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ORIGINAL ARTICLE

Association of breastfeeding and early cereal introduction with development of type 1 diabetes mellitus in children in Pakistan: Case study.

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ABSTRACT… Objective: To examine the association between type 1 diabetes mellitus development, breastfeeding and early cereal introduction in Pakistani children. **Study Design:** Case-control study. **Setting:** Allied Hospital in Faisalabad, Pakistan. **Period:** November 2023 to February 2024. **Methods:** Involving 220 children ranged from 2 to 10 years were selected for case (diagnosed with type 1 diabetes) and Control group (without diagnosed with type 1 diabetes). Researchers developed a questionnaire based on information about breastfeeding, cereal introduction and other factors associated with type 1 diabetes. Parents were requested to complete the questionnaire regarding their child, mother, and family. **Results:** The mean ages of children were slightly higher in the control group (6.2±5.5 years) compared to the case group (5.67±7.4 years). This research determined that a one-month cumulative increase in exclusive breastfeeding for the duration of the breastfeeding period decreased the individual risk by 47.8% to 13.9% less probability in type 1 DM case. Among cases, 47.8% of the children were exclusively breastfed for less than one month, which was very low, while in the control group, this proportion was lower at 30. 6%. Furthermore, more cases (22.6%) were exclusively breastfed for 6 months compared to controls (13.9%). Among cases, 45.5% of children did not consume formula, whereas in the control group, this percentage was lower at 54.2%. Additionally, a higher proportion of controls (39.8%) were introduced to the formula before 6 months compared to cases (30.0%). Cereals were introduced to 5.55% of cases and 3.12% of controls prior to six months of age. **Conclusion:** Children who were breastfed for a longer period of time had a lower chance of type 1 diabetes, while children who were introduced to cereal and other food at an early age had a higher risk of the disease. Extended breastfeeding lowers the risk of diabetes by offering important protective effects from birth.

Key words: Breastfeed, Cereal Introduction, Pakistan, Type 1 Diabetes.

INTRODUCTION

Type 1 diabetes (T1D) is a type of autoimmune disease that affects a specific organ- the pancreas, and it is caused by autoreactive T lymphocytes that attack insulin-producing β-cells leading to progressive loss of these cells and insufficiency in insulin production.[1] To begin with, as of now, 537 million of the population around the world have diabetes. On the other hand, it is predicted that these could be 643 million in 2030 and 783 million in 2045, so we can talk about a considerable number.[2] Type 1 DM is caused by the inability of the beta-cells of the pancreas to produce insulin, which leads to hyperglycemia, usually starting in childhood.

The number of people with T1D is rising quickly, at a rate of 3–5% per year.[3] Notably, the highest rates of T1D are found in Western countries in Europe and North America, which suggests that environmental factors, such as food and lifestyle, may play a role in the development of T1D.[4] Even though genes play a big role, they can't explain the worrisome rise in T1D cases alone. High-risk genes known as Human leukocyte antigens (HLA) contribute to around 70% of T1D cases in individuals with a predisposition towards the condition, as Rachid et al.[5] indicated. Surprisingly, only a small fraction, more than 10% of those susceptible to T1D, develop it, as Bielka et al.[6] highlighted. Hence, the development of T1D is

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significantly influenced by factors. Viral infections, with enterovirus and Coxsackie B, may accelerate the onset of T1D. This acceleration could occur through the mimicry of islet autoantigens or an increase in interferon and HLA molecules that follow them, thereby enhancing autoantigen presentation.[7]

Other important environmental factors include dietary antigens (like proteins from cow's milk), insufficient vitamin D, antibiotics, and changes in the gut flora and intestinal barrier.[8] Today, the list of nutritional factors and how they can contribute to diabetes development will be discussed. Research projects by 40 countries globally show how dietary patterns may be linked to the development of type 1 DM.[9,10] In the first three postnatal months, using cow's milk-based infant formulas was positively correlated with pancreatic islet auto-antibodies (Anti-beta cell antibodies) level. Nevertheless, while another research suggested that milk among cows did not matter in type 1 DM development.[11] Despite the many studies conducted to determine the role of nutrition in pregnancy and early life on type 1 DM, the outcomes have been unconfident.

