

Breastfeeding, Nutrition, Parental Smoking And Type 1 Diabetes: A Case-Control Study At Ege University Children's Hospital

İpek Çiçekli (✉ cicekliipek@gmail.com)

Acıbadem Mehmet Ali Aydınlar Üniversitesi: Acıbadem Üniversitesi <https://orcid.org/0000-0003-4717-6145>

Raika Durusoy

Ege University Faculty of Medicine: Ege Üniversitesi Tıp Fakültesi

Research

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Abstract

Background: It has been suggested that there may be a link between many environmental factors, including dietary antigens affecting diabetes epidemiology.

The main objective of this study is to investigate nutritional risk factors, especially breastfeeding early in life that may be associated with the development of Type 1 DM and to determine the relationship of these factors with the disease.

Methods: The research is a case-control study and was carried out in Ege University Children's Hospital. A total of 248 children aged between 4-14 years were included in the study. The case group was reached from patients diagnosed with Type 1 DM, who applied to the Ege University Children's Hospital; the control group was reached from non-diabetic children applying to the same hospital.

Results: The mean age was found 10.4 ± 3.3 years for cases and 7.4 ± 2.5 years for controls. It was found that each monthly increase in exclusive breastfeeding duration provided a 0.78 fold decrease in the risk of Type 1 DM. Introduction of cereals in the diet at 6th month or earlier was associated with an increased risk of 3.42 fold. Each unit increase in the total number of cigarettes that parents smoked at home had increased the risk of Type 1 DM by 1.15 times.

Conclusions: Prolonged exclusive breastfeeding duration was found to be a protective factor for Type 1 DM, while introducing cereals before the 6th month and parental smoking were found to be important risk factors, which might be another subject for further studies.

Introduction

Diabetes Mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia due to impairments in either insulin secretion and/or insulin effect (1). As of today, 463 million people worldwide have diabetes, 5–10% of which are Type 1 DM. This number is estimated to reach 578 million in 2030 and 700 million in 2045, which can be considered as alarming levels.

Type 1 DM is characterized by insulin deficiency and hyperglycemia, usually with onset in childhood, when the beta cells of the pancreas are destroyed by autoimmune or non-autoimmune reasons (2). In individuals with genetic predisposition (HLA groups at risk), autoimmunity is triggered by the effect of environmental factors (viruses, toxins, emotional stress, others) and progressive β -cell damage begins. Clinical symptoms of diabetes occur when β -cell reserve is reduced by 80–90% (3).

It has been suggested that there are many environmental factors, including dietary antigens (4–6), as well as genetic risk factors (7–11) that affect the epidemiology of Type 1 DM (12). Although not all genotypes with risk have yet been identified, only about 10–15% of individuals at genetic risk develop Type 1 DM (13). In studies conducted on migrants, it has been shown that the incidence of Type 1 DM increases in those who migrate from a region where the incidence of Type 1 DM is low to a region with

high incidence, and the effect of environmental conditions has been emphasized (14). These data were found to be consistent with the results of studies finding that environmental triggers increase and accelerate the development of clinical Type 1 DM despite lower genetic predisposition.

Some nutritional factors contribute to the development of Type 1 DM. Studies in 40 countries worldwide have shown that dietary patterns may impact the development of Type 1 DM (15). Vitamin D, another nutritional factor, may have a protective effect on glycemic control in patients with Type 1 DM (16) and according to a birth-cohort study, the provision of vitamin D supplementation for infants early in life could help to reduce the risk of Type 1 DM (17). The introduction of cow's milk-based infant formulas in the post-natal 1–3 months was found to be associated with an increase in pancreatic beta cell autoantibodies (18) however, another study had shown that cow's milk did not play an important role on the development Type 1 DM (19).

Although many studies have been performed to investigate the role of nutrition in pregnancy and early in life on Type 1 DM, the results have been inconsistent. Breastfeeding (20), probiotic supplementation (21), vitamin C, and zinc supplementation (22) have been shown as possible protective factors against Type 1 DM whereas early exposure to egg, gluten (13, 23) and vegetables (24) might increase risk.

Studies with school-age children have shown that diabetic children are significantly more prone to stress and depression compared to non-diabetic children (25). Beyond the somatic effects of the disease on individuals, diabetic individuals encounter socio-economic consequences affecting their families and entire societies. Frequent comorbidities further increase negative socioeconomic consequences, especially in low and middle-income countries (26).

