Frequency of major affective disorders in first-degree relatives of patients with type 2 diabetes mellitus

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Background & objectives: A genetic link between diabetes and depression has been proposed, but hardly explored. Data on family studies exploring relation between depression and diabetes are scanty. This study attempted to assess the prevalence of major affective disorders in first-degree relatives of patients with type 2 diabetes mellitus (T2 DM).

Methods: Fifty probands with T2 DM, in whom other psychiatric disorders had been excluded, were chosen. Morbid risks and prevalence figures for depression and mania were estimated in 481 first-degree relatives of these 50 probands using the family interview for genetic studies.

Results: Of the 481 first-degree relatives of probands, only six had affective disorders. The morbid risk for depression in first-degree relatives was 2.99 and 3.87 per cent, assuming age of risk at 15-60 and 15-50 yr respectively, while the morbid risk for mania was 0.59 and 0.77 per cent in these age groups.

Interpretation & conclusion: The morbid risks/prevalence rates among first-degree relatives of probands with T2 DM were not higher than those of the general population rates derived from earlier Indian and western studies. This study did not demonstrate a family aggregation of affective disorders in patients with T2 DM. Increased prevalence of affective disorders in diabetes could be due to non-genetic factors.

Key words Affective disorders - first-degree relatives - type-2 diabetes mellitus

An increased prevalence of affective disorders, especially depression, has been noted in diabetes mellitus. Meta-analyses of controlled data have yielded current prevalence rates of around 11 per cent, and lifetime prevalence rates of 28.5 per cent, for depression in diabetes, and a prevalence of
0.19 per cent for mania among diabetics; rates that are significantly higher than those found among controls\(^1\). Indian studies, though uncontrolled, have also reported prevalence rates between 22-29 per cent for depression in diabetes\(^2,3\).

In absence of a single comprehensive explanation various aetiological theories, ranging from psychosocial to biological, have been proposed to account for the increased prevalence of depression in diabetes. Several lines of evidence suggest that both depression and diabetes may share a common neurohormonal basis. Neuroendocrine abnormalities commonly found in depression such as increased plasma cortisol, abnormal dexamethasone suppression responses, or elevated growth hormone, have also been reported in depressed and non-depressed diabetic patients. This had led to the speculation that disturbances in the hypothalamo-pituitary-adrenal axis could lead to mood changes in patients with diabetes. Additionally, abnormalities of norepinephrine and serotonin, so characteristic of depression, have also been documented in animal models of diabetes\(^4\). Thus, there are several areas of commonality in neurohormonal disturbances, between depression and diabetes\(^5\). Further evidence from research on depression points to a genetic basis for these neurohormonal abnormalities, suggesting that some of the common neurohormonal disturbance between the two disorders could have a genetic basis. Genetic links between depression and diabetes have therefore been proposed\(^6\), but have hardly been explored.

The first step in establishing a genetic link between any two disorders is generally a family study, which aims to determine the degree of aggregation of the disorder in the first-degree relatives of persons with the disorder (probands), using the morbid risk statistics. Evidence of familial aggregation implies that the causes could be shared genes or shared environment.

Family aggregation studies usually rely on the ‘family study method’ that uses face-to-face interviews with relatives to determine the presence or absence of psychiatric illness in them. Alternatively, the ‘family history method’ in which probands and relatives are interviewed to determine which of the other relatives are affected, is used. Both methods have their advantages and disadvantages, and studies generally show modest overall agreement between the two methods. The family history method is especially useful when all eligible relatives are not available for direct interviews, or do not agree to be interviewed\(^7\).

There are very few family studies exploring the relation between depression and diabetes, and results are conflicting. Lustman et al\(^6\) have reported an increased prevalence of depression in non-diabetic first-degree relatives of patients with type 1 diabetes mellitus, while Popkin et al\(^8\) found that the first-degree relatives of patients of type 1 diabetes mellitus had only slightly, but not significantly, higher rates of depression than the general population.

The present study was thus carried out to assess the prevalence of depression and mania in first-degree relatives of patients with type 2 diabetes mellitus (T 2 DM).

**Material & Methods**

**Sample:** The study was conducted in the years 2000-2001. The population for this study included patients and their attendants attending the diabetes outpatient clinic, Department of Endocrinology, Nehru Hospital, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh. Consecutive patients who met selection criteria and their
attendants were inducted. The sample consisted of a group of 50 patients of T 2 DM, and 481 first-degree relatives of these patients.

Selection criteria:

Patients (probands) - Patients of either sex, aged ≥18 yr, with a diagnosis of T 2 DM according to American Diabetes Association criteria⁹, and accompanied by relatives, were chosen for the study. Patients with any co-morbid chronic physical illness (as per medical records), or lifetime history of psychiatric disorder (as per structured interviews), were excluded.

