Insulin "Dependent" Diabetes Mellitus in India: Classical versus Atypical

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INTRODUCTION

In the earlier part of the 20th century nutritional and infectious disorders were so overwhelming in developing countries, that chronic and degenerative disorders received little attention. Empirical experience led to the belief that chronic disease did not occur in the 'tropics'. For example, upto the 1930's, it was believed that rheumatic fever did not occur in India [1,2]. Now the prevalence of rheumatic fever/rheumatic carditis has been documented as 1-11/1000 [3], and rheumatic heart disease is recognized as one of the commonest chronic childhood illnesses. Similarly, several physicians from southeast Asia, Sri Lanka, and south India remark that they do not observe juvenile diabetes in their hospitals and clinics[4], leading to gross underestimation of the magnitude of the problem. In many medical facilities in India, sick children are not routinely evaluated for glycosuria or hyperglycaemia, and may be dying undiagnosed. These *DEATHS BEFORE DIAGNOSIS* of childhood diabetes mellitus (CDM) seem to be a preventable public health problem associated with lack of awareness and educational and economic impoverishment.

Hospital records and/or clinic data over the last 3 decades indicate that young diabetics (diabetes onset before 15 years) constitute 1-5% of the total diabetic subjects enrolled (i.e. those salvaged from death before diagnosis) [5-20] (Table I). The observed differences between reports and centres could be due to indirect factors (differences in socioeconomic status, health awareness, accessibility to quality medical care etc.), besides true variations in disease incidence (6-14). Increased salvage creates a fresh challenge. Providing care for chronic childhood disease like diabetes is a major economic and psychological burden on the family members, who have sometimes been seen to willfully deny insulin to the child, to let him/her die a 'natural' death.

Table I : Prevalence of Juvenile diabetes in India (onset * 15 yrs.)

S. No.	Region	Year	Prevalence %	Reference
1.	Ahmedabad	1964	< 1	Gupta OP [6]
2.	Delhi	1965	2.4	Ahuja MMS et al [7]
3.	Madras	1966	0.8	Viswanathan M [8]
4.	Bombay	1968	1.4	Udani PM et al [9]
5.	Delhi	1974	2.1	Vaishnava H et al [10]
6.	Cochin	1989	3.6	Abraham A et al [11]
7.	Cuttack	1989	2.0	Samal KC et al [12]
8.	Madras	1989	0.9	Venkataraman S et al [13]

Figures represent per cent of all diabetic patients in a given hospital or clinic.

REVIEW

Insulin-dependent diabetes mellitus(IDDM) is one of the most common chronic diseases in childhood. Very little is known about the epidemiology, determinants and clinical profile of childhood diabetes mellitus in India. Preliminary studies have confirmed the existence of islet cell autoimmunity and HLA association of classical type I diabetes mellitus (IDDM) in India with features similar to those observed in the west [21-23]. However besides IDDM, few other "types" or "variants" of diabetes in the young have been reported from India as well as the economically underprivileged developing countries [5-20]. They are described below:

1. **Non-alcholic chronic pancreatitis** (with or without pancreatic calculi) is seen in many parts of India and assumes endemic propor-tions in the southern costal state of Kerala (15). Despite incrimination of certain nutritional factors, the precise etiology of this form of diabetes is unknown.
2. Over the years several investigators have reported on a special clinical variant of diabetes in the young. This is variously referred to as **ketosis resistant diabetes of young, malnutrition related diabetes mellitus subtype protein deficient diabetes**

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mellitus (MRDM-PDDM). The associated features include a male preponderance, low socioeconomic status, absence of a family history of diabetes mellitus, onset of diabetes usually in the second or third decade, features of malnutrition, ketosis resistance, absence of pancreatic calcification and intermediate beta cell reserve (plasma C-peptide concentration between IDDM and NIDDM). Despite some studies and intense speculation, whether malnutrition is a cause or consequence is yet unclear [7-17].

