Review: Correlation between Type 1 Diabetes Mellitus and Gut Microbiome

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ABSTRACT:

Diabetes mellitus (DM) is one of the most common metabolic disorders all over the world. Type 1 diabetes (T1D) is a subtype of DM that is characterized by autoimmunity and B-cell destruction. T1D is considered a disease of multifactorial origin with genetic susceptibility and environmental factors. The environmental (triggering) factors are numerous and including gut microbiome (GM). GM is a humorous dynamic population of microbes that harbor the intestine and have a marked effect on our metabolic diseases and homeostasis. Many studies found that dysbiosis and compositional changes in GM play important roles in T1D development. The objective of this study was to determine the correlation between T1D and GM to establish the best strategies for microbiome alteration to assist in the prevention of T1D occurrence and for better glycaemic control in the near future. The search studies address the question of the relationship between T1D and GM. All available data provided by PubMed/MEDLINE, Google Scholar, Springer Link, EM base Medline, and Cochrane Library were reviewed to fulfill the required objectives. ***Conclusion:*** *Diet can alter the onset and course of autoimmune disorders including T1D by modifying the gut microbiome.*

Keywords*:* *Diabetes mellitus; T1D; Gut microbiome.*

Abbreviations

AAB	Autoantibody	G Hb	Glycosylated hemoglobin	LPS	Lipopolysaccharide	SPF	Specific pathogen-free
CD	Celiac diseases	GM	Gut microbiome	MHC	Major Histocompatibility complex	T1D	Type 1 diabetes
DM	Diabetes mellitus	HBM	Human breast milk	MYD88	myeloid differentiation response 88 protein	TLR	Toll-like receptors
GAD	Glutamic acid decarboxylase	HLA	Human leukocyte antigen	NOD mice	non-obese diabetic mice	T reg	regulatory T
GF	Germ-free	HMOs	Human milk oligosaccharides	PCR	Polymerase chain reaction	Zn T8	Zinc transporter 8
GFD	Gluten-free diet	IDF	International Diabetes Federation	RCT	Randomized control study		

INTRODUCTION

Diabetes is one of the most common metabolic disorders globally. According to the International Diabetes Federation (IDF), 537 million adults (20-79 years) are living with diabetes **(IDF Atlas, 2021).** More than 1.2 million children and adolescents (0-19 years) are living with type 1 diabetes (T1D) **(Mobasseri et al., 2020).** T1D accounts for about 10% of diabetic patients with an annual rise of 3 -5 % **(Patterson et al., 2019).** Patients with T1D are more susceptible to other auto-immune diseases, such as Addison's, celiac disease, Hashimoto's thyroiditis, myasthenia gravis, and vitiligo **(Draznin et al., 2022).** The sex distribution is equal despite the autoimmunity in pathogenesis and susceptibility to other autoimmune diseases **(Norris et al., 2020).** T1D has 2 types of idiopathic and the main one is autoimmune-mediated, and characterized by B-cell Destruction by T lymphocytes and other immune cells. The presence of one or more types of autoantibodies (A. A. Bs), markers of beta cell autoimmunity in type 1 diabetes include AAb against insulin, glutamic acid decarboxylase (GAD), protein tyrosine phosphatase IA-2 or IA-2β, and zinc transporter 8 (ZnT8), are indicative for the immunological onset of T1D (auto-immunity markers). These biomarkers could be detected months to years before the onset of manifestations and used to identify individuals who are at risk of developing T1D **(Draznin et al., 2022).** The type of autoantibody that appears first depends on the environmental trigger and on genetic factors **(Katsarou et al., 2017).**

The pathophysiology has three stages. Stage one is characterized by the presence of auto-antibodies with normal blood glucose levels and no symptoms **(Redondo et al., 2017).** In genetically pre-disposed individuals, environmental factors could act as a trigger of T-cell and humoral autoimmune responses against beta cells. This seroconversion to one or more autoantibodies including glutamic acid decarboxylase (GAD), anti-insulin, insulinoma-associated antigen 2 (IA2), and zinc-transporter 8 (Zn-T8) **(Insel et al., 2015)**. Stage 2 is defined by the positivity of two or more autoantibodies with alterations of glucose metabolism not diagnostic

for diabetes still in the absence of clinical symptoms. Stage 3 is characterized by the onset of clinical manifestations and the need for hormonal replacement therapy **(Pociot and Lernmark, 2016)**. The duration and progression from one stage to another are not completely known. The larger the number of islet autoantibodies, the higher the risk of progression to clinical onset **(Eringsmark and Lernmark, 2013).**

