

Environmental Factors before the Onset of Type 1 Diabetes Mellitus: A Case-Control Study

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Abstract

Objective: The role of environmental factors in the development of type 1 diabetes mellitus (T1D) is inconclusive. This study aimed to investigate the associations between selected environmental factors and T1D.

Materials and Methods: This group matched case-control study included diabetic and healthy subjects younger than 19 years old in 2017. Cases were diabetic subjects diagnosed before the age of 19 years and controls were healthy subjects with similar distributions of age, sex, and place of living. Information including demographic characteristics, birth season, duration of breastfeeding and major psychological stressors was obtained by a parent-administered questionnaire. Data were analyzed using SPSS version 16 and T-test and chi-square test. Statistical significance was defined as $P < 0.05$.

Results: The mean age of cases was 12.5 (± 5.2) years and 13 (± 6.7) in controls ($P: 0.55$). Compared to controls, children with T1D had a higher chance of having a major psychological stressor in the family before the onset of diabetes ($P: 0.0001$) with odds ratio (OR) 3.3, higher neonatal jaundice ($P: 0.01$, OR: 2.25), infection leading to hospitalization within the first year of life ($P: 0.007$, OR: 6.46), and lower family income ($P: 0.018$). Duration of breastfeeding was shorter in T1D group ($P: 0.018$, OR: 3.46) and they had started cereals one month earlier ($P: 0.015$).

Conclusion: Certain environmental factors including major psychological stressors, neonatal jaundice, infection leading to hospitalization within first year of birth and shorter duration of breastfeeding were associated with the development of T1D.

Keywords: Environmental factors, Diabetes Mellitus, Type 1

QR Code:



Citation: Zahra Z, Sadri H. Environmental Factors before the Onset of Type 1 Diabetes Mellitus: A Case-Control Study. IJDO. 2022; 14 (3) :152-158

URL: <http://ijdo.ssu.ac.ir/article-1-728-en.html>

 10.18502/ijdo.v14i3.10741

Article info:

Received: 08 April 2022

Accepted: 18 July 2022

Published in September 2022



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Introduction

Type 1 diabetes mellitus (T1D) is the most common chronic disease in children and adolescents caused by autoimmune selective destruction of insulin-producing beta cells (β -cells) in high-risk individuals. The etiology of T1D is multifactorial. HLA complex class II in chromosome 6 is major genetic susceptibility related to T1D and confers approximately half of the genetic risk for disease development (1,2). However, environmental factors are believed to provide essential components for the onset of the autoimmune process and eventually the clinical disease (3). It is unclear whether environmental factors influence T1D progression to clinical onset or they have any etiologic role in diabetes mellitus disease.

Epidemiologic studies have demonstrated that incidence of T1D varies widely between and within countries (4,5). The results of various studies also point to a remarkable and sustained increase in the incidence of T1D in children < 15 years with an estimated annual increase of approximately 3% globally (1,5). Given the stability of the genes related to T1D, increased global incidence of the disease may be explained by changes in environment or lifestyle (6,7). Possible triggers that may initiate the autoimmune process include chemicals, viruses, alterations in gut bacterial communities, infections in early life, climate, widespread usage of antibiotics, psychological stressors, maternal body mass index (BMI), and short duration of breastfeeding (7,8).

Because the genetic background cannot be changed, it is important to look for exposures that may initiate the autoimmune process or aggravate ongoing β -cells destruction and ultimately T1D development. Efforts to identify and eliminate the environmental triggers of T1D may make it possible to prevent or delay the disease. However, environmental factors that make the immune system mistakenly destroy β -cells remain largely unknown and need to be identified.

The aim of this study was to investigate some environmental factors before the onset of T1D.

Materials and Methods

This case-control study was conducted on diabetic and healthy subjects less than 19 years of age from July to December 2017. The sample size was calculated based on previous similar studies (9).

The cases comprised of 102 subjects age of 2–19 years who were diagnosed with T1D and were randomly selected from the children and adolescents attending Pediatric Endocrinology Clinic of Besat Hospital, Hamadan University of Medical Sciences, Hamadan, Iran. The control group included 99 healthy subjects who were selected from elementary and high school students or sports clubs. The diabetic and healthy subjects were strictly matched by sex, age, and residence or geographical distribution. Information on age, sex, place of living (urban, rural), birth seasonality, birth order, infant diet, duration of breastfeeding, age at introduction of cereals, major psychological stress (parental death, parental drug addiction, parental dispute, divorce, and parental job loss), neonatal jaundice, and average family monthly income was obtained. All collected data were evaluated by a valid researcher-made questionnaire completed by the parents through face-to-face interviews. For patients, additional information was extracted from the medical records as required. No private information was included in the study.

