Profile of young diabetes mellitus and its clinical implications

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BACKGROUND: The profile of diabetes mellitus in the young is changing and, without sophisticated markers, type segregation is often a dilemma. **METHODOLOGY:** This clinic-based study was planned to estimate the burden of the disease (over a period of one year); the presenting features; complications (i.e., retinopathy, nephropathy, neuropathy, hypertension, peripheral arterial disease, infections, and ketosis); and incident biochemical parameters. Type segregation was initially attempted by therapeutic titration, and the incident clinicobiochemical parameters (i.e., family history, body mass index, incident complications, glycemic status, and lipid profile) of the thus segregated groups were analyzed for any significant difference. **RESULTS:** The clinic prevalence of young diabetes was 4.08%. Overall, microvascular complications were present in 43%; hypertension was the commonest macrovascular complication. Type 1 diabetes was found in 68.7%, type 2 diabetes in 19.4% and fibrocalculus pancreatic diabetes in 11.9%. The predominant microvascular complications were nephropathy and retinopathy (~21%); patients with the fibrocalculus variety did not develop retinopathy. The family history, body mass index, fasting plasma glucose, and lipid profile revealed significant differences among the three predominant varieties segregated by therapeutic titration. Type 2 diabetes was strongly associated with a positive family history, higher body mass index, and high LDL cholesterol level. **CONCLUSION:** The tendency to consider all young diabetics as type 1 diabetics needs to be changed; a significant number have type 2 diabetes and, if identified, can be treated with oral drugs. Identification is possible by analyzing a few simple clinicobiochemical parameters like family history, body mass index, incident glycemic status, lipid profile, and abdominal ultrasonography.

KEY WORDS: Clinicobiochemical profile, complications, diabetes, India, prevalence, type segregation, young

The prevalence of diabetes mellitus (DM) as a whole is increasing throughout the world.[1,2] This phenomenon is also reflected in the younger population, especially for type 2 diabetes mellitus (T2DM).[3] It is probably more so in India because of the rapidly changing lifestyles and food habits in a population that is already ethnically predisposed to T2DM.[4] Without a study of the autoantibodies, C-peptide levels, and genetic markers, differentiating the varieties of DM in the young is often difficult.[5] T2DM in the young usually has higher prevalence in females and is often associated with relatively higher body mass index (BMI), cholesterol, and blood pressure.[2] Complications generally develop at around puberty or after, especially for type 1 diabetes mellitus (T1DM).[6] Though microvascular complications (retinopathy, nephropathy, and neuropathy) in the young may be present in up to 40%, macrovascular complications are infrequent and often subtle.[7] They are indicated by raised blood pressure, increased carotid intima-medial thickness, left ventricular dysfunction, abnormal ECG, and diminished peripheral pulses.[8] Prevalence of fibrocalculus pancreatic DM (FCPD) has been reported to be around 6–11%, with a male preponderance.[5] Data on the profile of T1DM are abundant,[9] whereas that on T2DM and FCPD are limited.[10,11] There are few reports from this part of the country about the prevalence patterns, as well as the clinicobiochemical aspects, of the predominant forms of DM in the young.[12]

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This study was planned to estimate the approximate burden of DM in the young, note their incident clinicobiochemical features and complications, and then attempt type segregation by identifying simple parameters. Initial type segregation of the prevalent varieties of DM (T1DM, T2DM, and FCPD) would be done according to the ultimate (at 3-8 months) therapeutic response (to insulin or oral drugs) and ultrasonographic findings of pancreatic calcification. Then the initially assessed (at presentation) simple clinical and biochemical parameters of these segregated varieties would be examined to identify those that were significantly different. Simple markers to differentiate between different types of DM might be helpful in planning therapy, as accurate genetic and autoimmunity markers for diagnosing the different varieties of DM are costly and not easily available.

