

**Chapter 17**

**Malnutrition related diabetes mellitus in Orissa**

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## Summary

*The links between malnutrition and diabetes are fascinating, and this is best exemplified by fibrocalculous pancreatic diabetes. In this article, the genesis of the term is described in detail, as are the associations with malnutrition. The earlier diagnosis of malnutrition-related diabetes mellitus has now given way to malnutrition modulated diabetes mellitus / protein deficient diabetes mellitus; in addition, criteria have been laid down for the diagnosis of the same. In addition, criteria have also been proposed for the diagnosis of fibrocalculous pancreatic diabetes. This article will also focus on the well-known link between malnutrition and diabetes in the state of Orissa, and provide a glimpse of the picture of the disease as seen in Orissa today.*

## Introduction

The concept of possible role of malnutrition in the genesis and modulation of clinical expression of diabetes mellitus emanated from Orissa. In late 1950s there came reports of young patients with diabetes who had severe hyperglycemia, were very lean and yet did not have ketone in urine. Further, these patients, unresponsive to sulphonylurea compounds, continuously required large doses of insulin for control. This picture did not fit in with juvenile diabetes who are depicted to be ketosis-prone and insulin sensitive so that minor changes in dose of insulin would cause wide alterations in the levels of glucose in blood.

Search into literature revealed description of clinically similar patients by Hugh Jones (1955)<sup>1</sup> from Jamaica. These were classified as J-type as it was not possible to fit them to either type 1 or type 2. None of these patients complained of abdominal pain to raise suspicion of pancreatic disease leading to diabetes. After the presentation by Geevarghese in 1962<sup>2</sup> and my personal discussion with him in 1963, we looked for pancreatic calcification by routine skiagram of abdomen of all such patients to find that some 25% of such patients had a calcific pancreatic disorder. By 1960-61 analysis of patients with features of J-type diabetes had revealed that all of such patients hailed from very poor families living in remote villages, so poor as to be unable to afford two ordinary meals in a day. Nutrition has to be inadequate for the mothers during

pregnancy and for the patients during their infancy and early childhood. This was confirmed by questionnaire method from the guardians of the patients and other family members. The complicity of over-nutrition and obesity with diabetes mellitus is age old. Sushruta (~600 BC) described diabetes in the obese and the indolent. The concept was revived by Bose in 1995<sup>3</sup> and taken up by Joslin in the early decades of the twentieth century.

On the reverse, the association of malnutrition with diabetes was possibly first brought out by Zuidema (1959)<sup>4</sup> from Indonesia, who found pancreatic calcification and diabetes in a group of patients majority of whom suffered from clinically evident protein malnutrition. Shaper (1960)<sup>5</sup> reported similar association from Uganda. Hugh Jones (1955)<sup>1</sup> 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 (type 1) did not have ketonuria and required high dose of insulin for control. He suggested the term 'J' (Jamaica) type for this clinical form of diabetes.

Subsequently (1959-61), similar patients were described from some African, south and South East Asian countries. They were observed only in the poor sections of the respective societies, yet it remained for Tripathy and Kar from Cuttack (Orissa) to implicate early childhood malnutrition as the underlying factor in their presentations in 1963-7<sup>6</sup>.

### **Pathophysiology**

The relevance of the hypothesis can be sought from the metabolic changes observed in starvation and malnutrition. Historically glucose intolerance in starvation and vagabond diabetes have been described by researchers such as Claude Bernard and Allen. Minkosky observed greater ease in inducing diabetes in animals on low food uptake. In contemporary literature prediabetic state has been observed in protein deficient litters of dogs and pigs (Heard et al. 1967)<sup>7</sup> and in childhood malnutrition (Baig and Endoziens 1965)<sup>8</sup> and several others<sup>6</sup>. Tripathy, Chhetri and their co-workers separately documented glucose intolerance, hypoinsulinaemia, insulin resistance and high growth

hormone levels in adult patients suffering from clinically evident chronic malnutrition<sup>6</sup>. Malnourished baby monkeys on low protein diet were shown to have similar aberrations by Khardori and Bajaj<sup>9</sup>.

