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

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Abstract

Recent studies indicate that the development of autoimmunity in T-cells develops within the first few years of life; in fact, autoantibodies are normally detectable by age 2 in the majority of cases. Due to this, researchers have been searching for environmental factors that influence early development, with a particular emphasis on the role nutrition plays in these processes. The gap between these results may also indicate the impact of genetic background on an individual's vulnerability to various environmental stimuli. In addition, the majority of these studies focused on the diets of adults, whereas more recent research has emphasized the significance of neonatal feeding practices and early nutrition in the onset of type 1 diabetes. Early nutrition is one of the earliest environmental factors to which a child is exposed. Given that the first signs of cell autoimmunity emerge during the first year of life in many subjects who later present with clinical type 1 diabetes and that the most conspicuous increase in the incidence of type 1 diabetes has been observed among those diagnosed before the age of 5 years, it is likely that the disease process is initiated in the majority of cases during childhood.

Keyword: *Early Feeding; Infant; Type 1 Diabetes*

INTRODUCTION

Type 1 diabetes mellitus is a chronic disease characterized by the body's inability to produce insulin due to autoimmune destruction of the beta cells in the pancreas.[1] Three-quarters of cases of type 1 diabetes are diagnosed in individuals aged <18 years. Type 1 diabetes is a chronic disease characterized by the body's inability to produce insulin due to autoimmune destruction of pancreatic beta cells. Most pediatric patients with diabetes have type 1 and lifelong dependence on exogenous insulin.[2,3]

The annual incidence varies from 0.61 cases/100,000 population in China to 41.4 cases/100,000 population in Finland. This variation is observed between countries with different lifestyles, such as Estonia and Finland, and between genetically similar populations, such as those in Iceland and Norway. Striking is the difference in incidence between mainland Italy (8.4 cases/100,000 population) and the island of Sardinia (36.9 cases/100,000 population). This variation strongly supports the importance of environmental factors in T1DM.[1]

Clear evidence points to a genetic component to type 1 diabetes mellitus. Monozygotic twins have a 60% lifetime concordance with T1DM, although only 30% within 10 years of the first twin being diagnosed. Environmental factors are important because even identical twins have only 30–60% concordance for T1DM and because incidence rates vary in genetically similar populations under different living conditions.[1]

No single factor has been identified, but infection and diet are considered the two most likely environmental candidates. Viral infection may be the most important environmental factor in T1DM. Nutritional management is one of the basic management and education of patients with DM.[4] Numerous environmental variables may contribute to the onset of T1DM in children, including viral infections, obesity, lack of exercise, puberty, rapid longitudinal growth, psychological stress, food, especially high glycemic index diets, vitamin D insufficiency, and poor variety of gut microbiota.[5]

A number of environmental factors, including baby food, have been proposed as potential contributors to the development of type 1 diabetes (T1D), in addition to a person's family history of the condition.[5,6] This article aims to look at research studies related to association early infant feeding and the risk of type 1 diabetes.

METHODS

Protocol

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 recommendations were followed in order to guarantee that this study was carried out in accordance with the standards that were cited. It was necessary to take these steps in order to ensure that the findings of this study were reliable.

Criteria for Eligibility

By assessing and analyzing the results of earlier research on the topic, the purpose of this review of the literature is to study the association between early baby feeding and the risk of developing type 1 diabetes. The ongoing probe has uncovered a substantial concern about the situation. Participation in research projects requires that they fulfill all of the following criteria:

1) In order for a publication to be taken into consideration for publishing, it must be written in English and the primary focus of the publication must be on the link between early baby feeding and the risk of type 1 diabetes.
2) The scope of this evaluation was expanded to include articles that were published after 2013 but before the time period that was the focus of this systematic review. Examples include editorials, submissions that do not have a DOI, review articles that have been previously published, and entries that are substantially identical to those that have been previously published in a journal.