Methodology

Patients with a definite diagnosis of DM[10] who were >6 years but ≤ 25 years of age were selected from all the new patients attending or referred to the diabetes clinic (of NRS Medical College, Kolkatta) between January 2004 and December 2004. They were either very recently diagnosed or had had the disease for some time. The selection of the upper age limit of 25 years was partly arbitrary and partly due to the prevailing concept that T2DM is uncommon below the age of 30 years.[10] Ultimate therapeutic response was defined as normalization of both fasting and postprandial plasma glucose, as well as an HbA_{1C} near 7%, with any particular therapy for at least 1 month. Insulin was the initial therapy for all patients. After stabilization of the patient and achieving euglycemia, sensitizers were introduced in patients without detectable pancreatic calcification.[13] If there was any therapeutic response by 4-6 weeks, then sulphonylureas were added with concurrent lowering of the insulin dose; depending on the response, insulin was progressively withdrawn.

The clinical parameters evaluated were age, sex, presenting history (polyuria, polydypsia, polyphagia, pain abdomen, etc.), family history of DM, BMI, blood pressure, peripheral arterial disease (PAD); by palpation of the posterior tibial and dorsalis pedis arteries of both sides), neuropathy (tested by vibration sense and monofilament test), limited joint mobility and retinopathy (tested by indirect fundoscopy with a dilated pupil).[11,12]

The biochemical investigations included urine for ketones (Ketostix) and albuminuria (after stabilizing the patient, albumin–creatinine ratio of spot urine was tested on two occasions within a span of 3 months); urine culture; fasting (FPG) and postprandial plasma glucose (PPPG); and HbA_{1C}. Fasting serum was examined for total cholesterol (TCHL), LDL cholesterol (LDLC), HDL cholesterol (HDLC), VLDL cholesterol (VLDLC), triglycerides (TGL), and creatinine (all by semi autoanalysar-MERCK-Microlab 200).

The other investigations included plain X-ray of the abdomen (for pancreatic calcification); X-ray chest (for pulmonary TB); ultrasonography of the whole abdomen (for pancreatic calcification-parenchymal or ductal-renal and hepatic abnormalities, ascites and to check the status of the ovaries); and resting 12-lead ECG (for any abnormality indicating coronary heart disease).[11,12]

Segregation was done by age (<10 years, 10–15 years, 16–20 years, and 21–25 years) and sex (male and female) for the various parameters of history, clinical, and laboratory findings. Patients were followed-up for around 3 to 8 months for therapeutic titration and finally segregated into the predominant varieties (T1DM, T2DM, and FCPD) according to the ultimate therapeutic response (i.e., to insulin, oral antidiabetics, or oral drugs plus insulin) and the ultrasonographic finding of pancreatic calcification (for the diagnosis of FCPD). Then their relevant parameters were analysed.

Serum C-peptide, autoantibodies (GAD65, ICA, IAA, and IA-2) and genetic markers were not examined. Pregnancy diabetes and secondary DM were excluded. Statistical analysis was done using the Student's t test (paired with unequal variance) and a P value of <0.05 was considered significant.

Results

A total of 1643 new cases of DM were recorded, of which 67 cases (4.08%) were classified as young diabetics (6–25 years);26 (38.8%) were male and 41 (61.2%) female. Below the age of 10 years there were 10 cases (M: 6, F: 4); between 10–15 years there were 17 cases (M: 8, F: 9); between 16–20 years there were 20 cases (M: 5, F: 15); and between 21–25 there were 20 cases (M: 7, F: 13). The distribution of the BMI according to age is shown in Table 1.