3. **Non-insulin-dependent diabetes of the young (NIDDY):** A high incidence of NIDDY has been reported from a few selected centres from South India [18]. NIDDY is characterized by strong family history of NIDDM (autosomal dominant inheritance with vertical transmission in families of 'MODY' - Maturity onset diabetes of young). About half of the off-springs of NIDDY patients subsequently develop diabetes mellitus. These children have reduced insulin secretion as judged by insulin and C-peptide response to glucose load [19]. NIDDY has also been reported among Indians in South Africa [20].

HLA studies in IDDM in India

HLA typing for detection of antigens in the HLA A and B loci (using the modified microlymphocytotoxicity test) in 54 unrelated North Indian insulin dependent diabetics with age of onset < 30 yr. showed that the frequency of HLA Bw21 was significantly increased (relative risk: 12.27: one of the highest ever reported for a single B locus antigen in IDDM) and of HLA B7 significantly reduced in diabetics compared to controls. This very strong positive correlation seems to be unique to India though the frequency of Bw21 in the normal Indian population is similar to that in other populations studied. On the other hand, the B allele conferring protection against IDDM (B7) appears to be common in different populations of the world [21].

In a second study, 88 North Indian patients with IDDM were typed for HLA DR antigens from DR1 to DR7. The frequency of HLA DR3 was significantly increased in patients as compared to controls (78% vs. 26%, corrected P <0.001), the relative risk of 10.52 being much higher than that reported in western IDDM populations. HLA DR2 showed significant negative association (RR=0.18, corrected P<0:001) [22].

The HLA haplotype segregation in 17 insulin dependent diabetic sibs (7 probands + 10 secondary cases) belonging to 7 multiplex families of North Indian origin were determined. Seven shared both haplotypes and 3 shared one haplotype with their proband; no HLA non-identical diabetic sibs were observed. This distribution of haplotypes was non-random (p=0.005) [23].

In North India, the 'high risk' IDDM haplotype appears to be A28, Bw2l, BfSl, DR3; the 'low risk' haplotype conferring resistance was A3, B7, DR2, a common finding in many other populations [24, 25].

Autoimmunity and islet cell autoantibodies in India

One hundred and ten North Indian IDDM patients (age of onset < 30 yr.) were screened for pancreatic islet cell antibodies (ICAb), gastric parietal cell antibodies, and adrenal antibodies (indirect immunofluorescence technique); and for thyroglobulin and thyroid microsomal antibodies (commercial haemagglutination kits) [26]. Overall (without consideration of diabetes duration), ICAb was present in 31% of the patients (vs. 0.8% of the controls), and had characteristics similar to those described in Whites, with maximum prevalence within a month of onset of diabetes (67%) and persistence for long periods in diabetics with coexistent autoimmunity. A second series of 51 North Indian IDDM patients has a similar ICAb prevalence of 29%[23]. These studies also demonstrated a higher prevalence of organ-specific thyrogastric antibodies in IDDM patients as well as their family members.

Childhood diabetes mellitus in migrant Asian Indians

It has been shown that the incidence of NIDDM increases significantly in Indians settled in more affluent societies (UK, Fiji, South Africa). Evidence for IDDM is not as conclusive, mainly due to lack of incidence/prevalence data from India. The prevalence of IDDM in Asian children under 15 yr. of age, settled in the UK has been reported as 36/10000 in West Yorkshire [27], and 54/10000 in Leicester [28], which is not significantly different from prevalence in British white Caucasian children. The incidence of CDM in Ugandan Indians was very low on their arrival in England because of expulsion from Uganda (<1-2/10000). Within 15

years this incidence increased over 10 times to approximate the incidence seen in the UK Indians. Is the incidence actually increasing due to changes in environment; or it is only apparently higher due to falsely low incidence reported in India and Africa due to death before diagnosis [29]? Without concrete population based data from India it would be difficult to draw any conclusions.

Diabetes of young in India: Recent studies

A consecutive unselected series of 201 patients with clinical diabetes mellitus before 30 years of age attending the Department of Endocrinology, Metabolism and Diabetes at All India Institute of Medical Sciences and collaborating institutions was recently studied.

Of the 201 patients 129 were males and 72 females. Eighty six (42.8%) patients gave a history of ketosis and 41 (20.4%) had experienced ketoacidosis/coma at least once (Tables 2 and 3).