Diagnosis of T1D as defined by the World Health Organization criteria (10), was based on the presence of classic symptoms of hyperglycemia (thirst, polydipsia, polyuria), weight loss, a random plasma glucose \geq 200 mg/dL fasting glucose level \geq 126 mg/dL at onset plus daily insulin injections requirement (10). A pediatric endocrinologist involved in the treatment and follow-up of these patients confirmed the criteria. Those with missing information required for the study and those

with monogenic or secondary diabetes were excluded from the study.

Statistical analysis

Data were analyzed using SPSS16. An independent T-test was used to investigate the quantitative data in two groups. The Chi-squared test or Fisher's exact test was used to compare qualitative data in two groups. A $P < 0.05$ was considered statistically significant.

Ethical considerations

The Ethics Committee of Hamadan University of Medical Sciences approved this study (No: p/16/35/1/649/1396). Parents of all children from both groups provided informed written consent before participation in the study.

Results

This group matched, case control study of 201 subjects included 102 patients ($n=53$ or 52% female) diagnosed with T1D and 99 healthy subjects ($n=56$ or 57% female). The mean age was 12.5 (± 5.2) years for case group and 13 (± 6.7) years for control group. There was no significant difference in type of feeding (breastfeeding, formula, or both) during the first 6 months of life between the two groups ($P: 0.57$). However, history of breastfeeding >1 year was less prevalent in the diabetic group than in the control group ($P: 0.018$) with odds ratio (OR) 3.46. Both groups received cereals and gluten-containing foods only after age of 6 months. However, compared with the healthy group, diabetic children started cereals one month earlier ($P: 0.015$). The major psychological stressors such as divorce or death of parents ($P: 0.0001$, OR=

3.3), neonatal jaundice ($P: 0.01$, OR= 2.25), and infection leading to hospitalization in the first year of life ($P: 0.007$, OR= 6.46) were more common in the patient group compared to the control subjects. The average family income was also lower in patient group compared to the control subjects ($P: 0.018$).

Quantitative and qualitative characteristics of both groups are summarized in Tables 1 and 2.

Discussion

The contribution of environmental factors to the development of T1D has been controversial for decades. This study evaluated the association between some environmental factors and the development of T1D. Our main findings demonstrate that certain previous environmental exposures are associated with the T1D. Diabetic children had experienced more stressful events years before the disease presentation compared to the control group. Divorce and parental drug addiction were the most common pre-disease stressors in our diabetic children. Stressful life events are thought to cause autoimmune diseases by altering the immune system. They may also increase susceptibility to infection in genetically susceptible individuals. The infection then may start or accelerates the autoimmune process (11).

The effect of psychological stress as a trigger and promoter of progression to T1D has been widely studied in the literature, but findings have often been inconclusive. Some previous studies have indicated that prolonged sorrow or stressful events including parental death, divorce, parental job loss, family financial hardship, parental dispute or adverse

Comparison of quantitative characteristics of cases With type 1 diabetes mellitus and their healthy Controls (N=201)

Characteristic	Case (n=102) Mean (\pm SD)	Control (n=99) Mean (\pm SD)	<i>P</i>
Age (Years)	13 (± 6.7)	12.5 (± 5.2)	0.55
Start of cereal and gluten (Months)	6.25 (± 1.33)	7.3 (± 0.83)	0.015
Birth weight (gr)	3057 (± 533)	3080 (± 533)	0.66
Monthly family income (Million Rials)	18.600 (± 700)	16.500 (± 600)	0.018a*

*:Indicates the *P* is less than 0.05 and the significance
a:The independent T-test was used

Table 2. Comparison of qualitative data related to environmental factors of cases with T1D and their healthy controls (N=201)

Characteristic	Case (n=102)	Control (n=99)	OR	P
Sex (girl)	53 (52%)	56 (57%)		0.57
Breastfeeding	89 (87.2%)	88 (88.8%)		0.57
Duration of breastfeeding >1 year	84 (82.3%)	95 (95.9)	3.46	0.018
Neonatal jaundice	34 (33.3%)	18 (18.2%)	2.25	0.01
Stressful events	34 (33.3%)	13 (13.1%)	3.3	0.00
Birth order:				
First child	38 (37.2%)	52 (52.5%)		
Second child	41 (40.1%)	28 (28.2%)		0.06
Third child	7 (6.8%)	13 (13.1%)		
Gestational age >37 weeks	99 (97%)	95 (95.5%)		0.67
Infection in the first year of life	12 (11.7%)	2 (2.02%)	6.46	0.007
Infection after the first year of life	5 (4.90%)	3 (3.03%)		0.29
Birth seasonality :				
Spring	22 (21.5%)	31 (31.3%)		
Summer	29 (28.4%)	21 (21.2%)		
Autumn	30 (29.4%)	31 (31.3%)		0.33
Winter	21 (20.5%)	16 (16.6%)		
Maternal type 2 diabetes mellitus	8 (7.8%)	9 (9.09%)		0.8

