ORIGINAL ARTICLE

The Association between Infant Feeding Patterns and Type I Diabetes in Children at Ministry of National Guard, Health Affairs Hospital, Riyadh

Reem F Alshammari*[1]

* For correspondence doctor-777@hotmail.com

[1]Department of Family Medicine and Health Care, King Abdulaziz medical city, National Guard Health affair, Riyadh, KSA

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Abstract

Introduction: There is little information on the association between early infant feeding and type 1 diabetes in children in Arabian countries. This study aimed to investigate the influence of breastfeeding on the onset of diabetes in children. **Methodology:** The study included 200 subjects (99 cases and 101 controls). Their age ranged between 1 and 14 years. They attended Ministry of National Guard - Health Affairs Hospital, Riyadh, (NGHA) during the study period (September to November 2013). Mothers were interviewed by research coordinator to fill the questionnaire. Descriptive analysis of cases and controls were carried out, and Chi-square, Odds-ratios and T-test estimates were utilized for analysis. **Results.** There was no difference between the two groups with regard to intake or duration of breastfeeding, the age of initiation of formula's milk and weaning. The study showed that subjects with type 1 diabetes had higher birth weight (p= 0.009). In addition, the study showed that the current daily consumption of cow's milk in subjects with type 1 diabetes were higher significantly in patients group (p= 0.04). Those in the type 1 DM group were more likely to have a sibling with type 1 diabetes (p=0.005). **Conclusions:** Patients did not differ significantly from the controls with regard to dietary practices.

Key Words: Type 1 diabetes mellitus; case-control study; infant feeding; birth weight; family history of type 1 diabetes.

الملخص

المقدمة: في الوقت الحالي لا توجد معلومات كافية عن العلاقة بين التغذية في الرضع في وقت مبكر وداء السكري من النوع الأول في أطفال الشرق الأوسط. **الهدف من الدراسة:** تهدف هذه الدراسة إلى التحقيق في تأثير الرضاعة الطبيعية على ظهور مرض السكري لدى الأطفال. **طرق البحث:** أجريت الدراسة على 200 شخص (99 طفل مصاب بمرض السكري و101 طفل غير مصاب) تتراوح أعمارهم بين 1-14 عاما الذين حضروا المستشفى الحرس الوطني الرياض، المملكة العربية السعودية، خلال فترة الدراسة (من سبتمبر إلى نوفمبر 2013). وقد تم اختيار كل من الأطفال المصابين وغير المصابين بالمرض عن طريق أخذ عينات عشوائية. وأجريت المقابلات مع الأمهات لجمع البيانات عن طريق فريق الأبحاث المعلومات التي تم جمعها من 200 طفل (101 طفل غير مصاب و99 طفل مصاب بمرض السكري). 51.2٪ من الأطفال غير مصابين بالمرض كانوا من الذكور و48.8٪ منهم إناث و50٪ من الأطفال المصابين بالسكري كانوا إناث و50 % من الذكور. لم يكن هناك فرق بين المجموعتين في متوسط العمر عند تناول الحليب لأول مرة أو مدة الرضاعة الطبيعية. لم يكن هناك اختلاف بين المجموعتين في متوسط العمر عند أخذ الأطعمة الصلبة لأول مرة لا تختلف كثيرا بين المجموعات (P=0.14). أظهرت الدراسة بأن الأوزان عند الولادة لأطفال المصابين كانت أعلى من أوزان أطفال غير مصابين بالمرض (P= 0.009). وأظهرت نتائج الدراسة أن الستة الأولى من الحليب البقري في الأطفال المصابين بمرض السكري كانت أعلى بكثير من الأطفال غير مصابين بالمرض (P-value 0.04). أيضا مجموعة الأطفال المصابين بالمرض لديهم أخوة أكبر سنا لديهم أخوة مصابين بمرض السكري (p=0.005). **الخلاصة:** المرضى في هذه الدراسة لا يختلفون كثيرا عن أطفال غير مصابين بالمرض في ما يتعلق بالعادات الغذائية، أول رضاعة الطبيعية، أو سن أول، أو تربية بالظلف في السنة. نحتاج إلى دراسات أكثر في المستقبل مع تقييم أوسع في المتغيرات قد تساعد على توضيح هذه العلاقة. لم نجد أي فرق في الوزن عند الولادة، السنة الأولى من الحياة، والتاريخ العائلي لأخوة مصابين بمرض السكري من النوع 1 ترتبط بعلاقة وثيقة مع خطر الإصابة بهذا المرض. **الكلمات الدلالية:** مرض السكري من النوع 1؛ دراسة التي تتبع الأطفال المصابين وغير مصابين بالمرض؛ عوامل الوراثية؛ التغذية في الرضع؛ وزن الولادة؛ التاريخ العائلي لمرض السكري من النوع.

