PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 12 (December 2024)

Original Article

OPEN ACCESS

A Comprehensive Analysis of Risk Factors Associated with Type 1 Diabetes Mellitus in Children and Adolescents at a Tertiary Healthcare Facility

Aamir Naseem[1*], Sommayya Aftab[1], Kashan Arshad[1], Sajjad Habib Ullah[1], Noor-Ul-Ain Mehak[1], Khandah Fishan Mumtaz[1] and Sumiya Abid[1]

[1]Department of Pediatric Endocrinology and Diabetes, University of Child Health Sciences, Lahore, Pakistan

ARTICLE INFO

Keywords:

Type 1 Diabetes, Risk Factors, Autoimmunity, Children

How to Cite:

Naseem, A., Aftab, S., Arshad, K., Habib Ullah, S., Mehak, N.- ul- ain, Mumtaz, K. F., & Abid, S. (2024). A Comprehensive Analysis of Risk Factors Associated with Type 1 Diabetes Mellitus in Children and Adolescents at a Tertiary Healthcare Facility: Risk Factors Associated with Type 1 Diabetes Mellitus in Children and Adolescents. Pakistan Journal of Health Sciences, 5(12), 56-61. https://doi.org/1 0.54393/pjhs.v5i12.2403

***Corresponding Author:**

Aamir Naseem
Department of Pediatric Endocrinology and Diabetes, University of Child Health Sciences, Lahore, Pakistan
danaseem7@gmail.com

Received Date: 28th September, 2024
Acceptance Date: 16th December, 2024
Published Date: 31st December, 2024

ABSTRACT

Type 1 Diabetes is an autoimmune condition affecting the pancreas. **Objectives:** To assess the associations between genetic and environmental risk factors and the development of Type 1 Diabetes Mellitus in children and adolescents. **Methods:** It was a case-control study conducted over 6 months at the Department of Pediatric Endocrinology and Diabetes, the Children's Hospital Lahore. The study population consisted of two groups. Cases consisted of children with Type 1 Diabetes while controls were without Type 1 Diabetes. Data were collected using a pre-designed questionnaire by interview method from parents of children participating in the study. The incidence of various environmental and genetic factors reported to be associated with Type 1 Diabetes was compared between the groups. **Results:** 300 children participated in the study (n=150 cases and n=150 control group). The mean age of the participants was 7.90 + 4.553 years. Pearson chi-square test revealed a significant association between Type 1 Diabetes and various factors like cow's milk in infancy, early weaning, and vitamin D supplementation. Amongst the genetic factors, the association was significant for history of autoimmunity, family history of autoimmunity and family history of Type 1 Diabetes (p-value=<0.05). **Conclusions:** It was concluded that children with a history of autoimmunity or Type 1 Diabetes in self or family, early introduction to cow's milk and supplementary foods are at higher risk for Type 1 Diabetes. Meanwhile, no relationship was established between Type 1 Diabetes and prior COVID-19 infection or recurrent infections. Further studies are needed to establish cause and effect relationship.

INTRODUCTION

Type 1 diabetes (T1D) is a chronic autoimmune disease with a significant impact on children and adolescents worldwide. It is a disease of the islet cells of the pancreas. Autoimmunity results in the destruction of islet cells and consequent insulinemia. About 17 –70 % of cases with T1D present with a life-threatening complication called diabetic ketoacidosis (DKA), due to delay in the diagnosis. Furthermore, mortality from DKA is <1 % in developed countries and 3-13% in developing countries [1]. Pathophysiology of T1D is complex and is a consequence of a combination of genetic predisposition along with largely unknown environmental factors. The increasing incidence of Type 1 Diabetes Mellitus (T1D) coupled with a reduction in the proportion of individuals with the highest risk of Human Leukocyte Antigen haplotypes, highlights the significant contribution of environmental exposures in the pathogenesis of T1D [2]. Other than genetic risk factors, several environmental risk factors were proposed to be linked with the pathogenesis of T1D. Age is considered an important risk factor, as studies have shown that T1DM commonly manifests during childhood and adolescence [3]. Research has now expanded from merely treatment to preventive strategies focusing on the risk factors and etiologies of the development of autoimmunity, aiming to identify individuals at risk before diabetes has set in and be able to modify the natural course of illness [4, 5].