Thirteen patients (19.4%) presented with DKA; of these, 70% were <10 years; 43 (64.2%) had polyuria, polydypsia, and polyphagia with weight loss; and few were >20

Table 1: Body mass index distribution according to age

Age group	Body mass index (kg/m.sq)				Total
	< 15	15-20	21-25	> 25	
< 10	n=7	n=2	n=1	n=0	10
10-15	n=3	n=10	n=4	n=0	17
16-20	n=3	n=13	n=3	n=1	20
21-25	n=2	n=8	n=8	n=2	20
Total	n=15	n=33	n=16	n=3	67
	(22.4%)	(49.3%)	(23.9%)	(4.5%)	(100%)

years of age. Nine patients (13.4%) had abdominal pain (4 > 20 years); 4 patients presented with foot ulcer; and 4 (6%, all <15 years) had joint symptoms. Pulmonary tuberculosis was found in 5 (7.5%) and culture-proven urinary infection was present in 7 (10.4%).

Retinopathy was found in 14 (20.8%; all >10 years; M: 8, F: 6), with one patient having proliferative retinopathy. Neuropathy was present in 9 (13.4%; M: 3, F: 6), of which 7 were between 10–20 years. Ketones were found in the urine in 16 (23.9%); 14 (20.8%; M: 4, F: 10) had microalbuminuria; and 1 had macroalbuminuria (F: 1). Family history of T2DM was present in 13 (19.4%) and 4 had both parents as diabetics. Only two patients gave a history of low birth weight. Seven patients had hypertension, of which 3 had a family history of the disease. PAD was found in 1 (22 years; F). None had resting ECG changes suggestive of coronary artery disease. Thyroid swelling was present in 6 of the cases (9%). Overall, microvascular complications were found in 29 patients (43%), and macrovascular in 8 (11.9%).

An initial fasting plasma glucose of >400 mg/dl was found in 12 cases (17.9%) and a PPPG >400 mg/dl was present in 36 (53.7%); there were 8 patients who had either FPG or PPPG in the diabetic range with the other value in the IGT/IFG range. Pancreatic calcification was identified in 8 cases by ultrasonography (4 were parenchymal and 4 ductal); only 4 of these cases had X–ray evidence of calcification. Renal parenchymal disease was evident in 7 (one patient being <10 years old); hepatomegaly, with or without altered echo texture (one case of cirrhosis and one of fatty liver), was seen in 6 (one patient <10 years and three >20 years); ascites was present in 3 (one cirrhosis, one TB peritonitis, and one renal parenchymal disease); and polycystic ovaries were found in one patient (in the age group of 16–20 years). The segregation of the predominant varieties of DM was roughly established depending on the therapeutic response after 3–8 months of follow-up and the ultrasonographic finding of pancreatic calcification. Table 2 depicts the ultimate therapy response data and Table 3 outlines the probable group segregations. T1DM was seen in 46 cases (M: 20, F: 26); T2DM in 13 (M: 3, F: 10); and FCPD in 8 (M: 3, F: 5).

These segregated groups were analyzed for their age distribution and the associated conditions. Table 4 shows the age-wise distribution of the types of DM and Table 5 enumerates the associated conditions.

These groups were then compared by the parameters of family history of DM, BMI, FPG, and lipid profile. Family history of T2DM was found in 11 of the 13 young T2DM patients (85%), with 4 having both parents suffering from T2DM.[7] A single parent having T2DM was found in one each of the T1DM (2.2 %) and FCPD (12.5 %) groups.[11] Table 6 depicts the mean values of BMI, FPG, and lipid parameters and Table 7 gives the *P* values of the statistically analyzed parameters. Three cases of T2DM had hypertension, and one had family history of hypertension.[14] Four cases of T1DM had hypertension and two had family history of hypertension.