Introduction: Type one diabetes mellitus (T1DM) is the most common chronic disease in childhood[1]. The incidence of childhood type 1 disease is rising worldwide, with reported annual increase of 2-5 percent in Europe, the Middle East, and Australia.[2-7]

Both genetic and non-genetic factors contribute to disease risk. Nonetheless, studies of familial clustering suggest that genetics accounts for only about half of the risk fraction.[8-9]

The only environmental trigger undergoing active investigation is early exposure to cow's milk proteins, which may be important in T1DM pathogenesis; conversely, breast milk may protect against triggering of the autoimmunity attacks.[10]

A series of studies has shown that children with newly diagnosed type 1 diabetes have increased concentrations of antibodies to dietary antigens and cow milk proteins in particular.[11-13] It is thought to be caused by inflammation and increased gut permeability which represent an early immune aberration that predisposes to b cell autoimmunity and type 1 diabetes. Gut permeability decreases faster over the first months of life in breastfed infants compared with infants given conventional or partly hydrolyzed formulas.[14] Early enterovirus infections have been implicated as a strong trigger candidate for b cell autoimmunity.[15] It is shown that breastfeeding protects against enterovirus infections in the infant period[16-17] and, accordingly, this would decrease the risk of enterovirus-triggered b cell autoimmunity. Whether or not breastfeeding protects against type 1 diabetes is a controversial issue and current evidence provides contradictory results in regards to the association of breastfeeding or early introduction of cow's milk and formula with the development of type 1 diabetes.

Although it is important to identify the association between breastfeeding and cow's milk and development of T1DM, we are not aware of any available studies in this regard in Arab countries.

This study aimed to assess the relationship between breastfeeding and development of T1DM in Saudi children.

Methodology

A case - control study was conducted over the period of 3 months starting September 2013. A total of 99 type 1 diabetic patients and 101 controls without diabetes mellitus were included in the study. Sample size of 100 cases and 100 controls was based on the assumption that cases would be 20% less likely to have been breastfed (40% cases vs 60% controls) or 20% more likely to have been bottle fed with (80% cases vs 60%), a power of 0.8 and alpha of 0.05.

Cases were defined as children diagnosed with type 1 diabetes under age of 14 years old attending pediatric endocrine clinic at NGHA, Riyadh. Equal number of non diabetic control child were selected from children attending Health Care Specialized Center (HCSC) primary health care in NGHA in Riyadh, systematically chosen by a random number from the daily appointment list. Adult and patients with type 2 DM were excluded.

Data on relevant exposures were asked from mothers by means of extensive interview done by a research coordinator to fill the questionnaire that is identical for case and control subjects.

The questionnaire was adopted from a similar study done in Germany[18] after taking permission from its primary author and was customized according to our culture and was validated by an expertise then it was translated to Arabic and back to English.

Basic information was collected on sex, age and diet. History of diet was taken through questions on the duration of overall breastfeeding and age at first introduction of breast milk substitutes, age at introduction of solid foods to infant feeding, type of breast milk substitute fed during the first year of life and current level of customary fresh cow's milk intake.

Mother's age at birth of the index child, child weight at birth, birth order, and the child's medical history were recorded. Further questions addressed family size. Genetic predisposition to of T1DM was covered through family history of T1DM.

Permission was procured from the king Abdullah international medical center in Riyadh, and a verbal consent of each participant `parents obtained before filling the questionnaire.

Statistical package for social sciences (SPSS) software version 19.0 was used for data entry and analysis. Descriptive statistics (e.g., number and percentage) were calculated for each and every variable wherever applicable. To see the significant difference between the two groups for the continuous variable, we had applied Student's T-test (unpaired). Chi-Square tests ($\chi 2$) were employed to test for the association between two categorical variables we had applied Chi-square test. P values of 0.05 or less were considered statistically significant.

Results

A total of 200 mothers of children below 14 year old including 101 controls and 99 type 1 diabetic patients were interviewed as shown in table 1. It illustrates that 51.2 % of controls were males and 48.8 % were females and 50 % of cases are female and 50 % were males. Subjects were divided into 4 groups depending on mothers' education level, namely illiterate, primary/ intermediate, secondary and university. No significant difference was observed in the distribution of patient or control subjects at any level. It was noticed that children born to mothers with high education level were at high risk of developing diabetes as compared to those who were born to illiterates, although it was not statistically significant (p= 0.17). Table 1 also illustrates that no significant difference exists between the patients and controls with regard to the history of bronchial asthma and eczema. Similarly, working status of the parents also did not differ significantly between the two groups.