Multiple Genetic and Environmental factors contribute to the pathogenesis of T1D. The risk for T1D is genetic primary and is strongly associated with human leukocyte antigen (HLA) genotype DR3/DR4 **(Pociot and Lernmark 2016).** The major histoco-mpatibility complex (MHC) encoding the HLA region confers 50% of the genetic risk for T1D **(Skyler 2013).** Genome-wide association studies have identified an additional 50 loci that confer susceptibility**.** Genetics alone is not enough and environmental factors are implicated to trigger T1D seroconversion and disease progression **(Pociot and Lernmark, 2016).**

Evidence had been expanded to support that interaction. Firstly, the incidence of T1D in recent decades is rising too rapidly to be explained by genetic changes alone **(Xia Y et al., 2019).** Secondly, the concordance rate of T1D between mono-zygotic twins is <50% **(Nistico et al., 2012).** Thirdly, significant geographic and positional differences, with a higher incidence of T1D in Northern countries **(Soderstrum et al., 2012).** Fourthly, the incidence is increasing across all age groups **(Norris et al., 2020).**

GUT Microbiome

The human intestine contains about 500 to 1000 different types of bacteria and creates a symbiotic relationship with the host and plays a vital role in both health and disease **(Bibbo et al., 2017).** This microbial composition is specific and varies among healthy individuals **(Ihekweazu and Versalovic, 2018).**

Generally, the microbiota is divided into gram-positive and gram-negative groups **(HMP 2012).** *Using* Culture-independent techniques such as DNA sequencing and fluorescence in situ hybridization (FISH) targeting the

16S ribosomal RNA gene sequence suggested that at least two-thirds of the gut bacteria in a western European cohort could have consisted of six groups at approximately the genus level: two *Bacteroides*, two *Clostridium*, *Streptococcus* / *Lactococcus*, and *Eubacterium rectale* **(Franks et al., 1998).** 16S rRNA studies also showed a large diversity in the taxonomic composition both between healthy people and among closely linked biogeographical sites within a single person such as mucosal and stool samples **(Walker et al., 2011).**

Microbiota refers to microorganisms in a particular environment and can be detected by 16S ribosomal ribonucleic acid gene sequence analysis (16S rRNA). However, micro-biome refers to a larger range, including not only the 16S rRNA region but also the whole bacterial genome and products **(Whiteside et al., 2015).**

Microbiome abundancy varies by age group, in Breast-fed infants Lactobacillus, Staphylo-coccus, and Bifidobacterium are dominant groups, as compared to formula-fed infants enriched by Roseburia, Clostridium, and Anaerostipes **(Rosenbauer et al., 2008),** and these groups associated with more inflammation and rapid maturation of groups towards adult-type groups composition **(O'Sullivan et al., 2015).**

Breast milk contains Human milk oligosaccharides (HMOs), the 3rd largest breast milk ingredient, and have prebiotic, antimicrobial, and antiadhesive properties and, increase specific bacterial populations in the gut of infants **(Robert., et al., 2006).** On the other side, Breastfed infants have reduced microbial diversity and increased genes for HMOs degradation **(Praveen et al., 2015).**

During the first year of life, the simple microbiome (functional similarity to mothers' gut) develops into a more complex adult gut microbiome with an increase of Bacteroidetes and Firmicutes (**Kaur et al., 2018)** with time and food introduction. Sustained change with an increase of Bacteroidetes **(Kaur et al., 2020)**. By the age of 3 years pediatric microbiome become relatively stable with adult configurations **(Ihekweazu and Versalovic, 2018)** but others suggest continuous development into teenagers **(LeBlanc et al., 2013).**

A study comparing 1-4 y children with adult microbiomes

found that adults have greater abundance and diversity **(Ringel-Kulka et al., 2013)** and also predominant group similarity at the phylum level including Bacteriodates, Firmicutes, and actinobacteria but differ at the genus level **(Russell et al., 2013).** In a study comparing 7-12y children with adults, the pediatric composition is found similar to adult composition with a lesser abundance of Bacteroidetes and greater actinobacteria and Firmicutes also many similarities were found in taxonomies but with a significantly different distribution **(Le-Blanc et al., 2013).**