According to the Social Security Institution's data in Turkey, the costs of diabetes and its complications amount to approximately 23% of the total health expenditure (27). In addition, indirect costs such as the loss of productivity of diabetics, the persons caring for the patient and their family are not included in these cost estimates. Therefore the cost does not reflect the psychosocial effects of the losses of quality-adjusted life years (QALY). Knowledge of modifiable environmental risk factors in Type 1 DM can assist authorities in planning and implementing preventive policies to reduce the burden of the disease. It is yet uncertain which nutritional or other environmental factors are important in the development of Type 1 DM. Moreover, epigenetic mechanisms are not clearly defined.

The main objective of this study is to investigate potential nutritional risk factors, especially breastfeeding early in life that may be associated with the development of Type 1 DM and to determine the relationship of these factors with the disease, independent of other established risk factors.

Methods

Subjects

A case-control study was carried out at the Ege University Children's Hospital, İzmir City, Turkey, over a period of two months from January to March 2020.

A minimum sample size of 105 cases and 105 control with a total of 210 participants was calculated with G-Power using the t-test group, with an effect size of 0.5, an error margin of 0.05, and a power of 95%. About 20% more sample size was added to account for possible non-response and a total of 248 children (122 cases and 126 controls) included in the study.

The data of the study were collected at Ege University Faculty of Medicine Children's Hospital in Bornova/Izmir between 13/01/2020 and 05/03/2020. Children and their parents who admitted to the general paediatrics and endocrinology/metabolic diseases outpatient clinic of the hospital and met the study criteria were examined. The case group comprised of 122 children in the age group of 4–14 years who were diagnosed with Type 1 DM based on World Health Organisation (WHO) and International Diabetes Federation guidelines (28) and who were on follow-up at Ege University Children's Hospital Endocrinology/metabolic diseases outpatient clinic.

The Diabetes outpatient clinic is held once a week (on Thursdays) and on the first Monday of every month. The mean number of diabetic patients attending to the research is 15 patients per day. The control group comprised of 126 non-diabetic children selected from the general pediatric outpatient clinic of the same hospital. A questionnaire was applied face-to-face to the parents of the children. All questions in the study were asked to the parents and separately written informed consent was obtained from children and their parents. In addition, the files of the case group were examined and the date of diagnosis, height, body weight and HbA1C levels at the time of diagnosis were also collected as data.

Children who followed in the Endocrine and Metabolic Diseases Outpatient Clinic, diagnosed with Type 1 DM and aged between 4–14 years were included in the case group. Children who applied to the General Pediatrics Outpatient Clinic, not diagnosed with Type 1 DM, aged 4–14 years were included in the control group. Those who did not want to share their information and could not remember the answers to the questions were excluded from the study. The response rates were 96% and 91% among cases and controls, respectively, for all eligible cases and controls admitting during the data collection period.

Questionnaires

A structured questionnaire was created by the researchers after reviewing the literature related to nutritional and other risk factors for Type 1 DM (13, 14, 22, 29–33). It was administered by interviewing the parents. The questionnaire was related to the child, mother and family of the child. For children; antropometric data, breastfeeding duration, formula consumption, the introduction of some foods to the diet, infections, supplementation (vitamin D and probiotic) early in life and physical activity were questioned; for mothers, anthropometric data and history during pregnancy; for the family sociodemographic characteristic such as education, whether the child lived with parents, smoking, family history were asked. In addition, the case group was examined about the age at diagnosis of the disease, the Hba1c level and the percentiles at diagnosis. In this study, breastfeeding duration was defined as the total duration of breastfeeding and exclusive breastfeeding meant that the child received only breast milk

(no other liquids or solids given, not even water with the exception of oral rehydration solution, or drops/syrups of vitamins, minerals or medicines) from the mother (34). The percentiles were calculated based on the percentile values table of Neyzi et al.(35). Parents' BMIs were classified according to WHO's obesity scale (36). Finally, high-intensity physical activity was defined as "physical activities that increase the maximum heart rate by 70–85%" (37). Examples of physical activities were given (running, basketball, football, tennis, swimming, skipping rope) by the researcher.