Table 2: Therapeutic response

Age group (years)	Inj. insulin (%)	OAD + MNT (%)	Combination (%)
< 10 (n=10)	n=10 (100)	-	-
10–15 (n=17)	n=14 (82.4)	n=2 (11.8)	n=1 (5.9)
16–20 (n=21)	n=18 (85.7)	n=3 (14.3)	-
21–25 (n=19)	n=12 (63.2)	n=7 (36.8)	-
Total (n=67)	n=54 (80.6)	n=12 (17.9)	n=1 (1.5)

OAD - Oral anti diabetics, MNT - Medical nutrition therapy

Table 3: Probable varieties

Type of DM	Male (%)	Female (%)	Total no. (%)
T1DM	20 (43.5)	26 (56.5)	46 (68.7)
T2DM	3 (23.1)	10 (76.9)	13 (19.4)
FCPD	3 (37.5)	5 (62.5)	8 (11.9)

Table 4: Distribution of different types of diabetes according to age

Type	< 10 years	10-15 years	16-20 years	21-25 years	Total no.
T1DM	10	13	15	8	46
T2DM	0	3	3	7	13
FCPD	0	0	3	5	8
Total	10	17	21	20	67

Ketosis, limited joint mobility, polyuria, polydypsia, polyphagia and foot ulcer were more frequently associated with T1DM.[15] Infections like tuberculosis and UTI were more common in T2DM.[14] Neuropathy (13.1% *vs* 15.4% *vs* 12.5%) and nephropathy (21.7% *vs* 23% *vs* 25%) were rather evenly distributed among the three predominant varieties. Retinopathy was similar in T1DM and T2DM (23.9% *vs* 23.1%), with none having it in the FCPD group.[16] Abdominal pain was highest in FCPD (50%)[17] [Table 5].

The highest FPG was associated with T1DM followed by FCPD and T2DM. BMI was lowest in the FCPD group and similar in T1DM and T2DM (age-matched). All the lipid parameters were significantly low in FCPD; TGL was highest in T1DM, and TCHL and LDLC was significantly high only in T2DM. HDLC was highest in T2DM [Table 6]. Below the age of 10 years all cases were T1DM, with few complications (10%). Complications as well as the various varieties started appearing and increasing from the age of 12 years onwards. Mean insulin requirement for initial control was highest for the FCPD group, followed by T1DM and T2DM.

Between groups A and B (T1DM), only the parameter of BMI was significantly different; this difference was also true when groups A and C (T1DM) were compared. This is natural considering the age. Between groups B and C (T1DM) only VLDL and TGL were significantly different, being higher in group C, probably again age is the factor. Between groups D and E (T2DM and FCPD), all parameters were significantly higher in group D except FPG, VLDL, and TGL, which were similar; probably the cause for altered TGL in FCPD is different. Between groups C and D (older age group T1DM and T2DM), the parameters of BMI, TCHL, LDLC, and HDLC were significantly higher in T2DM, while TGL did not differ; FPG was significantly higher in T1DM (P=0.0001). Between groups C and E (older age group T1DM and FCPD), all parameters except FPG and HDL were significantly lower in group E (FCPD) [Tables 6 and 7].

Table 5: Distribution of associated conditions according to type of diabetes

Associated condition	T1DM (*n*=46)	T2DM (*n*=13)	FCPD (*n*=8)	Total (*n*=67)
Pain abdomen	3	2	4	9
Ketosis	13	3	0	16
L J M	3	1	0	4
UTI	1	5	1	7
Tuberculosis	0	4	1	5
3 Ps	34	3	6	43
Ascites	2	1	0	3
Foot ulcer	3	0	1	4
Nephropathy	10	3	2	15
Neuropathy	6	2	1	9
Retinopathy	11	3	0	14
PAD	0	1	0	1
PCOD	0	1	0	1
HTN	4	2	1	7

LJM - Limited joint mobility, UTI - Urinary tract infection, 3 Ps - Polyuria, polydypsia, polyphagia, HTN - Hypertension; PAD - Peripheral arterial disease, PCOD - Polycystic ovarian disease

