 2: Clinical Features of PDDM

1. Severe diabetes - fasting blood glucose more than 200 mg/dl.
2. Onset of diabetes before the age of 30 years.
3. Leanness. Body-mass index $< 18 \text{ kg/m}^2$
4. Absence of ketosis on withdrawal of insulin
5. Poor socio-economic status, history of childhood malnutrition.
6. Insulin requirement more than 60 U/day or more than 1.5 to 2 U/kg/day.
7. Of rural origin.
8. Absence of radiographic or sonographic findings of pancreatic calculi ductal dilatation and fibrosis; laboratory evidences of exocrine pancreatic dysfunction.

The very poor rural background of the patients suggests that they could not have appropriate nourishment during their infancy and early childhood as well as in course of their fetal life. In most cases, dietary history could be ascertained from parents and other accompanying persons and the diet was found to be utterly deficient.

Height and body weight indicated retardation of growth. Marks of micronutrient deficiency were evident in many cases. High levels of free fatty acids (FFA) and marginal increase in plasma ketones were lower than seen in type 1 diabetes. Insulin and C-peptide levels were somewhat lower at fasting but much more in response to carbohydrate load, as compared to controls. Growth hormone levels were high and not suppressed by glucose administration.

A score system for the firm diagnosis of PDDM devised at Cuttack is presented in Table 3.

Table 3: Score System for the Clinical Diagnosis of PDDM

Clinical Profile	Score
Age at onset 10-30 years	1
Poor economic status (Rural Origin)	1
Leanness, BMI < 16 kg/m ²	2
< 18 kg/m ²	1
History of malnutrition in childhood	2
Stigmata of malnutrition (clinical) (past or present)	1
Severe hyperglycemia (fasting blood glucose > 200 mg/dl)	1
Lack of proneness to ketosis: (Absence of ketonuria on withdrawal of insulin for long periods)	3
Insulin requiring. Over 60 U/day (2 U/day/kg body wt.) unresponsive to sulphonylurea compounds	2
Absence of X-ray / Ultrasound evidence of pancreatic calculi and ductal dilatation	3
Total Score	17
Diagnostic score - 13	
Suggestive score - 12	

FCPD

Most patients seen in the hospital diabetes clinic present with symptoms usual for young patients with diabetes. In a small proportion of cases, particularly those seen in private clinics, may have milder symptoms. Another small group of patients have history of abdominal pain and therefore more commonly report to the Gastroenterology wing.

Over two thirds of patients attending the hospital are poor compared to 25% of those seeking private consultation. At Cuttack and Chennai about 10% complain of abdominal pain while another 30% give history of digestive problems on asking leading questions. Mohan's criteria for diagnosis of FCPD (Table 1) have been accepted widely as the most appropriate.

Broad differences between PDDM and FCPD as observed at our center where both types are seen in fair numbers are summarized in Table 4.

Table 4: Distinguishing Features between PDDM and FCPD

Comparison:	PDDM (General)	FCPD
Age at onset	10-30 yrs	10-40 yrs or older
Rural	All	78%
Socio Economic Status: Poor	All (100%)	60%
BMI < 16 kg/m ²	92%	60%
Ketonuria	Nil	16%
C-peptide (2hr post parandial)	0.6	1.0 pmol/l
Fecal fat (On 100g fat diet/day)	6.2 g/d	29 g/d

Data from Patients Presented at the Workshop

	PDDM	FCPD
Mean age	22.1 ± 3.1 yrs	29.8 ± 4.4 yrs
Poor	All	54.5%
History of childhood malnutrition	All	54.5%
Mean BMI (Kg/m ²)	13.7 ± 1.6	15.4 ± 3.1
W/H Ratio	0.7 ± 0.12	0.8 ± 0.07
Fasting blood glucose (mean)	278 ± 79	235 ± 72 mg/dl
Current insulin dose (mean)	78.3 ± 10.4	46.4 ± 12.1 u/d

WORKSHOP 1995

Despite discussion at several conferences and two international workshops (10, 11), controversies on the term MRDM and its placement along with the two sub classes PDPD and FCPD in the WHO (1985) table of classification remained highly controversial.

It was felt that this situation persisted mostly due to lack of opportunity for diabetologists from other areas to have first hand exposure to clinical material. With the above in view, we planned to hold a workshop at Cuttack, Orissa where contrary to the places of the previous workshops (UK and Japan), typical clinical material could be displayed for observation and analysis.

The workshop, held in October 1995, was attended by medical scientists from various specialities covering different aspects of diabetes and nutrition from both developing countries such as India, Bangladesh, China and Ethiopia and developed nations, namely USA, UK, Belgium and Sweden. Twelve patients with PDDM and 11 with FCPD were placed before the participants for clinical examination and analysis of records. Data were presented from various centres from the participating countries. After thorough and threadbare discussions, unanimous statements were issued on the concluding day (Tables 5 and 6). These have been widely published in several international journals. Both ADA and WHO classification committees have taken these into consideration and partly adopted the recommendations.

