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EARLY INFANT FEEDING AND THE RISK OF TYPE 1 DIABETES AGE : A SYSTEMATIC REVIEW

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Abstract

Background: *In addition to genetic background, a number of environmental factors have been claimed to influence the development of type 1 diabetes (T1D), including infant diet*

The aim: *This study aims to show incidence, risk of early infanft feeding of DMT1*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 146 articles, whereas the results of our search on SagePub brought up 74 articles. The results of the search conducted for the last year of 2013 yielded a total 49 articles for PubMed and 34 articles for SagePub. In the end, we compiled a total of 5 papers, 3 of which came from PubMed and 1 of which came from SagePub. We included five research that met the criteria.*

Conclusion: *Understanding the incidence, risk of early infanft feeding of DMT1*

Keyword: *Early infant feeding, type 1 diabetes, risk of type 1 diabetes*

INTRODUCTION

Type 1 diabetes is a common disease in childhood, type 1 diabetes results from immune-mediated destruction of pancreatic β-cells, eventually leading to complete and lifelong dependence on exogenous insulin.[1] Although genetic susceptibility variants play a role in the development of type 1 diabetes, increased incidence over the past 50 years strongly suggests an important role for nongenetic factors.[2]

Diabetes is a serious issue tackled globally. It's considered one of the top 10 causes of death in adults. According to the International Diabetes Federation Atlas, in 2019, the number of people with diabetes was ~463 million. Children represent 5–15% of total diabetic patients. Type 1 diabetes (T1D) is an autoimmune disease resulting from the destruction of insulin-producing β-cells in the pancreas which is promoted by T-cells, producing autoantibodies. Although the disease can occur at any age, T1D develops mostly in youth as 85% of all cases worldwide are diagnosed in individuals under 20 years of age.[3]

Diabetes mellitus is potentially reversible but the disease continues to present a large social, financial and health system burden across the world. Lifetime cost of treating type 2 diabetes mellitus (T2DM) in has been estimated to range from USD 50000 to USD 130000 in United States of America and SGD 70000 to SGD 130000 in Singapore depending on age of diagnosis.[4]

Human milk contains biologically active substances, including antibodies, cytokines, and hormones, that may influence the infant immune system. A number of biologically plausible mechanisms have been hypothesized for the potential protective effect of breast milk against type 1 diabetes, such as protection against potentially diabetogenic infections, postponed exposure to dietary antigens including cow's milk, healthier infant gut microbiota, and optimal maturation of the infant gut.[2]

Breastfeeding has been associated with a number of positive health outcomes, and a possible protective effect against type 1 diabetes in children has been cited as evidence for the importance of breastfeeding. Previous systematic reviews and meta-analyses of observational studies have suggested that breastfeeding more than 3 months, and exclusive breastfeeding for more than 2 weeks, are associated with an approximately 15–30% lower risk of type 1 diabetes. However, data were almost exclusively from case-control studies and therefore susceptible to recall bias and selection bias. Recent prospective studies of genetically susceptible children have had limitedvsample sizes and inconsistent results.[5]

The prevalence of T1D varies considerably by geographical region, but in many regions it is rising. In addition to genetic background, a number of environmental factors have been claimed to influence the T1D epidemiology, including infant diet. A recent, large, individual patient data meta-analysis (43 studies, 9874 patients with T1D) suggested a weak protective association between exclusive breastfeeding in the first weeks of life and development of T1D (15% risk reduction in children who were exclusively breastfed for >2 weeks). Duration of breastfeeding (anywhere between <2 weeks and >6 months) was not associated with altered risk of T1D. These results were not affected by the incidence of T1D (low- or high-incidence countries subgroup analysis) or geographic region (European vs non-European countries).[1]

By means of this systematic review, we aimed to answer the questions of whether breastfeeding at the time of introducing gluten, and the timing of gluten introduction, influence the risk of T1D development. Understanding these associations could facilitate early disease prevention. Two clinical questions were posed.