Table 2 : "Diabetes in the young" in India

Clinical Groups	(n)	Male/Female (ratio)	Age at onset yrs, mean (SD)	Family History of Diabetes (%)
IRD	(168)	0.64	15.1 (6.6)	53
KP	(22)	0.45	15.63 (7.7)	59
KR	(34)	0.67	20.48 (6.12)	73
NIRD #	(23)	0.69	24.2 (3.9)	39
CCP-DM	(10)	0.60	22.3 (6.4)	80

#: 8/21 initially requiring OHA, later developed secondary drug failure after a mean duration of 5 years; one required only dietary regulations for glycaemic control.

Table 3 : "Diabetes in the Young" in India

Clinical Groups	(n)	Duration of Diabetes (yrs) Mean (SD)	History of Ketosis (%)	History of Ketoacidosis /coma (%)	Body Mass Index (kg/m^2) Mean (SD)
IRD	(168)	3.6 (4.2)	48	24	17.9 (2.8)
KP	(22)	6.5 (7.3)	100	50	19.2 (3.1)
KR	(34)	5.2 (5.1)	2	2	17.8 (2.9)
(NIRD)	(23)	5.36 (6.6)	17	0	20.2 (4.0)
CCP-DM	(10)	2.4 (2.5)	0	0	19.3 (3.8)

RESIDUAL BETA CELL FUNCTION

Table 4 illustrates the basal and glucagon stimulated C-peptide levels in normal controls and the three groups of young diabetics.

Table 4: Residual betal cell function

Clinical Groups		Plasma C-peptide, mean (SD) (pmol/ml)		
	(n)	Basal	Stimulated	Incremental
Controls	(6)	0.35 (0.08)	0.55 (0.14)	+ 0.20 (0.09)
IRD	(77)	0.11 *** (0.10)	0.15 *** (0.14)	+ 0.04 (0.06)
NIRD	(12)	0.32~~~ (0.14)	0.42~~~ (0.19)	+0.11~ (0.12)
CCP-DM	(9)	0.19* (0.20)	0.24** (0.21)	+ 0.04*** (0.04)