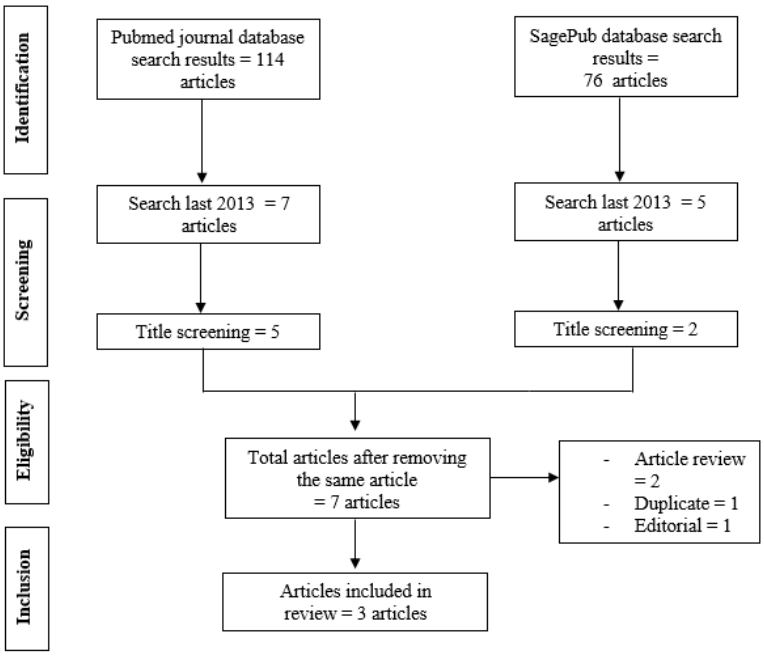

Figure 1. Article search flowchart

Search Strategy

The search for studies to be included in the systematic review was carried out from February, 5th 2023 using the PubMed and SagePub databases by inputting the words: “early infant feeding” and “risk of type 1 diabetes”, and than "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 ("risk"[MeSH Terms] OR "risk"[All Fields] OR "risk of"[All Fields]) AND ("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields] OR "type 1 diabetes"[All Fields]) is used as search keywords.

Data retrieval

After reviewing the titles and abstracts of past research, the author decided to make adjustments to the inclusion criteria. The details of the amended criteria can be found in the additional materials that accompany this study. This made the scope of the problem as well as its numerous dimensions clear, both of which call for additional examination. Following a thorough examination of a number of research that were carried out in a comparable manner, the author arrived at this verdict. In the systematic reviews, consideration was given only to those studies that fulfilled all of the inclusion criteria. This narrowed the scope of the search to only include pertinent material.

Those research proposals that did not comply with our requirements were turned down by our staff. This assured that the study was carried out completely. During the course of this examination, many pieces of information such as names, authors, publication dates, places, study activities, and parameters were found. The following is a list of the different product categories that can be purchased. Developing these skills through repeated practice is possible. It's possible that the origin of this information will have an impact on how it's displayed.

Quality Assessment and Data Synthesis

Each author carried out their own individual analysis of a distinct piece of research presented in the titles and abstracts of the publications before picking which studies to study further. After that, we will proceed to read all of the publications that qualify for inclusion in the systematic review because they satisfy the inclusion criteria and are therefore suitable for inclusion in the review. After that, we'll pick which papers to include in the review depending on the findings that we uncovered. The pieces of writing that will be assessed have been chosen based on these criteria, which were utilized to choose them. in order to simplify the procedure of choosing articles for review as much as is humanly practicable. Which earlier investigations have been carried out, and which aspects of those studies make it possible for them to be included in the review?

RESULT

The first study found that breast-feeding for 12 months or longer was associated with a lower risk of developing type 1 diabetes compared with any breast-feeding for less than 12 months before and after adjusting for factors such as having a first-degree relative with type 1 diabetes, vitamin D supplementation, maternal education, sex, and type of delivery (hazard ratio [HR] = 0.37 [95% confidence interval [CI] = 0.15-0.93]). The second study found that breast-feeding for less than 12 months Islet autoimmunity was not related with breast-feeding for 12 months or longer, but it did indicate a lower probability of progression from islet autoimmunity to type 1 diabetes (HR = 0.35; 95% CI = 0.13-0.94). There was no significant association found between the duration of full breast-feeding and the risk of islet autoimmunity or type 1

diabetes. Neither was there a significant association found between the age at which solid foods were introduced or between breast-feeding and the introduction of any solid foods.[7]