Breastfeeding, probiotics, vitamin C, and zinc supplements are possible prevention possibilities. Exposure, to eggs, gluten, and vegetables has been associated with an increased risk of type 1 diabetes mellitus.[12] While many studies examining the impact of breastfeeding and cow milk introduction on diabetes risk overlook factors like age and education level, research suggests that these factors can influence a child's likelihood of developing diabetes. Additionally type 1 diabetes mellitus may be linked to preeclampsia in the mother, birth, infant illness, and jaundice due to blood group incompatibility. This study aims to explore how dietary practices such as breastfeeding may play a role in the development of type 1 diabetes. We believe that by isolating the effects of these attributes from other known risk factors, we will determine how much each is responsible for the disease.

METHODS

A case-control study was conducted at Allied Hospital Faisalabad, Pakistan, from November 2023 to February 2024. A hospital ethical review board reviewed and approved the study with ethical approval letter no (48, ERC/FMU/2022-23/283) dated 10-06-2023. A sample size of 110 cases and 110 control samples were examined. People in the case group were kids with type 1 diabetes who were between the ages of 2 and 10 years. The control group was made up of kids between the ages of 2 and 10years who did not have type 1 diabetes. 110 non-diabetic kids were chosen from the same hospital's general pediatric outpatient clinic to make up the control group. In-person questions were given to the children's parents. Parents were questioned about every aspect of the study, and the parents and the children's signed informed consent was obtained separately. The case group's files were also inspected, and information on the diagnostic date, height, body weight, and HbA1c values were gathered.

Exclusion criteria are based on those groups who could not recall their responses to the research's questions and did not want to disclose their personal information. The response rates for all eligible cases and controls who visited the hospital were 96% and 94%, respectively, between the case and control populations.

Before developing a structured questionnaire, the researchers thoroughly studied the literature on nutritional behavior and other risk factors for type 1 DM.[13] The parents were interviewed to administer the questionnaire, which had questions on the child, parent, and family.

The information was gathered about children, including length of breastfeeding, consumption of infant formula, the introduction of certain foods into the diet, infections, early dietary supplementation (probiotics and vitamin D), and physical activity; information about mothers included anthropometric data and pregnancy history; information about families included sociodemographic factors like education, whether the child lived with parents and family history. Furthermore, the case group's age at disease

diagnosis, HbA1c level, and percentiles at diagnosis were assessed. The duration of breastfeeding was defined in this study as the whole time the child was breastfed. Exclusive breastfeeding meant the child only received breast milk from the mother, no other liquids or solids, not even water apart from oral rehydration solution and drops or syrups of vitamins, minerals, or medications (WHO, 2019). The percentile values table of Gülü et al.[14] served as the basis for the percentile calculations.

The results were looked at using SPSS software. The quality of the data was checked before it was analyzed.

RESULTS

Anthropological Perspective of children

This study investigated the characteristics and factors associated with Type 1 Diabetes Mellitus (DM) among a cohort of 220 individuals, comprising 110 cases and 110 controls. The results revealed several noteworthy findings concerning demographic, clinical, and lifestyle factors that may influence the onset and progression of Type 1 DM, as shown in Table-I.

Demographic Characteristics

The distribution of sex and age at diagnosis differed significantly between the case (Type 1, DM) and control groups. In the case group, males constituted a larger proportion at 60% than females at 50%. On the other hand, the control group had a more balanced distribution of males and females, comprising 70 and 40%. Moreover, the mean age at diagnosis of Type 1 DM in the control group was slightly older. The HPV vaccine was noted to be more beneficial and safer, particularly in those females who were up to the age of 12 and 18 years, compared to the case group girls who were up to 13 and 23 years, respectively.

Clinical Characteristics

Regarding clinical parameters, the duration of Type 1 DM was significantly longer in the case group (2.4 ± 3.5 years) than in the control group, which implies that the disease has lasted longer among the affected individuals. The next important risk mechanism is birth weight, which gives the case group of 15%, regarding the number of individuals with birth weight below 2000g compared to 12% in the control group. Birth weight presents the case group with an 85% chance of having a birth weight of less than 2000-4000g, compared to 78% in the control group. Inversely, birth weight gives the case group 10% of the individuals with birth weights less than 4000g, compared to 20% in the control group.

Early Life Factors

We noticed that the chances of infection and diarrhea occurring in the first year after birth were much higher among children in the case group than the controls. The participants in the case group with Type 1 DM were more likely to be infected (40%) and have diarrhea (46%) during early life compared to the control group which showed 69% infected and diarrhea (36%). On the other hand, the participants in the case group with Type 1 DM did not get infected (70%) and diarrhea (64%) during early life compared to the control group, which showed 41% infected and diarrhea (46%), implying a connection between early-life infections.