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast the incidence, risk of early infanft feeding of DMT1. This is done to provide an explanation and improve the handling of type 1 diabetes mellitus in infant. As the main purpose of this paper, to show the relevance of the difficulties that have been identified as a whole.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used "early infant feeding"; "early infant feeding in type 1 diabetes" as keywords.The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *("early"[All Fields] AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields] OR "infant s"[All Fields]) AND ("feeding"[All Fields] OR "feedings"[All Fields] OR "feeds"[All Fields]) AND ("early"[All Fields] AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields] OR "infant s"[All Fields]) AND ("feeding"[All Fields] OR "feedings"[All Fields] OR "feeds"[All Fields]) AND ("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields] OR "type 1 diabetes"[All Fields])))* AND *((clinicaltrial[Filter]) AND (2013:2023[pdat]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

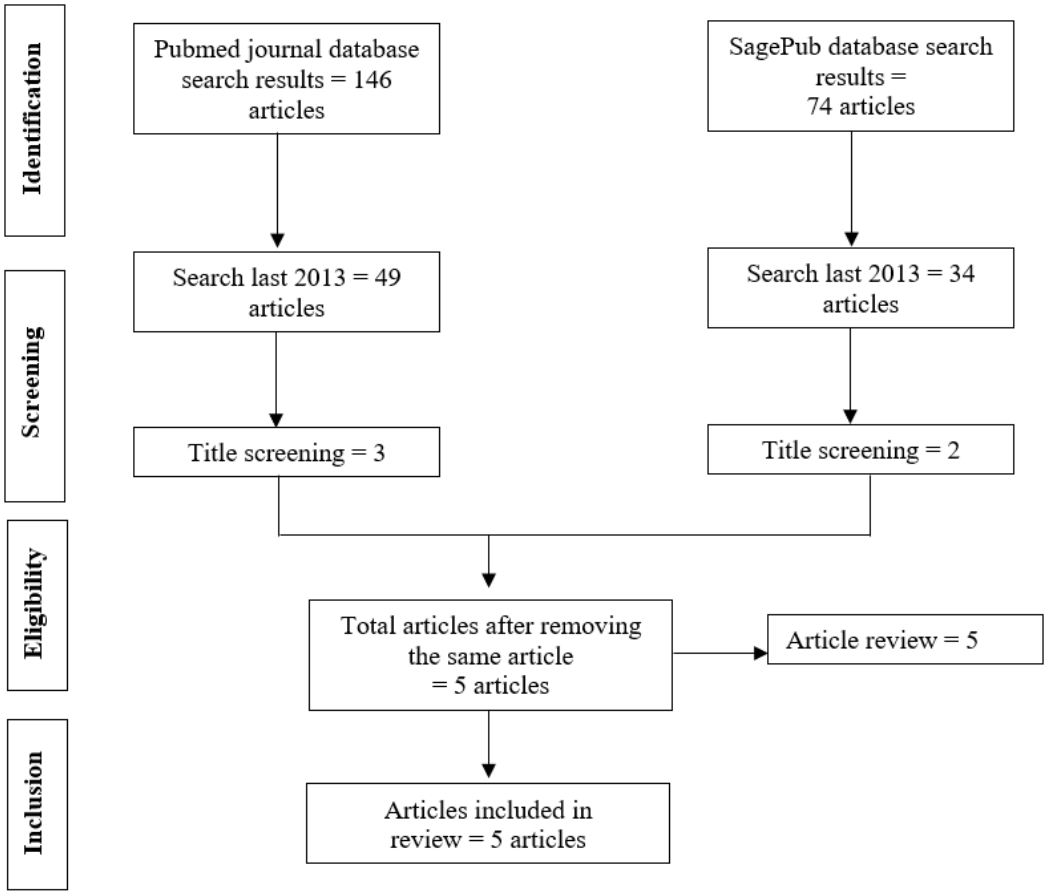

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 146 articles, whereas the results of our search on SagePub brought up 74 articles. The results of the search conducted for the last year of 2013 yielded a total 49 articles for PubMed and 34 articles for SagePub. In the end, we compiled a total of 5 papers, 3 of which came from PubMed and 1 of which came from SagePub. We included five research that met the criteria.

Siljander, et al[6] (2021) showed that it is possible to decrease intestinal permeability in infancy through weaning to an extensively hydrolyzed formula. This may reduce the early exposure to dietary antigens. Clinical visits of this resarch took place at 3, 6, 9, and 12 months of age. The infants were provided either EHF or conventional formula whenever breastfeeding was not available or additional feeding was required over the first 9 months of life. The main outcome was the lactulose to mannitol ratio (L/M ratio) at 9 months. The secondary outcomes were L/M ratio at 3, 6, and 12 months of age, and fecal calprotectin and human beta-defensin 2 (HBD-2) levels at each visit.

