GENDER DIFFERENCES IN CHILDHOOD DIABETES

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It is accepted wisdom that childhood diabetes is rare in India. Most published series quote a prevalence of less than five percent of all persons with diabetes [1]. Majority of the reports are based on hospital and clinic based data (Table 1).

Table 1
Gender differences in Young/childhood diabetes

Area	Diagnosis	Age group	Male : Female	Ref
Orissa, Cuttack	PDDM*	< 30 y	2.7 : 1	2
Orissa, Cuttack	FCPD**	< 30 y	3 : 1	2
Orissa, Cuttack	IDDM	< 30 y	2 : 1	3
New Delhi, AIIMS	IRD***	< 30 y	0.64 : 1	1
New Delhi, AIIMS	KP****	< 30 y	0.45 : 1	1
New Delhi, AIIMS	KR@	< 30 y	0.67 : 1	1
New Delhi, AIIMS	NIRD@@	< 30 y	0.69 : 1	1
New Delhi, AIMS	CCP@@@	< 30 y	0.6 : 1	1
Kerala, Cochin	IDDM	< 20 y	20 : 19	4
Kerala, Cochin	NIDDM	< 20 y	3 : 5	4
Kerala, Cochin	FCPD	< 20 y	2 : 9	4
T Nadu, Chennai	All groups	< 20 y	3 : 1	5
T Nadu, Chennai	FCPD	< 20 y	17 : 11	6
T Nadu, Chennai	NIDDY	< 30 y	188 : 126	7
T Nadu, Chennai	IDDM	< 30 y	73 : 46	7
T Nadu, Chennai	FPD	< 30 y	17 : 4	7
T Nadu, Chennai	PDPD	< 30 y	6 : 1	7
Andhra P, Vizag	IDD, MRDM	< 20 y	2 : 8	8
T Nadu, Kudremukh		< 25 y	0 : 0	9
Fiji		< 25 y	0 : 0	10
Tanzania		< 25 y	0 : 0	11
Africa	MRDM		M>F	12
Africa, Uganda	PDDM		16 : 6	13
Africa, Ethiopia		< 15 y	32 : 48	14
Malta		< 32 y	52 : 65	15
Africa, Sudan	IDDM	7-14 y	More in girls	16
United Kingdom	IDDM	< 14 y	26.8% more in males	17
United Kingdom	IDDM	< 30 y	65 : 45	18
Europe, Norway	IDDM	< 14 y	12% more in boys	19

*protein deficient diabetes mellitus
** fibro calculous pancreatic diabetes
*** insulin requiring diabetes
**** ketosis prone
@ ketosis resistant
@@ non insulin requiring diabetes
@@@ chronic calcific pancreatitis, with diabetes.

Not unexpectedly, a wide range of age groups, diagnostic criteria and differences in gender were reported. Diabetes was more prevalent in males, with few exceptions in New Delhi[1], Kerala[4], Andhra Pradesh [8], Ethiopia[14], Maltese islands [15] and Sudan[16].

Childhood diabetes from Visakhapatnam

Data from out Centre on children with diabetes starting at or below the age of 15 years is given in Table 2. The male female ratio continued to favor females (i.e. more females), consistent with our earlier data[8].

Table 2

Childhood diabetes: EDC, Visakhapatnam (1988-1996)

Characteristic	Boys (n = 24)	Girls (n = 34)	P*
Sex Ratio (M : F)	24	34	
Onset of diabetes (years)	9.62± 3.82	8.5± 3.99	NS
Duration of diabetes (years)	2.58± 3.45	3.38± 5.7	NS
Newly diagnosed DM	5(20.83%)	6(17.65%)	NS
Duration DM = < 6mo.	19(79.17%)	19(55.88%)	NS
Geographic origin			
Andhra Pradesh: rural	5(20.84%)	6(17.65%)	NS
Andhra Pradesh: urban	16(66.67%)	27(79.41%)	NS
Other states	3(12.5%)	1(2.94%)	NS
Height (cm)	125.85± 43.68 (n : 20)	122.3± 23.28 (n : 20)	NS
Weight (cm)	28.93± 13.85 (n : 23)	26.62± 12.43 (n : 32)	NS
Body mass index	15.5± 2 : 65 (n : 20)	15.12± 2 : 42 (n : 20)	NS

* NS : not significant.