Discussion

There has been an increase in the prevalence of both T1DM and T2DM. However, T1DM probably still remains the main form of DM in the young, with a female preponderance. Heredity, strong family history, obesity, physical inactivity and the intrauterine environment, all probably contribute to the development of T2DM.[10] The organ complication that is most commonly reported is nonproliferative retinopathy (40–80%).[18,19] Microalbuminuria (10–60%),[20] limited joint mobility (7%),[15] and peripheral neuropathy were less common (40–18%).[16] Population data about T1DM is widely available but T2DM data is predominantly clinic based.[3] There is no uniformity in the methodologies of the various studies, especially with regard to the age-groups studied and the clinicobiochemical parameters selected and so our data cannot always be compared with that collected by others.[5,7,12,19]

Compared to other studies the clinic prevalence of young DM is still small (4.08%) in our setup.[2,4] Beyond the age

Table 6: Distribution of anthropometric and biochemical parameters according to diabetes type (mean ± SD)

Groups (years)	DM type	No.	BMI (kg/m.sq)	FPG (mg/dl)	TCHL (mg/dl)	LDLC (mg/dl)	VLDLC (mg/dl)	HDLC (mg/dl)	TGL (mg/dl)
A (<10)	T1DM	*n*=10	13.3 ± 1.9	407 ± 118	153 ± 61	100.9 ± 36.4	46.6 ± 33	30.5 ± 8.8	265.5 ± 152.7
B (10-15)	T1DM	*n*=13	16.9 ± 2.2	332.4 ± 173	181.6 ± 42.7	103 ± 29	37.3 ± 6.4	30.7 ± 7.1	180.6 ± 42.2
C (15-25)	T1DM	*n*=23	18.3 ± 2.8	337.9 ± 127	179.4 ± 31.3	101.3 ± 34.6	60.7 ± 35.1	29.1 ± 11.5	211.7 ± 103.4
D	T2DM	*n*=13	21 ± 4.5	180.6 ± 52.2	255.3 ± 60.5	168.6 ± 52.3	29.8 ± 12.3	39.9 ± 8.5	185 ± 87.8
E	FCPD	*n*=8	15.6 ± 2.5	253.7 ± 78.9	114.7 ± 45.2	63.8 ± 26.6	26.5 ± 19.5	26.3 ± 12.3	114 ± 49.8

Table 7: *P* value distribution of the compared parameters

Groups	BMI	FPG	TCHL	LDLC	VLDLC	HDLC	TGL
A: B	0.002	0.2	0.2	0.5	0.2	0.5	0.09
B: C	0.1	0.5	0.5	0.5	0.007	0.4	0.04
A: C	0.00002	0.1	0.2	0.5	0.2	0.4	0.2
D: E	0.01	0.05	0.0003	0.0004	0.4	0.03	0.05
C: D	0.08	0.0001	0.006	0.005	0.002	0.01	0.3
C: E	0.03	0.05	0.01	0.01	0.006	0.3	0.004
B: D	0.03	0.03	0.01	0.007	0.09	0.02	0.5
B: E	0.2	0.2	0.01	0.02	0.1	0.03	0.02
A: D	0.001	0.0005	0.003	0.007	0.1	0.03	0.1
A: E	0.06	0.009	0.1	0.03	0.1	0.3	0.02

of 10 years, female predominance of not only T2DM but also the other varieties is significant.[10] Both T2DM and FCPD could not be identified below the age of 10 years;[10,17] T1DM had the highest prevalence in the second decade, while the others were more prevalent in the third decade[11] [Table 4]. Complications were predominantly microvascular (43%) and were uncommon below the age of 10 years.[7] They expressed a surge after the age of 12 years (around puberty).[6,21] Retinopathy was associated more with males and was not seen in FCPD[17] and, unlike other reports, the prevalence was not significantly higher than the other microvascular complications. It had a prevalence similar to that of nephropathy (~21%). Nephropathy and neuropathy were more commonly associated (83% of neuropathy had nephropathy, while only 33% had retinopathy, $P<0.05$) and both exhibited a female preponderance and were similar in distribution among the three main groups. Neuropathy was present in 13.4% and joint symptoms in 6%; this is similar to international data, though slightly on the lower side.[7,16,22] Probably our population is prone to develop nephropathy early.[23,22]

Patients responding only to insulin and having no pancreatic calcification were classified as T1DM, those with calcification were considered as FCPD, and the rest were T2DM. T2DM cases were those that responded to oral drug therapy alone or required some insulin with the oral drugs (sensitizers) [Table 3]. Therapeutic titration can be used for probable type segregation but it is a long-drawn process, which requires meticulous patient follow-up and can only be used for a programmed research purpose.