DOI: https://doi.org/10.54393/pjhs.v5i12.2403

International research has shown that both genetic and environmental factors have a relationship with the onset of T1D [6, 7]. Amongst the genetic factors, the most strongly associated with T1D are the Major Histocompatibility Complex Human Leukocyte Antigen (MHC/HLA) and non-MHC/HLA genes [8].

This study aims to determine the association of various genetic and environmental risk factors with T1DM. It will provide a better understanding of the pathogenesis of T1DM in children and adolescents of our local population as such extensive data is missing in previously published literature. Identifying these potential risk factors will provide valuable insights for the development of targeted preventive strategies and risk factor modification. It will also help us in making guidelines for screening T1DM in our local population which helps in early diagnosis and prevention of Diabetic ketoacidosis (DKA).

METHODS

A case-control study was conducted at the University of Child Health Sciences, the Children's Hospital, Lahore. The study was carried out in the Department of Pediatric Endocrinology and Diabetes over 6 months from November 2023 to May 2024 after prior approval from the Ethical Review Board from the respected hospital vide letter no. 694. Open-Epi online calculator was used to calculate the sample size. Sample size was calculated with a 2-sided confidence interval of 95% and power of 80% taking the equal ratio of controls and cases. The hypothetical incidence of T1D amongst those who were breastfed was taken as 11% while the incidence of T1D amongst those who were not was taken as 55% [9]. Convenience sampling was used to include 150 children diagnosed with T1D from the outpatient department and wards of Children's Hospital, Lahore. Similarly, 150 children were enrolled in the control group of the study who did not have T1D. This method was employed because of its simplicity, efficiency and its cost-effectiveness. The inclusion criteria for the case group were all children between the ages of one year and 18 years and diagnosed with Type 1 Diabetes Mellitus. Both male and female were included in the study. Controls were children of both genders between the ages of one year and 18 years who were not diagnosed with T1D and did not have any symptoms of polyuria, polydipsia, or unexplained weight loss. Exclusion criteria were formulated extensively to ensure the removal of any confounders in the study. Any child who was found to have Maturity Onset Diabetes of the Young, Type 2 Diabetes Mellitus, neonatal diabetes, or diabetes secondary to other illnesses like cystic fibrosis, thalassemia, chronic pancreatitis, or drug-induced. Also, children with any history of chemotherapy or radiotherapy or history of intake of a drug that might contribute to diabetes were excluded. Any child with syndromic features, developmental delay, or disorders of sexual development was also excluded from the study. Chronic infections like hepatitis B, Hepatitis C, tuberculosis and human immunodeficiency virus (HIV) were also part of the exclusion criteria. Non-probability consecutive sampling technique was used to gather the samples. All patients and controls participating in the study gave informed consent for enrollment in the study. Data were collected on a predesigned questionnaire by one-to-one interview. The questionnaire consisted of three parts. The first part had questions about age, gender, demographic data and questions regarding any of the above-mentioned conditions to rule out any of the exclusion criteria. The second part was regarding genetic factors that may or may not have any association with T1D. The third part concerned the environmental factors investigated for a possible association with T1D. It was validated by experts in the field of pediatric endocrinology and by researchers constituting the Research Ethics Board (ERB) of our hospital. Avoidance of breastfeeding was defined as the deliberate decision or practice of not breastfeeding (either from a biological mother or donor) either partially or entirely to a child below one year of age. Early introduction of cow's milk was defined as the addition of cow's milk to an infant's diet before the completion of 12 months. Similarly, early weaning was defined as the introduction of supplementary foods before the completion of six months. Vitamin D supplementation was taken as any oral supplements given to children in the form of syrups, tablets, drops or mega dose ampoules. Recurrent infections were defined as two or more severe infections in any one year or three or more infections in one year. Family history of Autoimmune illnesses like celiac disease, Hashimoto's thyroiditis, Grave's disease, Addison's disease, juvenile idiopathic arthritis, autoimmune hepatitis, autoimmune hepatitis, autoimmune thrombocytopenia purpura, and systemic lupus erythematosus were also excluded by interview to remove any confounding factors. Data were analyzed using a statistical package for social sciences version 23.0. Descriptive statistics were employed to describe the data. Mean and standard deviation were calculated for age in years. Discrete data regarding the frequency of genetic and environmental factors was expressed as percentages. Both groups were analyzed for any differences in the relationship of various genetic and environmental factors between the two groups. Pearson chi-square test was employed to determine if the difference between the two groups was statistically significant. The difference was considered statistically significant if the p-value was less than or equal to 0.05.