Key informants - Healthy close relatives of these patients, spouses or first-degree relatives aged 18 yr or above were included as key informants.

First-degree relatives - For this study, the first-degree relative of probands referred to parents, siblings or children who were biologically related to the patient.

Assessments: Sociodemographic details and clinical information regarding diabetes were recorded on structured proformas. Probands were screened for psychiatric disorders using the Schedule for Affective Disorders and Schizophrenia - Lifetime Version (SADS-L)¹⁰ to rule out the presence of depression or other psychiatric disorders in them, which could have affected the results. This study used the family history method to determine the presence/absence of depression or mania in first-degree relatives of probands with diabetes. The instrument used was the family interview for genetic studies (FIGS)¹¹. As a part of the FIGS a pedigree chart was prepared initially for each proband, followed by general screening questions to detect psychiatric pathology in pedigree members, and finally the application of symptom-checklists to determine the presence/absence of psychiatric illness in them. The FIGS has symptom-checklists for a number of psychiatric conditions including depression and mania.

Procedure: The plan of the study was approved by the research and ethics committees of the Institute. Patients (and key informants) attending the diabetes clinic and fulfilling selection criteria were approached. The purpose of the study was individually explained and written informed consent was taken. Sociodemographic and clinical details were obtained from patients and their medical records. The SADS-L was used to screen for psychiatric disorders in the index patients. The FIGS was then administered to assess the prevalence of depression and mania in first-degree relatives of probands. To increase the reliability of this process information was also obtained from a key informant (spouse/relative) in addition to the proband. All assessments were non-blind and were completed over one or two sessions.

Results

Sociodemographic profile: Sociodemographic profiles of probands with diabetes, key informants and first-degree relatives are depicted in Table I. The mean age of probands was 47.28 ± 8.23 yr and 44 per cent were males.

Clinical profile of patients with diabetes (probands): The mean age of detection of diabetes was 41.2 ± 8.19 yr, the mean duration of illness being 6.01 ± 4.72 yr. The treatment of diabetes was predominantly with oral hypoglycaemic drugs (72%). The mean blood sugar levels at the time of assessment were 158.72 g per cent (SD= 61.55).

Affected first-degree relatives of diabetic probands:

First degree relatives with depression or mania - Of the 481 first-degree relatives, only 6 (1.25%) (3 males, 3 females with mean age 56.50 ± 22.0 yr) had a diagnosis of affective disorder based on the FIGS, 5 with a diagnosis of depression (1.04%) and 1 with mania (0.21%). Four of these first-degree relatives had had a single episode of depression (without psychotic symptoms), one had a diagnosis
of recurrent depression, and one was diagnosed to have recurrent mania (with psychotic episodes). All 4 cases of depression were of major depression that roughly corresponds to the older category of endogenous depression. Age of onset varied from 22-58 yr, the longest duration of an episode was 14 wk (range 3-14 wk).

Demographic and clinical characteristics - All 6 relatives with affective disorders were married, 5 had 12 yr of schooling and three were unemployed). Of these, 3 were parents, 2 siblings and one child of the probands.

First-degree relatives with diabetes - Information from patients and informants also revealed that of the 481 first-degree relatives of diabetic probands, 53 (11.02%) had a diagnosis of diabetes mellitus. Morbid risk for affective disorders: Morbid risk figures for affective disorders among first-degree relatives of probands with diabetes were calculated using the Weinberg equation\(^1\) and assuming age of risk to be both 15-50 yr as well as 15-60 yr, to allow better comparison with previous studies (Table II).

**Discussion**

Family aggregation studies are a useful first step to determine genetic links between any two disorders. This study chose to examine the prevalence of depression and mania in first-degree relatives of probands with T2 DM, an area seldom explored.

Previous (western) studies\(^13\)-\(^18\) have varied in the consideration of the age at risk for affective disorders for calculation of morbid risk figures, assuming

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**Table I.** Sociodemographic profile of probands, informants and first-degree relatives