Statistical Analysis

The obtained data were analyzed by using SPSS software. The quality of the data had been checked prior to analysis. Descriptive variables of cases and controls were compared with Student t-test (continuous variables), Mann Whitney U test (non-parametric) and chi-square test (categorical variables). In order to reveal the relationship between significant parameters and the development of Type 1 DM independently from other factors, age and sex-adjusted logistic regression analysis were performed. Since the difference in mean ages of the two groups was found to be significant, other variables were evaluated adjusting for age and gender. Sex and age adjusted multivariable logistic analysis, adjusted odds ratios (aORs) and 95% confidence intervals (95% CIs) were used to identify possible risk factors of the disease. In all analyzes, $p < 0.05$ was considered statistically significant. The dependent variable was having Type 1 DM. Maternal factors, family history, family characteristics, nutritional characteristics early in life were the independent variables.

Results

Characteristics of children

Totally 248 children were included in the study, with 122 cases and 126 controls. The mean age of the case and control groups were 10.44 ± 3.30 and 7.48 ± 2.56 years, respectively ($p < 0.05$). The mean height percentiles were higher in controls (means 45.66 ± 31.16 and 58.00 ± 31.88 , $p = 0.003$) and mean BMI percentile was higher in the case group (means 55.20 ± 29.86 and 40.32 ± 35.02 , $p < 0.001$). The cases' mean age at diagnosis was found 6.30 ± 4.03 years and the mean disease duration was 4.20 ± 3.85 years. A significant difference was found in the family history of Type 1 DM. There was a type 1 DM history in 10.7% of the case group and only 0.8% in the control group ($p = 0.001$). No significant difference was found child's living status with parents and parents' education status. However a significant difference was found in physical activity level. There was no difference between the duration of vitamin D use. In both groups, no one was supplemented with probiotics in the postpartum first year. The controls' rate of living in urban was found significantly higher (Table 1).

Table 1
The main characteristics of children

	Cases	Controls	<i>p</i>
Sex (n = 248)			
<i>Female</i>	65 (53.3%)	54 (42.9%)	0.101
<i>Male</i>	57 (46.7%)	72 (57.1%)	
Age (n = 248)	10.44 ± 3.30	7.48 ± 2.56	< 0.001
Age at diagnosis of Type 1 DM (years, n = 117)	6.30 ± 4.03	-	
Duration of Type 1 DM (years, n = 117)	4.20 ± 3.85		
Birth weight (n = 243)			
< 2500 g	15 (12.3%)	12 (9.8%)	0.548
2500–3999 g	99 (81.1%)	105 (86.1%)	
> 4000 g	8 (6.6%)	4 (4.1%)	
Having an infection in the first year after birth (n = 243)			
<i>Yes</i>	65 (53.7%)	55 (45.1%)	0.178
<i>No</i>	56 (46.3%)	67 (54.9%)	
Having diarrhoea in the first year after birth (n = 191)			
<i>Yes</i>	37 (44.6%)	38 (35.2%)	0.188
<i>No</i>	46 (55.4%)	70 (64.8%)	
Physical activity (n = 243)			
<i>None</i>	68 (56.2%)	89 (73.0%)	0.018
<i>Once or twice a week</i>	38 (31.4%)	21 (17.2%)	
<i>Three or more times a week</i>	15 (12.4%)	12 (9.8%)	
Transportation to school			
<i>Not going to school</i>	11 (9.1%)	11 (9.1%)	0.057
<i>On foot</i>	56 (46.3%)	61 (50.4%)	
<i>By school bus</i>	23 (19.0%)	26 (21.5%)	
<i>By car/bus</i>	31 (25.6%)	22 (18.2%)	
<i>By bicycle</i>	-	1 (0.8%)	

	Cases	Controls	<i>p</i>
Residence (n = 245)			
<i>Urban</i>	35 (28.7%)	54 (43.9%)	0.011
<i>District</i>	84 (68.9%)	62 (50.4%)	
<i>Rural</i>	3 (2.5%)	7 (5.7%)	

Maternal characteristics of mothers

The mean year of birth interval was higher in cases. A significant difference was found in the birth intervals with univariate analysis but not in multivariate analysis ($p = 0.036$). Those with a birth interval of more than 6 years constituted 20.7% of the cases, 8.0% of controls (Table 2). In the case group, no mother supplemented with probiotics during pregnancy and 98.4% of the control group did not supplement with probiotics during pregnancy.

