Association between Breastfeeding Patterns and Type 1 Diabetes among Children

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ABSTRACT
Background: Though factors such as breastfeeding (BF), cow's milk formula, and cereals are among the dietary factors linked to T1D development, their role is still debatable.
Objective: This study aimed to assess the relationship between BF patterns and the development of T1D.
Subjects and Methods: The study is an epidemiologic hospital-based case-control study in Ismalia city, Egypt. 140 children 15 months- to 13 -year-old, from both sexes were included in two groups; the T1D cases (n=70) and the nondiabetic; age-and-sex-matched, control group (n=70).
Results: The proportion of children who received exclusive breastfeeding (EBF) was low in both cases and controls but significantly lower among cases (11% vs 53% respectively, P<0.05) with almost nine times rise in the odds of T1D. More T1D children depended on formula feeding (FF) during their infancy than controls (40% vs 14% respectively, P<0.05) with four folds rise in the odds of T1D. T1D patients who had FF (n= 28) started it at an earlier age compared to controls who had FF (n=10) (mean age 3.2 vs 12.3 months respectively, P<0.05). Likewise, the onset of weaning took place at the age of four months among T1D cases vs five months among controls (P<0.05). No association was detected between T1D and the sociodemographic or maternal obstetric factors.
Conclusion: Short-term BF or no BF at all may be a substantial risk factor for T1D. FF and the early age at its start increase the odds of T1D.
Keywords: Type 1 diabetes, Children, Exclusive breastfeeding, Formula feeding, Egypt.

INTRODUCTION

Type 1 diabetes (T1D) is defined as high blood sugar levels brought on by a deficit in the production, function, or both, of insulin leading to a variety of metabolic disorders [1] and in the long run, damage to tissues and organs [2] in addition to the emotional and physical burden on patients and families [3]. T1D could develop at any age but most commonly in childhood and young adulthood [4].

It is the third most common noncommunicable disease (NCD) in children and its annual incidence has been increasing by about 2%-5% worldwide [1]. Genetic susceptibility plays a role in the development of T1D, yet, the increased incidence during the past five decades strongly suggests an important role for nongenetic factors such as environmental or nutritional factors [1, 4]. About 129,000 children in the Middle East have T1D of whom nearly 50% exist in Egypt and Saudi Arabia [5]. In Egypt, the estimated T1D age-adjusted incidence was 3.1 % and the age-adjusted prevalence was 26.8 % [6].

Recent researches indicate that the increasing rates of NCDs, including T1D, in Egypt are probably linked with the decline in BF practice with subsequent use of complementary and/or FF. This suggests that early life exposures to some environmental or dietary factors may have a significant role in the development of T1D [2, 7]. Also, large ecological and case-control studies supported the hypothesis that BF features a protective effect against T1D [4, 8].

According to research on animal models, a gluten-free diet greatly lowered the likelihood of developing T1D compared to a cereal-based diet. Thus, the pathogenesis of T1D is assumed to be influenced by food. Additionally, two significant, human prospective cohort studies have found a relationship between an early gluten-containing infant diet and the development of autoantibodies against pancreatic islets. As well, there is evidence that the intestinal immune system plays a major role in the pathogenesis of T1D. According to certain research, the development of T1D is correlated with short-term BF and early introduction of complex proteins like cow's milk protein. The immune system's maturation is thought to be aided by substances found in human milk, which help prevent the onset of T1D [9, 10].

Other research, however, did not discover such a connection, and other research had even contradictory or insufficient findings to establish a causal relationship [11]. Thus, though factors such as BF, cow's milk formula, and cereals are among the dietary factors linked to T1D development, their role is still debatable. This study aimed to assess the relationship between BF patterns and the development of T1D.

PATIENTS AND METHODS

This was an epidemiologic case-control study conducted in the health insurance hospital in Ismailia city, Egypt, between 12 September 2019 to 12 March 2020. 140 children 15 months- to 13 -year-old, from both sexes were included in two groups: The case group (T1D children) (n=70) and the control group (nondiabetic children) (n=70). Both groups were age-

Received: 19/09/2022
Accepted: 22/11/2022

and-sex-matched. The sample size was calculated using an online tool accessed through: https://clincalc.com/stats/samplesize.aspx where the expected percentage of BF in diabetic children was set to 32% and that of the control children was set to 68% [11]. The case group included T1D patients who were diagnosed and followed up by the hospital's endocrinology outpatient of the hospital. The control group comprised non-diabetic children who attend the pediatric general outpatient at the same hospital. T1D diagnosis was made according to the diagnostic criteria of the American Diabetes Association [12].

Exclusion criteria: Patients with autoimmune diseases, inborn errors of metabolism, and other chronic conditions were excluded.