Figure 1 shows that there is a positive association between birth weight and development of the T1DM. The patients group tend to be heavier than those with no diabetes are and the difference was statistically significant (p= 0.009).

Table 1: Baseline demographic characteristics of patients and control subjects

Item	No	Cases		Controls		P-value
		No	%	No	%	
Age, years (Means, SD(	**200**	8.86±2.80		6.33±2.22		**0.000**
Gender						
Female	**114**	57	**50.0**	57	**50.0**	**0.871**
Male	**86**	42	**48.8**	44	**51.2**	
Child weight in gm (Means, SD)	**200**	3140.9±561.3		2929.7±564.4		**0.009**
Mother with DM						
Yes	**16**	4	**25.0**	12	**75.0**	**0.039**
No	**183**	95	**51.9**	88	**48.1**	
Mother with GDM						
Yes	**17**	7	**41.2**	10	**58.8**	**0.434**
No	**180**	92	**51.1**	88	**48.9**	
Mother age at child birth						
≤ 20	**28**	15	**53.6**	13	**46.4**	**0.903**
21-25	**72**	35	**48.6**	37	**51.4**	
26-46	**99**	49	**49.5**	50	**50.5**	
Order of birth of child						
First born	**46**	24	**52.2**	22	**47.8**	**0.88**
Second born	**65**	31	**47.7**	34	**52.3**	
Third or more in birth	**87**	44	**50.6**	43	**49.4**	
Sibling with DM						
Yes	**25**	19	**76.0**	6	**24.0**	**0.005**
No	**175**	80	**45.7**	95	**54.3**	
Gender of sibling with DM						
Female	**14**	10	**71.4**	4	**28.6**	**0.26**
Male	**10**	9	**90.0**	1	**10.0**	
No. of sibling ≤ 18 years (mean ±SD)	**198**	4.32±1.97		3.22±1.60		**<0.001**
Mother education						
Illiterate	**24**	8	**33.3**	16	**66.7**	**0.170**
Primary/intermediate	**61**	30	**49.2**	31	**50.8**	
Secondary	**61**	36	**59.0**	25	**41.0**	
University	**54**	25	**46.3**	29	**53.7**	
Mother work status						
Housewife	**160**	79	**49.4**	81	**50.6**	**0.710**
Employee	**36**	19	**52.8**	17	**47.2**	
Asthmatic						
Yes	**28**	15	**53.6**	13	**46.4**	**0.640**
No	**172**	84	**48.8**	88	**51.2**	
Eczema						
Yes	**7**	5	**71.4**	2	**28.6**	**0.230**
No	**193**	94	**48.7**	99	**51.3**	

Table 2: Details of breast-feeding and consumption of food among the patients and control subjects

Item	No	Case		Control		P-value
		No	%	No	%	
Breastfeeding given						
No	**34**	14	**41.2**	20	**58.8**	**0.280**
Yes	**166**	85	**51.2**	81	**48.8**	
Bottle feeding given						
No	**25**	16	**64.0**	9	**36.0**	**0.115**
Yes	**91**	82	**90.1**	9	**9.9**	
Type of breastfeeding						
Breastfeeding only	**25**	15	**60.0**	10	**40.0**	**0.231**
Bottle feeding only	**141**	70	**49.6**	71	**50.4**	
Mixed feeding	**32**	12	**37.5**	20	**62.5**	
Duration of breastfeeding						
≤ 4 months	**69**	34	**49.3**	35	**50.7**	**0.742**
5-6 months	**33**	16	**48.5**	17	**51.5**	
> 6 months	**64**	35	**54.7**	29	**45.3**	
Age at introduction of solid food						
3-4 months	**37**	19	**51.4**	18	**48.6**	**0.480**
5-6 months	**100**	65	**65.0**	35	**35.0**	
≥ 7 months	**20**	7	**35.0**	13	**65.0**	
Current cow milk consumption						
Non	**22**	8	**36.4**	14	**63.6**	**<0.001**
< 200 ml	**66**	27	**40.9**	39	**59.1**	
≥ 200 ml	**111**	64	**57.7**	47	**42.3**	

There was no difference between the 2 groups with regard to intake or duration of breastfeeding (p= 0.28) as shown in Table 2. It also shows that there was no significant difference between the 2 groups with regard to the age of initiation of formula's milk and weaning. Interestingly we have noticed that with postponing formula's milk introduction to children, less cases of type 1 DM was diagnosed. Only 25 % of the cases developed if formula's milk postpone until after age of 7 months as compared to 57 % if it introduced before 4 months, however it was not statistically significant (p= 0.48).