Table 2
Maternal factors

	Cases	Controls	<i>p</i>
Mean age at birth (years) (n = 248)	27.59±5.33	27.89±5.41	0.662
BMI classification before pregnancy (n = 237)			
<i>Under weight</i>	6 (5.2%)	8 (6.6%)	0.476
<i>Normal weight</i>	73 (63.5%)	85 (69.7%)	
<i>Over weight</i>	26 (22.6%)	18 (14.8%)	
<i>Obese</i>	10 (8.7%)	11 (9.0%)	
Mean of total weight gained during pregnancy (n = 239)	14.41±12.45	13.06±8.53	0.324
OGTT during pregnancy (n = 245)			
<i>Yes</i>	85 (71.4%)	96 (76.2%)	0.396
<i>No</i>	34 (28.6%)	30 (23.8%)	
Gestational Diabetes Mellitus during pregnancy* (n = 190)			
<i>Yes</i>	17 (18.7%)	13 (13.1%)	0.295
<i>No</i>	74 (81.3%)	86 (86.9%)	
Form of delivery (n = 246)			
<i>Vaginal</i>	40 (33.1%)	43 (34.4%)	0.824
<i>C-section</i>	81 (66.9%)	82 (65.6%)	
Mean of birth order (n = 246)	1.64±0.74	1.68±0.83	0.666
Birth interval (n = 246)			
<i>First child</i>	49 (40.5%)	54 (43.2%)	0.036
<i>< 3 years</i>	20 (16.5%)	24 (19.2%)	
<i>3–6 years</i>	27 (22.3%)	37 (29.6%)	
<i>> 6 years</i>	25 (20.7%)	10 (8.0%)	
Supplemented with iron during pregnancy (n = 248)			
<i>Yes</i>	100 (82.0%)	97 (77.0%)	0.332
<i>No</i>	22 (18.0%)	29 (23.0%)	
Supplemented with Vitamin D during pregnancy (n = 232)			

	Cases	Controls	<i>p</i>
<i>Yes</i>	62 (57.9%)	75 (60.0%)	0.751
<i>No</i>	45 (42.1%)	50 (40.0%)	
Supplemented with probiotic during pregnancy (n = 248)			
<i>Yes</i>	-	2 (1.6%)	
<i>No</i>	122 (100.0%)	124 (98.4%)	

Nutritional profiles of children

It was found that the mean duration of exclusive breastfeeding was higher in the control group ($p=0.009$). In the case group, the rate of exclusive breastfeeding for less than 1 month was found to be 47.5%, and 30.6% in the controls (Table 3). This difference was found statistically significant ($p = 0.040$). No statistically significant difference was found between colostrum consumption, total breastfeeding duration, formula consumption and formula preferences.

No statistically significant difference was observed between the introduction month of cow's milk, eggs, fruits, vegetables, and berry fruits. However the introduction of cereals was found to be statistically significant and the cases' introduction was found earlier. 7% of the case group had been introduced to cereals before 6th month as compared to 3.3% of controls, while 34.4% of controls were introduced to cereals after 8 months, compared to 16.7% of cases (Table 3).

Table 3. Nutritional characteristics of children early in life

	Cases	Controls	<i>p</i>
Breastfeeding			
<i>Received within first hour after birth</i>	104 (86.0%)	102 (82.3%)	0.430
<i>Colostrum fed</i>	116 (95.9%)	111 (89.5%)	0.057
Exclusive breastfeeding duration (n=244)			
<i>Any or less than 1 month</i>	57 (47.5%)	38 (30.6%)	0.040
<i>1-2 month</i>	19 (15.8%)	28 (22.6%)	
<i>3-5 month</i>	27 (22.5%)	30 (24.2%)	
<i>6 month</i>	17 (14.2%)	28 (22.6%)	
Total breastfeeding duration (n=246)			
<i><6 month</i>	21 (17.2%)	21 (16.9%)	0.887
<i>6-12 month</i>	29 (23.8%)	27 (21.8%)	
<i>13-18 month</i>	31 (25.4%)	27 (21.8%)	
<i>19-24 month</i>	28 (23.0%)	35 (28.2%)	
<i>≥ 24 month</i>	13 (10.7%)	14 (11.3%)	
Formula consumption			
<i>Not consumed</i>	59 (49.2%)	63 (51.2%)	0.057
<i>< 6th month</i>	38 (31.7%)	49 (39.8%)	
<i>≥6th month</i>	23 (19.2%)	11 (8.9%)	
Introduction of complementary foods (n=245)			
<i>Before 6st month</i>	28 (23.0%)	23 (18.7%)	0.602
<i>6th month</i>	79 (64.8%)	87 (70.7%)	
<i>>6th month</i>	15 (12.3%)	13 (10.6%)	
	Mean ± SD	Mean ± SD	
Exclusive breastfeeding duration (month)	1.88±2.23	2.67±2.38	0.009
Total breastfeeding duration (month)	16.05±10.72	16.38±10.08	0.802
Introduction of complementary foods (month)	5.91±1.37	6.08±2.06	0.436
Cow's milk (n=237)			