Patients with type-J diabetes manifest significant insulinopaenia, high growth hormone and severe insulin resistance<sup>6</sup>.

Neel (1962)<sup>10</sup> enunciated his famous dictum "thrifty" genotype rendered detrimental by "progress" as cause of increase in the incidence of diabetes, speculating genetic adaptation of metabolic processes for survival during periods of famine and food deprivation. More recently, Hales and Barker<sup>11</sup> enunciated 'thrifty phenotype' referring to lasting adjustments in the metabolic set up of the fetuses in case of maternal undernutrition as a cause of high susceptibility to diabetes and cardiovascular disease in the offsprings later in life in situations of relative affluence. These observations provide strong support to our concept of the nutritional basis of development of diabetes with atypical presentations when severe undernutrition continues beyond infancy and early childhood as it is not unusual in a number of developing countries with a proportion of population living far below poverty line. Diabetes develops in those who are otherwise susceptible as in case of some with obesity.

Clinical, experimental and other laboratory data clearly indicate that diabetes evolves primarily from a critical fall in insulin secretion, not from destruction of beta cells as in type 1 diabetes (IDDM) but from functional alteration possibly as an adaptation to nutritional deprivation in the developing phases viz; foetal, infancy and early childhood. This has been corroborated both by mathematical models<sup>12</sup> and autopsy studies<sup>13</sup>. Insulin and C-peptide levels are low, both basal and in response to secretagogues. Long term observations (over 10 years) have revealed absence of decline in b-cell function in J-type diabetes in contrast to type1<sup>6</sup>. The other mechanism involved is insulin resistance observed both in patients with J-type diabetes and chronic malnutrition<sup>6</sup>.

J-type was described as Ketosis Resistant Young Diabetes (KRYD) in the North (Delhi) and Insulin Requiring Diabetes Mellitus (IRDM) in the South (Chennai). On the other hand, young patients with pancreatic calculi

and diabetes were less severely malnourished before onset of diabetes in patients under our observation. In Kerala where incidence was much higher all such patients observed, as belonged to poor families, those subsisting mostly on very low protein containing tapioca (cassava) as staple food. Further these tubers usually boiled and consumed contain cyanogenic glycosides, which have the potential to damage pancreatic constituents as well as the thyroid gland. These findings implicated nutritional deficiency to be involved in the pathogenesis of the condition. Yet I had suggested to Geevarghese not to consider malnutrition as the critical factor, which he has acknowledged in his first monograph published in 1968<sup>14</sup>.

### **Recognition**

Global acceptance of the association of malnutrition with diabetes was first expressed by the National Diabetes Data Group (1979)<sup>15</sup> and subsequently corroborated by WHO Expert Committee (1980)<sup>16</sup>. Describing "Special types" of diabetes, the technical report acknowledged two sub type 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 and also excessive consumption of cyanide especially from cassava.

These "special classes" were described under other types of clinical diabetes-subhead miscellaneous<sup>16</sup>. In the final classification by WHO Study Group (1985)<sup>17</sup>, the position was altered. Next to the well recognized classes (1) IDDM and (2) NIDDM, Malnutrition-related Diabetes Mellitus (MRDM) was placed 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 a good number of patients from both these categories. The recognition of our reports

and views were very much welcomed. 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 or 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 13<sup>th</sup> 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, gallbladder disease or hyperparathyroid states where malnutrition could be ruled out. Further, as, in the case of FCPD, diabetes occurs in association with florid exocrine pancreatic disorders, to classify it along with primary 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. The 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 quite severe but urine tests negative for ketones. Oral hypoglycemic agents are ineffective. Insulin in relatively high doses is required for control (Fig. 1).

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 (Fig. 2).

