Effect of breastfeeding on the gut microbiota and the risk of type-1 diabetes mellitus in childhood - A mini review.

Metallinou Dimitra[1], Karamitrou Christina[2], Nanou Christina[3], Sarantaki Antigoni[3]

[1] Academic Fellow, PhD, Department of Midwifery, University of West Attica, Athens, Greece
[2] Registered Midwife, MSc, Department of Midwifery, University of West Attica, Athens, Greece
[3] Assistant Professor, PhD, Department of Midwifery, University of West Attica, Athens, Greece
Corresponding Author: MetallinouDimitra, PhD, Department of Midwifery, University of West Attica, Ag. Spyridonos Street, 12243 Egaleo, Greece;

ABSTRACT: Type 1 diabetes mellitus (T1DM) constitutes a chronic autoimmune disease whose onset occurs more commonly during childhood. Several studies have demonstrated the relationship between dietary patterns and the risk of developing T1DM, with breast milk gaining much attention due to its beneficial bacteria and protective effectvia numerous antipathogenic and anti-inflammatory bioactive molecules. Recent evidence suggests that breast milk might have a potential impact on the onset of T1DM by influencing the infant's immunity and gut microbiota. The aim of this mini narrative review is to analyze the association of breastfeeding and the risk of T1DM in childhood, focusing on the effect on gut microbiota.
KEYWORDS: Breastfeeding, Gut microbiota, Type-1 diabetes mellitus, Childhood

I. INTRODUCTION

Type 1 diabetes mellitus (T1DM), once known as juvenile diabetes or insulin-dependent diabetes, constitutes a chronic autoimmune disease which is characterized by autoimmune destruction of the pancreatic β-cells. The onset of this endocrine and metabolic condition occurs more commonly during childhood [1]. Recent research data show that new cases of T1DM are rising by 3.4% per year across Europe. Rates are increasing similarly in boys and girls when age is between 0-9 years old but are higher in boys when the age is between 10-14 years old [2].

Several studies have demonstrated the relationship between dietary patterns during early childhood and the risk of developing T1DM [3,4]. Breastfeeding for the first 5-6 months of life is strongly associated with lower risk of developing T1DM during childhood [5,6] and the benefits seem relative to the duration of breastfeeding [7], although results from various studies are still controversial [8,9]. The protective effect of breast milk has been strongly linked to its numerous antipathogenic and anti-inflammatory bioactive molecules which reduce insulin resistance, prevent excessive weight gain during childhood and support the immune system through life against many diseases, such as T1DM [10].

Breastfeeding has a crucial role in influencing immunity and gut microbiota. Breast milk is consisted of nutrients and bioactive substances (cytokines, growth factors, immunomodulators, oligosaccharides) that promote the maturation of immune system and adjust its functions. Components like oligosaccharides and glycoproteins modulate the neonatal gut microbiota composition and contribute significantly to the growth of specific bifidobacteria [11,12]. Additionally, breast milk microflora serves as an unfailing source of colonizing bacteria to the infant. These insights are important because it has been proposed that the establishment of a healthy gut microbiota in neonatal period and infancy influences lifelong metabolic health. Thus, the aim of this mini narrative review is to analyze the association of breastfeeding and the risk of T1DM in childhood, focusing on the effect on gut microbiota.

II. BREASTFEEDING AND THE RISK OF TYPE-1 DIABETES MELLITUS IN CHILDHOOD

Findings from the Diabetes Prediction and Prevention study [13] demonstrated that diabetes autoantibodies can appear as soon as the age of 2-3 years old and that a child may be double or triple antibody positive for up to 7 years before the onset of T1DM. These findings urged researchers to investigate environmental factors that act early in

life and nutritional factors were those that gained most attention.

Breastfeeding, beyond nutritional value for the infant, may have a potential impact on the onset of T1DM. Many studies have examined this hypothesis ending though in debatable results. Lund-Blix et al [8], in two large cohort studies with 155.392 children coming from two Scandinavian countries, concluded that breastfeeding reduces the risk of T1DM among those who are breastfed, however, duration of breastfeeding was not significantly associated with that reduced risk. Furthermore, Yan et al [14] in a meta-analysis of 25 studies with 226.508 participants from 12 countries, found that breastfeeding was a significant protective factor against obesity in children. Besides, breastfeeding reduced the risk of T1DM to be triggered.