<i>0-6th month</i>	14 (11.9%)	16 (13.4%)	0.900
<i>7-12th month</i>	76 (64.4%)	77 (64.7%)	
<i>> 12th month</i>	28 (23.7%)	26 (21.8%)	
Cereals (n=236)			
<i>< 6th month</i>	8 (7.0%)	4 (3.3%)	0.005
<i>6-7th month</i>	87 (76.3%)	76 (62.3%)	
<i>≥ 8th month</i>	19 (16.7%)	42 (34.4%)	
Egg (n=239)			
<i>< 6th month</i>	5 (4.3%)	8 (6.5%)	0.266
<i>6-7th month</i>	65 (56.0%)	78 (63.4%)	
<i>≥ 8th month</i>	46 (39.7%)	37 (30.1%)	
Fruits and vegetables (n=244)			
<i>< 6th month</i>	22 (18.2%)	16 (13.0%)	0.520
<i>6-7th month</i>	89 (73.6%)	95 (77.2%)	
<i>≥ 8th month</i>	10 (8.3%)	12 (9.8%)	
Berry fruits (n=244)			
<i>< 6th month</i>	-	16 (13.0%)	0.706
<i>6-7th month</i>	91 (75.2%)	95 (77.2%)	
<i>≥ 8th month</i>	10 (8.3%)	12 (9.8%)	

Parental smoking

In the case group, the mean number of cigarettes that parents smoked daily was 10.08 ± 12.89 , while it was 7.13 ± 8.57 in the control group ($p = 0.042$). Similarly, the mean number of cigarettes smoked at home was significantly higher in the case group (Table 4).

Table 4. Pre-natal, post-natal and daily parental smoking

	Cases	Controls	<i>p</i>
Smoking during pregnancy (n=247)			
<i>No smoking</i>	16 (13.1%)	18 (14.4%)	0.769
<i>Smoking</i>	106 (86.9%)	107 (85.6%)	
Smoking during lactation (n=243)			
<i>No smoking</i>	16 (13.3%)	15 (12.2%)	0.790
<i>Smoking</i>	104 (86.7%)	108 (87.8%)	
Smoking at home (n=242)			
<i>No smoking anywhere at home</i>	51 (42.1%)	49 (40.5%)	0.794
<i>Smoking at home</i>	70 (57.9%)	72 (59.5%)	
	Mean ± SD	Mean ± SD	
The number of cigarettes parents smoke			
<i>Daily smoked (n=229)</i>	10.08±12.89	7.13±8.57	0.042
<i>Daily smoked at home (n=235)</i>	3.51±5.41	2.12±3.28	0.018
Smoking near the child until the diagnosis of Type 1 DM (n=118)			
<i>No smoking</i>	54 (45.8%)		
<i>Smoking</i>	64 (54.2%)		
	Mean ± SD		
Number of cigarettes parents smoked daily at home until the diagnosis (n=62)	18.44±12.63		
Smoking pack-years (n=61)	6.09±6.43		

Multivariate analysis

According to non-parametric correlation analyzes, exclusive breastfeeding duration and total breastfeeding duration were not found to be associated with the age at diagnosis of Type 1 DM.

According to the multivariate logistic regression, prolonged exclusive breastfeeding duration and living in a rural area were found as protective factors (respectively aOR = 0.78, %95 CI: 0.66–0.93, aOR = 0.10, %95 CI: 0.01–0.89). Although there was no significant difference found in Type 1 DM risk with introduction to cereals 12th months and after, it was found that introduction to cereals at 6th month and before increased the risk of Type 1 DM by 3.42 (1.42–8.24) times compared to between 7-11th months, independent of other risk factors. Similarly formula consumption after the 6th month was associated with an increased risk of Type 1 DM compared to no formula consumption. Moreover it was determined that each unit of increase in the total number of cigarettes parents smoked daily at home and near the child increased the risk of Type 1 DM by 1.15 (1.03–1.29) times (Table 5).