## 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 gallbladder disease, there can be little doubt about its diagnosis. PDDM on the 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 there is a 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, insulin requiring diabetes mellitus (IRDM), J-type or M (malnutrition) type have been applied. During the 60s and 80s 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 of Delhi where KRYD was seen almost exclusively and in Madras where FCPD was much more common. Investigators at both places considered J-type as an 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 that Mohan<sup>18</sup> came out with clear cut criteria required for the diagnosis of FCPD (Table 1), thus squashing the speculations on its identity with PDDM. Further, reports on pancreatic function tests from Cuttack, Delhi, Lucknow, Chennai and Dhaka clearly established pancreatic acinar dysfunction in FCPD and 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 b-cell function over the long period of time<sup>6</sup> (Fig. 3).

**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.

**Table 2. Clinical features of PDDM (MMDM)**

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 < 18kg/m<sup>2</sup>
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 foetal 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 increases in plasma ketones were lower than seen in type 1 diabetes. Insulin and C-peptide levels were somewhat lower at fasting but much more so in response to carbohydrate load, as compared to controls. Growth hormone levels were high and not suppressed by glucose administration<sup>6</sup>.

A scoring system for the firm diagnosis of PDDM (MMDM) devised at Cuttack is presented in Table 3.

**Table 3. Scoring system for the clinical diagnosis of PDDM (MMDM)**

Clinical profile	Score
Age at onset 10-30 years	1
Poor economic status (Rural origin)	1
Leanness, BMI < 16 MG/m <sup>2</sup> < 18 mg/m <sup>2</sup>	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 of ketosis: (absence of ketonuria on withdrawal of insulin for long periods)	3
Insulin requiring over 60 U/day (2 U/day/kg/body weight) unresponsive to sulphanylurea 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. 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 (MMDM) 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 (General)**

Comparison	PDDM (MMDM)	FCPD
Age at onset	10-30 years	10-40 years or older
Rural	All	78%
Socioeconomic status: Poor	All (100%)	60%
BMI < 16 kg/m <sup>2</sup>	92%	60%
Ketonuria	Nil	16%
C-peptide (2 hour post prandial)	0.6	1.0 pmol/l
Fecal fat (on 100g fat diet/day)	6.2 g/d	29 g/d
<b>Patients presented at the Workshop (1995)</b>		
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 <sup>2</sup> )	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

Despite discussions at several conferences and two international workshops<sup>10,11</sup> 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 specialties covering different aspects of diabetes and nutrition from many nations, viz; 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 by medical scientists from the participating countries. After thorough and threadbare discussions, a unanimous statement was 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 malourishment
- 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 glycemic control but are not ketosis prone

Essentially there was unambiguous and unreserved recognition of the two variants PDDM and FCPD, that were different from each other. Regarding PDDM, it was felt that evidences were 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.

**Table 6. Evidence summary: 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 calculus pancreatopathy, not due 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 dilation are essential features. Recurrent abdominal pain and steatorrhoea 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 FPCD 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 etiology 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. These recommendations have been adopted by both ADA and WHO committees..

### Data from Orissa

#### Incidence

As presented in Table 7, MMDM constituted 5.2% of all patients of diabetes seen at our hospital at Cuttack compared to FCPD, which accounted for 2.2 and IDDM for 0.9%. Among young patients (9% of total) around half were noted to have MMDM. Proportion of the above 3 categories of cases and of NIDDM in the young seen in the hospitals and comparative incidence among patients seen in private clinics<sup>6</sup> at Cuttack are presented in Fig 5. Patients with so called MRDM are much more often seen in charitable hospitals compared to private clinics obviously for economic reasons.

**Table 7. Comparison of two types of youth onset diabetes**

	MMDM	FCPD
<b>Incidence among diabetics</b>		
All ages	5.2%	2.2%
Upto 30 years	52.5%	22.4%
Age at onset	10-30	10-40
Male/female ratio	2.5:1	3:1

Relative proportion of patients with MMDM, FCPD, Type 1 and Type 2 diabetes among cases with onset by 30 years as documented at Berhampur (Orissa), Cuttack (Orissa) and Dhaka (Bangladesh)<sup>6</sup> is illustrated in Fig. 6. Geographic distribution of FCPD in Orissa is presented in Fig. 7.