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Period	Result
Lund-Blix, 2015[7]	Norway	Prospective cohort study	50,000 newborns	2001-2007	Breast-feeding for 12 months or longer was associated with a lower risk of developing type 1 diabetes before and after controlling for having a first-degree relative with type 1 diabetes, vitamin D supplementation, maternal education, sex, and delivery type (HR = 0.37 [95% CI = 0.15-0.93]). Breast-feeding for 12 months or longer did not predict islet autoimmunity but did predict a lower risk of progression from islet autoimmunity to type 1 diabetes (HR= 0.35 [95% CI = 0.13-0.94]). The duration of full breast-feeding was not associated with the risk of islet autoimmunity or type 1 diabetes, nor was the age at solid food introduction or breast-feeding at the time of solid food introduction.
Welander, 2014[8]	Sweden	Population-based prospective study	9,414 children	October 1, 1997, through October 1, 1999	T1D was diagnosed in 46 children (0.5%), who were compared to 9368 control children from the general population. Ten of 46 children with later T1D (22%) had an infection at the time of gluten introduction, compared to 2520 control children (27%, P=0.43). Age at the end of breastfeeding, age at any infection, or age at gluten introduction were not associated with later T1D. Breastfeeding at the time of gluten introduction was not associated with a lower risk of future T1D (HR= 1.2; 95% CI = 0.5-2.7). When we adjusted for age at gluten introduction, age at infection, and breastfeeding duration, we found that infection at the time of gluten introduction had no effect on the risk of future T1D (HR= 0.8; 95% CI = 0.3-1.6).
Beyerlein, 2013[9]	Germany	RCT	150 children younger than 3 months	2000 and 2006	Breastfeeding with gluten had no effect. Intention-to-treat analyses of the 120 children who completed the follow-up to age 3 in the original trial yielded comparable results. The BABYDIET study's follow-up suggests that newborns' gluten introduction age and method may affect type 1 diabetes risk. Even with longer follow-up time and better outcome definition, our findings do not suggest that a delayed gluten introduction intervention above what is currently suggested in most countries will reduce the incidence of type 1 diabetes autoimmunity.

Welander, et al (2014)[8] showed forty-six children (0.5%) developed T1D and were compared with 9368 reference children from the general population. Some 10 of 46 children with later T1D had an infection at time of gluten introduction (22%) compared with 2520 reference children (27%, P=0.43). Age at the end of breastfeeding, age at any infection, or age at gluten introduction were not associated with later T1D. Breastfeeding at the time of gluten introduction was not associated with a lower risk of future T1D (HR= 1.2; 95% CI = 0.5-2.7). When we adjusted for age at gluten introduction, age at infection, and breastfeeding duration, we found that infection at the time of gluten introduction had no effect on the risk of future T1D (HR = 0.8; 95% CI = 0.3-1.6).

The consumption of gluten during breastfeeding had no effect on any of the outcomes studied. When we restricted the intention-to-treat analyses to only those 120 children who participated in the initial trial and completed the follow-up until they were 3 years old, the results remained the same. The follow-up findings of the BABYDIET trial do not rule out the possibility that the age at which gluten is introduced into the diet of infants as well as the manner in which it is given can have an effect on the risk of developing type 1 diabetes.[9]

In spite of this, and despite the fact that we followed the participants for a longer period of time and refined our definition of the outcome, our findings do not suggest that an intervention based on delayed gluten introduction, as opposed to what is currently recommended in the majority of countries, will reduce the risk of developing autoimmunity related to type 1 diabetes.[9]

DISCUSSION

Diabetes mellitus (DM) is a condition in which a person experiences dysfunction characterized by hyperglycemia and the effects of resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion.[1] Diagnostic criteria for diabetes according to the American Diabetes Association (ADA) include: fasting plasma glucose level (126 mg/dL) (7.0 mmol/L) or higher, or 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/ L) or higher during a glucose tolerance test of 75 g (OGTT), or random plasma glucose of 200 mg/dL (11.1 mmol/L) or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.[1,4]

The most easily recognized symptoms of T1DM are hyperglycemia, glycosuria, and DKA. Symptoms of diabetes mellitus can be divided into acute and chronic. Acute symptoms of diabetes mellitus are: polyphagia, polydipsia, polyuria (urinating a lot / frequent urinating at night), increased appetite but rapidly losing weight (5-10 kg within 2-4 weeks), and

get tired easily. Chronic symptoms of diabetes mellitus are: Tingling, skin feeling hot or like being pricked by a needle, numbness in the skin, cramps, fatigue, easy drowsiness, vision starting to blur, teeth move easily and fall out easily.[1]

The development of autoimmunity in -cells occurs in the first years of life, according to recent studies; in fact, autoantibodies can typically be identified by the age of 2 in the majority of instances. Because of this, researchers have been looking for environmental elements that affect early in life, with a particular focus on the role that nutrition plays in these processes.[10] Numerous studies, both retrospective and prospective, have been carried out in an effort to clarify the role that dietary factors play in the development of type 1 diabetes; nevertheless, the results are still debatable.[11,12]