situations in very early childhood might affect the onset of diabetes in genetically at-risk children (12). In contrast, Cosgrove cited one large well-controlled trial and stated that stressful life events do not cause T1D (13). Similarly, studies by Lloyd et al. and Littorin et al. failed to support the concept that stress causes type 1 diabetes (14,15).

Our study found that having history of neonatal jaundice requiring phototherapy was more prevalent among diabetic cases compared to the control group. In confirmation of the results of this finding, a previous study has suggested an association between neonatal jaundice and the risk of developing T1D (16). It is unclear how jaundice is involved in diabetes development, but it seems to be related to the underlying disease leading to jaundice rather than icterus itself as a potential cause of T1D. Our data add to our understanding of the potential contribution of neonatal jaundice to T1D etiology. However, this association needs further exploration. Although others have shown no association between diabetes development and economic status (17), the data of this study revealed that the average family income was significantly lower in diabetic group compared to the control group. We have no explanation for this unexpected finding. It can be assumed that the

triggers for diabetes may be different around the world.

In confirmation of study by Beyerlein (18), in our study having self-reported history of lower respiratory tract infections leading to hospitalization in the first year of life associated with the T1D. Multiple mechanisms of action have been proposed to explain the role of viral infections (bacterial infections are rarely discussed) as biological agents linked to type 1 diabetes development. One group of viruses can directly infect and destroy pancreatic β -cells independent of autoimmune processes. Viral infections may have the potential to induce islet autoimmunity and β -cell damage (bystander activation of auto reactive T cells, loss of regulatory T cells and by the introduction of an antigen that cross-reacts with islet cell antigens) (19).

Evidence regarding the association of infection with diabetes mellitus is inconsistent and remains inconclusive. Some prospective studies have reported that multiple exposures and more frequent infections might increase the risk of islet autoimmunity and speed up the development of diabetes in children (18,20). On the contrary, some recent reports suggest that infectious agents may play a protective role against diabetes development. It is assumed that improved hygiene and lack of

exposure to childhood infection and so less antigenic stimulation in early life may increase an individual's chances of developing autoimmune disease including T1D because immune system is less trained for its main task namely host defense (Hygiene hypothesis) (21). Nevertheless, hygiene hypothesis is not widely accepted, and further investigations are warranted to elucidate whether infections contribute to diabetes or have a protective effect on the expression of the disease (7).

Consistent with previous studies (22,23), there was no significant difference between the two groups in terms of breastfeeding rate. So, the data of this study failed to confirm earlier findings of an association between T1D and infant feeding in the first 6 months of life. The justification for this finding may be that breastfeeding rates are high in our area. However, in contrast to data from the Frederiksen and Lund-Blix (24,25), a lower number of patients in the diabetic group had experienced duration of breastfeeding longer than one year compared to the control group.

Previous studies show that A1 beta-casein of cows' milk is one putative environmental factor that increases the risk of T1D in the child (26,27). Hyytinen et al. and Alves JG et al. have shown that avoidance of cow's milk-based formula for infants with genetic susceptibility for T1D may reduce the cumulative incidence of diabetes-associated autoantibodies (28,29). Earlier studies have suggested that protective effect of breastfeeding may be related to its influence on changing the role of dietary factors on the risk of developing T1D (7).

With respect to birth seasonality, this study showed no evidence of an association between the birth season and development of T1D, a finding that contradicts the results of previous studies (30,31). A series of population-based studies found association between the risk of T1D and past environmental exposures such as gestational age, birth weight, birth order, infection leading to hospitalization after 1 year of birth, and positive familial history of type 2 diabetes mellitus. In this current study, no

association was found between T1D and these variables.

This study had several limitations that should be considered. Firstly, questionnaire information was self-reported by the participants and therefore was prone to misreporting and recall bias. Secondly, this was a case-control study whose results were not as conclusive as those of well-controlled trials and cohort studies. Thirdly, this study was conducted with a small sample size. The present findings cannot prove causality, but only show a link between T1D and exposure to certain environmental factors before the onset of the disease. However, the present study reinforces previous findings on the association of T1D with environmental factors.