## Complications

A variety of pyogenic and fungal infections of skin, mucous membrane and tissues, as well as pulmonary tuberculosis occur frequently in patients with MMDM; and relatively less commonly in patients with FCPD (Table 8). Features of neuropathy (reversible, distal symmetrical, sensory polyneuropathy) are extremely common in undernourished patients with MMDM (77%) as well as in FCPD (40%). These complications are noted at first observation, or early during the course of treatment. Macrovascular complications are rare, except peripheral vascular disease, which is elicited by bedside clinical tests rather than by symptoms such as claudication or dry gangrene.

**Table 8. Incidence of complications (%)**

	PDDM (MMDM)	FCPD
Infection	38	10
Macrovascular		
Coronary artery disease	-	-
Cerebrovascular disease	-	-
Peripheral vascular disease	10	20
Microvascular		
Nephropathy	10.2	10.4
Retinopathy	21.4	14.4
Neuropathy	77	40

## Immunogenetics

Genetics and immunological studies of patients with MMDM (71) and FCPD (47) as well as type 1 (74) and type 2 (216) diabetes along with 122 controls from Cuttack have been carried out at the laboratory of C.B. Sanjeevi of the Karolinska Institute, Stockholm, Sweden. Either

GAD or 1A-2 Ab test was positive in around 25% of patients with MMDM. The association was significantly higher than controls while it was much lower relative to type 1 and similar to that in patients with type 2 diabetes.

There are differences in the incidence of genetic markers of MMDM and type 1 diabetes. In antibody positive patients HLA DR<sub>3</sub>-DQ<sub>2</sub> set up was common but not DR<sub>4</sub>-DQ<sub>8</sub>. In the larger fraction of patients who were Ab negative there was increased association of MMDM with DR<sub>7</sub>-DQ<sub>9</sub>. Further, MMDM was positively associated with allele 9 of MIC-A in the class 1 region and negatively so with allele 5 only. These findings suggest that MMDM is immunogenetically different from type 1 diabetes in several respects<sup>21,22</sup>.

Incidence of antibody positivity among patients with FCPD was not different from those in controls. There was no HLA identity either except that some positive association was observed with DQ<sub>9</sub>.

### **Epilogue**

There has been a decline in the number of new cases of MMDM and FCPD reporting to the diabetes clinics at Cuttack in the course of the last 5-6 years. Incidence of cases of Tropical Calcific Pancreatitis observed at the Gastroenterology Section is also on the decline. This may be due to improvement in the nutritional status of the rural poor particularly in the endemic coastal districts of Orissa.