DOI: https://doi.org/10.54393/pjhs.v5i12.2403

RESULTS

A total of 300 subjects were enrolled in this study. 150 were allotted to the control group and 150 to the cases group. 172 subjects were male and 128 were female. The mean age of all participants was 7.90 ± 4.55 years. In the total study population, 125 children were a product of consanguineous marriages. 68 had a history of avoidance of breastfeeding. 93 children were introduced to cow's milk before the age of one year while 73 children were weaned with supplemental foods before the age of six months (Table 1).

Table 1: Demographic Features of Children Participating in the Study (n=300)

Variables	Frequency (%)
Age (Years)	
Mean ± SD	7.90 ± 4.553 Years
Gender	
Male	172 (57.3%)
Female	128 (42.7%)
Consanguinity	
Yes	125 (41.7%)
No	175 (58.3%)
Avoidance of Breastfeeding	
Yes	68 (22.7%)
No	232 (77.3%)
Cow's Milk Introduction in Infancy	
Yes	93 (31%)
No	207 (69%)
Early Weaning	
Yes	73 (24.3%)
No	227 (75.7%)

When the two groups were compared it was found that there were 83 males amongst the cases and 89 amongst controls. The p-value was 0.484 and hence the difference was not significant. Similarly, there were 66 products of consanguineous marriages amongst cases and 59 of the controls were products of consanguinity. The difference was not statistically significant as the p-value was 0.412. 15 patients amongst cases had a history of other co-existing autoimmune illnesses besides type 1 diabetes mellitus. At the same time, only three of the controls had such diseases. The p-value was 0.004. History of autoimmune illness besides type 1 diabetes mellitus in the family was found in 10 of the cases while only five of the controls had such history. The p-value was 0.003. Family history of type 1 diabetes mellitus was found in 46 of the cases and 10 of controls. The p-value was <0.001. Hence, amongst the genetic factors, the difference between the two groups was statistically significant for autoimmunity in self, and family history of autoimmunity or T1D while being most striking for family history of T1D (Table 2).

Table 2: Association between Genetic Factors and Type 2 Diabetes (*= Pearson Chi-square)

Genetic Factor	Cases	Controls	p-Value
Gender			
Male	83 (55.3%)	89 (59.3%)	0.484*
Female	67 (44.7%)	61 (40.7%)	
Consanguinity			
Yes	66 (44%)	59 (39.3%)	0.412*
No	84 (56%)	91 (60.7%)	
History of Autoimmune Illness in Self			
Yes	15 (10%)	3 (2%)	0.004*
No	135 (90%)	147 (98%)	
Family History of Autoimmunity			
Yes	19 (12.7%)	5 (3.3%)	0.003*
No	131 (87.3%)	145 (96.7%)	
Family History of T1D			
Yes	46 (30.7%)	10 (6.7%)	<0.001*
No	104 (69.3%)	140 (93.3%)	

Similar tests were employed to establish whether there was a statistically significant relationship between environmental factors and T1D. 60 children from amongst cases and 33 children from amongst controls had a history of early cow's milk introduction. The p-value was 0.001. Statistical analysis of early weaning trends yielded similar results. 49 cases and 24 individuals from the control group had a history of weaning before six months. The p-value was calculated to be 0.001. Avoidance of breastfeeding was observed in 39 cases and 29 controls. The p-value was 0.168. Vitamin D supplementation revealed the most striking difference among the environmental factors. 61 of those with type 1 diabetes mellitus had been supplemented with some form of vitamin D while only 18 of those without type 1 diabetes mellitus had received any supplements of vitamin D. Thus the p-value was less than 0.001. The incidence of recurrent infections amongst diabetics was 34 while amongst the non-diabetics it was 41. Covid-19 infections were low in both groups with 5 individuals from cases and 4 individuals from the control group being infected. The p-value was statistically non-significant for both at 0.351 and 0.735, respectively (Table 3).