Conclusions

In conclusion, the present study found that certain environmental factors including major psychological stressors, neonatal jaundice, infection leading to hospitalization in the first year of birth, low family income, earlier introduction of cereals, and discontinuation of breastfeeding after the first year were associated with T1D. The results of this study may also indicate that the distribution of triggers or accelerators of T1D development may vary around the world. To fully understand the effects of environmental factors on autoimmunity and T1D risk, additional large-scale cohort studies will be of importance.

Acknowledgements

This paper was funded by Clinical Research Development Center of Besat Hospital, Hamadan, Iran. We express our thanks to all patients and their parents for their consent and cooperation in completion of the questionnaires and data collection.

Funding

The authors received no funding from an external source.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Sugihara S. Genetic susceptibility of childhood type 1 diabetes mellitus in Japan. *Pediatr Endocrinol Rev.* 2012;10(1):62-71.
2. Černá M. Genetics of autoimmune diabetes mellitus. *Wiener Medizinische Wochenschrift.* 2008;158(1):2-12.
3. Fazeli Farsani S, Souverein PC, van der Vorst MM, Mantel-Teeuwisse AK, Knibbe CA, de Boer A. Disease history and medication use as risk factors for the clinical manifestation of type 1 diabetes in children and young adults: an explorative case control study. *PLoS one.* 2014;9(2):e87408.
4. Patterson C, Guariguata L, Dahlquist G, Soltész G, Ogle G, Silink M. Diabetes in the young—a global view and worldwide estimates of numbers of children with type 1 diabetes. *Diabetes research and clinical practice.* 2014;103(2):161-75.
5. Mamoulakis D, Vrouvaki F, Louvari V, Galanakis E. Incidence of childhood Type 1 diabetes mellitus in Crete. *Diabetic Medicine.* 2018;35(9):1210-5.
6. Patterson CC, Gyürüs E, Rosenbauer J, Cinek O, Neu A, Schober E, et al. Trends in childhood type 1 diabetes incidence in Europe during 1989–2008: evidence of non-uniformity over time in rates of increase. *Diabetologia.* 2012 ;55(8):2142-7.
7. Rewers M, Ludvigsson J. Environmental risk factors for type 1 diabetes. *The Lancet.* 2016;387(10035):2340-8.
8. Sharif K, Watad A, Coplan L, Amital H, Shoenfeld Y, Afek A. Psychological stress and type 1 diabetes mellitus: what is the link?. *Expert review of clinical immunology.* 2018;14(12):1081-8.
9. Majeed AA, Mea KH. Risk factors for type 1 diabetes mellitus among children and adolescents in Basrah. *Oman medical journal.* 2011;26(3):189.
10. Razavi Z, Hamidi F. Diabetic ketoacidosis: demographic data, clinical profile and outcome in a tertiary care hospital. *Iranian Journal of Pediatrics.* 2017;27(3).(in Persian)
11. Roth R, Lynch K, Hyöty H, Lönnrot M, Driscoll KA, Bennett Johnson S, et al. The association between stressful life events and respiratory infections during the first 4 years of life: The Environmental Determinants of Diabetes in the Young study. *Stress and Health.* 2019;35(3):289-303.
12. Sipetic S, Vlajinac H, Marinkovi J, Kocev N, Milan B, Ratkov I, et al. Stressful life events and psychological dysfunctions before the onset of type 1 diabetes mellitus. *Journal of Pediatric Endocrinology and Metabolism.* 2007;20(4):527-34.
13. Cosgrove M. Do stressful life events cause type 1 diabetes?. *Occupational Medicine.* 2004;54(4):250-4.
14. Littorin B, Sundkvist G, Nyström L, Carlson A, Landin-Olsson M, Ostman JA, et al. Family characteristics and life events before the onset of autoimmune type 1 diabetes in young adults: a nationwide study. *Diabetes Care.* 2001 ;24(6):1033-7.
15. Lloyd C, Smith J, Weinger K. Stress and diabetes: a review of the links. *Diabetes spectrum.* 2005;18(2):121-7.
16. Waernbaum I, Dahlquist G, Lind T. Perinatal risk factors for type 1 diabetes revisited: a population-based register study. *Diabetologia.* 2019;62(7):1173-84.
17. Connolly V, Unwin N, Sherriff P, Bilous R, Kelly W. Diabetes prevalence and socioeconomic status: a population based study showing increased prevalence of type 2 diabetes mellitus in deprived areas. *Journal of Epidemiology & Community Health.* 2000;54(3):173-7.
18. Beyerlein A, Wehweck F, Ziegler AG, Pflueger M. Respiratory infections in early life and the development of islet autoimmunity in children at increased type 1 diabetes risk: evidence from the BABYDIET study. *JAMA pediatrics.* 2013 ;167(9):800-7.
19. Van der Werf N, Kroese FG, Rozing J, Hillebrands JL. Viral infections as potential triggers of type 1 diabetes. *Diabetes/metabolism research and reviews.* 2007;23(3):169-83.
20. Stene LC, Oikarinen S, Hyöty H, Barriga KJ, Norris JM, Klingensmith G, et al. Enterovirus infection and progression from islet autoimmunity to type 1 diabetes: the Diabetes and Autoimmunity Study in the Young (DAISY). *Diabetes.* 2010;59(12):3174-80.
21. Morgan E, Halliday SR, Campbell GR, Cardwell CR, Patterson CC. Vaccinations and childhood type 1 diabetes mellitus: a meta-analysis of observational studies. *Diabetologia.* 2016;59(2):237-43.
22. Norris JM, Barriga K, Klingensmith G, Hoffman M, Eisenbarth GS, Erlich HA, Rewers M. Timing of initial cereal exposure in infancy and risk of islet autoimmunity. *Jama.* 2003;290(13):1713-20.
23. Knip M, Akerblom HK, Becker D, Dosch HM, Dupre J, Fraser W, Howard N, Ilonen J, Krischer JP, Kordonouri O, Lawson ML. Hydrolyzed infant formula and early β -cell autoimmunity: a

