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Association between Type 1 Diabetes Mellitus in Offspring with Positive Parental History of Diabetes

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ABSTRACT

Objective: To measure the association between parental history of diabetes and the odds of an offspring having T1DM.
Study Design: Case-control study.
Place and Duration of Study: Specialized Pediatric Centers across Pakistan from Oct 2017 to Aug 2018.
Methodology: The total number of enrolled participants was n= 375 (125 cases and 250 controls). Individuals aged ≥ 2 years and ≤20 years with T1DM and on insulin for the last one-year and positive for one or more islet cell autoantibodies were included. Primary data was collected at the time of enrolment. Participants were then contacted telephonically after 15 days for follow-up.
Results: Overall, 218(58%) participants were males (mean age 10.66±3.40 years; HbA1c 7.05±2.78%). Amongst the cases, 14(11.0%) reported to have a family history of diabetes (T2DM=13[10.4%]; T1DM=1[0.8%]). Regarding the parental history of diabetes, 10(8.0%) mothers reported having diabetes as compared to 4(3.2%) fathers. No statistically significant association (p= 0.83, OR= 0.92, 95% CI: 0.404 -2.077) was observed between parental history of diabetes and the odds of an offspring being T1DM.
Conclusion: The results of the study suggest no association between parental diabetic history and odds of occurrence of T1DM in offspring in a Pakistani cohort.

Keywords: Insulin auto-antibodies, Pakistan, Parental history, Type 1 diabetes mellitus.

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INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) is a metabolic disorder characterized by the depletion of β-cells leading to lifelong reliance on exogenous insulin.[1] and may result in severe health repercussions such as vision loss, accelerated vascular disease, and renal failure, if left unchecked.[2,3]. Three decades ago, the model proposed by Dr. Eisenbarth hypothesized T1DM as a chronic autoimmune disorder, and this model remains valid today.[4] The autoimmune process is marked by the presence of circulating autoantibodies to islet cell autoantigens.[5]

Previous studies suggest that parental history of diabetes increases the risk of incidence of diabetes in offspring as genetic association. with up to a six-fold risk when both parents are affected, although multifactorial etiology plays a predominant role.[6] The risk of developing T1DM is 8-15-fold higher in first-degree relatives and twice as much in second-degree relatives. FINNDIANE study revealed that 12.2% (father 6.2%, mother 3.2%, and sibling 4.8%) of the children with newly diagnosed T1DM had at least one affected first-degree relative with either T1DM or T2DM (13). Despite this, most patients are diagnosed with a sporadic form of diabetes.[7,8]

As per the International Diabetes Federation, diabetes affects 26.7% of adults in Pakistan in 2022, bringing the total to approximately 33,000,000 people.[9,10] There is a lack of data on risk factors that may be associated with the development of T1DM in the pediatric population in Pakistan. This study was conducted to evaluate if parental history of diabetes is a risk factor associated with the onset of T1DM in offspring in Pakistan.

METHODOLOGY

The case-control study was conducted at five Specialized General Pediatrics and Endocrinology

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Centers, across four major cities of Pakistan, from October 2017 to August 2018 with a ratio of 1:2, recruited 375 subjects (125 cases: 250 control).

Inclusion Criteria: Patients of either gender, aged ≥ 2 years and ≤ 20 years having T1DM and on insulin for the last one year were included in the study as cases. Similarly, subjects of either gender aged ≥ 2 years and ≤20 years who were non-diabetic were included in the study as controls.

Exclusion Criteria: For the cases, patients having any other pre-existing auto-immune disease, gestational Diabetes, and pregnant women were excluded. In addition, people having positive history of T1DM or T2DM in siblings were excluded from the study as controls.

In order to identify the true T1DM cases; Insulin autoantibodies testing was done (i.e., IAA, GADA and IA2-A), for which ELISA kits from Medizyme® were used; a positive result for any one or more of these autoantibodies was considered as having T1DM. Non-diabetic status was determined if all three insulin autoantibodies were negative at the time of enrolment. For sample size calculation, publicly available sample size calculator Open EPI was used. Assuming the proportion of controls with exposure 0.5 (50%), proportion of cases with exposure 0.666 (66.6%)[11] with power of study 80%, 95% confidence level, age-matched controls were inducted for each case, ratio of cases to controls of 1:2 with odds ratio of 2. The number of cases 112 and controls 223, a total sample size 335 was needed but on account of 10% missing information a total sample size of 375 was required with cases 125 and controls 250 for this study.