Table 5
Multivariate logistic regression analysis of selected variables

Risk factors	aOR
	(%95 CI)
Risk factors (if categorical, reference categories in superscript)	
Age(<i>continuous variable</i>)	1.47 (1.28–1.68)
Sex ^{girl}	0.78 (0.36–1.67)
Birth interval ^{first child}	
< 3 years	1.66 (0.55-5.00)
3–6 years	0.99 (0.36–2.73)
> 6 years	2.20 (0.65–7.46)
Exclusive breastfeeding (month)	0.78 (0.66–0.93)
Introduction to cereal ^{7–11.month}	
≤ 6th month	3.42 (1.42–8.24)
≥ 12th month	0.57 (0.17–1.95)
Mother's education level (high school degree and above)	0.53 (0.21–1.36)
Father's education level (high school degree and above)	0.95 (0.38–2.40)
Family history of Type 1 DM	7.13 (0.70-72.74)
Residence ^{urban}	
District	1.86 (0.84–4.11)
Rural	0.10 (0.01–0.89)
Formula consumption ^{no formula}	
< 6th month	0.63 (0.26–1.51)
≥ 6th month	3.82 (1.18–12.41)
The parents smoke cigarette/day at home	1.15 (1.03–1.28)

Discussion

Elimination of preventable environmental risk factors associated with Type 1 DM is an important step in the prevention of the disease. However, it has not been precisely explained which factors play a key role

and when and in which situations the factors should be eliminated (13). In this research we have explored possible preventable environmental triggers and determinants, especially nutrition early in life.

We found that each monthly increase in the duration of exclusive breastfeeding provides reduction in Type 1 DM risk. However introducing the cereals before the 6th month was found to be an important risk factor. Similarly each one-unit increase number of cigarettes parents smoke daily at home increased the risk of the disease. Birth interval which was found significant in univariate analyzes, lost its meaning in multivariate analysis.

Breastmilk

The effect of breast milk, which is the first food of the newborn, on Type 1 DM is a controversial issue. There are many studies in the literature that show a protective effect, an effect and even a predisposing effect (22). It has been suggested that the protective effect of breastmilk is through reducing neonatal intestinal permeability. WHO recommends exclusively breastmilk in the first six months of life and breastmilk up to the age of two because feeding children with exclusively breast milk for the first six months after birth prevents diarrhea, respiratory diseases and provides all the nutrients and fluids the infant needs for optimal growth and development.

Holmberg et al. (2007) found that the duration of total breastfeeding for less than 4 months is a risk factor for the development of beta cell autoimmunity in children under five years of age (OR: 2.09). In the same study, it was concluded that breastfeeding for less than 4 months increased the risk of developing beta cell autoantibodies (38). One study has shown that the risk of Type 1 DM in childhood can be reduced risk, even with breastfeeding only in the first weeks of life. However, the relationship observed between breastfeeding alone and Type 1 DM was unexplained independently of certain risk factors for DM such as gestational DM, birth weight, gestational age, maternal age, birth order and mode of delivery (20). Unlike these studies in a series of prospective studies investigating the relationship between breast milk and the development of pancreatic beta cell autoimmunity, no effect of breastfeeding has been reported (39, 40).

We found that prolonged exclusively breastfeeding duration was a significantly protective factor against Type 1 DM. The same effect was not observed with total breastfeeding duration. In some studies, exclusive breastfeeding and total breastfeeding duration were not compared and the duration of general breastfeeding was taken as a variable. Moreover, while asking the duration of exclusive breastfeeding, the definition of exclusive breastfeeding was explained as "the total time in which the baby takes only breast milk, and no other liquid (including water) or solids other than oral rehydration solution or vitamins, minerals or drugs/syrups are given" in this study. While making statement, after the parents answered, "Have you ever given water during this period?" was asked again to be sure. In this process, there were parents who changed their answers after the second question. Therefore, different results may have been obtained in studies where this distinction was not made clearly.