Data types and collection tools: Data were collected by reviewing patients' medical records and performing anthropometric assessments as follows:

A. Patients' medical records:

I. **Socio-demographic characteristics:** Age in years, sex.

II. **Medical and nutritional history:** Medical condition of the children, family history, perinatal history, and child nutritional history during the first 12 months of life as follows [12,13]:

- ***Type of feeding:***
  - ***Exclusive breastfeeding (EBF):*** The infant received only breast milk for the first six months without any other items except for nutritional supplements such as vitamins or minerals, or medications
  - ***BF and formula feeding (FF):*** The infant received both breast milk and formula milk
  - ***Only FF:*** The infant received formula milk only
- ***Child age (in months) at the onset of weaning:*** Weaning meant the process of switching the infant's meal from breast/formula milk to other foods or drinks including water.

B. Anthropometric assessments: Assessing the height, weight, and body mass index of a child based on age- and sex-specific WHO reference values and standards [13] as follows:

Weight (kg) for age: The weight status was categorized according to WHO z-score growth reference curves as follows:

- Normal weight: ranges from –2 SD to +2 SD.
- Underweight: less than -2 SD
- Overweight: more than +2 SD

Height (cm) for age: Height status was categorized according to the WHO z-score of reference growth curves [13] and categorized into:

- Normal: height ranges from –2 SD to +2 SD
- Stunted: height is < -2 SD

Body Mass Index (BMI) by age (kg/m^2):

The BMI is calculated by the equation of the weight (kg) divided by the square of height (meters), then the result of the equation of each participating child was plotted against the WHO age- and sex-specific BMI Z-score growth curves and categorized as:

- Normal weight: BMI between -2 SD to +2 SD
- Overweight: BMI > +2 SD
- Obese: BMI > +3 SD
- Underweight= BMI < -2 SD

Glycated hemoglobin (HbA1c):

Is the hemoglobin to which glucose is bound. This test is done to measure the average level of blood glucose over the past three months and thus is useful in monitoring the long-term control of diabetes mellitus and the detection of the prediabetic state. It was done in the laboratory department of the health insurance hospital in Ismailia by quantitative colorimetric determination of glycohemoglobin in whole blood. The value of HbA1c is classified as follows [12]:

- Normal blood sugar level: HbA1c is < 5.7%.
- Prediabetic: HbA1c is 5.7% to < 6.5%.
- Diabetic: HbA1c is ≥ 6.5%.
- Controlled diabetes: HbA1c is < 7%.
- Poor diabetic control: HbA1c is ≥ 7%

Statistical Analysis

Data were entered, coded, and analyzed using the Statistical Package for the Social Sciences (SPSS) version 21. To summarize data, the mean ± standard deviation (SD) was used for data in quantitative variables while frequency and percentages were used for data from categorical variables. Comparisons between data groups were done using a Mann-Whitney U test for quantitative variables and a Chi-square or Fisher exact test for categorical variables. A P-value ≤ 0.05 was considered statistically significant.

Ethical consideration:

The study protocol was revised and permitted by The Research Ethics Committee at the Egypt National Nutrition Institute. Informed consent was obtained from each parent after properly orienting them with the study objectives, and implications, and assuring data confidentiality. The study was conducted according to the Helsinki declaration of biomedical ethics.

RESULTS

As displayed in table (1), cases and controls showed no significant differences regarding sociodemographic characteristics (age, sex, and residence).

Table (1) Sociodemographic Characteristics of T1D and control children

Sociodemographic Characteristics	T1D	Control	p-value	OR	95% CI
Age (years) (mean ± SD)	7.69±1.93	7.03±2.07	0.054	NA	1.32, 0.01
Sex (n, %)					
- **Male**	37 (53.0)	35 (50.0)	0.866	1.12	0.58, 2.18
- **Female**	33 (47.0)	35 (505)			
Residence (n, %)					
- **Urban**	45 (64.3)	41 (58.6)	0.487	1.27	0.64, 2.52
- **Rural**	25 (35.7)	29 (41.4)			

NA: not applicable

Regarding growth parameters, table (2) showed that the mean height of T1D children was 125 cm compared to 119 cm for the control group and the mean weight of diabetic children was 27 kg compared to 23 kg for the control group. Most diabetic children (77%) had normal BMI but they had poor glycemic control as indicated by HA1c (the mean was 7% in the diabetic group compared to 4.4% in the control group).