The primary objective of this study was to evaluate the association between T1DM in offspring with a positive parental history of diabetes among both groups. The secondary objective was to document the profile, glycemic parameters and current therapeutic management of T1DM patients. The study was conducted as per the International Conference on Harmonization Guideline for Good Clinical Practice (ICH-GCP-E6) and the Declaration of Helsinki. The Institutional Review Board (IRB) approval was obtained from each of the 5 sites participating in the study. The sites and their respective IRB approval numbers are: The Children's Hospital and The Institute of Child Health, Multan; Khyber Medical College, Peshawar (19/ADR/KMC); National Institute of Child Health, Karachi (08/2017); King Edward Medical University, Lahore; (122/RC/KEMU); The Children's Hospital and The Institute of Child Health, Lahore (76/CH/LCH). Written Informed consent was obtained from all recruited subjects or their parent[s]/guardian[s] (for subjects below 18 years of age) before study enrolment. The study had two visits upon recruitment, information like patient demographics anthropometrical data/ vital signs diabetes mellitus history, antidiabetic therapy and glycemic parameters, history of hypoglycemia, diabetes education and frequency of consultations were also collected.

The data was analyzed using the Statistical Package for the Social Sciences (SPSS version 22). Baseline characteristics were reported using descriptive statistics such as mean and standard deviation for continuous variables, and frequencies and percentages for categorical variables. Independent sample t-test was used to assess mean differences between continuous variables, whereas, chi-square test was used to assess differences between categorical variables among both groups. The 2x2 contigency table was used to calculate measures of disease frequency and association i.e. Odds ratio (OR) from discordant pairs

RESULTS

A total of 375 subjects (125 cases and 250 controls) were included in the study, out of which 218(58%) were males. The mean age of participants was 10.6+3.4 years (Table-I). It was observed that 262(70%) of the participants had a BMI <18.5 kg/m2, whereas 82(22%) had their BMI between 18.5-22.9 kg/m2.

The mean HbA1c of the participants was 7.05±2.8. FBG was recorded on historic basis and values were available for 51(40.8%) cases, in whom the mean FBG was 143.49±66.15 mg/dL. Overall, 30(8.0%) of the participants reported having a positive parental history of diabetes, out of which 15(4.0%) were reported among mothers and 15(4.0%) reported among fathers. Most of the parents, 27(7.2%) reported having T2DM, while only 3(0.8%) of the parents reported having T1DM. The mean duration of diabetes in parents was 4.82±4.5 years. Regarding parental diabetes history in cases, 10(8%) mothers reported to have diabetes compared to 4(3.2%) fathers .

Table-I: Baseline Characteristics of the Study Participants (n=375)

Characteristics	Cases (n=125)	Controls (n=250)	p-Value	Total (n=375)
Demography	**Mean SD/n(%)**	**Mean±SD/n(%)**		**Mean±SD/n(%)**
Age	10.63±3.4	10.68±3.5	0.91	10.66±3.4
Gender				
Male	60(48.0%)	158(63.0%)	0.006	218(58.1%)
Female	65(52.0%)	92(37.0%)		157(41.9%)
Anthropometrical data/ Vital Signs/Glycemic Parameter				
Weight (kg)	32.24±11.75	30.63±14.6	0.25	31.16±13.73
Height (cm)	133.12±21.34	130.65±20.1	0.28	131.5±20.52
BMI (kg/m2)	18.58±10.56	17.2±5.02	0.087	17.7±7.35
Waist Circumference (cm)	133.12±9.64	62.16±13.54	0.78	62.3±12.37
Systolic BP (mmHg)	99.22±12.77	103.3±11.63	0.128	101.26±12.05
Diastolic BP (mmHg)	68.40±10.34	71.35±10.28	0.01	70.37±70.37
Heart Rate (b/m)	92.00±13.42	88.08±13.85	0.01	89.34±13.82
HbA1c (%)	10.41±2.38	5.40±0.65	-	7.05±2.78
Parental history of diabetes				
Positive	14(11.2%)	16(6.4%)	-	30(8%)
Mother	10(8.0%)	5(2.0%)	-	15(4%)
Father	4(3.2%)	11(4.4%)	0.08	15(4%)
Duration of Diabetes in Parents				
Duration (years)	4.33±4.44	5.19±4.65	-	4.82±4.5
Types of diabetes in parents				
T1DM	1(0.8%)	2(0.8%)	-	3(0.8%)
T2DM	13(10.4%)	14(5.6%)	0.16	27(7.2%)

Table-II: Association of Type 1 Diabetes Mellitus in offspring with Parental History of Diabetes

Cases	Controls		Odds ratio	*p*-Value	95% Confidence Interval
	Parental History	**Positive (n=13)**	**Negative (n=112)**			
	Positive	1(7.7%)	11(9.8%)	0.92	0.83	(0.40-2.077)
	Negative	12(92.3%)	101(90.2%)			

Table-III: Type 1 Diabetes Mellitus related Complications

Diabetes related complications	Cases(n=125)
	n(%)
Overall positive	60(16%)
Diabetic ketoacidosis	52(86%)
Sensory neuropathy	06(10%)
Retinopathy	02(3.3%)
Unknown	26(6.9%)

In our study, among the cases (n=125), IAA was positive in 72(58.0%), followed by GADA being positive in 63(50.0%) and IA-2A in 50(40.0%).