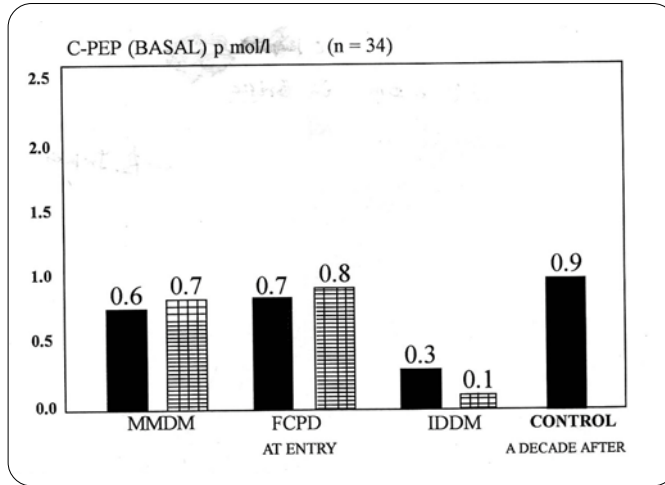
**Fig. 1 Typical patients with MMDM**



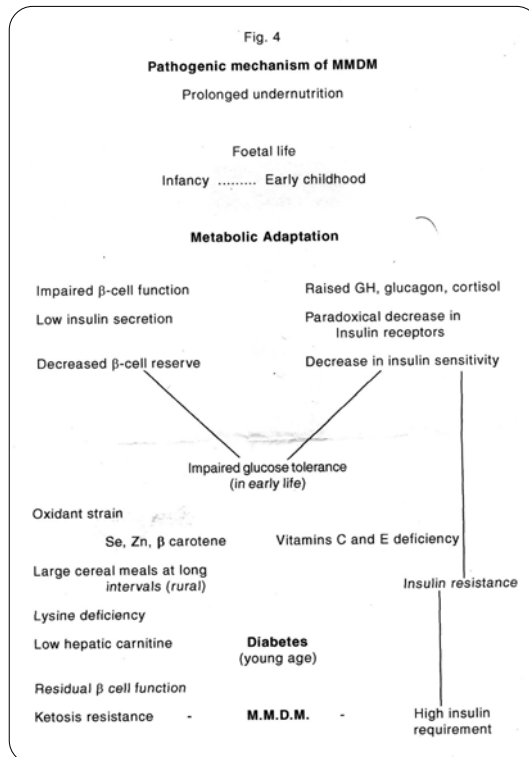
**Fig. 2 Patients of FCPD. Abdominal scar of pancreaticolithotomy in one patient**



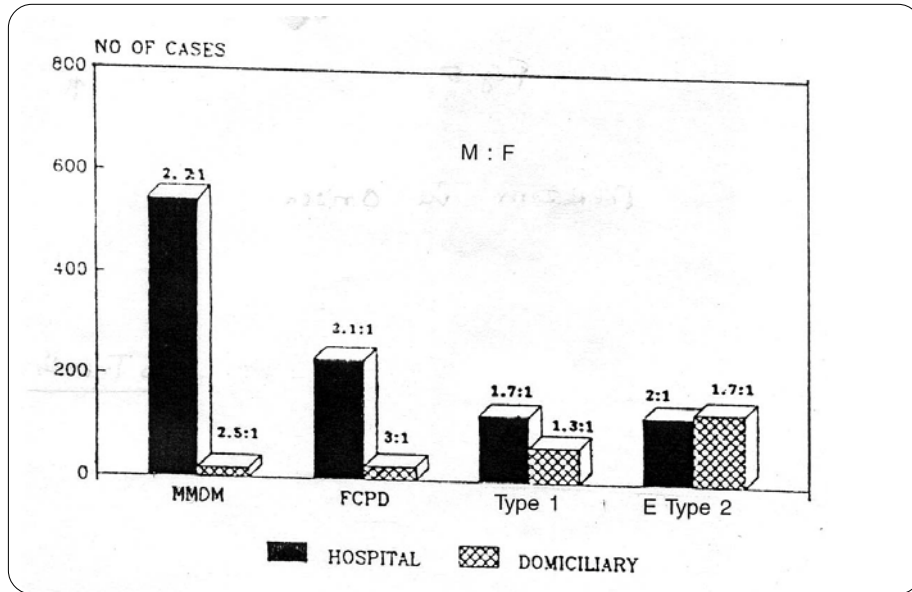
**Fig. 3 Basal C-peptide levels at admission and after ~10 years of follow up**



**Fig. 4 Hypothesis of the pathogenetic mechanism of MMDM**



**Fig. 5 Incidence of clinical types of diabetes among young patients in Hospital and Domiciliary practice**



**Fig. 6 Hospital based incidence of clinical types of diabetes among young patients observed at Berhampur, Cuttack and Dhaka**

