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Excess Maternal Transmission of Type 2 Diabetes Mellitus in South India: Indication from Sibling Recurrence Risk Ratio Analysis

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ABSTRACT

Sibling recurrence risk ratio (λ_S), defined as the ratio of risk of disease manifestation in siblings of probands compared with risk of disease in general population, is an extensively used measure of familial aggregation. A λ_S>1 is suggestive of familial aggregation. To assess the extent of familial clustering according to parental history of type 2 diabetes mellitus, the sibling recurrence risks (K_S) and the sibling recurrence risk ratios (λ_S) were estimated in a randomly selected sample of 275 subjects with type 2 diabetes mellitus. A total of 325 out of 1125 siblings were affected giving an overall K_S of 28.90% (95%CI: 26.21%-31.51%) and a λ_S of 2.31x (95%CI: 2.09x-2.50x) which is suggestive of a complex aetiology involving both genetic factors and environmental triggers. The K_S and the λ_S values were elevated in families with one or two diabetic parents indicating that susceptibility to type 2 diabetes mellitus is transmitted primarily through an affected parent. The risk varied with respect to the status of the probands' parents with K_S (49.21%; 95%CI: 43.04%-55.38%) and λ_S (3.94x; 95%CI: 3.41x-4.43x) when both parents were affected being the highest reflecting a predominant influence of the predisposing genetic factors. The λ_S was found to be significantly higher (Z = 2.05; p = 0.04) when the affected parent was the mother (2.59x; 95%CI: 2.20x-3.06x) rather than the father (1.81x; 95%CI: 1.31x-2.31x) indicative of an excess of maternal transmission of type 2 diabetes mellitus. This is the first study on sibling recurrence risk ratio estimates for type 2 diabetes mellitus from India.

Key words: Type 2 diabetes mellitus, familial aggregation, sibling recurrence risk ratio, maternal transmission, South India

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM), characterized by a persistent elevation in plasma glucose levels, is rapidly increasing at alarming proportions across the world and has become one of the foremost epidemics in today's world. The World Health Organization (WHO) estimates that the global prevalence of T2DM would reach 5.4% by the year 2025 which translates into nearly 300 million affected individuals (King *et al*., 1998). According to the estimates presented by WHO, a substantial measure of the increase in prevalence of T2DM would occur in the developing countries and by the year 2025, India, China and the United States would harbour the maximum numbers of diabetics in the world. Additionally, in line with these estimates, the International Diabetes

Federation evaluated that about 19% of the world's diabetic population, i.e., nearly 49 million diabetic individuals were in India as of 2006 and by 2025 this figure would rise to 70 million (Sicree *et al.*, 2006). Consequently, experts in the field were led to label India as the "Diabetes Capital of the World" (Mohan *et al.*, 2007).

The massive and rapid increase in the prevalence of T2DM, principally, in the case of India, is considered to be an offshoot of the dietary and lifestyle modifications accompanying the contemporary fast-paced, urbanised societal influences (Ramachandran *et al.*, 2002). However, the crucial role played by genetic predisposition in the causation of T2DM just cannot be dismissed. The presence of familial aggregation in T2DM has been documented in several previous studies. The Framingham offspring study showed that if either parent was affected, the Odds Ratio (OR) of the offspring being affected was 3.4-3.5 and if both parents were affected the OR was 6.1 (Meigs *et al.*, 2000). Studies by Arfa *et al.* (2007) and Benrahma *et al.* (2011) have revealed familial aggregation as well as maternal transmission of type 2 diabetes in African populations. Likewise, increased frequency of diabetes among relatives of diabetics has been reported in numerous epidemiological studies conducted in Asian populations (Sheu *et al.*, 1999; De Silva *et al.*, 2002; Kim *et al.*, 2004). Systematic analyses conducted in Indian population have demonstrated familial clustering in these study populations as well (Ramachandran *et al.*, 1988; Viswanathan *et al.*, 1996; Ramachandran and Snehalatha, 1999; Deo *et al.*, 2006).