* significant ($p<0.05$) when compared to the controls
** significant ($p<0.01$) when compared to the controls
*** significant ($p<0.001$) when compared to the controls
~ significant ($p<0.05$) when compared to IRD
~~~ significant ($p<0.001$) when compared to IRD

Table 5 : Plasma C-Peptide in relation to age at onset in all young diabetic patients

Age at onset		Plasma C-Peptide, mean (SD) (pmol/ml)		
(yrs)	(n)	Basal	Stimulated	Incremental
0 - 5	(3)	0.04 (0.02)	0.07 (0.04)	+0.02 (0.02)
6 - 10	(13)	0.04 (0.05)	0.06 (0.05)	+/ 0.01 (0.01)
11-15	(23)	0.09 (0.08)	0.13 (0.11)	+0.03 (0.04)
16-20	(27)	0.16 (0.14)	0.21 (0.15)	+0.05 (0.06)
21-25	(13)	0.14 (0.16)	0.25 (0.25)	+0.11 (0.14)
26 -30	(19)	0.25 (0.16)	0.32 (0.19)	+0.07 (0.07)

The basal and stimulated plasma C-peptide levels correlated with age at onset ($r=0.45$, $P<0.001$). This indicates that the later the onset of diabetes better preserved is the beta cell function. The non-insulin requiring group and the chronic calcific pancreatic group have a later age at onset and better preserved beta cell function.

Analysis of the beta cell function in relation to the age at onset in IRD also showed that the basal and stimulated C-peptide levels correlated with age at onset of diabetes ($r=\sim0.3$, $p<0.05$).
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The duration of diabetes was inversely retated to plasma C-peptide levels ($p<0.05$, Table 6).

Table 6: Duration of diabetes and beta cell reserve

Duration of Diabetes (yrs)	(n)	Plasma C-Peptide, mean (SD) (pmol/ml) Basal	Stimulated	Incremental
Upto 1	(14)	0.17 (0.12)	0.20 (0.13)	+ 0.04 (0.05)
> 1	(63)	0.09* (0.10)	0.14 (0.14)	+0.04 (0.06)

* : significant ($p < 0.05$) when compared to duration of diabetes up to one year.

C-peptide levels and diabetic ketoacidosis/coma:

Table 7 : Plasma C-peptide levels in relation to history of ketosis

History of Ketosis	Plasma C-Peptide, mean (SD) (pmol/ml) Basal	Stimulated	Incremental
No History of Ketosis (60)	0.17 (0.15)	0.23 (0.19)	+ 0.07 (0.09)
History of all Ketosis# (38)	0.11* (0.12)	0.14* (0.15)	+0.03* (0.03)
History of Ketoacidosis/ coma (13)	0.07* (0.09)	0.09* (0.09)	+0.02* (0.02)

* Inclusive of Ketosis and Ketoacidosis/coma.

* : $p < 0.05$ when compared to those with no history of ketosis.

The subjects with a history of ketoacidosis/coma had a significantly lower age at onset and a longer duration of disease (12.8 ± 4.9 years and 5.1 ± 7.5 years respectively) compared to those without history of ketosis (19.5 ± 7.1 and 4.0 ± 4.5) ($p < 0.01$ and $p < 0.05$ respectively).

C-peptide levels and 'ketosis-resistance' (insulin abstinence

Due to certain social and economic reasons it is not uncommon to find insulin treated patients withdrawing insulin against medical advice. Presence of such a history gives us a unique opportunity to determine the difference between those patients who develop ketosis, and those who do not do so despite insulin abstinence.

Table 8 : Plasma C-peptide levels in groups of patients who developed or did not develop ketosis after stopping insulin treatment

Clinical Groups	Plasma C-Peptide, Mean (SD) (pmol/ml) (n)	Basal	Stimulated	Incremental
Ketosis Prone	(16)	0.11 (0.12)	0.13 (0.15)	+0.03 (0.04)
Ketosis Resistant	(30)	0.15 (0.14)	0.21 (0.17)	+0.07(0.09)*

* : significant ($p < 0.05$) when compared to the ketosis prone group

The subjects with relative ketosis resistance had a significantly later age at onset (20.1 ± 6.1) when compared to the ketosis prone group (14.4 ±6.1) ($p<0.01$).

Plasma C-peptide levels - other correlates

The body mass index, age at sampling and family history of diabetes did not correlate with either the basal or stimulated C-peptide levels.

Islet cell autoantibodies (ICAbs)

The overall ICAb prevalence (irrespective of diabetes duration) was 24% in the insulin requiring group. The clinical correlates in relation to the ICAb positivity are indicated in the following tables (9 to 11).

Table 9 : ICAb positivity and age at diabetes onset

Age at onset (years)	Total	ICAb positive	% Positive
1 - 5	7	2	28.6
6 - 10	24	6	25.4
11 - 15	37	11	29.7
16 - 20	39	9	23.1
21 - 25	17	3	17.7
26 - 30	24	5	20.8

Table 10 : ICAb positivity and duration of diabetes

Duration of Diabetes (months)	N	ICAb +VE	%
1 - 3	18	6	33
4 - 12	25	7	28
13-60	73	16	21.9
61 - 120	22	4	18.2
> 120	10	7	70.0

Table 11: Islet cell antibody status and endogenous insulin reserve

ICAb STATUS	Plasma C-Peptide, mean (SD) (pmol/ml)		
(n)	BASAL	STIMULATED	INCREMENTAL
POSITIVE (11)	0.13 (0.13)	0.17 (0.14)	+0.07 (0.10)
NEGATIVE (66)	0.15 (0.15)	0.20 (0.19)	+0.05 (0.07)

When the IRD was analyzed as a group, the basal, the stimulated and the incremental C-peptide levels were not significantly different in the ICAb positive and negative sub-groups.

Table 12 : ICAb positivity and ketosis 'proneness' vs 'resistance'

Ketosis	Total	ICAb Positive	% Positive