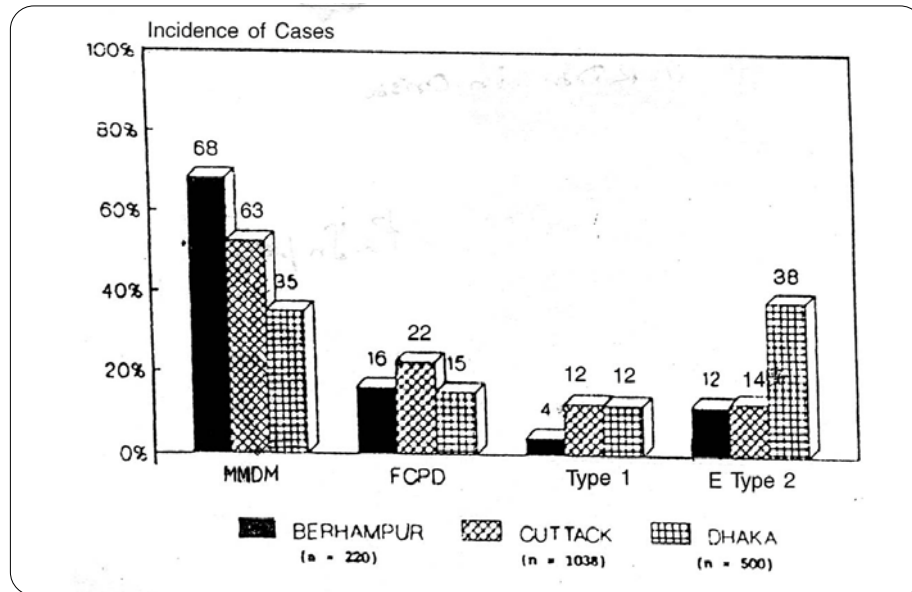
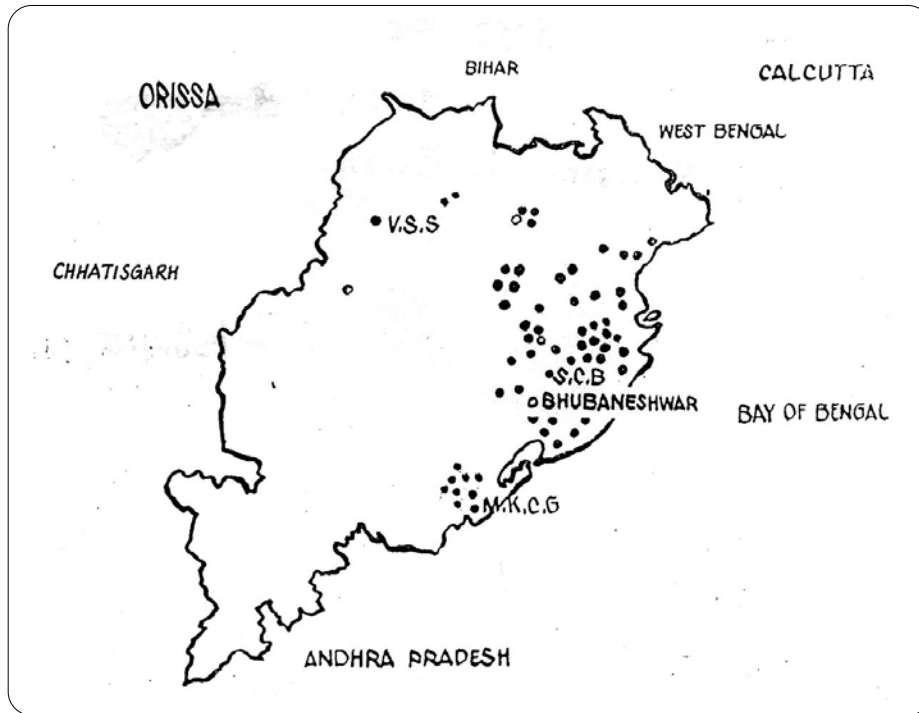


Fig. 7 Map depicting the geographic distribution of FCPD in Orissa



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