In the clinic setup T1DM still predominates, as T2DM is commonly asymptomatic or presents with nonspecific symptoms to start with.[8,24] It was not infrequent for T2DM to present as abdominal pain (15%) or ketosis (23%), though infections were more common (70%)[10,14] [Table 5]**.** Our clinic prevalence of T2DM, as DM in the young, was around 20%. These patients, if identified, can be treated with oral drugs. No study has so far conclusively established the superiority of insulin therapy over oral drugs as initial therapy of T2DM.

The family history, BMI, FPG and lipid profile revealed striking differences among the three predominant varieties [Tables 6 and 7]. These can be simple markers of segregation in a situation where the markers of autoimmunity (T1DM), genetic markers (MODY, etc.), and C-peptide assays are not easily available. Patients with no family history of DM, low or near normal BMI, high presenting plasma glucose and TGL, and normal or slightly raised TCHL can be classified as T1DMs. Definite family history with normal to high BMI and high LDLC are T2DMs.[12] Negative family history, with low lipid parameters of all varieties and low BMI, with or without abdominal pain, indicates FCPD.

There is a significant and strong association between family history of DM and high BMI with T2DM. The strikingly high level of LDL, without any changes in the resting ECG, is a matter of concern as they are known to have early cardiovascular events.[25] This mandates counseling the older T2DM patients on the need for proper screening of their offspring (especially the females, who would additionally increase their risk of T2DM with future pregnancies)[10] for obesity, sedentary lifestyle, DM, and lipid abnormalities. The quick-fix method used for the diagnosis of diabetes in patients below 25 years needs to change. This study establishes that a significant number of diabetics below 25 years are also non-T1DMs, mainly being T2DM. Genetic and antibody studies to diagnose T2DM, MODY, or FCPD are not possible routinely in our resource-limited situation. T2DM in the young can be clinically diagnosed, based on BMI, features of insulin resistance, absence of recent weight loss, absence of ketonuria, presence of a strong family history and finally, drug response. If any confusion arises, treatment should be started with insulin, subsequently changing over to oral drugs, as we have done in our study.

Conclusion

The clinic prevalence of young DM is still small (4.08%). Female preponderance is significant beyond the age of 10 years.[10] Polyuria, polydypsia and polyphagia were

the predominant presenting features. Microvascular complications were significant (43%), with nephropathy and retinopathy predominating (~21%). Nephropathy and neuropathy appeared to have some association and had a female preponderance, while retinopathy was more common in males. Hypertension was the commonest macrovascular complication. The predominant varieties could be reasonably segregated, depending on therapeutic response along with ultrasonographic studies, but this was cumbersome. T1DM, being more commonly symptomatic, forms the bulk (68.7%) of the cases; T2DM more commonly presents with infections (70%). Prevalence of FCPD was 11.9% and abdominal pain was a common association. Such segregated patients expressed striking differences in their family history, BMI, lipid profiles and degree of incident hyperglycemia. These incident clinicobiochemical parameters can be of immense help in early variety segregation and in deciding on initial therapy. Young age diabetes is not necessarily T1DM, and therapy with oral drugs can be tried out after checking a few simple parameters.[10] Probably asymptomatic T2DM has been under-detected and FCPD slightly over-detected as this is primarily a clinic-based data. We might have also missed a few cases of uncommon genetic forms of DM (e.g., MODY, etc.).

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