Table (2): Comparison between T1D and control children regarding growth parameters

Growth parameters	T1D	Control	P-value	OR	95% CI
Height (cm) (mean ±SD)	125.39±13.17	119.31±16.03	0.016	NA	1.18, 10.98
Weight (kg) (mean ±SD)	27.29±8.41	23.39±8.23	0.006	NA	1.17, 6.63
BMI (kg/m^2)					
- **Normal**	54 (77.0)	42 (60.0)	0.01	0.3*	0.13, 0.73
- **Underweight**	9 (13,0)	23 (33.0)		1.09**	0.32, 3.68
- **Overweight/ Obese**	7(10.0)	5 (7.0)		3.58***	0.9, 14.25
HA1c %	7.09±0.90	4.43±0.40	0.0001	NA	2.43, 2.89

NA: not applicable *: OR between underweight and normal weight groups **: OR between overweight/obese and normal weight groups, ***: OR between overweight/obese and underweight groups

Table (3) showed a comparison between T1D cases and controls regarding nutritional and family history. Most children in both groups received some sort of BF (not necessarily EBF) for some duration during their infancy.

The proportion of children who did not receive EBF was high in both T1D cases and controls but significantly higher among cases (89% vs 53% respectively, P<0.05) with a rise in the odds of T1D (OR 8.6, 95% CI 3.63, 20.81). More diabetic children depended on formula feeding during their infancy than control children (40% vs 14% respectively) with four folds rise in the odds of T1D (P<0.05, 95% CI 1.76, 9.11). T1D patients (n= 28) who had formula feeding started it at an earlier age (mean= 3.2 months) compared to controls (n=10) (mean= 12.3 months) (P<0.05). Likewise, the onset of weaning took place at age four months among T1D children versus five months among controls (P<0.05).

Table (3): Comparison between T1D and control children regarding the nutritional history

Nutritional history	T1D	Control	P-value	OR	95% CI
Any breastfeeding *(n, %)*					
- *Yes*	61 (87.0)	63 (90.0)	0.791	0.02	0.01, 0.05
- *No*	9 (13.0)	7 (10.0)			
Exclusive breastfeeding *(n, %)*					
- *Yes*	8 (11.0)	37 (53.0)	0.0001	8.6	3.63, 20.81
- *No*	62 (89.0)	33 (47.0)			
Formula feeding *(n, %)*					
- *Yes*	28 (40.0)	10 (14.0)	0.001	4	1.76, 9.11
- *No*	42 (60.0)	60 (86.0)			
Child's age at the start of artificial feeding (months) *(mean ± SD)*	3.2±1.6	12.3±0.22	0.001	NA	-9.48, -8.72
Duration of breastfeeding (months) (mean ± SD)	15 ± 10	16 ± 6.1	0.61	NA	-3.74, 1.74
Child's age at onset of weaning (months)	4±0.51	5.1±0.88	0.001	NA	-1.34, -0.86

NA: not applicable.

Table (4) demonstrated no significant difference between diabetics and controls who received any BF during their infancy in respect of sociodemographic characteristics (child's sex, mother's education, and residence) or maternal obstetric factors.

Table (4): Comparison between T1D and control children (who received any breastfeeding during their infancy) regarding sociodemographic and maternal obstetric factors

sociodemographic and obstetric factors	Breastfed T1D (n=61)	Breastfed Control (n=63)	p-value	OR	95% CI
Sex					
- **Male**	32 (52.5)	33 (52.4)	0.349	1	0.5, 2.03
- **Female**	29 (47.5)	30 (47.6)			
Habitus					
- **Rural**	22 (36.1)	26 (41.3)	0.577	0.8	0.39, 1.66
- **Urban**	39 (63.9)	37 (58.7)			
Mother education					
- **Primary**	2 (0.0)	6 (9.5)	0.273*	0.32	0.06, 1.66
- **Secondary or High Education**	59 (32.8)	57 (90.5)			
Mode of delivery					
- **CS**	23 (37.7)	27 (42.9)	0.172	0.81	0.39, 1.66
- **Normal**	38 (62.3)	36 (57.1)			
Duration of pregnancy					
- **Preterm (< 38 weeks)**	3 (4.9)	5 (7.9)	0.717*	0.6	0.13, 2.62
- **Term (38 - 40 weeks)**	58 (95.1)	58 (92.1)			

NA: not applicable *****Fischer exact test

DISCUSSION

Although the proportion of children who did not receive EBF was significantly higher among cases, it was high in both cases and controls. These alarming figures are consistent with what was detected by national studies such as the Egypt Demographic and Health Survey (EDHS) in 2014 where 71% of newborns younger than two months old were found to be exclusively breastfed but the percentage steadily declined among older infants [14]. The reasons why so many Egyptian mothers struggle to start and continue EBF for the first six months of an infant's life and instead introduce formula feeding are not fully understood. Nevertheless, some studies pointed to that there are several variables that influence the decision to begin and continue EBF, such as sociodemographic characteristics (mother's education level, household income, and parity), residence, cultural attitudes, biopsychosocial variables, health-related variables, and women's employment policies. A study conducted in Egypt in 2021 revealed that mothers who worked longer hours and those who took longer to go to work had poor BF practices more frequently [15]. Similar reasons were stated in other studies conducted outside Egypt such as in Tanzania and Malaysia [16, 17, 18]. In order to focus governmental intervention efforts to reduce newborn morbidity and mortality, it is crucial to understand these reasons.