Table 3: Pearson Chi-Square Test for the Relationship of Various Environmental Factors with T1D. (*= Pearson Chi-square)

Environmental Factor	Cases	Controls	p-Value
Avoidance of Breastfeeding			
Yes	39 (26.0%)	29 (19.3%)	0.168*
No	111 (74.0%)	121 (80.7%)	
Cow's Milk Introduction in Infancy			
Yes	60 (40%)	33 (22%)	0.001*
No	90 (60%)	117 (78%)	
Early Weaning			
Yes	49 (32.7%)	24 (16%)	0.001*
No	101 (67.3%)	126 (84.0%)	

DOI: https://doi.org/10.54393/pjhs.v5i12.2403

Vitamin D Supplementation			
Yes	61 (40.7%)	18 (12%)	<0.001*
No	89 (59.3%)	132 (88%)	
Recurrent Infections in 1st Year of Life			
Yes	34 (22.7%)	41 (27.3%)	0.351*
No	116 (77.3%)	109 (72.7%)	
Prior Covid-19 Infection			
Yes	5 (3.3%)	4 (2.7%)	0.735*
No	145 (96.7%)	146 (97.3%)	

DISCUSSION

Pakistan is a population of over 200 million individuals with almost two-thirds of the population being under 18 years [10]. While the incidence of T1D is estimated to be less than five per 100,000, it still amounts to a staggering figure of more than 6500 patients per year [11]. Previously, the environmental factors mostly included infections and dietary supplements. However, recently it has expanded to the relationship between the timing of food introduction and the role of gut microbiome with T1D, as was shown by our results. Though cause and effect have not been established as yet there is evidence that they may alter the course of illness [8]. While recent advances are changing the management landscape of T1D, they are still widely unavailable for the developing world. Considering their cost and technological requirements the hope for resource-limited countries relies mostly on insulin therapy. However, that is not to say technology cannot be employed to improve patient outcomes in third-world countries. Studies have shown how telemedicine has widened the scope of treatment and how mobile phones can play a role in the management of T1D. A recently published study from Pakistan proved how health education regarding various aspects of T1D was imparted via a short messaging service and results have been promising for HbA1c and most of the secondary outcomes [12]. Infections play a two-way role in association with T1D. While poorly controlled diabetes increases the risk of susceptibility to infections, infection itself may be a contributing factor to poor glycemic control and resultant decompensation leading to a diagnosis of T1D. Though, in our study, we did not find a significant relationship between infections and diabetes, Piccolo et al postulated otherwise [13]. Other studies also reveal that repeated infections could potentially disrupt immune regulation and increase the risk of developing T1D [14]. Our findings were similar to that of Rahmati *et al.* Their meta-analysis comprising seven studies involving more than 11 million participants revealed that the risk of T1D in patients with a history of COVID-19 infection was not found in any studies except those from the United States. This further extrapolates to their being a geographic link that has remained unexplored by researchers [15]. The association of the Covid pandemic with a new surge of T1D is still undergoing investigation and some studies reported a fair rise in T1D cases after the Covid pandemic [16]. Similarly, another systematic review and meta-analysis by Lampoussi *et al.*, from the world over concluded that the risk of T1D was lower in individuals who were exclusively breastfed and those introduced to cow's milk and supplemental foods at a later age. Our result was similar except for breastfeeding which did not establish a significant difference. One explanation could be that Lampoussi *et al.*, focused on exclusive breastfeeding while our study included both exclusive and partially breastfed children in the cohort [17]. Various studies have proposed a link between autoimmunity among diabetics and their relatives [18, 19]. Lorini *et al.*, while studying 55 children found that 58% of these children had one or more autoantibodies [18]. Family history was investigated by Gilliam *et al.* Their results were supportive of our findings during the study. They further found that age at diagnosis was directly related to the age of a family member at the time of diagnosis. Hence, the sooner the history of presentation in the family, the more likely the child to be diagnosed at a younger age [20].