Cow's milk and formula consumption

Early exposure to cow's milk proteins has been studied in terms of beta cell autoimmunity and the risks of clinical disease development. Early introduction of cow's milk proteins into the diet may trigger inflammation of the intestinal mucosa and increase intestinal permeability. Some studies have shown that early exposure to cow's milk proteins increases the risk of beta cell autoimmunity and Type 1 DM. However, Knip and Simell (2012) found no relationship between Type 1 DM and cow's milk proteins (14). We also did not find an association with the timing of cow's milk introduction. It has been observed that consumption formula at 6 months and later increased the risk of Type 1 DM in this research. However, while the risk of Type 1 DM was expected to increase with the consumption of formula 6 months and before compared to those who did not consume, it a statistically significant change was not observed. As in our study, case-control studies always have the potential for bias. It is not easy to collect accurate and unbiased data on past exposures. This result may be explained in three ways: First; there may be a bias in choosing the control group from the same tertiary care and university hospitals with Type 1 DM patients. Considering the socioeconomic status of children admitting to a university hospital, formula may have been introduced earlier than the community and could not represent clearly the healthy control group. Second; there may have been a response bias. Third; since the mean age of children with Type 1 DM is significantly higher, parents may have recall bias. Although it is easy to identify potential sources of bias, it is not possible to predict the true impact of these biases on results.

Introduction to cereals

A study in non-obese diabetic rats concluded that decreased the intraepithelial infiltration of T cells and decreased incidence of autoimmune Type 1 DM and enteropathies with a gluten-free diet compared to the controls. This result was explained by the hypothesis that the gluten-free diet may prevent gliadin peptides from crossing the intestinal barrier by reducing intestinal permeability, thus preventing the development of pancreatic autoimmunity (13). Our study supports this argument since introducing cereals before the 6th month was found to be an important risk factor. In our study, were not separated according to their gluten content, they were questioned overall, but wheat production and consumption ranks in the first place among cereals in Turkey (41). So wheat containing cereals (including gluten) are expected to be added in the diet of infants in the transition to complementary foods at first. Nevertheless, it could not be confirmed specifically that gluten exposure was earlier in cases, but it was found that cereal introduction prior to 6th month was associated with an increased risk of Type 1 DM.

Parental smoking

Smoking and/or passive smoking is another risk factor associated with DM. It can mediate insulin resistance through changes in insulin secretion secreted by the beta cell of the pancreas, causing impaired glucose metabolism that can lead to diabetes (42). There are studies in the literature that confirm (43,44) this result or contradict (45). We found that a one-cigarette increase in the total number of cigarettes that parents smoked daily at home was associated with an increased risk of Type 1 DM, independent of other risk factors.

We have many limitations in the study. Case-control studies are prone to some sources of bias like recall bias, or the control group's selection from the hospital. Many of the established risk factors were questioned, in order to overcome confounding. The gestation week was not questioned at birth, so it could not be evaluated whether the birth weight was normal for gestational age. In addition, the vaccination status of the children was not asked, and, abortion was not researched while questioning the birth interval and birth order so it may be a confounding factor. Since infections in the first three years were questioned by anamnesis, their bacterial/viral status could not be determined and their relationship with enteroviruses could not be investigated.

Determining the contribution of nutritional factors and their interactions with predisposing and/or protective genes to the disease is important in establishing preventive policies. Considering the limitations of the study, it is thought that large-scale cohort studies may be useful in determining the risks of birth interval, birth weight, postpartum vitamin D supplementation, nutrition early in life and other risk factors in the development of Type 1 DM. In the researches, the mechanisms of risk factors should be defined precisely and new approaches could be applied.

Conclusions

Independent of all other risk factors, prolonged exclusive breastfeeding duration was found to be a protective factor for Type 1 DM, while introducing cereals before the 6th month was found an important risk factor. Similarly, the Type 1 DM risk increased as the total number of cigarettes that parents smoked daily at home increased, which might be another subject for further studies.

Declarations

Authors' contributions

R.D., and İ.Ç. contributed to the design and implementation of the research, to the analysis of the results. İ.Ç. contributed to the writing of the manuscript. R.D. encouraged İ.Ç. to investigate and supervised this work. All authors read and approved the final manuscript for submission.

Availability of data and materials

The dataset could be obtained from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The research was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ege University Faculty of Medicine Clinical Research Ethics Committee (decision no.10059, dated 9 January 2020). Written approval was obtained from the administration of the Department of Child Health and Diseases before starting the study.

Competing interests

We have no known conflict of interest to disclose.

Consent for publication

Not applicable.

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