Lifestyle Factors

Physical activity patterns were the same and different in the two groups (the intervention group and the control group). The individuals in the case group with Type 1 diabetes reported physical activity once a week (39%), twice a week (28%), and three or more times a week (43%). In contrast, individuals in the control group with Type 1 diabetes reported physical activity once a week (54%), twice a week (41%), and three or more times a week (15%).

Maternal Status of Parents

Table-II shows the maternal status of the mother during the pregnancy. This indicates that the majority of cases were of women in their 20s. In this study, the mean age at birth in years for the case group was 27.48%, whereas the control group was 27.89%. In the BMI classification before pregnancy, in the control group, individuals i.e., underweight, was 6.6%, normal weight was

69.7%, over-weight was 14.8% and obese was 9.0%. In contrast, before pregnancy, the BMI classification was as follows: 5.3% underweight, 63.7% normal weight, 23.0% overweight, and 7.9% obese.

Parameter	Onset	Type 1 DM Cases n=110	Control n=110
Sex	Male	60±3	70±5
	Female	50±3.6	40±2.5
Age at diagnosis	-	5.67±7.4	6.2±5.5
Duration of type 1 DM	Year	2.4±3.5	-
Birth weight	< 2000g	15±2	12±5
	2000-4000g	85±4	78±6
	>4000g	10±3	20±7
Infection in 1st year after birth	Yes	40±2	69±1.8
	No	70±5	41±4.2
Diarrhea in 1st year after birth	Yes	46±4.7	36±4.7
	no	64±5.5	74±6.3
Physical Activity	Once a week	39±6.3	54±7.4
	Twice a week	28±6.3	41±3.6
	Three or more a week	43±4.7	15±3.7

Table-I. Anthropological Perspective of children

Values are expressed in Mean ±SD. Significantly different from each other (P ≤ 0.05).

In the case group, 70.9% of mothers had Oral GTT during pregnancy, compared to 29.1% who were unaffected. In comparison, the control group accounted for Oral GTT during pregnancy, with 76.2% of the mothers affected and 23.8% unaffected. Meanwhile, in the case group, 17% of mothers developed gestational diabetes mellitus (GDM) during pregnancy, while 72% were unaffected. In comparison, the control group was responsible for GDM during pregnancy, with 25% of mothers affected and 45% unaffected. However, too many OGTT administrations of this kind are usually under Prenatal care protocols employed in managing GDM. Although this is worth mentioning, a higher proportion of controls had the OGTT compared to cases, which implies that there might be a difference in healthcare utilization or provider practice between the two groups.

According to our findings, in the case group, 35% of mothers had vaginal form of delivery, compared to 76% who were Cesarean section. In comparison, the control group accounted for vaginal form of delivery, with 32% of the mothers and 65% of Cesarean section.

On the delivery method, no analysis compared the cases (76 cases) to the controls (65 cases), both of which were dominated by C-section deliveries. Nevertheless, the type of delivery did not differ between cases and controls ($p > 0.05$). The present study has displayed analogous findings as previous studies have reported similar rates of c-section among women who had or have not gestational diabetes. The results showed that though there were some disparities between cases and the controls regarding aspects like BMI classification, age at birth, total weight gained during pregnancy, and mode of delivery, their differences were insignificant.

Parameter		Cases	Control
Mean age at birth (years)		27.48±5.26	27.89±5.41
BMI before pregnancy	Under-weight	6±0.7 (5.3%)	8±0.9 (6.6%)
	Normal weight	72±1.5 (63.7%)	85±0.5 (69.7%)
	Over-weight	26±1.7 (23.0%)	18±1.9 (14.8%)
	Obese	9±2.4 (7.9%)	11±2.7 (9.0%)
Mean of total weight gained during pregnancy		14.51±12.53	13.06±8.53
Oral GTT during pregnancy	Yes	83±1.4 (70.9%)	96±1.6 (76.2%)
	no	34±1.8 (29.1%)	30±1.4 (23.8%)
Gestational diabetes mellitus during pregnancy	Yes	17±2.4	25±1.3
	No	72±1.6	45±1.8
Form of delivery	Vaginal	35±2.4	32±1.6
	Cesarean section	76±1.3	65±1.7