While the presence of familial clustering in T2DM has been reported in various populations, the extent of genetic contribution towards familial aggregation of the disease has not been quantified in most of them. The magnitude of genetic contribution to a disease is measured by employing the familial recurrence risk ratios, of which the sibling recurrence risk ratio (λ_S) is the most extensively used parameter. Defined as the ratio of the risk of disease manifestation in siblings of index cases compared with the disease risk in the general population, λ_S was first used by Pincus and White in the early 1930s, for estimating familial aggregation of T2DM (Pincus and White, 1934). Subsequently, some researchers have used similar approaches for analysing T2DM families, especially among the Caucasian populations (Meigs *et al.*, 2000; Weijnen *et al.*, 2002). So far, however, risk estimates for siblings of those affected with T2DM akin to those reported among Caucasians are lacking among the Indian diabetic population. In view of that, the sibling recurrence risk ratios for T2DM according to parent affected were analyzed in this study.

MATERIALS AND METHODS

Ascertainment of study population: A total of 275 unrelated, randomly selected T2DM patients visiting the endocrinology unit of Deccan Hospital were recruited for this study. All the subjects were diagnosed as type 2 diabetic according to criteria laid by the WHO. Subjects with type 1 diabetes, ketoacidosis at diagnosis and subjects with an age at onset of less than 35 years were excluded from the study. Presence of diabetes was documented by testing for Fasting Blood Sugar (FBS) $\geq$126 mg dL^{-1} and Post Lunch Blood Sugar (PLBS) $\geq$200 mg dL^{-1}.

Collection of data: Demographic information including age, gender, age at onset of T2DM, duration of diabetes, height, weight and pedigree data extending up to two generations was obtained through a specified questionnaire from all the index cases. Biochemical measurements including FBS, PLBS, fasting lipid profiles were obtained from the hospital case records and all these details were recorded in a specified proforma. The study protocol was approved by the ethical committees of the participating institutions and written informed consent was obtained from all the participants of the study.

Calculation of sibling recurrence risk ratio: The population approach of calculating λ_S was used in this study. The population prevalence of type 2 diabetes at the time of sample collection was used as measure of population risk (K). The sibling recurrence risk (K_S) is the proportion of siblings of the index cases who are affected. This was estimated from the formula given below:

$$K_s = \frac{\sum_{s=1}^{\infty}\sum_{a=1}^{s}(a-1)n}{\sum_{s=1}^{\infty}\sum_{a=1}^{s}(s-1)n}$$

where, 'n' is the number of families, 's' is the total number of offspring, 'a' is the number of affected offspring (Olson and Cordell, 2000). Only those siblings of the index cases who were aged 35 years or older were considered while calculating the sibling recurrence risk. The sibling recurrence risk ratio λ_S was estimated according to the formula $\lambda_S = K_S/K$.

Statistical analysis: Statistical analyses were performed using SPSS system (version 11.5). All the quantitative and continuous variables were expressed as mean ($\bar{X}$) along with Standard Error of Mean (SEM) and 95% Confidence Interval (95%CI) of mean. Comparison of quantitative variables between the various groups was done using Student's t-test or One way Analysis of Variance (One way ANOVA) and comparison of frequencies between the groups was done using Z-test. A two tailed p-value less than 0.05 was considered as statistically significant.

RESULTS

Of the 275 subjects with T2DM included in this study, nearly 77% (211/275) reported positive family history of T2DM. The mean age at onset in the total T2DM subjects was 46.0±0.6 years (Table 1) and a significant difference (p = 0.0002) with respect to mean age at onset was observed between familial and non familial subjects (44.8±0.6 years and 49.9±1.1 years, respectively). The difference with respect to the mean age at onset remained significant even after stratification of cases with respect to gender as illustrated in Table 2.