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There was no statistically significant difference in the various parameters studied, although there was a trend towards a greater proportion of urban boys from rural areas, and boys from other states being brought for attention (Table 2). Similarly, there was a greater proportion of boys with duration of diabetes less than six months.

Community based prevalence studies in India

There are few community based prevalence studies of childhood diabetes in India, that employed well established criteria for diagnosis. Ramachandran et al estimated the prevalence of childhood diabetes in an urban population in south India (the city presently known as Chennai), the overall prevalence was 0.26/1000. Among 30 IDDM patients with onset of diabetes below 15 so identified, there were 13 boys and 17 girls[20].

The other major prevalence survey in the community was conducted all over India by P.V. Rao, under the supervision of M. M.S. Ahuja. The prevalence of diabetes mellitus in the age group 15-19 years was 0.34% in males (n=3) and 0.19% among both males and females (3 boys, no girls)[21].

Is childhood diabetes truly common in boys?

Most studies show that boys are more prone to develop diabetes mellitus compared to girls. The difference exists in both community based surveys as well as hospital based reports. Given the interaction of genetics, environment and the immune system in the pathogenesis of IDDM, the male preponderance has been well established [17], Exposure to possible environmental toxins, such as N-nitroso compounds has been implicated as a contribution factor.

However, a closer examination of children who presented below the age of five from United Kingdom shows that more girls than boys developed diabetes in this age group[18]. Perhaps a difference in the genetic susceptibility and environmental insult could explain the difference in gender difference in the very young.

Age at presentation: gender differences in relation to puberty.

An interesting sex difference in the age at presentation was shown by Ramachandran et al[22]. The peak age of diagnosis was 11 years in girls (n : 293), while boys 9n : 321) showed multiple peaks between 11 and 18 years. In urban patients the maximum occurrence of the disease was at 11 years in contrast to a delayed peak at 18 years in the rural group. This demonstrates that the peak was delayed in children from the rural areas and more markedly in those from the lower income group.
The peak occurrence of IDDM at puberty could partly result form high susceptibility at that time [23]. It is probably caused by decreased insulin sensitivity at that age, which also explains why girls develop diabetes early, as they undergo pubertal development earlier than boys [24].

Islet cell antibody (ICA) positivity, a surrogate of smouldering autoimmune pancreatic beta cell destruction was seen in girls at a younger age, suggesting that beta cell destruction is faster, and total destruction occurs earlier in girls [25]. On the other hand, ICA positivity in boys with longer duration of diabetes might be associated with slow progression of diabetes mellitus [26].

The precise reason for the difference is not known, although influence of sex hormones can one factor responsible for diabetes occurring in girls at a younger age [25]. Estrogens and progesterone, the principal sex hormones in girls which rapidly increase during puberty, are known to decrease during puberty, are known to decrease insulin levels, and decrease glucose tolerance [27]. However they do not appear to produce clinical glucose intolerance.

When autoimmune diseases are common in women, why isn't childhood diabetes so?

It is well recognised that autoimmune diseases are far more common in women that in men[28]. the logical cause for this difference would be the sex hormones. Women might respond more to conventional antigens, due to sex hormones[28]. The interaction of gonadal steroids and the immune system is another area for further study. Genetic control of autoantigen presentation to T lymphocytes by specialised cells might be affected by sex hormones [29,30].

The other reason why childhood diabetes is not uniformly more common in girls is, it is not all autoimmune. Contributions from genetic, environmental and immunological factors ensure that. Besides, a variety of clinical syndromes are seen in young diabetes, especially from India and other developing countries. Whereas childhood onset diabetes below 15 years of age is more often classical, Type 1 autoimmune mediated, youth onset, i.e. 16-30 years appears to be more heterogeneous [31].

Studies on residual beta cell function in young diabetics showed a spectrum of changes, from insulin requiring diabetics (n = 77) who were ketosis prone (40%) to ketosis resistant insulin requiring (60%) patients. Twenty three patients were non-insulin

requiring, they had calcification of the pancreas [32], and are included in the generic term of malnutrition related diabetes mellitus [33].

Clinicians are aware of unusual variants, including those simulating non-insulin depended diabetes mellitus [34]. A variety of types including insulin debates mellitus, non insulin depended diabetes of young, maturity onset diabetes of young [34a] are all described, which could account fo0r the skewed gender prevalence of childhood diabetes.