In order to observe the association of parental diabetes history and T1DM in offspring, an odds ratio was calculated for matched case controls at 1:2 ratio and 23 discordant pairs observed. Overall, our results observed that with an OR= 0.92, 95% CI: 0.404 -2.077 and p= 0.83, the parental history of diabetes was not associated with T1DM in the offspring (Table-II).

Among the cases, Diabetic ketoacidosis was the most commonly occurring complication, affecting 52(86.0%). For more details kindly refer to (Table-III).

Table IV: History of Hypoglycemia

History of Hypoglycemia	
Hypoglycemia Parameters	**Cases(n=125)**
	Mean±SD/n(%)
Experience of hypoglycemia	
Yes	74(59.2%)
UNK	1(0.8%)
Severity of hypoglycemia (n=74)	
Severe hypoglycemia (60 mg/dl)	52(70.2%)
Moderate hypoglycemia (60-70 mg/dl)	10(13.5%)
Mild hypoglycemia (70-80 mg/dl)	2(1.6%)
Experience of hypoglycemia in last 3 months	
Yes	63(50.4%)
UNK	5(4.0%)
1. At least once a month	46(73.0%)
2. At least once a week	14(22.0%)
3. Unknown	3(4.7%)
Mean no. of severe hypoglycemic episodes	1.65±1.04
Emergency room visits in last 6 months	1.50±1.28

Among cases, 74(59.0%) reported having hypoglycemic events, out of which 52(70.2%) reported severe hypoglycemia. Medical assistance was required

among 52(41.6%) cases who experienced severe hypoglycemic events in the last three months (Table-IV).

All cases were on insulin therapy. The most common single-insulin regimen was premix (Isophane/regular 70/30) taken by 41(33%) patients with mean dose of 29.2±12.6 IU. It was also observed that 77(62%) cases took Dual-insulin therapy. Short acting insulin (Human regular) plus Intermediate acting insulin (human NPH) was found to be most common combination taken by 66(53%) cases (Table-V).

Table-V: Anti-Diabetic Insulin Therapy

Insulin Therapy	Cases (n=125)
Insulin therapy Class	n(%)
Rapid Acting Insulin	3(2.4%)
Basal Insulin analog	3(2.4%)
Premix Insulin	41(33.0%)
Rapid Acting Insulin + Basal Insulin ANALOG	9(7.2%)
Short Acting Insulin + Basal insulin Analog	1(0.8%)
Short Acting Insulin + Intermediate Acting Insulin	66(53.0%)
Short acting insulin + Premix	1(0.8%)
Others	1(0.8%)

DISCUSSION

In our study, no association was observed between positive parental history of diabetes and odds of occurrence of T1DM in offspring. It could reflect that in Pakistan, other environmental factors may play a role in the pathogenesis of T1DM including swift rate of urbanization, increasing trend of consuming fast food among children and adolescence, limited physical activity, increase usage of modern gadgets.[12-16]

Previous studies suggest that parental history of diabetes increases the risk of diabetes in offspring. In particular, studies conducted in Denmark and Finland had concluded that parents with diabetes double the risk of diabetes in offspring, with up to six times the risk when both parents are affected, although multifactorial etiology plays a predominant role and control individual susceptibility to progress towards disease.[17-18] Another Finland study showed that approximately 22% of newly diagnosed T1DM children have a first or second-degree relative with T1DM.[19]

The study opened the doors for future researchers to explore other risk factors that may contribute to the development of T1DM in pediatric population in Pakistan.

LIMITATIONS OF THE STUDY

Chances of recall bias might have been introduced as no antibody testing has been done to collect parental diabetic information due to limited resources. The HLA complex – which accounts for approximately 50% heritability of T1DM - was not included as a part of investigation and can be considered as one of the limitations of this research.

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Conflict of Interest: Nabeea Junaid, Danish Tariq and Navira Chandio are employees of Sanofi Pakistan and may hold shares and/or stock options in the company. Remaining authors have nothing to disclose.

CONCLUSION

The findings from this study conclude that in Pakistan, the parental history of diabetes was not associated with the onset of T1DM in the offspring. This study highlights the need of large-scale interventional studies to explore other genetic and environmental risk factors which may contribute to the onset of T1DM in local pediatric population.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SJR & MA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

JM & WIK : Data acquisition, data analysis, critical review, approval of the final version to be published.

SA & MNI & NC & DST & NJ: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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