Table 1: Age at onset of T2DM with respect to familial incidence

Category	N	Mean±SEM	95% CI
Total T2DM	275	46.0±0.6	44.8-47.2
Familial	211	44.8±0.6	43.5-46.2
Non familial	64	49.9±1.1	47.6-52.2

Familial vs. non familial t-value: 3.75, p = 0.0002

Table 2: Age at onset of T2DM with respect to family history and sex

	Familial			Non familial			Total		
Category	N	Mean±SEM	95% CI	N	Mean±SEM	95% CI	N	Mean±SEM	95% CI
Males	162	44.3±0.7	42.8-45.8	40	49.2±1.5	46.1-52.3	202	45.3±0.6	43.9-46.6
Females	49	46.1±1.5	43.2-49.4	24	51.1±1.6	47.4-54.8	73	47.8±1.2	45.3-50.2
Total	211	44.8±0.6	43.5-46.2	64	49.9±1.1	47.6-52.2	275	46.0±0.6	44.8-47.2

Familial male vs. non familial male t-value: 2.94, p = 0.0047, Familial female vs. non familial female t-value: 2.23, p = 0.03

Table 3: Characteristics of index cases of T2DM according to familial incidence

	Familial T2DM cases (N = 211)		Non familial T2DM cases (N = 64)		
Parameters	Values	95% CI	Values	95% CI	p-value
BMI (kg m^{-2})	27.2±0.4	26.4-27.9	26.8±0.7	25.3-28.3	0.66
FBS (mg dL^{-1})	146.2±6.7	132.8-159.5	137.5±12.0	112.6-162.5	0.53
PLBS (mg dL^{-1})	213.3±12.2	188.7-237.9	215.7±22.8	167.6-263.8	0.92
TC (mg dL^{-1})	165.3±6.3	152.6-178.0	165.5±13.1	137.0-194.0	0.98
HDL (mg dL^{-1})	35.9±1.3	33.4-38.5	40.9±2.4	35.7-46.1	0.08
LDL (mg dL^{-1})	95.9±4.9	85.8-105.9	89.1±13.7	58.9-119.3	0.65
TG (mg dL^{-1})	184.0±19.6	144.7-223.4	204.2 ±33.3	130.9-277.4	0.61
SBP (mmHg)	133.9±2.4	129.0-138.8	133.7±3.6	126.3-141.1	0.25
DBP (mmHg)	81.2±1.2	78.8-83.5	83.5±1.2	80.9-86.1	0.19

Values are Mean±SEM, BMI: Body mass index; FBS: Fasting blood sngar; PLBS: Post lunch blood sngar; TC: Total cholesterol; HDL: High density lipoprotein cholesterol; LDL: Low density lipoprotein cholesterol; TG: Triglycerides; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Table 4: Characteristics of index cases of T2DM according to parent affected

	Affected parent				
Characteristics	Neither (N = 125)	Father (N = 43)	Mother (N = 60)	Both (N = 47)	p-value
Male					
No.	91	30	48	31	
Percentage	72.7	70.0	79.1	65.5	
AAO (years)	47.7±0.9	44.7±1.7	44.5±1.3	44.6±1.2	0.07
DOD (years)	9.8±0.6	9.2±1.3	12.2±1.3	10.4±1.2	0.19
AAS (years)	57.1±0.8	56.1±1.3	56.1±1.3	54.5±1.4	0.32
Obese					
No.	83	29	46	30	
Percentage	66.2	66.7	76.2	64.3	
No. of siblings	3.5±0.2	3.7±0.3	4.1±0.3	4.5±0.4	0.17
BMI (kg m^{-2})	27.1±0.5	28.3±1.1	26.5±0.6	26.9±0.9	0.48
FBS (mg dL^{-1})	135.5±7.8	136.3±13.5	134.8±7.7	161.9±14.4	0.31
PLBS (mg dL^{-1})	201.7±14.0	247.7±41.1	172.6±19.5	201.0±26.5	0.26
TC (mg dL^{-1})	161.4±7.8	160.7±15.1	167.8±10.4	155.7±8.1	0.90
HDL (mg dL^{-1})	40.6±1.7	37.0±2.7	36.1±1.9	33.6±1.8	0.07
LDL (mg dL^{-1})	96.7±8.5	97.2±10.9	95.6±8.3	90.9±8.3	0.98
TG (mg dL^{-1})	218.2±32.4	169.7±30.5	162.7±20.5	157.0±20.6	0.43
SBP (mmHg)	132.2±2.4	135.0±6.2	135.8±4.4	135.8±7.9	0.87
DBP (mmHg)	82.0±0.9	79.4±2.4	82.2±2.3	83.0±4.5	0.75