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Probands (patients) (N= 50)</th>
<th>Key informants (N= 50)</th>
<th>First-degree relatives* (N=481)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) (mean ± SD)</td>
<td>47.28 ± 8.23</td>
<td>43.92 ± 11.44</td>
<td>40.72 ± 21.38</td>
</tr>
<tr>
<td>Sex males</td>
<td>22 (44)</td>
<td>35 (70)</td>
<td>252 (52.4)</td>
</tr>
<tr>
<td>females</td>
<td>28 (56)</td>
<td>15 (30)</td>
<td>229 (47.6)</td>
</tr>
<tr>
<td>Marital married</td>
<td>45 (90)</td>
<td>45 (90)</td>
<td>339 (70.5)</td>
</tr>
<tr>
<td>Status others</td>
<td>5 (10)</td>
<td>5 (10)</td>
<td>142 (29.5)</td>
</tr>
<tr>
<td>Education (yr of schooling)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 12</td>
<td>34 (68)</td>
<td>25 (50)</td>
<td>343 (71.3)</td>
</tr>
<tr>
<td>&gt; 12</td>
<td>16 (32)</td>
<td>25 (50)</td>
<td>138 (28.7)</td>
</tr>
<tr>
<td>Occupation employed</td>
<td>24 (48)</td>
<td>33 (66)</td>
<td>208 (43.2)</td>
</tr>
<tr>
<td>unemployed</td>
<td>26 (52)</td>
<td>17 (34)</td>
<td>273 (56.7)</td>
</tr>
<tr>
<td>Family income (Rs./month)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6000</td>
<td>34 (68)</td>
<td>34 (68)</td>
<td></td>
</tr>
<tr>
<td>&gt; 6000</td>
<td>16 (32)</td>
<td>16 (32)</td>
<td></td>
</tr>
<tr>
<td>Family type</td>
<td></td>
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</tr>
<tr>
<td>nuclear</td>
<td>32 (64)</td>
<td>32 (64)</td>
<td></td>
</tr>
<tr>
<td>non-nuclear</td>
<td>18 (36)</td>
<td>18 (36)</td>
<td></td>
</tr>
<tr>
<td>Locality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>urban</td>
<td>41 (82)</td>
<td>41 (82)</td>
<td></td>
</tr>
<tr>
<td>rural</td>
<td>9 (18)</td>
<td>9 (18)</td>
<td></td>
</tr>
<tr>
<td>Relationship with proband</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>spouse</td>
<td>30 (60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>parent</td>
<td>-</td>
<td></td>
<td>99 (20.6)</td>
</tr>
<tr>
<td>sibling</td>
<td>8 (16)</td>
<td></td>
<td>245 (50.9)</td>
</tr>
<tr>
<td>children</td>
<td>12 (24)</td>
<td></td>
<td>137 (28.5)</td>
</tr>
</tbody>
</table>

Figures in parentheses are percentages
*of the 481 first-degree relatives only 281 were still alive
15-50, 15-60, 15-70 yr, etc., as the age of risk (Table III). Hence, in the current study, the morbid risk figures for two age groups of 15-60 yr and 15-50 yr were calculated. These studies\textsuperscript{13,16,18} have shown morbid risk estimates ranging between 0.7 and 10.6 per cent with weighted average of morbid risk for unipolar disorder being 4.8 per cent. Morbid risk figures for unipolar disorder obtained from our study were similar to these. For bipolar disorder the morbid risk estimates ranged between 0.2 and 1.8 per cent with a weighted average of 0.6 per cent. The figures in the current study were 0.59 to 0.77 per cent. Thus, the morbid risks for depression or mania in first-degree relatives of probands of T 2 DM as estimated by the current study were not greater than the morbid risks in first-degree relatives of general population probands obtained from other studies. The cases of depression found in first-degree relatives were of major depressive type, which is similar to the older category of ‘endogenous depression.’ However, a distinction between ‘neurotic’ and ‘endogenous’ depression is no longer made because of the similarities/overlap in genetic loading, clinical features, course and outcome, etc. Therefore, this fact was unlikely to have a significant bearing on the results of the study.

Prevalence of unipolar disorder ranged from 3.6-6.9 per cent, while that of bipolar disorder ranged from 0-3.8 per cent, in first-degree relatives\textsuperscript{13-18}. In the current study the prevalence of depression (unipolar disorder) was 1.04 per cent, and that of mania (bipolar disorder) was 0.21 per cent, among the first-degree relatives of diabetic probands. This was considerably lower than the other studies, particularly for depression.

