



# Association between environmental factors and risk of type 1 diabetes — a case-control study

Czynniki środowiskowe a ryzyko cukrzycy typu 1 — badanie kliniczno-kontrolne

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## Abstract

**Introduction:** While many studies support the theory that environmental factors play a role in the development of type 1 diabetes mellitus (T1DM), controversy exists as to the contribution of any individual factor. The aim of the present study was therefore to investigate the associations of T1DM with several environmental factors.

**Material and methods:** A case-control study was conducted on children  $\leq 16$  years old who were diagnosed with T1DM and healthy age- and sex-matched controls. Data regarding the socio-demographic status, gestational and neonatal risk factors were evaluated.

**Results:** One hundred and one children with T1DM (41 males and 60 females), and the same number of age- and sex-matched controls, were included in the present study (mean age  $10.3 \pm 4.5$  years). On multivariable logistic regression analysis, maternal age  $> 35$  years at delivery, duration of  $> 6$  months of cow milk feeding, lack of vitamin D supplementation and caesarean delivery were significantly associated with diabetes.

**Conclusion:** In the present case-control study, certain environmental risk factors were associated with the development of T1DM.

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**Key words:** type 1 diabetes mellitus, risk factor, environmental factors

## Streszczenie

**Wstęp:** Mimo że wyniki wielu badań potwierdzają teorię o wpływie czynników środowiskowych na rozwój cukrzycy typu 1, nadal istnieją kontrowersje co do znaczenia poszczególnych czynników w patogenezie tej choroby. Celem badania było zbadanie zależności między występowaniem cukrzycy typu 1 a obecnością niektórych czynników środowiskowych.

**Materiał i metody:** Badaniem kliniczno-kontrolnym objęto dzieci w wieku  $\leq 16$  lat, u których rozpoznano cukrzycę typu 1 i dopasowaną pod względem płci i wieku grupę kontrolną złożoną ze zdrowych dzieci. Analizowano dane socjodemograficzne oraz czynniki ryzyka związane z przebiegiem ciąży i porodu oraz okresem niemowlęcym.

**Wyniki:** Do badania włączono 101 dzieci chorych na cukrzycę typu 1 (41 chłopców i 60 dziewcząt) i taką samą liczbę zdrowych dzieci stanowiących grupę kontrolną. Średnia wieku wynosiła  $10,3 \pm 4,5$  lat. W wieloczynnikowej analizie regresji wykazano istnienie związku wieku matki w czasie porodu  $> 35$  lat, podawania dziecku mleka krowiego przez  $> 6$  miesięcy, braku suplementacji witaminy D i cesarskiego cięcia z cukrzycą u dzieci.

**Wnioski:** W niniejszym badaniu kliniczno-kontrolnym niektóre czynniki środowiskowe wiązały się z rozwojem cukrzycy typu 1.

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**Słowa kluczowe:** cukrzyca typu 1, czynniki ryzyka, czynniki środowiskowe

## Introduction

Type 1 (insulin-dependent) diabetes mellitus (T1DM) is an autoimmune disease resulting in destruction of pancreatic  $\beta$ -cells [1, 2]. It affects about 35 million people worldwide, and its incidence exhibits significant geographic variation, ranging from  $< 1/100,000$  to  $> 35/100,000$  per year [3].

Many studies support the hypothesis that environmental factors play a role in the development of T1DM

[4–6]. However, controversy still exists as to which factors may be responsible for the disease's susceptibility. These factors may differ substantially from population to population.

Epidemiologic studies have indicated the incidence of T1DM in Iran to be low (3.7/100,000) [7]. This makes this region a particularly suitable area to investigate the association between T1DM and different environmental factors, since the attributed risk for a single factor will be greater in low-risk areas than in high risk ones [8].



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Therefore, in the present study, we aimed to investigate the associations of T1DM with several environmental factors in order to better understand the factors that could initiate or accelerate the autoimmune process leading to the disease.

## Material and methods

A case-control study was conducted in the Children's Medical Centre Hospital, Ali Asghar Hospital and the Diabetes Association between 2004 and 2009. These hospitals are referral centres for childhood endocrinopathies in Iran. Informed consent was obtained from all patients and the study was approved by the Ethics Committees of Tehran University of Medical Sciences.

The index group comprised children  $\leq 16$  years old who were diagnosed or referred to the Children's Medical Centre Hospital for diagnoses of T1DM. Subjects were classified as T1DM based on WHO criteria.

The control group comprised healthy subjects who were below 16 years old with blood glucose levels  $> 6.1$  mmol/L and who did not have any history of taking diabetic medication. The control group was matched by age and gender to the studied population.