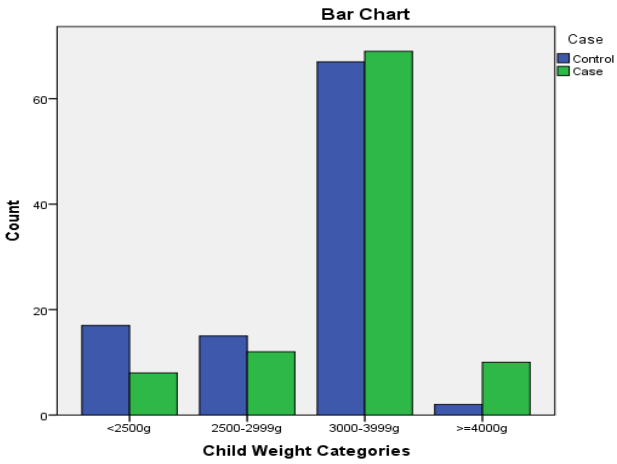


Fig. 1: Association of T1DM with birth-weight among cases and controls.

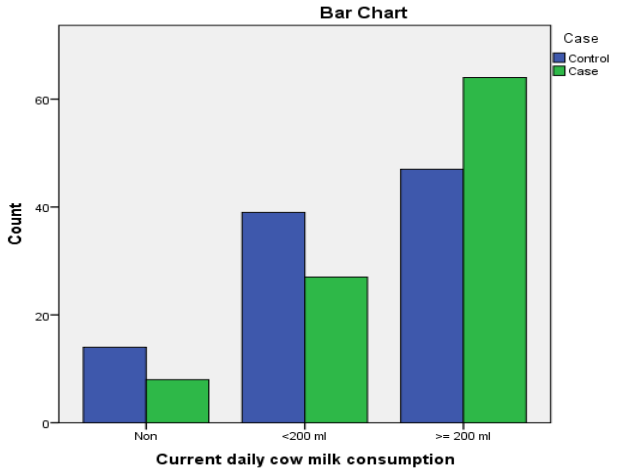


Fig. 2: Cases and controls current daily cow's milk consumption.

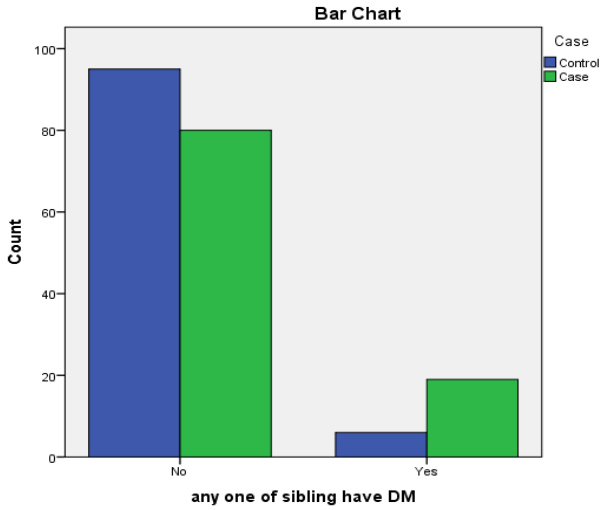


Fig. 3: Cases and controls with siblings with T1DM

Similar finding with solid food introduction with 35 % of cases of T1DM was diagnosed if it was after age of 7 months as compared to 52 % if started earlier but it was not statistically significant (p= 0.14). The age at which the subjects were fed solid food for the first time did not differ significantly between the 2 groups (p= 0.14). The study results showed in Fig. 2 that the current daily consumption of cow's milk in subjects with diabetes were higher significantly in patients group (p=0.04).

Interestingly, it was found that children with T1DM were less likely to have a mother with diabetes than controls (p=0.039) as seen in Table 1. Also patients with T1DM were more likely to have a sibling with T1DM as over 75 % of patient with T1DM have sibling with DM as compared to 24 % in normal controls (p=0.005) as shown in figure 3.

Discussion

This case control study in children attending NGHA showed no statistically significant association between breastfeeding, bottle feeding, age at introduction of solid food, or mother age at childbirth, was found with T1DM in children. Factors associated with type 1 diabetes in children were found to be family history of T1DM in siblings, larger birth weight, and high current cow's milk.