Since no Indian study that had estimated morbid risks of affective disorders in a general population could be identified, comparisons with other Indian studies were carried out solely on the basis of percentage prevalence rates. Comparisons with general population prevalence studies of affective disorders in India were nevertheless difficult, because of the considerable variation in diagnostic criteria/categories among these studies. Moreover, such studies have been carried out in different parts of the country, where the composition of the population

\begin{table}[h]
\centering
\caption{Morbid risk\textsuperscript{a} for affective disorders among first-degree relatives of probands with type 2 diabetes mellitus}
\begin{tabular}{llll}
\hline
Diagnosis & Unipolar disorder (depression) & Bipolar disorder (mania) & Unipolar disorder (depression) & Bipolar disorder (mania) \\
\hline
Authors & Gershon et al\textsuperscript{12} & 0.7 & 0.2 & 6.8 & 3.8 \\
 & Gershon et al\textsuperscript{13} & 5.8 & 0.5 & 5.8 & 0 \\
 & Weissman et al\textsuperscript{14} & 5.6 & 1.8 & 5.1 & 0.2 \\
 & Weissman et al\textsuperscript{15} & 10.1 (age of onset <30 yr) & 6.7 (age of onset >30 yr) & \\
 & Kutcher et al\textsuperscript{16} & 10.6 & 1.8 & 6.9 & 1.2 \\
 & Maier et al\textsuperscript{17} & 10.6 & 1.8 & 6.9 & 1.2 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a}Weighted average of morbid risk for unipolar disorder was 4.8 per cent, and for bipolar disorder was 0.6 per cent
studied was quite different from the subjects of this study. For purposes of comparison, the categories of endogenous and neurotic depression in these Indian studies were lumped together as unipolar depression. Manic affective psychosis and manic depression were considered equivalent to bipolar disorder. In a comprehensive, meta-analytic, review of this area by Reddy and Chandrashekhar\textsuperscript{19}, the authors had estimated weighted prevalence rates for unipolar and bipolar depression, from 13 community prevalence studies (both rural and urban) carried out in different parts of India between 1967 and 1995. Results revealed that such rates for unipolar depression were 1.2 per cent, and those for bipolar depression were 0.34 per cent. Somewhat similar results were reported by Kapoor and Singh\textsuperscript{20}, the authors of a community prevalence study from rural Punjab, 3.57 per cent for manic depressive psychosis- unipolar subtype, and 0.57 per cent for the bipolar subtype. Although the population of the latter study was from an area similar to the current study, comparisons were still difficult since subjects and relatives in the current study were from hospital clinics, and predominantly, from urban backgrounds. Nevertheless, the prevalence figures for depression and mania among first-degree relatives of diabetic probands in the present study were not greater than those reported in any of the Indian general population surveys of affective disorder.

Overall, the above comparisons suggest that morbid risks and prevalence of depression and mania in first-degree relatives of probands with T 2 DM was not higher than general population, implying a lack of familial aggregation of affective disorders in first-degree relatives of probands with T 2 DM.

The lack of aggregation of affective disorders in relatives of diabetic probands needs to viewed in the context of the methodological strengths and weaknesses of the present study. The strengths of the current study included selection of probands with T 2 DM, which is more common than type 1 diabetes, and with a better established genetic basis\textsuperscript{6}. The family history (and not the family study method) was chosen since it was easier to execute, less expensive and also less time consuming. To increase the reliability of the information obtained, the FIGS was administered to a key informant as well as the proband, and data collated from both sources. Andreasen \textit{et al}\textsuperscript{21} have pointed out that the inclusion of additional informants increases the reliability of data obtained by the family history method. The fact that there was complete concordance between probands and informants also suggests that the information obtained was genuinely reliable.

The characteristics of the probands with diabetes in the current study did not differ significantly from previous studies\textsuperscript{22} in terms of sociodemographic profiles of probands and first-degree relatives, clinical features and family history data, suggesting that the sample was fairly representative of patients with type 2 diabetes attending hospital clinics in India.

The limitations included the restricted nature of the sample which prevents generalization of results to patients of type 1 diabetes, inpatients, and patients from the community. The lack of a suitable comparison group necessitating comparison with morbid risk/ prevalence percentages of other studies was another major limitation.

Family studies exploring the link between affective disorders and diabetes are scarce, and their results inconclusive. These studies only pertain to depression and there is no study on the prevalence of mania in relatives of patients with diabetes. Lustman \textit{et al}\textsuperscript{6} reported an increased prevalence of depression in non-diabetic first-
degree relatives of patients with type 1 diabetes mellitus. In another study, an evaluation of risk factors for psychiatric disorders following diagnosis of IDDM in the young, revealed that the presence of maternal depression specifically increased the risk of depression in the offspring. Popkin et al could not find a significantly increased prevalence of depression in their first-degree relatives of patients with type 1 diabetes mellitus.

While our study was unable to find familial aggregation of affective disorders in T2DM probands, more family studies with improved methodology may be required, before it can unequivocally stated that this is indeed so. In the absence of a genetic link, other non-genetic factors, such as illness related causes will then need to be explored to unravel the aetiology of depression in diabetes. A better understanding of the aetiology is expected to lead to improved detection and treatment of depression in diabetes, thereby reducing the additional morbidity.

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