Frederiksen, et al[7] showed the safest age to introduce solid foods in children at increased genetic risk for T1DM is between 4 and 5 months of age. Breastfeeding while introducing new foods may reduce T1DM risk. Infant exposures as risk factors for the development of T1DM in children at increased genetic risk. While much of the focus of infant diet and T1DM research has been on the timing of the introduction of a single antigen (ie, milk or gluten), our data suggest multiple foods/antigens play a role and that there is a complex relationship between the timing and type of infant food exposures and T1DM risk. In summary, there appears to be a safe window in which to introduce solid foods between 4 and 5 months of age; solid foods should be introduced while continuing to breastfeed to minimize T1DM risk in genetically susceptible children. These findings should be replicated in a larger cohort for confirmation.

Table 1. The litelature include in this study

Author	Origin	Method	Sample	Result
Siljander et al, 2021[6]	USA	Retrospective cohort study	1468 patients	Compared with controls, the median L/M ratio was lower in the EHF group at 9 months (.006 vs .028; P = .005). Otherwise, the levels of intestinal permeability, fecal calprotectin, and HBD-2 were comparable between the two groups, although slight differences in the age-related dynamics of these markers were observed.
Frederiksen et al, 2013[8]	Colorado	Prospective cohort study	1835 patients	Both early and late first exposure to any solid food predicted development of T1DM (hazard ratio [HR], 1.91; 95% CI, 1.04-3.51, and HR, 3.02; 95% CI, 1.26-7.24, respectively), adjusting for the HLA-DR genotype, first-degree relative with T1DM, maternal education, and delivery type. Specifically, early exposure to fruit and late exposure to rice/oat predicted T1DM (HR, 2.23; 95% CI, 1.14-4.39, and HR, 2.88; 95% CI, 1.36-6.11, respectively), while breastfeeding at the time of introduction to wheat/barley conferred protection (HR, 0.47; 95% CI, 0.26-0.86). Complicated vaginal delivery was also a predictor of T1DM (HR, 1.93; 95% CI, 1.03-3.61).
Lund et al, 2017[9]	Norway	Cross sectional study	908 patients	Any breast-feeding for 12 months or longer predicted a decreased risk of developing type 1 diabetes compared with any breast-feeding for less than 12 months before and after adjusting for having a first-degree relative with type 1 diabetes, vitamin D supplementation, maternal education, sex, and delivery type (hazard ratio 0.37 [95% CI 0.15–0.93]). Any breast-feeding for 12 months or longer was not associated with islet autoimmunity but predicted a lower risk of progression from islet autoimmunity to type 1 diabetes (hazard ratio 0.35 [95% CI 0.13–0.94]). Duration of full breast-feeding was not significantly associated with the risk of islet autoimmunity or type 1 diabetes nor was age at introduction of solid foods or breast-feeding at the time of introduction of any solid foods.
Beyerlein et al, 2014[10]	Germany	Cross sectional study	150 patients	No associations between any definition of exposure (intention to treat or per protocol) and any outcome in either unadjusted or adjusted analyses. Relevant to the question of a potential benefit of delayed gluten introduction, hazard ratios comparing delayed exposure to standard exposure provided no suggestion of protection and were rather increased for islet autoantibody outcomes reaching a hazard ratio of 2.4 (95% CI 0.9−6.8) in the per-protocol analysis. This would be consistent with the findings from the Diabetes Autoimmunity Study in the Young (DAISY). Gluten introduction while breast-feeding was not associated with any outcome. Results were similar if we restricted the intention-to-treat analyses to those 120 children who completed the follow-up until age 3 years in the original study (data not shown).
Cicekli et al, 2022[11]	Turkey	Retrospective cohort study	246 patients	The mean age at diagnosis was 6.30 ± 4.03 years for cases and 7.48 ± 2.56 years for controls. We found that each monthly increase in exclusive breastfeeding duration provided a 0.83-fold (95% CI 0.72, 0.96) decrease in the risk of type 1 DM. Introduction of cereals in the diet at the sixth month or earlier was associated with a 2.58-fold (95% CI 1.29, 5.16) increased risk.

Lund, et al[9] (2015) showed that breast-feeding for 12 months or longer predict a lower risk of progression from islet autoimmunity to type 1 diabetes among genetically predisposed children.

Beyerlein, et al[10] (2014) showed the follow up findings of the BABYDIET study do not exclude that the age and manner that gluten is introduced into the diet of infants can affect the risk of type 1 diabetes. Even with increased follow up time and refined outcome definition, the data do nto indicate that an intervention based on delayed gluten introduction over what is currently recommended in most countries will reduce the risk of developing autoimmunity related to type 1 diabetes.

Cicekli, et al[11] (2022) showed determining the contribution of exclusive breastfeeding to the disease is important in establishing preventive policies. A longer duration of exclusive breastfeeding may be an important role in preventing the disease. This free intervention that truly works will be cost-effective. Future studies are needed to clarify the role of both exclusive and non-exclusive breastfeeding on the development of type 1 DM.