Values are Mean± SEM, AAO: Age at onset of diabetes; DOD: Duration of diabetes; AAS: Age at sampling

An analysis of epidemiological and biochemical parameters between familial and non familial cases is presented in Table 3. A quick perusal of the table reveals that the mean levels of FBS (146.2±6.7 and 137.5±12.0 mg dL^{-1}, respectively), HDL (35.9±1.3 and 40.9±2.4 mg dL^{-1}, respectively) and LDL (95.9±4.9 and 89.1±13.7 mg dL^{-1}, respectively) are higher in the familial T2DM subjects in comparison with the non-familial T2DM subjects. However, no statistical significance in this difference was observed with respect to mean levels of FBS and LDL and a marginal significance ($p = 0.08$) was observed in the case of mean HDL levels. Table 4 presents the epidemiological characteristics or clinical profile of the index cases when they were categorized

Table 5: Sibling risk ratios (λ_S) for T2DM according to parent affected

	Affected cases				
Statistics	Neither (N = 125)	Father (N = 43)	Mother (N = 60)	Both (N = 47)	Total (N = 275)
Total No. of siblings	460	172	241	252	1125
No. of affected siblings	84	39	78	124	325
K_S (95%CI)	18.26 (14.73-21.79)	22.67 (16.41-28.93)	32.37 (26.46-38.28)	49.21 (43.04-55.38)	28.90 (26.21-31.51)
λ_S (95%CI)	1.46x (1.17x-1.74x)	1.81x (1.31x-2.31x)	2.59x (2.20x-3.06x)	3.94x (3.41x-4.43x)	2.31x (2.09x-2.50x)

according to the parent affected. The mean AAO was observed to be the highest (47.7±0.9 years) in index cases with neither parent affected in comparison with index cases with either or both of their parents affected. The difference, however, was only marginally significant ($p = 0.07$). While not statistically significant, the mean levels of FBS were observed to be the highest in the index cases with both parents affected (161.9±14.4 mg dL^{-1}) and the mean HDL levels were observed to be the least (33.6±1.8) in this category of patients.

The sibling recurrence risk ratio estimates are presented in Table 5. A total of 325 siblings out of 1125 siblings were affected giving an overall K_S of 28.90% (95%CI: 26.21%-31.51%) and a λ_S of 2.31x (95%CI: 2.09x-2.50x). The risk varied with respect to the status of the proband's parents and a perusal of Table 5 reveals that the sibling recurrence risk K_S (49.21%; 95%CI: 43.04%-55.38%) and the λ_S (3.94x; 95%CI: 3.41x-4.43x) when both parents were affected was the highest. The λ_S was found to be significantly higher ($Z = 2.05$; $p = 0.04$) (calculation not shown in table) when the affected parent was the mother (2.59x; 95%CI: 2.20x-3.06x) rather than the father (1.81x; 95%CI: 1.31x-2.31x).

DISCUSSION

Familial aggregation of a disease refers to the occurrence of the disease more frequently in the relatives of an affected individual than in the general population which cannot be readily accounted for by chance. It serves as an evidence of the contribution of genetic factors in disease predisposition because it is thought that there is an increased number of shared genes between family members of a proband, including those genes that are involved in disease predisposition. However, familial aggregation of a trait is a necessary but not sufficient condition to infer the importance of genetic susceptibility as shared family environment also could lead to occurrence of a disease among families of affected individuals (Khoury *et al*., 1988).