The current study revealed that non-exclusive breastfed children have an 8.6 times higher risk of developing T1D than the control group. Additionally, the percentage of T1D cases who depended on artificial feeding during their infancy was higher than that of the controls, indicating that artificial feeding could raise the possibility of developing T1D. This result is consistent with other various studies [19, 20, 21]. BF is linked to decreased rate of diabetes triggers according to **Yan *et al.*** 2014's meta-analysis of 25 studies with a total of 226,508 participants from 12 different countries [22].

In another meta-analysis comprising 155,392 children from Norway and Denmark, FF was linked to T1D, with a two-fold higher risk of T1D among non-breastfed compared to breastfed infants [4]. However, a meta-analysis encompassing 43 observational studies and 9,874 T1D patients failed to detect a protective role of BF against T1D [23]. However, this analysis did not study the BF role in T1D before age of three months. These inconsistent findings may be caused, among other things, by the various experimental approaches used in these studies and the diversity in BF practices across nations. Additionally, many studies documenting the minimal or adverse effects of BF frequently track it imprecisely without considering whether it is exclusive or supplemental [24]. Furthermore, the timing of events in infant feeding seems to have a role in T1D epidemiology.

Our study analyzed the durations of EBF and any BF separately. We found that the mean age at the start of weaning (introduction of any complementary food) was four months in diabetics compared to five months in controls, supporting the idea that protection against T1D increases with the increased duration of EBF during the first six months of life, which is consistent with other studies [25, 26, 27]. BF for more than three months and EBF for longer than two weeks has been linked to an estimated 15–30% decreased risk of T1D [25]. As well, regardless of the feeding type, the early start of weaning (before age of four months) appears to be associated with T1D development. This finding is similar to that of other studies where the risk factors for T1D included not only short-term BF (three months or less) but also, the early or late start of complementary feeding (four and six months, respectively) [4, 28]. The introduction of complex dietary proteins, cereals, fruits, berries, and roots during early infancy has also been linked to an increased risk of T1D [28]. A study in Saudi Arabia with 200 T1D children found a correlation between T1D and extended cow's milk consumption (OR = 4.3) and short-term BF (for less than three months after birth) (OR = 3.5) [29]. Some birth cohort studies showed that BF for less than two to four months and cow's milk introduced before the age of four months are associated with T1D development [30]. How these predispositions function exactly is still uncertain. According to recent studies, breast milk possesses several bioactive compounds, such as immunoglobulins, oligosaccharides, insulin, lactoferrin, lysozyme, cytokines, epidermal growth factors, leukocytes, nucleotides, beneficial bacteria, and vitamins. Such compounds promote the infant's immune system indirectly by improving thymus function and directly by increasing gut microbiota diversity and combating pathogenic bacteria and pro-inflammatory chemicals. In light of this, lacking or insufficient BF may increase the risk of developing T1D among other autoimmune diseases. [31].

While there are currently insufficient studies on this topic to substantiate such a link, in T1D patients, there appears to be less microbial biodiversity and a predominance of a microbiome less supportive of maintaining intestinal integrity [32].

Our study did not detect an association between T1D development and sociodemographic or parity status. To the best of our knowledge, current evidence indicated that T1D risk increases with positive family history while low socioeconomic status is associated with an increased risk of poor disease control and complications [33, 34, 35].

CONCLUSION

The current study revealed that a lack of EBF increases the odds of T1D by almost nine times. As well, short-term BF or no BF at all may be a substantial risk factor for T1D. FF and the early age at its start increase the odds of T1D.

IMPLICATIONS

This study helps identify and understand the environmental/dietary exposures influencing the risk of T1D and consequently informs policies and strategies for prevention.

RECOMMENDATIONS

It is important that every mother should try to initiate BF as early as possible and be encouraged to practice EBF for an appropriate duration (preferably six months) to receive beneficial effects for her child, including reducing the risk of diabetes. Collaboration across many medical and social subspecialties is necessary for the beginning and maintenance of EBF.

ACKNOWLEDGEMENTS: The researchers would like to thank all study participants.
CONFLICT OF INTEREST: No conflict of interest was reported by the authors
FUNDING: None stated by the authors.

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