

Familial aggregation of Diabetes: a study based on Patients and Controls in Pune

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ABSTRACT

Type 2 Diabetes prematurely kill two-thirds of people in industrialized nations. Large numbers of diabetics in Indian sub continent and their ever-growing numbers are because of rapidly changing lifestyles compounded with inherent susceptibility of Indians to the disease. The study therefore aimed to undertake an anthropological investigation of 'familial clustering of diabetes' among Indian population with its possible linear transmission from one generation to other. A study of 1150 subjects was carried that included 750 patients, 400 nested case controls. Diagnosis of disease was based on 'WHO criteria. Data was collected from various hospitals from Pune such as K.E.M, AFMC, Sassoon Hospital, Poona Hospital, Nandadeep Hospital. Structured questionnaires, in-depth interviews were used. Family History Index (FHI) was calculated. Conventional statistical methods like Yates correction, Odds Ratio (OR), 95 % CI were used. Analysis showed that more than half of diabetic patients had positive family histories. Family History Index (FHI) showed a strong exposure to diabetes with presence of significant familial clustering of diabetes among first degree relatives. The prevalence of diabetes was relatively high among one or both parents, siblings of patients. Thus, it was observed that parents and siblings were the maximum sufferers of diabetes along with strong paternal inheritance. The study reflected the fact that linear transmission of diabetes was strongest among first degree relatives followed by second degree relatives of patients. This implies the fact of presence of strong genetic component in the etiology of the disease which becomes more severe, with various lifestyle factors.

Keywords: Family History, diabetes, linear transmission.

Introduction

Degenerative diseases such as cardiovascular diseases, cancer and diabetes prematurely kill over two-thirds of the people in industrialized nations. 'American Journal of Clinical Nutrition' looked at the reason for the world-wide shift towards degenerative diseases, rather than infectious diseases, being the dominant form of illness. The World Health Organization and World Health Forum jointly reported that India will have a loss of US \$ 237 billion by 2015 due to wide spread chronic diseases like diabetes among the working population.

The report also revealed that countries like Brazil, China, Russia and India currently loses more than 20 million productive life-years annually to chronic diseases like cardio-vascular disorder, stroke, cancer and diabetes, and the number is expected to be 65 % by 2030 [1]. Diabetes Mellitus, a type of degenerative non-communicable disease, once regarded as a single disease entity is now seen as a heterogeneous group of diseases characterized by a state of chronic hyperglycemia, resulting from a diversity of etiological, environmental and genetic factors acting jointly. This metabolic disorder was observed among the senior age group once upon a time and was found to be the leading cause of death, but today even the younger age groups are affected. Most of the chronic problems of today like limb amputation, blindness, cardiac failure, stroke, deafness, neuron-problems and kidney failure are due to the incidence of Type 2 Diabetes [2]. It is observed that a large numbers of diabetics in the Indian sub continent and their ever-growing numbers are largely because of rapidly changing lifestyles due to industrialization,

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modernization, urbanization, compounded with the inherent susceptibility of Indians to the disease [3]. The small numbers of genetic factors identified with Type 2 Diabetes are likely to be factors that are expressed but no genes much in particular to Type 2 Diabetes have as yet been identified along with the pattern of inheritance of the disease. The study therefore aimed to undertake an

Material and Methods

A study of 1150 subjects was carried by the present researcher. 750 patients were diabetics and had clinical symptoms of Type 2 Diabetes. A comparison of the data was conducted with 400 control subjects coming from the same socio-economic group. The patients hailed from different communities within Pune city from Western India. These subjects' belonged to different ethnic groups had different cultures, customs and socio-economic status. They were grouped as Marathas, Brahmins, Backward Caste and the Migrants (Marwaris, Gujaratis, Punjabis, Sindhis and Bengalis) who hailed from other places but settled in Pune. Since the data comprised of 750 diabetic patients, there were more males (N = 487) than females (N=263). The nested case control group consisted of 400 (males =180, females = 220) normoglycemic subjects. These normoglycemic or controls subjects accompanied the patients in the hospitals and data was taken from them; thus reflecting more or less the same socio-economic and cultural group as that of the patients [4].