Data about study participants was obtained from their parents, most frequently from their mothers, within 12 weeks of the diagnosis of diabetes being established. The information on each patient was obtained by trained health professionals and nurses.

A two page questionnaire was designed to meet the objective of this study. The data was obtained from both cases and controls using the same questionnaires. Accordingly, data regarding the socio-demographic status, gestational and neonatal risk factors was evaluated.

### Statistical analysis

Student's *t* test was used to ascertain the significance of differences between mean values of two continuous variables, and non-parametric Mann-Whitney test was used. Chi-square analysis was performed to test for differences in proportions of categorical variables between two or more groups.

Univariable and multivariable conditional logistic regression methods were also performed. Variables which were related to diabetes at significance level of  $p$  value  $< 0.1$  in univariable analysis were entered into the multivariable analysis. The level  $p < 0.05$  was considered as the cut-off value for significance.

## Results

### Socio-demographic data

In this study, the data of 101 patients with T1DM was gathered for final analysis. There were 41 (40.6%) males

and 60 (59.4%) females with a mean age of 10.3 years (SD 4.5 years). For each case, one control subject, matched for both age and sex, was selected. The mean age at the time of diabetic diagnosis was 6.7 years (SD 3.2 years). In seven cases, a positive family history of diabetes was present among the parents. Also, in eight cases, a sibling was found to be diabetic at the time of evaluation.

Forty eight patients developed polyphagia, polydipsia or polyuria as the first clinical manifestations of the disease, while in 17 patients, diabetic ketoacidosis was the initial clinical presentation. Also, the presence of diabetes in a first degree relative led to the diagnosis of diabetes in six patients. In the other patients, routine laboratory tests revealed the presence of diabetes.

Table I shows the socio-demographic characteristics of the studied children according to diabetic and healthy subjects.

### Gestational risk factors

Among the risk factors being present in the gestational period of the mothers, maternal age at the time of delivery, the child's birth order and weight, and the medical events during gestation were evaluated.

The mean age of mothers at the time of delivery for both cases and controls were 26.2 (SD 6.22) and 24.3 (SD 4.45) years, respectively ( $p$  value = 0.017). This variable also showed a significant difference between the two groups on univariable analysis for the two cut-off points of 25 and 35 years (Table II). However, such an effect was only observed for the cut-off point of 35 years on the multivariable model (Table III).

There was no difference in either the order of the birth child or birth weight between the groups (Table II). The mean weight and height at birth were 3.27 kg (SD 0.5) and 49.7 cm (SD 2.63) for cases and 3.18 kg (SD 0.45) and 49.12 cm (SD 2.8) for the controls, respectively.

Maternal events including the incidence of pre-eclampsia and the amount of increase in weight gain during pregnancy were also not significantly different between the two groups.

### Neonatal risk factors

The type of delivery, type and duration of child feeding and the presence of vitamin D supplementation during the first year of life were investigated in all subjects.

The rate of caesarean section was significantly increased in the cases (Table II).

The mean duration of breast feeding was 16.2 (SD 8.37) and 20.3 (SD 8.69) months for the cases and control groups respectively ( $p$  value  $< 0.001$ ). While univariable analysis revealed total durations of breast feeding of more than 12 months to have a protective effect against the development of T1DM, such associations were not

**Table I. Socio-demographic characteristics of the studied diabetic and healthy subjects****Tabela I. Charakterystyka socjodemograficzna dzieci chorych na cukrzycę i dzieci z grupy kontrolnej**

Variables	Cases n = 101	Controls n = 101
<b>Age group (years)</b>		
< 5	11	11
5–10	49	49
11–16	41	41
<b>Sex</b>		
Male	41	41
Female	60	60
<b>Education of father</b>		
Illiterate	11	8
Primary	31	34
Intermediate	25	28
Secondary	17	21
University	16	10
<b>Education of mother</b>		
Illiterate	9	5
Primary	45	51
Intermediate	29	27
Secondary	10	10
University	7	8
<b>Occupation of father</b>		
Not working	6	6
Manual	25	22
Sedentary/professional	30	37
Businessman	35	32
Government officer	5	4

present on the multivariable analysis (Table III). On the other hand, the number of cases who were fed for more than six months exceeded significantly that in the control group ( $p$  value = 0.03) and were shown to be an independent risk factor for diabetes (odds ratio = 4.38, 95 CI 1.05, 18.20). Also, for the time of introduction of supplementary feeding, no difference was observed between the groups.