IRD -`KP'	18	2	11
IRD - `KR'	29	6	21

DISCUSSION

Classical IDDM (`ketosis-prone') versus atypical `ketosis-resistant' form of diabetes in young in India

Our recent studies confirm the previous observations on the existence of autoimmunity related 'classical' type I diabetes mellitus in India. These patients (diabetes onset before 15 years) were characterized by presence of islet cell autoantibodies (associated with younger age at onset and shorter diabetes duration), obligatory insulin dependence, proneness to ketoacidosis and minimal serum C peptide responses. Hence, childhood onset diabetes even in India appears to be homogeneously 'classical' type I/IDDM.

In contrast the group of youth onset diabetes (onset between 16 and 30 years) appears to be heterogeneous, consisting of (a) 'classical' type I/IDDM: 'ketosis-prone' and autoimmunity related, (b) a relatively 'ketosis-resistant' form of insulin requiring diabetes (associated with features of malnutrition), (c) non-insulin-dependent diabetes of the young (NIDDY/MODY) in the relatively higher socioeconomic-economic groups and (d) diabetes associated with tropical calcific pancreatitis.

Of the sub-groups of youth onset diabetes, the `ketosis-resistant' form appears to be the most enigmatic. It is obvious that the relative ketosis resistance is due to better preserved endogenous beta cell function. Despite the smaller number of subjects studied, the lack of differences in the prevalence of ICAbs in the `ketosis-prone' (11%) versus 'ketosis-resistant' (21%) forms of young diabetics, raises the possibility that the 'ketosis-resistant' form is a variant of autoimmunity related, classical type I/IDDM. This hypothesis is supported by a recent observation from Africa, where HLA-DR associations were found to be similar in the so called 'malnutrition related' diabetes mellitus and classical type I/IDDM [30]. Thus it is suggested that, the 'ketosis-resistant' subgroup is probably a milder variant of classical Type I/IDDM. Further in-depth comparative studies (islet cell autoantibodies and insulin autoantibodies at diabetes onset, HLA-DR typing, H LA DQ beta 57 asp/non-asp typing) in a larger number of well defined 'ketosis-prone' and 'ketosis-resistant' young Indian diabetics are necessary to clarify the hypothesis. Novel experimental paradigms (in BB/W rats, NOD mice) also need to be examined to analyze the effects of nutritional factors/deficiencies and infectious processes on the magnitude and character of anti-islet autoimmune responses and resulting beta cell destruction.

Beta-cell dysfunction

Our recent studies primarily evaluated the endogenous insulin reserve of young diabetics as reflected by their basal and glucagon stimulated C-peptide levels. Majority of young diabetics (84.1 %) required insulin for management from the onset of the disease. A small subset of 23 patients (11.4%) however could be managed with oral hypoglycaemic agents. Basal as well as glucagon stimulated C-peptide levels in IRD were significantly lower than those in normal controls but

the NIRD group showed levels comparable to the controls, though the incremental response of C-peptide to glucagon stimulation was less than that in normal controls. It is thus clear that insulin requirement for clinical management is indicative of seriously compromised endogenous insulin reserve in the insulin requiring young diabetics seen in the North India. Comparative evaluation of endogenous insulin reserve in the ketosis prone and ketosis-resistant subgroups of IRD showed that the reserve was higher in the group who were not prone to ketosis.

On the basis of the observations made in the present study, the young diabetics are a heterogenous group from the point of view of proneness to ketoacidosis and endogenous insulin reserve even adopting a cutoff point of 30 yrs of age, a decade earlier than that used in western countries to define young diabetics. Thus as much as 11.4% of the present group of young diabetic patients showed features of relative insulin independence, preserved endogenous insulin reserve and resistance to development of ketoacidosis on deferment of insulin treatment. These are features of type II diabetes (NIDDM). The classification of this subset of young diabetic patients remains an open issue.

The remaining young diabetics in the present study are comparable to the insulin dependent, type I diabetic patients (IDDM) described from the West. The relatively low positivity rate of ICAb in them, however, is one point that makes them different from the IDDM groups reported in the Western literature where an average of 30-40% is shown to be ICAb positive on cross sectional studies. However this difference could be partly because of the delay (mean 5 yrs) from the diagnosis of diabetes when we studied ICAb status in these patients.

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