Why does diabetes favor boys?

Given that IDDM is autoimmune medicated, why is it that girls are relatively spared, at least when compared to other autoimmune disease such as rheumatoid artiritis? Delayed diagnosis, missed diagnoses, not being brought to medical attntion, all as part of social deprivation [35] are obvious reasons. But could there be something else? Some of the other reasons, particularly in out country can be speculated upon.

The pathogenesis of IDDM can be summarized as follows: (a) IDDM is a polygenic disorder, in which genetic susceptibility is conferred by an unfavorable combination of common alleles of normal genes (b) each gene involved in IDDM susceptibility quantitatively controls a part of the pathogenetic process which is initiate by (c) release of islet beta cell antigen, process and presented by mononuclear cells to T lymphocytes. There is a self-perpetuating and self limiting circuit of cytokine production of which IL-1 is islet beta cell cytotoxic an effect potentiated by tumour necrosis factor alfa [36]

In other words, there is a role for environmental agents to initiate the autommune process. Efforts are on to identify the environmental agent. Putative mediators include dietary toxin [17,33], consumption of caffeine by the mother during pregnancy [37], nutrients and food additives [38].

Recently interest has been focussed on the role of breast-feeding in preventing IDDM. A Swedish study has shown that breast-feeding could decrease the risk of IDDM in certain subgroups [39]. The reasons seems to be early exposure to foreign proteins, such as cow's milk, which can trigger the autoimmune process of IDDM [40]. Another reason for high risk in non-breast-fed infants could be that breast-fed infants less weight compared with non-breast-fed children, which may protect against Type-1 diabetes later on [41].
The protective effect of breast-feeding seems to be lost in Indian children differently, depending on the gender of the child. Recent studies have shown that girls are breast-fed for a shorter length of time that girls are breast-fed for a shorter length of time [42-43]. The differential was shown to occur across socio-economic disparity, where breast-feeding continued for a longer period among land-owners than among landless laborers [44].

Nutritional status of the female child is poor compared to male[42]. Besides, boys are more likely to be given nutritionally rich food such as milk[43]. Lastly, boys were attended by the doctor on the very first day of illness,. compared to girls. A combination of all these environmental factors on genetic susceptibility, along with increased mortality of Indian girls in the first five years of life[44] make more diabetic boys present for attention.

A recent study from Bangladesh also showed that the duration of breast feeding was decreasing in younger mothers, compared to older women [45].

Associations by themselves do not imply causality; risk factor stratification has shown that increased risk of childhood IDDM in Northern Ireland and Scotland was seen with delivery by cesarean section[46].

Diabetes begins in the womb: Barker's hypothesis

Following a series of painstaking and elegant epidemiological studies, Barker and Hales proposed that diabetes mellitus in later life., had its genesis from a combination of undernutrition early in life and overnutrition later on[47].

Peak pancreatic beta cell mass may be determined early in life, even during gestation and the factors that influence it are important in the development of diabetes [48]. Infants with poor intrauterine nutrition were shown to have fewer beta cells, a finding in line with Barkers' hypothesis which was put forth later. Overnutrition or obesity in later life leads to insulin resistance, and the functional beta cell mass, programmed in leaner times, may then be unable to meet the rising demand for insulin [48].
Give that etiology of IDDM is multifaceted, early undernutrition can contribute to its pathogenesis, although not as significantly as in adult onset or Type 2 diabetes (NIDDM).

It seems possible therefore that susceptibility to Type 1 diabetes could be determined during gestation or fandancy in response to nutrition. the out come in Type 1 diabetes can be logically influenced by the peak beta cell mass, which in turn could depend on early maternal nutrition[48].

A combination of poor antenatal nutrition, commonly seen in women in developing countries combined with relative post natal overfeeding of boys… could be the right mix for Barker's hypothesis to take effect in these boys.

In collaboration with Barker, C.S. Yajnik from Pune, has been undertaking an ambitious project in which women of childbearing age from the community are screened periodically, through to the time of their delivery and later. The ongoing project should generate invaluable data that throws light on early life nutrition as a cause of insulin resistance and insulin deficiency.