- randomized clinical trial. *Jama*. 2014 ;311(22):2279-87.
24. Frederiksen B, Kroehl M, Lamb MM, Seifert J, Barriga K, Eisenbarth GS, et al. Infant exposures and development of type 1 diabetes mellitus: The Diabetes Autoimmunity Study in the Young (DAISY). *JAMA pediatrics*. 2013;167(9):808-15.
25. Lund-Blix NA, Dydensborg Sander S, Størdal K, Nybo Andersen AM, Rønningen KS, Joner G, et al. Infant feeding and risk of type 1 diabetes in two large Scandinavian birth cohorts. *Diabetes Care*. 2017 ;40(7):920-7.
26. Verge CF, Howard NJ, Irwig L, Simpson JM, Mackerras D, Silink M. Environmental factors in childhood IDDM: a population-based, case-control study. *Diabetes care*. 1994 ;17(12):1381-9.
27. Chia JS, McRae JL, Enjapoori AK, Lefèvre CM, Kukuljan S, Dwyer KM. Dietary cows' milk protein A1 beta-casein increases the incidence of T1D in NOD mice. *Nutrients*. 2018;10(9):1291.
28. Hyytinen M, Savilahti E, Virtanen SM, Härkönen T, Ilonen J, Luopajarvi K, et al. Avoidance of Cow's Milk-Based Formula for At-Risk Infants Does Not Reduce Development of Celiac Disease: A Randomized Controlled Trial. *Gastroenterology*. 2017 ;153(4):961-70.
29. Alves JG, Figueiroa JN, Meneses J, Alves GV. Breastfeeding protects against type 1 diabetes mellitus: a case-sibling study. *Breastfeeding Medicine*. 2012;7(1):25-8.
30. Mikulecky M, Rausova Z, Dedik L, Mojto V. Does seasonality of births in diabetes mellitus reflect pathogenetic differences?. *Bratislavske Lekarske Listy*. 2016;117(9):501-4.
31. Samuelsson U, Ludvigsson J. Seasonal variation of birth month and breastfeeding in children with diabetes mellitus. *Journal of Pediatric Endocrinology and Metabolism*. 2001 ;14(1):43-6.
32. Haynes A, Bower C, Bulsara MK, Finn J, Jones TW, Davis EA. Perinatal risk factors for childhood Type 1 diabetes in Western Australia—a population-based study (1980–2002). *Diabetic Medicine*. 2007;24(5):564-70.
33. Abebe W, Abebe B, Molla K, Alemayehu T. Tuberculous dactylitis: an uncommon presentation of skeletal tuberculosis. *Ethiopian Journal of Health Sciences*. 2016;26(3):301-3.
34. Li S, Zhang M, Tian H, Liu Z, Yin X, Xi B. Preterm birth and risk of type 1 and type 2 diabetes: systematic review and meta-analysis. *obesity reviews*. 2014 ;15(10):804-11.
35. Cardwell CR, Stene LC, Joner G, Davis EA, Cinek O, Rosenbauer J, et al. Birthweight and the risk of childhood-onset type 1 diabetes: a meta-analysis of observational studies using individual patient data. *Diabetologia*. 2010;53(4):641-51.