DISCUSSION

Type 1 diabetes mellitus (DM) is a chronic disease of unknown etiology with a preclinical phase characterized by autoimmunity against pancreatic islet cells. A genetic susceptibility is well documented and an environmental influence is assumed. The autoimmunity that precedes type 1 DM can appear in the first years of life, suggesting that environmental agents encountered early in life could be triggers of the disease process. Notably, the early introduction of cow's milk and short duration of breastfeeding have been reported to be associated with increased risk of type 1 DM.[3]

Type 1 diabetes mellitus (DM) is a chronic disease of unknown etiology with a preclinical phase characterized by autoimmunity against pancreatic islet cells. A genetic susceptibility is well documented and an environmental influence is assumed. The autoimmunity that precedes type 1 DM can appear in the first years of life, suggesting that environmental agents encountered early in life could be triggers of the disease process. Notably, the early introduction of cow's milk and short duration of breastfeeding have been reported to be associated with increased risk of type 1 DM.[12]

The main findings of our study suggest that, based on evidence from observational data, breastfeeding at the time of gluten introduction has no effect on the risk of developing T1D or T1DA. In addition, the timing of gluten introduction into the infant's diet, at the specific timeframes evaluated in the included studies, has no effect on the risk of developing T1D or T1DA. One exception was very early gluten introduction (at 3 months or younger). The certainty of this evidence is very low because of the study design (observational), and the CI was very wide because of the small number of events. Because of these considerations, it would be premature to suggest formulating a future recommendation on gluten introduction in the context of the risk of T1DA based on this finding.

An important strength of this systematic review and meta-analysis is the use of rigorous methodology developed by the Cochrane Collaboration. We employed several methods to reduce bias (ie, comprehensive literature search, prespecified criteria for methodological assessment and analysis, no restrictions by language or year of publication, attempts to identify unpublished trials). Important limitations of our study are that mainly observational studies were available, and the number of studies was relatively small. Also, data on the amount of gluten were not available in these studies. Although this was not specified as a variable of interest in the protocol of the current systematic review, we did search for it in the identified studies.[13]

This is an important issue for parents who would like to know not only at what age should gluten be introduced to their child who is at risk of T1D, but also what are the needed quantities, and how should the amount be increased (dosage and intervals). Recently released results from a Swedish case-control study suggest that high-dose gluten consumption is associated with increased risk of CD at the age of 2 years. These issues, however, remain unanswered for T1D, which shares a common genetic background with CD.[14]

Although the methodological quality of the included observational trials was generally high, the observed associations do not allow one to establish causality, and potential biases and confounding variables can only be partially considered. Therefore, results from RCTs are needed. Although randomly assigning infants enrolled in trials to breastfeeding or formula feeding would not be ethical, determining the effects of earlier versus later gluten introduction in RCTs is feasible and may result in different conclusions, compared with those in some large observational studies, as shown recently for gluten introduction and CD. The longest follow-up in the included trials was 8 years. Thus, our results are limited to the studied time periods. Studies with long-term follow-up are needed.[15]

T1D is a life-long condition with a great effect on both health and the quality of life, which results in the onset of systemic complications along the course of the disease. These complications include retinopathy, nephropathy, neuropathy, and most of all, cardiovascular disease, a condition with a 10 times higher risk of occurrence and less favorable treatment outcomes in individuals with T1D compared with nondiabetic individuals. These complications contribute to the great health and economic burden of T1D. The annual cost of the disease has been estimated at >$14 billion in the USA. The incidence of T1D is rising worldwide.[1] Despite broad organizational, research, and financial investments, no preventive strategies exist. Identifying early nutrition modification as a means for disease prevention would allow its population-level implementation. Preventing or even delaying the occurrence of this debilitating, life-long condition would have a major health impact. Therefore, the notion that early infant feeding practices may prevent the occurrence of T1D was an attractive option that found its way into previous infant feeding guidelines. Unfortunately, our systematic review was unable to support these claims.[4]

CONCLUSION

In summary, we can conclude that the influence of early exposure to foods on the subsequent development of diseases, including T1D, remains uncertain. Current evidence, mainly from observational studies, fails to provide support that early infant feeding practices, such as breastfeeding at gluten introduction and age of the infant at the time of gluten introduction, may decrease the risk of developing T1D. More robust data are needed, including data from RCTs.

Until more data are available, none of these practices can be viewed or recommended as a means of reducing the risk of developing T1D.

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