An earlier study on infant study on infant aged 3.5 to 4.5 years was carried out to see whether there was a difference in metabolic profile depending on birth weight[49]. At the age of four, girls had smaller head circumference and greater skinfold thickness than boys. Plasma glucose was not different between boys and girls, but plasma insulin concentration in girls were consistently higher implying insulin resistance. pooling the data, the highest 30 minute plasma glucose concentration were in children who were light at birth and heavy at four years[49].

Considering that IDDM consists of insulinopenia, with insulin resistance partly contributing, fetal undernutrition could be partly responsible for diabetes. Correction of maternal undernutrition in pregnancy, and appropriate nutrition for both boys and girls are necessary goals.

Adolescence and changes in fuel metabolism

There is a difference in the microvascular diabetic complication rate and mortality, depending on whether IDDM develops before puberty or not. Studies from the Children's Hospital of Pittsburgh Insulin-Dependent diabetes Mellitus Registry has shown that postpubertal duration of IDDM may be a more accurate determinant of the development of microvascular complications and diabetes-related mortality than total duration [50].

By implication, girls, due to their earlier puberty would be expected to be exposed to a longer duration of diabetic complication risk, and could have greater microvascular complications. The same group has shown that girls have a more prominent association of glyucaemic control with albumin excretion rate, systolic blood pressure, presence of microaneurysms, serum triglyceride and serum cholesterol concentration during the first five years of IDDM[51].

Similarly, elevation of lipoprotein (a) have been shown to occur during puberty in IDDM children[52].

Differences were also found in the metabolism of triglycerid-rich subfractions in IDDM males and females [53]. the composition of subfractions 100 to 400 and 20 to 100 lipoproteins was abnormal in IDDM by higher total cholesterol/triglycerid, total cholesterol/protein, and triglyceride/protein, and triglyceride/phospholipid ratios both fasting and postprandially. A similar enrichment in total cholesterol was observed in diabetic versus normal women following fat ingestion in subfractions greater than 400 only[53].

Late teenage period is associated with improved insulin sensitivity, caused partly by changes in growth hormone [54].

Gender differences in access to diabetes management

Given that diabetes mellitus is the most complex of all common metabolic disorders to manages [55], in terms of physical discomfort, mental strain and economic factors, it is not surprising there could be differences in the way boys and girls have access to modern management.

Among 614 IDDM patients with onset of diabetes at or before 20 years of age registered at the Diabetes Research Center, 234 belonged to the high income group (family income Rs.> 2000/- per month) and 380 belonged to the low income group (monthly family income Rs.< 2000/-). Interestingly, the proportion of females in the high income group was more (115/119;0.967), compared to the low income group (178/202; 0.88). Whether the differences is due to difference in prevalence or due to difference in access to medical care between sexes cannot be ascertained; the latter possibility however is likely [43].

Psychosocial aspects – gender differences

Diabetes being so complex to manage, compliance to treatment can be expected to be difficult. In a study performed at all India Institute of Medical Sciences, New Delhi, more males than females were likely to be irregular in their contact and follow-up with diabetes education programme [56]. Childhood and early adolescence is the period of intense change and necessity to cope up, even without the additional burden of managing diabetes mellitus. Given that manifest needs differ in the genders[57], it is likely that diabetes and its treatment could adversely affect meeting these needs in the adolescent period.

Gender differences in parenting of IDDM

IDDM affects not only the child but the immediate family as well. Management depends on adult intervention, especially in the pre-school and early school going age group[58]. Often, the mother carries a disproportionate share of the burden of diabetes care[59]. When father do not participate in the initial period of diabetes management, they feel out of touch with the complexities of its management. Therefore care should be taken to distribute the responsibility between the two parents.

Gender differences in IDDM parents as transmitters of their disease

IDDM being partly genetic, the risk of transmission to further generations is real. Studies have shown that there could be gender differences in the risk of transmission between the mother with IDDM and father with IDDM. Warram et al suggested that offspring of Type 1 diabetic father were at higher risk for developing autoimmune diabetes than offspring of Type 1 diabetic mothers[60]. this difference appeared to be confined to fathers with a DR4 allele, and was not due to selective loss of diabetes susceptible fetuses in the perinatal period[61].

In conclusion, a variety of differences were reported, both in the presence and absence of gender differences between boys and girls with diabetes. Such information gives insights into possible differences in pathogenesis, intervention strategies, as well as ways to overcome obstacles in delivering health care between the sexes.

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