CONCLUSIONS

It was concluded that current study has conclusively established a relationship between T1D and autoimmunity in self and family history of both and also for early introduction of cow's milk and supplementary foods being risk factors. It is pertinent that further research is carried out to establish a more strong relationship between these factors and T1D. These factors could be used later on to predict and prevent T1D. A multi-center study may reflect more reproducible results.

Authors Contribution

Conceptualization: AN
Methodology: SHU, NUAM, KFM, SA
Formal analysis: AN
Writing review and editing: AN, SA, KA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

REFERENCES

[1] Curtis JR, To T, Muirhead S, Cummings E, Daneman D. Recent Trends in Hospitalization for Diabetic Ketoacidosis in Ontario Children. Diabetes Care. 2002 Sep; 25(9): 1591-6. doi: 10.2337/diacare.25.9.15

DOI: https://doi.org/10.54393/pjhs.v5i12.2403

91.
[2] Fourlanos S, Varney MD, Tai BD, Morahan G, Honeyman MC, Colman PG *et al.* The Rising Incidence of Type 1 Diabetes Is Accounted for by Cases with Lower-Risk Human Leukocyte Antigen Genotypes. Diabetes Care. 2008 Aug; 31(8): 1546-9. doi: 10.2337/dc08-0239.
[3] American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. Diabetes Care. 2021 Jan; 44(Supplement_1): S15-33. doi: 10.2337/dc21-S002.
[4] Sherr JL, Laffel LM, Liu J, Wolf W, Bispham J, Chapman KS *et al.* Severe Hypoglycemia and Impaired Awareness of Hypoglycemia Persist in People with Type 1 Diabetes Despite Use of Diabetes Technology: Results from A Cross-Sectional Survey. Diabetes Care. 2024 Jun; 47(6): 941-7. doi: 10.2337/dc23-1765.
[5] Gregory GA, Robinson TI, Linklater SE, Wang F, Colagiuri S, de Beaufort C *et al.* Global Incidence, Prevalence, and Mortality of Type 1 Diabetes in 2021 with Projection to 2040: A Modelling Study. The Lancet Diabetes and Endocrinology. 2022 Oct; 10(10): 741-60. doi: 10.1016/S2213-8587(22)00218-2.
[6] Vurallı D, Jalilova L, Alikaşifoğlu A, Özön ZA, Gönç EN, Kandemir N. Cardiovascular Risk Factors in Adolescents with Type 1 Diabetes: Prevalence and Gender Differences. Journal of Clinical Research in Pediatric Endocrinology. 2024 Mar; 16(1): 11. doi: 10.4274/jcrpe.galenos.2023.2023-12-12.
[7] Ramos EL, Dayan CM, Chatenoud L, Sumnik Z, Simmons KM, Szypowska A *et al.* Teplizumab and β-cell Function in Newly Diagnosed Type 1 Diabetes. New England Journal of Medicine. 2023 Dec; 389 (23): 2151-61. doi: 10.1056/NEJMoa2308743.
[8] Ramaphane T, Gezmu AM, Tefera E, Gabaitiri L, Nchingane S, Matsheng-Samuel M *et al.* Prevalence and Factors Associated with Microalbuminuria in Pediatric Patients with Type 1 Diabetes Mellitus at a Large Tertiary-Level Hospital in Botswana. Diabetes, Metabolic Syndrome and Obesity. 2021 Nov; 14: 4415-22. doi: 10.2147/DMSO.S322847.
[9] Oza C, Khadilkar V, Karguppikar M, Ladkat D, Gondhalekar K, Shah N *et al.* Prevalence of Metabolic Syndrome and Predictors of Metabolic Risk in Indian Children, Adolescents and Youth with Type 1 Diabetes Mellitus. Endocrine. 2022 Mar; 75(3): 794-803. doi: 10.1007/s12020-021-02924-6.