Methodology and Study Design

The diagnosis of the disease was based on 'WHO criteria of Diagnosis of Type 2 Diabetes[5].and as per confirmed by the doctors. The Data was collected from K.E.M (King Edward Memorial Hospital), AFMC (Armed Force Medical College), Sassoon Hospital, Poona Hospital and Nandadeep Hospital. A written informed consent letter was obtained by the researcher from all participants who had willingly taken part in the research work. Structured questionnaires and in-depth interviews were used for the family history of the study. The patients were available to the researcher only after the concerned doctors had seen them and not repeated again for the same patients on whom data was collected once. Family History Index (FHI) was also calculated based on the presence or absence of diabetes in paternal and maternal grandparents (PGP and MGP); father (F);

anthropological investigation of 'familial clustering of diabetes' (Type 2 Diabetes) among Indian population, which continues to be the geneticist' nightmare for the risk of developing diabetes among more and more population due to linear transmission of this disease from one generation to other.

mother (M); brother (B) and sister (S) according to the given formula: $FHI = F+M+B+S + (PGP+MGP)/2$ [6].

Statistical Considerations

Conventional statistical methods were applied and the differences were considered to be statistically significant, $p < 0.01$. The calculation of odds ratio (OR) with 95 % CI was used to study the disease exposure association. The odds ratio is widely used statistic to compare the frequency of exposure to risk factors in epidemiological studies [7].

Results

In the present study, out of the total diabetic patients, approximately more than half (58 %) of them had positive family histories for diabetes. Two-third of them were male patients (66%) and the rest were female patients (34%). Analysis showed that Family History Index (FHI) for the diabetic patients under study was 126.5 showing a strong exposure to diabetes among them. It was $FHI = 6.0$ for the control which was relatively weak as compared to the patients.

Further studies were carried out in order to have a clear picture about the transmission of the disease. Therefore First-degree and Second degree pattern of inheritance of the disease [8] was studied. The data pertaining to the positive family histories of the first degree relatives and second degree relatives of the patients were analyzed. The data showed that the relatives of the diabetic patients had strong positive family histories of diabetes. The family histories of diabetes denoted a significant elevation of odds ratio for diabetes (Table 1) in both the parents (10.22). One or both the parents and siblings also had elevated odds ratio (9.04). Odds ratio for diabetes was also found to be high in aggregates with uncles / aunts and grandparents and parents (8.18); parents with uncles/ or aunts (7.76); parents with uncles / aunts and sibling (7.30) followed by the single siblings alone (4.16) which strengthened the phenomenon of strong familial aggregation of Type 2 Diabetes.

Table: 1 Positive Family Histories of Diabetes among First Degree and Second Degree Relatives (Overall)

Relatives positive:	Patients		Control		Odds Ratio (OR)	95% Confidential Interval (CI)	Yates Corrected (d.f=1)	Remark
	No.	%	No.	%				
Siblings	17	2.27	2	0.55	4.16	0.24– 12.24*	2.76	N.S
One or both the parents	111	14.77	7	1.66	10.22	10.64– 81.64*	34.26***	0.001 Sig
One/both parents Sig and siblings	128	17.04	9	2.22	9.04	10.90 – 93.90*	37.23***	0.001
One/both parents, Sig Siblings + uncles and/or aunts	113	15.0	9	2.22	7.76	8.36 – 82.36*	31.06***	0.001
One or both the Sig parents + uncles and / or aunts + siblings	130	17.27	9	2.77	7.30	8.62 – 94.62*	34.19***	0.001
One or both sets of Sig grandparents + and one or both the parents + uncles and / or aunts	118	15.68	9	2.22	8.18	9.20 – 86.20*	33.14***	0.001

* 95% exact Confidential Limits; Sig: Significant; N.S: Non-Significant.