A widely used measure of familial aggregation is the sibling recurrence risk ratio, also referred to as λ_S which is defined as the ratio of the risk of disease manifestation in siblings of index cases compared with the disease risk in the general population. This ratio is usually used in genetic epidemiology to determine the power to detect genetic influences (Burton *et al*., 2005). A ratio above unity suggests familial aggregation. A λ_S value >2 is suggestive of a substantial genetic component as opposed to the environmental factors in the predisposition of the disease (Weijnen *et al*., 2002).

Apart from the estimation of λ_S, the study involved the examination of the age at onset of T2DM with respect to familial incidence and status of parent of index cases. A significant difference in the age at onset between familial and non familial cases was observed even when stratified by gender indicating that the familial cases developed the disease at a relatively lower age. This finding of the study is in keeping with previous literature on predictors of age at onset of diabetes wherein it has been demonstrated that familial influences may advance the age at onset of T2DM (Bo *et al*., 2000; Lee *et al*., 2001; Molyneaux *et al*., 2004). However, a similar difference was not obtained when the

index cases were stratified according to parent affected. It can be surmised that the category of neither parent affected is also a familial subgroup as the siblings or a second degree relative are affected in most families and this might explain the result.

The overall λ_S of 2.31x obtained by us is suggestive of a complex aetiology involving both genetic factors and environmental triggers. The λ_S was observed to be the highest when both parents were affected reflecting a predominant influence of the predisposing genetic factors. The risk varied with respect to the status of the parents of the proband and the recurrence risk ratios were elevated in families with one or two diabetic parents. These data are consistent with the results of earlier studies involving analysis of sibling recurrence risk ratios among Caucasian populations indicating that susceptibility to T2DM is transmitted primarily through an affected parent (Meigs *et al.*, 2000; Weijnen *et al.*, 2002).

How does one explain the modest risk when neither parent is affected? It might be easy to consider this risk to be an offshoot of shared family environment. Instead, the answer lies in the polygenic threshold theory of diseases that has been put forth to explain the occurrence of complex dichotomous traits such as T2DM (Falconer, 1981). It is assumed that for disease manifestation, there is a certain threshold, determined in a large measure, by a collection of susceptibility genes. This genetically determined risk is called liability. If an individual's liability (in other words, the required susceptibility gene complement) exceeds the threshold, then he/she will be affected. We infer that each of the parents in the neither parent affected subgroup had a liability lower than the threshold. However, the cumulative effect of the susceptibility gene complements transferred from both parents resulted in some of their offspring whose liability exceeded the threshold. In this context, we submit that those individuals who have no parent affected should also be cautious and aware of future risk of T2DM as they too have an underlying latent genetic susceptibility, though in a lesser measure when compared with those with stronger family history of the disease.

Of particular interest in this study is the significantly higher sibling risk ratio when the affected parent was the mother than the father. Hitherto, maternal excess in transmission of T2DM has been documented in Caucasian, African and Asian populations (Karter *et al.*, 1999; Sheu *et al.*, 1999; De Silva *et al.*, 2002; Arfa *et al.*, 2007; Benrahma *et al.*, 2011). Studies conducted in south Indian population have, however, not observed this phenomenon (Viswanathan *et al.*, 1996).

A possible explanation for the observed maternal excess could be the *additional* influence of mitochondrial genes in disease susceptibility. In an earlier study from the subcontinent it has been reported that nearly 10% of the total cases studied (or nearly 42.5% of cases where maternal parent was affected) showed maternal mode of inheritance and it had been proposed by the authors that mutations in mitochondrial DNA (mtDNA) could account for this phenomenon Khan *et al.* (2004). With mutations in mitochondrial genes having been reported to be associated with maternally inherited diabetes (Tawata *et al.*, 1998, 2000), it would be interesting and informative to study the association of mtDNA mutations with susceptibility to T2DM in this subgroup of patients.

CONCLUSION

Besides the reaffirmation of the existence of familial aggregation of T2DM, the study demonstrated the presence of excess maternal transmission of the disease in the study population. Analysis of sibling recurrence risk ratios while indicating the complex aetiology of T2DM, reflected a predominant influence of parental transmission of susceptibility to T2DM.

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