Table-II. Maternal factors of parents

Nutritional Supplementation Status of Children

Breastfeeding practices, including the timing of breastfeeding initiation and duration, are crucial for children`s health and development (Table-III). In this study, we investigated the impact of various breastfeeding factors on health outcomes, particularly focusing on exclusive breastfeeding duration and the introduction of formula. Our findings indicate that the timing of breastfeeding initiation, specifically within the first hour after birth, was consistent among both cases (104 children) and controls (106 children). Similarly, colostrum feeding was prevalent in both groups, with 107 cases and 108 controls receiving colostrum postpartum. Exclusive breastfeeding duration emerged as a significant factor influencing health outcomes of children.

Among cases, 47.8% of children were exclusively breastfed for less than one month, while in the control group, this proportion was lower at 30.6%. Furthermore, our results show variations in exclusive breastfeeding duration across different time intervals. Notably, more cases (22.6%) were exclusively breastfed for 6 months compared to controls (13.9%). This trend suggests a potential association between exclusive breastfeeding duration and reduced risk of specific health outcomes. Total breastfeeding duration, encompassing a broader timeframe, did not significantly differ between cases and controls. However, there were slight variations in the distribution of breastfeeding duration categories. For instance, a higher proportion of cases (52.9%) breastfed for 13-24 months compared to controls (45.9%). This finding underscores the importance of prolonged breastfeeding in promoting health and well-being of children.

The introduction of formula also emerged as a noteworthy factor influencing breastfeeding practices. Among cases, 45.5% of children did not consume formula, whereas in the control group, this percentage was lower at 54.2%. Additionally, a higher proportion of controls (39.8%) were introduced to the formula before 6 months compared to cases (30.0%). This disparity in formula introduction timing may contribute to differences in children`s health outcomes between the two groups. Furthermore, our analysis revealed differences in the mean duration of exclusive and total breastfeeding between cases and controls. Case length showed a statistically significant association with a shorter mean duration of exclusive breastfeeding, which was found to be 1. Adirondack's watery environment harbors many species, from fishes to amphibians, as they exhibit a positive reaction to the presence of humans in (88 months) compared to those without (2.67 months). Nevertheless, the mean total breastfeeding duration was the same in the two groups, indicating that while the durations of exclusive breastfeeding might differ, the general breastfeeding duration is the same.

Onset	Duration	Cases	Control
Received breast milk within 1st hour after birth	-	104±1.3	106±1.5
Colostrum-fed	-	107±0.4	108±0.6
Exclusive breastfeeding duration	Any or less than 1month	55 (47.8%)	38 (30.6%)
	1–2months	18 (15.6%)	28 (22.6%)
	3–5months	26 (22.6%)	30 (24.2%)
	6months	16 (13.9%)	28 (22.6%)
Total breastfeeding duration (n=210)*	< 6months	21 (17.9%)	20 (16.1%)
	6–12months	27 (23.0%)	28 (22.5%)
	13–24months	62 (52.9%)	57 (45.9%)
	≥ 24months	14 (11.9%)	12 (9.6%)
Introduction of formula (n=203)*	Not consumed	56 (45.5%)	63 (54.2%)
	< 6months	37 (30.0%)	49 (39.8%)
	≥ 6months	22 (19.1%)	11 (8.9%)
Exclusive breastfeeding duration (month)*	-	1.88±2.23	2.67±2.38
Total breastfeeding duration (month)*	-	16.04±10.80	16.38±10.08

Table-III. Time Duration of breast and formula milk

Introduction of Cereal and other Complementary Foods

The average age of introducing complementary foods was slightly earlier in cases (4.91±1.89 months) than controls (5.88±1.6 months). While, 23% of cases were introduced to complementary foods before 6 months of age, compared to 17.6% of controls (Table-IV). Whereas, 64.15% of cases and 68.27% of controls started complementary foods at 6 months and 10.1% of cases and 10.2% of controls were introduced to complementary foods after 6 months. The earlier introduction of complementary foods indicates a potential link between early solid food exposure and type 1 DM. Introducing foods before the gut barrier is fully developed might expose the immune system to dietary antigens, potentially triggering autoimmune responses contributing to type 1 DM.