On the other hand, data from a meta-analysis of 43 studies, including 9.874 patients with T1DM, revealed weak protective associations between exclusive breastfeeding and T1DM [9]. Further studies with strict design, well defined population and breastfeeding patterns could possibly clarify these inconsistent results in the future.

III. EFFECT OF BREASTFEEDING ON GUT MICROBIOTA ASSOCIATED WITH T1DM

Recent studies suggest that fetuses are exposed to colonization of bacteria even from intrauterine life. This finding has been confirmed by the presence of bacteria in meconium samples [15]. The variability of infants' microbiota is influenced by many factors such as the mode of delivery, vaginal birth or caesarean section, duration of gestation, antibiotic exposure, genetics, mother's and infant's health status as well as lactation stage [16,17]. Breastfeeding however, is the most important determinant of infant gut microbial colonization which influences T1DM development via affecting the immune response.

Breastfeeding forms the gut microbiota in early life, both directly by exposure of the infant to the milk microbiota and indirectly, via maternal milk factors that influence bacterial growth and metabolism such as human milk oligosaccharides, secretory immunoglobulin (Ig) A and anti-microbial factors [18]. More specifically, non-digestible oligosaccharides contained in breast milk impact favorably on gut microbiota's balance as they support the growth of probiotic species, such as Lactobacillus and Bifidobacterium, leading therefore to a balanced microbiota [19]. They seem also to protect from viral pathogens, like rotavirus and norovirus infections, through numerous

mechanisms [20]. Moreover, big amounts of Igs are included in breast milk which aim to protect infant's intestinal system from pathogenic organisms. Interestingly, deficiency of serum levels of IgA and IgG have been reported in children newly diagnosed with T1DM [21]. Besides, children with T1DM are more prone to enterovirus infections featuring the linkage between healthy intestinal microbiomeand the presence of T1DM [22].

Furthermore, breast milk is a complex fluid composed of heterogeneous population of antipathogenic and anti-inflammatory biologically active molecules, some of which can contribute potentially to infants' lifelong immunity against many diseases, including T1DM. In particular, insulin and leptin are hormones found in breast milk with very important role on gut microbiota and T1DM prevention. These hormones improve gut maturation and enhance gut diversity of the microbiota, factors critical in the aetiology and prevention of T1DM [23,24]. Reduction of microbial diversity is associated with intestinal inflammation and is frequently reported before the onset of T1DM [24]. Lactoferrin, is another key player molecule in breast milk with wide-ranging effects on the infant's protection against infections in gut. This glycoprotein is lactation-stage related with its highest concentration being found in colostrum. Lactoferrin is able to destroy the cell membrane of Gram-negative bacteria, constrain the growth of viruses and increase membranepermeability of fungal species, causing therefore their death, featuring in this way an anti-microbial, antiviral and antifungal efficacy, respectively [25]. Specifically, it has been associated with improvement in diabetic conditions in obese diabetic pediatric population [26]. Finally, breast milk contains growth factors and adipokines whichhave an effect on β-cell size and function respectively [27-29].

Following on, different groups of beneficial bacteria in breast milk support the immunological and metabolic function through the reduction of gut permeability and the enhancement of gut microbiota diversity and maturation. The Bifidobacteriumlongum subspecies infantis, which belongs to the genus of Bifidobacterium and is present mainly in the gut microbiota of exclusively breastfed infants, accelerates the immune's system maturation, alleviates gastrointestinal and infectious diseases and improves intestinal barrier function. Thus, this multifunctional probiotic is closely involved in child's immunity early in life and its limited colonization is linked to a higher incidence of childhood-onset T1DM [30].

Additional beneficial bacteria contained in breast milk are Lactobacillus species and Firmicutes subspecies which also strengthen immunity and have anti-infectious function. Decrease in these populations has been reported in diabetic individuals [10].

IV. CONCLUSION

Type 1 diabetes mellitus is a chronic autoimmune disorder with multiple factors, including environmental, dietary, genetic and individual, contributing on the trigger of islet autoimmunity. Breast milk undoubtedly, is a living tissue whose immunomodulatory constituents are crucial for the adjustment of the development of a competent innate immunity and hence the decrease of T1DM risk. It can therefore be described as a "weapon of self-defence" that a mother can give to her child to fortify its immunity. Yet, further studies are required to clearly define the exact gut microbial profile of patients diagnosed with or susceptible to T1DM.

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