Table: 2 Positive Family Histories of Diabetes among First Degree Relatives and Second Degree Relatives

Relatives positive:	Patients		Control		Odds Ratio (OR)	95% Confidential Interval (CI)	Yates Corrected (d.f=1)	Remark
	No	%	No.	%				
Siblings	17	2.27	2	0.55	4.16	0.24– 12.24*	2.76	N.S
One or both the parents	111	14.77	7	1.66	10.22	10.64– 81.64*	34.26***	0.001 Sig
Offs springs	0		0		0	-	-	-
Grandparents (Maternal + Paternal)	5	0.68	0		0	1.73 – 1.26	0.95	N.S
Paternal Uncles N.S	8	1.0	0		0.40*	2.26 – 0.74		0.02

* 95% exact Confidential Limits; Sig: Significant; N.S: Non-Significant

Transmission of disease among the First – Degree Relatives

When data was scrutinized separately for the first degree and second degree relatives, it was observed that in the first degree relatives, nearly 15 percent of the diabetic patients had family histories of diabetes among the parents, with the differences to be statistically significant compared to two percent of the siblings who showed positive family histories of diabetes (Table 2). Also it was observed that odds ratio was high among the parents (10.22) compared to the siblings (4.16) of the patients (Table 2). There were no off springs reported who had family histories of diabetes. Thus the study denoted a significant elevation of Odds Ratio (10.22) in diabetic patients among the parents followed by the siblings of the patients (Yates Corrected = 34.26***, $p = 0.001$).

Transmission of Disease among the Second – Degree Relatives

Approximately one percent of the diabetic patients reflected positive family histories of diabetes among the paternal grandparents and among the paternal uncles. However, the odds ratio among the grandparents was negligible as compared to the paternal uncles, which was observed to be 0.44 (Table 2). Thus, it was observed that familial aggregation of diabetes among the second degree relatives was relatively less with marked paternal inheritance of the disease.

Discussion

There is a clear relationship between the magnitude of the diabetic risk of Type 2 Diabetes observed and the degree of genetic relationship of the patients. This statement is based on the observation that as the degree of genetic relationship decreases from monozygotic twins to first, second and third degree relatives, as the lifetime risk for developing diabetes decreases in a non-linear fashion 9 .

The study thus analyzed familial aggregation of Type 2 Diabetes. The advantage of this study was that in most of the families, one or both the parents were still alive. However, many of the cousins, siblings, off springs of the patients were too young, that might have not expressed the disease. The observations based on the present analysis indicated the presence of significant familial clustering diabetes among the first degree relatives, especially when the parents and siblings were affected. The prevalence of Type 2 Diabetes was relatively high among one or both the parents' (Odds Ratio: 10.22; $p = 0.001$) of the patients to be diabetic. This was followed by family histories of diabetes among the patients having parents and siblings (clubbed

together) to be diabetic (Odds Ratio: 9; $p = 0.001$). Thus, it was observed that parents and siblings were the maximum sufferers of diabetes along with the patients. Also the paternal inheritance was stronger than the maternal which was deliberately observed among the second degree relatives of diabetes (maternal uncles). The study thus reflected the fact that the transmission of Type 2 Diabetes among the patients was strongest among the first degree relatives followed by second degree relatives and thereafter.

Samocha Bonet *et al.* [10] stated that healthy people with a genetic predisposition to Type 2 diabetes gained more weight by overeating over the short period of time than their non-genetically-prone counterparts and thus accelerate faster towards the incidence of diabetes. According to Mohan *et al* [11]. Genetic factors of diabetes were stronger in Indian population than the European populations where diabetes was significantly higher among subjects with both parents having diabetes compared to those with one parent diabetic and those with no family history. The impact of paternal history of diabetes among the off-springs has been extensively reviewed in many studies[12-14]. Where it was observed that for the first degree relatives of diabetes, the impact of family history of diabetes on the patients was relatively strong. McCarthy *et al.* [15]. Also stated that paternal influence was stronger than maternal influence in the transmission of diabetes.

Conclusion

More than half of the diabetic patients showed a strong exposure to diabetes. The presence of the disease among the first- degree relatives was well marked with strong paternal inheritance. Thus, it was observed that parents and siblings were the maximum sufferers of diabetes first degree relatives. Since the disease showed a considerable familial clustering of diabetes, the fact of presence of strong genetic component in the etiology of the disease cannot be denied.

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