Table 5: Malnutrition Modulated Diabetes Mellitus

- There is a clinical syndrome of diabetes mellitus that occurs in developing countries in young individuals with a history of, or signs of malnourishment.
- The physical characteristics of the patients with this syndrome at presentation and the metabolic course of the treated disease differ from those that are usual among patients with NIDDM in developed countries. These patients do not have FCPD.
- The patients require insulin for glycaemic control but are not ketosis prone.

Essentially there was unambiguous and unreserved recognition of the two clinical variants PDDM and FCPD, that were different from each other. Regarding PDDM, it was felt that evidences was not adequate to accept that protein deficiency was the sole cause, while the role of overall malnutrition was obvious in modifying the clinical behaviour and early onset. The term Malnutrition Modulated Diabetes Mellitus (MMDM) was therefore, unanimously adopted as more suitable for this clinical form of diabetes (12).

Table 6 : Fibrocalculous Pancreatic Diabetes

1. Fibrocalculous Pancreatic Diabetes (FCPD) is a form of diabetes seen mainly in tropical and developing countries.
2. FCPD is due to chronic calculous pancreatopathy, not to chronic alcoholism or other recognized causes of pancreatitis such as hyperparathyroidism.
3. It is usually seen in young and malnourished individuals but also occurs in others.
4. Diabetes and pancreatic calculi and/or ductal dilatation are essential features. Recurrent abdominal pain and steatorrhea are other important features but absence of these does not preclude the diagnosis.
5. Hyperglycemia may vary from severe to mild. Ketosis is uncommon.
6. Pancreatic calculi are usually large, multiple and intraductal. Marked ductal dilatation and fibrosis are usual; inflammatory changes are uncommon.
7. Abnormal exocrine pancreatic function is invariably present but is often demonstrable only following investigations.
8. FCPD is associated with an increased risk of pancreatic carcinoma.
9. Management of FCPD includes treatment of diabetes, oral pancreatic enzyme replacement and relief of pain. Surgery may be required for severe intractable pain and for other indications.
10. The aetiology of FCPD is uncertain. The roles of nutrition (including intrauterine nutrition), other environmental exposures and genetic factors need further investigation.

Further, it was felt that malnutrition as a factor could not be paramount in the genesis of FCPD. Moreover, as diabetes occurred obviously in association with pancreatic ductal and acinar disorder, it was to be classified with other secondary forms of diabetes (12). These recommendations have been adopted by both ADA and WHO Committees on classification.

Unfortunately, controversy still remains regarding acceptance of MMDM as a separate clinical class. There has been no suggestion from any quarter as what could be the alternative. The tentative classification proposed by WHO Consultation group

has not provided a place for MMDM, although they have discussed the current views on the topic. But the matter is not yet over. Genetic and autoimmune status of MMDM so far investigated, justify the separate identity of MMDM. Dissertations on the topic continue to appear in world literature including one recent one in the *Annals of New York Academy of Sciences* (2002). It may yet be hoped that immunogenetic data worked out at the Karolinska Institute, Stockholm, on material collected from India may convince the skeptics among the IDF and WHO mandarins dealing with this topic.

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DIABETES UPDATE AND CME ANNOUNCEMENT

Research Society for the Study of Diabetes in India (Maharashtra Chapter)

Diabetes Update: A diabetes update will be conducted at Lilavati Hospital, Bandra, Mumbai from **13th-14th September 2003**

- **Course Director** Dr H B Chandalia
- **Co-Directors** Dr P S Lamba, Dr Vijay Panikar
- **Faculty** comprising of eminent Diabetologists, Endocrinologists and related specialties from all over India. We are planning to make the course fully interactive.
- **Eligibility** – Minimum qualification MBBS (Please enclose a copy of degree certificate)
- Likely to be valid for 20 credit hours of RSSDI for first attendance and ten credit hours for subsequent attendance.
- Number of delegates attending: limited to a maximum of 100.
- Registration charges Rs 1500/- (Rupees fifteen hundred only). Pay by demand draft addressed to "RSSDI Maharashtra Chapter" payable at Mumbai. This includes the CME program on 13th September 2003.
- Last date of registration is 30 August 2003.
- Application forms available at
 1. www.rssdi.com
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103-104, Lady Ratan Tata Medical Research Centre, Maharshi Karve Road, Mumbai 21
Phone: 22871613, 22840244. Fax: 22840255
 3. Endocrine and Diabetes Management Center,
111, Big Splash, Sector 17, Vashi, Navi Mumbai 400 703.
Phone: 27891432. E-mail: drlambaps@hotmail.com
- All delegates must arrange for their own accommodation in Mumbai. A limited amount of Hostel/ Dormitory type inexpensive accommodation is being arranged. Book early to avail this facility, as it will be offered on first come basis.

CME program will be held on 13th September 2003 from 1800 – 2100 hours. Those only interested in CME are required to pay Rs 50/- as delegate fee.

Dr P S Lamba
Secretary,
RSSDI (Maharashtra Chapter)