Infant's diet has been hypothesized to be involved in the initiation of the T1DM autoimmune process by impairing the

maturation of the gut-associated immune system and or by providing antigens cross–reactive to islet cell antigens (molecular mimicry).[19] The results of this study on infant diet didn't support any protective role of breastfeeding or a late introduction of breast milk substitute as it didn't find any association between duration of breastfeeding between the 2 groups. The diabetogenic effect of animal milk is also a matter of debate. Earlier retrospective studies did not consistently find evidence for a protective effect of breastfeeding and late exposure to formulas or cow's milk.[21-24]

Recent prospective investigations, which were not subject to recall bias, also produced conflicting evidence on the association between infant diet and the risk of beta cell immunity. Some studies did not find an association between diabetes autoimmunity and breastfeeding duration or early formula's milk introduction, whereas other studies did.[25-29] Recently, a randomized double-blinded dietary intervention pilot trial in newborns genetically at increased risk for T1DM provided first evidence that casein hydrolysate formulas may protect against the development of islet cell autoimmunity.[33]

Recent prospective studies found association between increased beta cell autoimmunity and early or late introduction of cereals /gluten or early introduction of fruits and roots into infant diet.[26-28] Both early and late first exposure to any solid food predicted development of T1DM was shown in one cohort study done in Colorado.[34] The data in this issue is conflicting. The present study did not find any association between the early introduction of solid food and the development of the type 1 diabetes.

Cow's milk influences the composition of the gut flora,[35] In addition cow's milk contains bovine IgG and IgA which could further modify the flora and modulate the immune response to the flora.[36] In the current study, it was noticed that there is significant increase in current daily cow's milk intake inpatient with diabetes. The result of the present study was contrary to the result of one study done in Germany[18] where it showed an inverse relationship in this issue.

A positive family history of T1DM has consistently been reported to raise type 1 diabetes risk among relatives.[20, 37-43] It is known that sibling of a diabetic probands have a higher risk of T1DM than unrelated individuals in the general population at about 3-10%.[43-46] The current study evaluated risk of T1DM in family member and found that T1DM in siblings determines a 3.7 times higher risk of the disease. This is similar to what has been found in study done in Lancashire and Cambria, UK.[36]

The study results showed more cases of maternal T2DM among controls than among cases of T1DM, which support the evidence that there is no association between T1DM and T2DM. This is consistent with studies done in UK[36] and Italy[47] which showed that family

history of type 2 doesn't influence the risk of T1DM in first degree relative.

Epidemiological evidence on the association between level of education of parents and T1DM risk in children is conflicting. In the present study, parents educational background didn't vary between patients and control although there was an interesting finding that mothers with higher education level were having more chance to have diabetic child but it wasn't statistically significant. If we increase the sample size, it may become significant.

Crowded household which was reflected by number of sibling has been observed to be associated with reduced risk for T1DM in case control and recent cohort studies,[20,48-50] Our study did not show any association between the number of sibling and the development of T1DM. The study results did not support the hygiene hypothesis which suggesting that more siblings could lead to earlier and more antigens exposure in life. The hygiene hypothesis suggests that improved hygiene and living conditions have decreased the frequency of childhood infections, leading to a modulation of the developing immune system and increasing risk for autoimmune such as T1DM.[51,52]

There is a considerable body of evidence that higher maternal age at childbirth is associated with a higher risk of T1DM.[39,40,49,53-57] The present study results did not show any association in this regards.

Results in the relation between birth weight and T1DM risk are conflicting. Some studies observed an increased risk in children with high birth weight and lower T1DM risk among children with low birth weight.[57-59] But other studies observed also low birth weight to be associated with increased risk[60-62] while others found no association.[20,55,63] In concordance with the study done in Germany,[18] present study indicated a relationship between higher birth weight and T1DM risk as cases tend to be heavier than control subjects. Data with regard to the order of birth were comparable between the 2 groups in the current study. Other studies have found an increased risk of T1DM among low birth order children.[64-65]

We did not find any significant difference among either sex in developing T1DM which is consistent with one German study[66] which did not find significant difference, whereas the Hawaiian IDDM registry[67] showed a higher incidence among girls. In another study done in India there was a male predominance.[68] Therefore, influence of sex in etiology is not clear.

Regarding the association between atopy and T1DM, one meta-analysis[69] found that there is an inverse relationship between asthma and T1DM. Failure to detect such like association between asthma or eczema and T1DM in the present study may be attributed to the small sample size of our study.

This study has some limitations that should be mentioned. A case control study design generally depends on the collection of retrospective data, thus introducing the possibility of recall bias. The study was conducted in limited area and does not necessary reflect the characteristic of the general population. Finally, there was wide age range (1-14 years). This is because the fact those available cases were limited.

Conclusively, children with T1DM do not differ significantly from their healthy peers in nutritional status. However, child birth-weight, current cow's milk ingestion, and family history of siblings with type 1 diabetes show a significant association with T1DM.

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