Vitamin D supplementation was present in only 27% of patients during their first year of breast feeding; while in the control group 65% received vitamin supplementation which was significantly higher than the cases group in both univariable and multivariable analyses.

## Discussion

In recent years, many environmental factors have been implicated as risk factors for the development of T1DM [5, 6, 9–18]. Controversy however exists among these

**Table II. Comparison of risk factors between the cases and controls****Tabela II. Porównanie występowania czynników ryzyka w grupie dzieci chorych na cukrzycę i dzieci z grupy kontrolnej**

Variables	Cases n = 101	Controls n = 101	p value
<b>Gestational risk factors</b>			
<b>Maternal age at delivery</b>			
> 35 years	12 (12.1%)	3 (3%)	<b>0.015</b>
> 25 years	54 (53.5%)	40 (40.4%)	<b>0.013</b>
<b>Child birth order</b>			
1	45 (44.6%)	40 (39.6%)	0.47
2	30 (29.7%)	41 (40.6%)	0.12
3+	26 (25.7%)	20 (19.8%)	0.3
<b>Child birth weight</b>			
> 4,000 g	5 (5.6%)	4 (4.4%)	0.7
<b>Maternal events</b>			
Pre-eclampsia	9 (8.9%)	10 (10.8%)	0.67
Weight gain > 10 kg	56 (55.5%)	59 (58.3%)	0.6
<b>Neonatal risk factors</b>			
<b>Type of delivery</b>			
Caesarean	41 (40.6%)	23 (22.8%)	<b>0.006</b>
<b>Type of feeding</b>			
Breast feeding > 6 months	78 (78.2%)	90 (89.1%)	0.3
Breast feeding > 12 months	72 (72.2%)	87 (87.1%)	<b>0.009</b>
Cow milk fed > 6 months	90 (90.9%)	82 (81.9%)	<b>0.03</b>
<b>Vitamins</b>			
Vitamin D supplementation	27 (27.5%)	65 (65%)	<b>0.07</b>

**Table III. Factors related to T1DM according to multivariable logistic regression analysis****Tabela III. Czynniki ryzyka związane z cukrzycą typu 1 zgodnie z wynikami wieloczynnikowej analizy regresji**

Variable	OR (95% CI)	p value
Maternal age > 35 years at delivery	11.96 (1.33, 17.67)	0.027
Caesarean delivery	5.75 (2.45, 13.47)	< 0.001
Cow milk fed > 6 months	4.38 (1.05, 18.20)	0.03
Lack of vitamin D supplementation	3.78 (1.60, 8.89)	0.002

studies, giving conflicting findings in this regard. Also, very few studies have investigated multiple environmental factors in the development of T1DM [5, 6, 11, 18]. In the present study, maternal age at delivery, duration of cow milk feeding, vitamin D supplementation

and the type of delivery were significantly associated with diabetes.

Although in the present study, longer duration of breast feeding was associated with protection against T1DM, we did not identify any relationship between early introduction of cow or formula feeding and development of T1DM. Also, while we observed a protective effect for breast-feeding of more than 12 months on univariable analysis, such an effect was not encountered in the multivariable model. The only independent infant nutritional factor associated with the development of T1DM was the total duration of cow milk consumption. The data regarding the associations between the parameters of infant nutrition and the development of diabetes are conflicting. While most studies report a protective role of breast feeding [19–21], there are studies which do not support this hypothesis [22]. Since most studies are performed retrospectively, the presence of recall bias may be responsible for these discrepancies. Therefore, prospective interventional studies may provide final answers for the role of nutritional risk factors in the development of diabetes.

Data regarding the role of caesarean section as a risk factor for the development of T1DM is conflicting [23–26]. In a previous large study performed in Sweden, relatively small increases in the risk of T1DM were reported [23]. However, the observation of a large odds ratio (5.75) in our study suggests that this factor could be considered as a strong independent risk factor for the future development of DM.

In the present study, vitamin D supplementation during the first year of breast feeding was associated with a decreased risk of T1DM development. This observation has also been supported by other studies [13, 27]. In a large European multicentre survey, vitamin D supplementation during infancy was associated with a reduced risk of T1DM [27]. Therefore, based on these findings, vitamin D supplementation has protective effects against T1DM and should be administered for all infants, at least during their first year of life.

## Conclusions

In conclusion, environmental factors play an important role in the pathogenesis of T1DM. Identification of such factors is crucial, since they offer potential means for intervention aimed at the prevention of the disease. As most children with newly diagnosed diabetes are sporadic cases, such environmental modifications may affect the natural history of T1DM in future.

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