The discrepancy of these results may also be a reflection of the influence that an individual's genetic background has on their susceptibility to different environmental influences. In addition, the majority of these studies concentrated on the diets of adults, while more recent studies have highlighted the importance of newborn feeding practices and early nutrition in the progression of type 1 diabetes. Following this, we will examine and discuss the information that is currently available about the role of breastfeeding and the introduction of supplementary and single foods, such as cow milk and gluten, in the beginning of type 1 diabetes.[13,14]

Table 2. Proposed mechanistic pathways for nutrition-related exposures during infancy that increase or decrease the risk of β cell autoimmunity and T1DM

Factor	Proposed mechanisms
Breastfeeding	Decreased intestinal permeability
	Decreased frequency of early enterovirus infections
Early introduction of cow milk proteins	Inflammation in intestinal mucosa
	Dysregulated immune response to cow milk proteins
	Increased intestinal permeability
Early introduction of cereals	Inflammation in intestinal mucosa
Early introduction of fruit, berries, and root vegetables	Presence of toxic contaminants?
Weaning to a highly hydrolyzed formula	Postponed introduction of cow milk proteins that includes bovine insulin
	Decreased intestinal permeability?
	Induction of regulatory T cells in gut-associated lymphoid tissue?
	Increased diversity of gut microflora?
Vitamin D deficiency	Decreased suppression of pathologic Th1 immune responses
Accelerated infant growth	Induced β cell stress and insulin resistance

Breastfeeding may give a potential protection against type 1 diabetes, and there is a good possibility that this protection is mediated by a number of different molecular routes. When compared to infants who were given standard or partly hydrolyzed formulas, breastfed infants see a more rapid reduction in gut permeability over the first few months of life.[6,15,16] Early enterovirus infections have been suggested as a strong candidate for the role of a trigger in the development of autoimmune disease involving beta cells. We and others have demonstrated that nursing provides protection against enterovirus infections throughout the baby period; thus, this would result in a lower risk of enterovirus-triggered cell autoimmunity.[14,16–18]

Proposed mechanistic pathways for nutrition-related exposures during infancy that increase or decrease the risk of β cell autoimmunity and type 1 diabetes. A study conducted on diabetes-prone rats showed that breastfeeding decreases the number of activated lymphocytes and the production of pro-inflammatory cytokines (IL-4, IL-10, IFN-γ) while it increases the number of T regulatory cells (CD4+ CD25+ FoxP3+). In particular, long-term exclusively breastfed rats have reduced number of CD4+ T cells in the mesenteric lymph nodes and an expansion of both effector and natural T regs. Exclusive and prolonged breastfeeding reduced the risk of autoimmunity by limiting the introduction of external antigens and by shifting the balance between tolerogenic cells and autoreactive cells.[6,19]

When introduced at a young age, the proteins found in cow's milk have the potential to cause mucosal inflammation as well as increased intestinal permeability. According to the findings of a number of studies that were published in the last few years, people who have exhibited type 1 diabetes have symptoms of intestinal inflammation. Westerholm-Ormio et al.[20] reported an increase in the expression of HLA–class II molecules, adhesion molecules, and proinflammatory cytokines in small intestine biopsy samples taken from children with type 1 diabetes.[21]

About half of the children that Auricchio et al[22] studied for type 1 diabetes had an increased density of CD3-positive and / T cells within the intraepithelial lining as well as CD25-positive T cells within the lamina propria. These findings indicated that the children's intestinal immunity had been activated. Intestinal inflammation may represent an early immune aberration that predisposes to beta cell autoimmunity and type 1 diabetes. Whether or not such intestinal inflammation is characteristic of children with preclinical type 1 diabetes remains questionable; however, one may speculate that intestinal inflammation may represent such an aberration.

The mechanisms of action for the predisposing effect of the early introduction of fruit, berries, and roots on the emergence of β cell autoimmunity are not defined. One may speculate that such food items contain toxic contaminants.[23] Toxic plecomacrolide antibiotics with a 16- or 18-member macrolactone ring are bafilomycins and concanamycins. Streptomyces species produce bafilomycins, which can specifically infest tuberous plants, potatoes, and sugar beets. Streptomyces infection produces common scab disease in potatoes, which manifests as crusted lesions or pits on the tuber surface and occurs wherever potatoes are cultivated.[24]

CONCLUSION

Early nutrition represents one of the first environmental determinants to which an infant is exposed. Given that the first signs of β cell autoimmunity emerge during the first year of life in many subjects who later present with clinical type 1 diabetes, and that the most conspicuous increase in the incidence of type 1 diabetes has been observed among those diagnosed under the age of 5 y, it is likely that the disease process is initiated early in life in most cases.

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