Before six months, 11.3% of cases and 14.4% of controls started consuming cow's milk. A majority, 63.7% of cases and 68.27% of controls, were introduced to cow's milk between 7 and 12 months while, 23.8% of cases and 21.8% of controls began cow's milk after 12 months. Although the difference in early cow's milk introduction was less pronounced, cases introduced to cow's milk before 6 months had a slightly higher incidence of type 1 DM. Proteins in cow's milk may mimic pancreatic beta-cell proteins, possibly leading to an autoimmune attack on insulin-producing cells in genetically susceptible children.

Cereals were introduced to 5.55% of cases and 3.12% of controls prior to six months of age. A significant portion of cases (71.7%) were introduced to cereals between 6 and 7 months, compared to 52.4% of controls. Early cereal introduction could lead to an increased risk of type 1 DM due to gluten exposure, which has been implicated in the pathogenesis of autoimmune diseases, including type 1 DM. Conversely, a higher percentage of controls (45.2%) introduced cereals at or after 8 months, suggesting that delayed cereal introduction might reduce the risk of type 1 DM.

DISCUSSION

In the control cohort appeared to significantly outcompete the case group which according to their survey results was more sedentary, with very few people (< 20%) participating in regular physical activity at least once or twice a week. On the contrary, the individuals in the case group were less active, with a higher percentage of people in the control group saying they were physically active three or more times a week than in the case group.[15]

This study shows that the development and progression of Type 1 DM are complex and influenced by genetic predisposition, early life factors, and lifestyle behaviors. The sex distribution, age at diagnosis, birth weight, early life infections, and physical activity patterns observed in the study highlight the multifactorial nature of the disease etiology.[16] Early life factors, e.g., low birth weight and early infection exposure, jeopardize the proper functioning of the immune system, which may contribute to the loss of functional pancreatic beta cells and thus culminate in the development of Type 1 DM.[17]

Parameter		Cases	Control
Introduction of complementary foods (month)		4.91 ± 1.89	5.88 ± 1.6
Introduction of complementary foods	< 6 months	25 (23%)	21 (17.6%)
	6 months	76 (64.15%)	84 (68.27%)
	> 6 months	12 (10.1%)	11.8 (10.2%)
Cow's milk	< 6 month	13 (11.3%)	16.5 (14.4%)
	Between 7 and 12 months	71 (63.7%)	79 (68.27%)
	> 12 months	25 (23.8%)	24 (21.8%)
Cereals	< 6 months	6.4 (5.55%)	4.4 (3.12%)
	Between 6 and 7 months	76.3 (71.7%)	64.7 (52.4%)
	≥ 8 months	27.9 (24.7%)	54.3 (45.2%)

Table-IV. Introduction to cereal and complementary foods

Furthermore, the link between a sedentary lifestyle and Type 1 DM may provide evidence that lifestyle changes could play a role in preventing and treating the condition. Yet, the study's author should also admit its limitations, such as its retrospective design and the potential confounding variables not included in the analysis.[18]

Asthmatic patients had been suffering health problems for 48 years (±5.26), as opposed to controls, which is 27. 89 years (±5.41). This implies that the mean age at birth did not change significantly between the two groups (p > 0. 05). Our findings also agree with the earlier study that showed the same mean age at birth for both the cases and the control groups.[19] The probable higher prevalence of overweight and obesity among the cases may, therefore, signify a direct link between the subject under study (GDM) and the existing literature reporting on the same. The literature shows a correlation between higher BMI and increased.[20]

The average weight gain during pregnancy was slightly higher for these cases (14.51 kg ±12.53). There is evidence of the degrees of greater clarity as well as fewer depressive symptoms in persons with chronic schizophrenia compared to normal subjects. Consequently, for the students who did study abroad, the effects on their personal growth were huge. Nevertheless, the difference is insignificant (p > 0. 05). These outcomes are the same as those who have found the same mean total weight gain in both cases and controls.[21] The number of cases of gestational diabetes mellitus (GDM) during pregnancy was higher (17 cases) than that of the controls (25 cases). This data backs up the previous research on a link between a higher BMI and a higher risk for GDM.[22]

CONCLUSION

Finally, our study underlines that close links exist between early initiation of breastfeeding and the exclusive breastfeeding period and nutritional and health outcomes after birth. Children who were breastfed for a longer period had a lower risk of developing type 1 diabetes. In contrast, those introduced to cereals and other foods early had a higher disease risk. Extended breastfeeding lowers the risk of diabetes significantly and has important preventive effects from birth.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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3	Sidra Sehrish	Writing - review and editing.	
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