[10] Abrahim AM, Tilahun T, Gelana B. Glycemic Control and Associated Factors Among Children and Adolescents with Type 1 Diabetes Mellitus, Southwest Ethiopia. Diabetes, Metabolic Syndrome and Obesity. 2023 Dec; 16: 2025-37. doi: 10.2147/DMSO.S412529.
[11] Patterson CC, Karuranga S, Salpea P, Saeedi P, Dahlquist G, Soltesz G *et al.* Worldwide Estimates of Incidence, Prevalence and Mortality of Type 1 Diabetes in Children and Adolescents: Results from the International Diabetes Federation Diabetes Atlas. Diabetes Research and Clinical Practice. 2019 Nov; 157: 107842. doi: 10.1016/j.diabres.2019.107842.
[12] Rahman A, Razzaq A, Khan MS, Nawaz S, Akhtar S. Short Message Service as a Tool for Health Education in Families of Children with Type 1 Diabetes in Pakistan: A Randomized Control Trial. Pakistan Armed Forces Medical Journal. 2024 Apr; 74(2): 506-511. doi: 10.51253/pafmj.v74i2.10215
[13] Piccolo G, De Rose EL, Bassi M, Napoli F, Minuto N, Maghnie M *et al.* Infectious Diseases Associated with Pediatric Type 1 Diabetes Mellitus: A Narrative Review. Frontiers in Endocrinology. 2022 Aug; 13: 966344. doi: 10.3389/fendo.2022.966344.
[14] Calliari LE, Almeida FJ, Noronha RM. Infections in Children with Diabetes. Journal of Pediatric. 2020 Apr; 96(Suppl-1): 39-46. doi: 10.1016/j.jped.2019.09.004.
[15] Rahmati M, Yon DK, Lee SW, Udeh R, McEvoy M, Kim MS *et al.* New-Onset Type 1 Diabetes in Children and Adolescents as Postacute Sequelae of SARS-Cov-2 Infection: A Systematic Review and Meta-Analysis of Cohort Studies. Journal of Medical Virology. 2023 Jun; 95(6): e28833. doi: 10.1002/jmv.28833.
[16] D'Souza D, Empringham J, Pechlivanoglou P, Uleryk EM, Cohen E, Shulman R. Incidence of Diabetes in Children and Adolescents During the COVID-19 Pandemic: A Systematic Review and Meta-analysis. Journal of the American Medical Association. Network Open. 2023 Jun; 6(6): e2321281-. doi: 10.1001/jamanetworkopen.2023.21281.
[17] Lampousi AM, Carlsson S, Löfvenborg JE. Dietary Factors and Risk of Islet Autoimmunity and Type 1 Diabetes: A Systematic Review and Meta-Analysis. E Bio Medicine. 2021 Oct; 72: 103633. doi: 10.1016/j.ebiom.2021.103633.
[18] Lorini R, Larizza D, Livieri C, Cammareri V, Martini A, Plebani A *et al.* Auto-Immunity in Children with Diabetes Mellitus and Their Relatives. European Journal of Pediatrics. 1986 Aug; 145: 182-4. doi: 10.1007/BF00446060.
[19] Frazzei G, van Vollenhoven RF, de Jong BA, Siegelaar SE, van Schaardenburg D. Preclinical Autoimmune Disease: A Comparison of Rheumatoid Arthritis, Systemic Lupus Erythematosus, Multiple Sclerosis and Type 1 Diabetes. Frontiers in Immunology. 2022

DOI: https://doi.org/10.54393/pjhs.v5i12.2403

Jun; 13: 899372. doi: 10.3389/fimmu.2022.899372.

[20] Gilliam LK, Liese AD, Bloch CA, Davis C, Snively BM, Curb D *et al* SEARCH for Diabetes in Youth Study Group. Family History of Diabetes, Autoimmunity, and Risk Factors for Cardiovascular Disease among Children with Diabetes in the SEARCH for Diabetes in Youth Study. Pediatric Diabetes. 2007 Dec; 8(6): 354-61. doi: 10.1111/j.1399-5448.2007.00241.x.