The intestinal communities of children shared 35–46% similarity to each other taxonomically, but they had substantially greater overlap at the functional level **(LeBlanc et al., 2013).** This difference explains the higher functional capacity of microbes present in the pediatric gastrointestinal tract. These microbes play important roles in homeostasis, providing essential nutrients **(Flint et al., 2012),** metabolizing dietary fiber **(Russell et al., 2013),** and ensuring proper development of the immune system, Therefore, GM is considered an essential factor for proper early life development and lifelong health **(Round and Mazmanian, 2009).**

Disruption of the GM's balance can lead to immunologic dysregulation and the development of diseases including; inflammatory bowel disease **(Frank et al., 2011),** irritable bowel syndrome **(Mayer et al., 2014),** asthma **(Marra et al., 2009),** obesity **(Kalliomaki et al., 2008),** and neuro-developmental disorders such as autism **(Finegold et al., 2010).**

Dysbiosis is defined as any change that occurs in the composition of resident commensal communities relative to the other community found in healthy individuals. In the last decade, several studies have reported significant changes in the structure of microbial communities in patients and mouse models of such disorders and loss of beneficial microbes and diversity **(Petersen and Round, 2014).**

Role of GM and T1D

GM is in dynamic and homeostatic condition and is affected by several factors such as mode of delivery. In babies delivered by caesarean section

(CS), GM resembles are close in composition to that of the mother's vagina **(Dominguez-Bello et al., 2010**). In the same context, Biasucci and colleagues demonstrated that CS causes early biodiversity of newborn gut bacteria **(Biasucci et al., 2008).**

Multiple factors affect GM and include antibiotic use, diet, drinking water PH, and medicine use. High-sugary diets cause dysbiosis by increasing Bifido-bacterial species raising the incidence of DM **(Brown et al., 2012).** Dysbiosis occurred in early life and can provoke and augment inflammation with resulting immune system provocation before the onset of T1D **(Siljander et al., 2019).**

In the longitudinal study, stool samples were collected from children aged 3 months to 5 years, T1D children have increased levels of Roseburia hominis, Bifidobacterium pseudocatenu-latum, and Alistipes shahii, Moreover, the GM of control children contained more geneus that were related to fermentation and the biosynthesis of short-chain fatty acids (SCFAs), supporting the protective effects of SCFAs in early-onset T1D **(Vatanen et al., 2018).**

A case-control study was conducted by **Murri and colleagues** (2013), they collected stool samples from 16 children with T1D and 16 healthy controls, and samples were examined by polymerase chain reaction (PCR). They found that GM in children with T1D significantly differed from those found in healthy control. Significant differences were reported with regard to the number of Bifidobacterium, Lactobacillus, and Clostridium and the Firmicutes to Bacteroidetes ratio. In addition, the number of butyrate-producing bacteria. Lactic acid-producing bacteria and mucin-degrading bacteria, essential to maintain gut integrity were significantly lower in the children with diabetes than in the healthy control. These differences could alter the gut permeability reported in patients with T1D. These results could be beneficial for developing new strategies to control the development of T1D by modifying the GM.

Groele and colleagues (2021) conducted a randomized control study for the effects of *Lactobacillus rhamnoses* GG and *Bifidobacterium lactis* Bb12 on β-cell function in children with newly diagnosed T1D. A C-peptide level

between the groups was similar to the residual β-cell function. It was unclear which probiotic should be administered alone or in combination for T1D management**.**

In non-obese diabetic (NOD) mice, a broad-spectrum antibiotic affected the composition of the microbiome and decreased the proportion of regulatory T cells (T-reg) in the gut lamina propria, resulting in an increased incidence of T1D **(Candon et al., 2015).** On the contrary, **Hu and colleagues (2017)** reported that NOD mice were protected from the development of T1D and of the unknown mechanism if their mothers were treated with antibiotics.

Another study showed that antibiotic treatment in NOD mice could change the composition of GM as well as insulin sensitivity, but gut permeability was not altered in the following 2 months (**Geach, 2016)**. These studies suggest that diabetic patients had an alteration in GM, and the impact of antibiotic treatment on GM and T1D was inconclusive and might depend on the nature of the used antibiotic and the time window of its usage **(Tormo-Badia et al., 2014)**.

GM interaction with diabetes

- **Immune system alteration**

T1D is considered a state of a pro-inflammatory condition mediated by innate and adaptive immunological pathways **(Dev-araj et al., 2010).** GM is associated with molecular patterns like lipoproteins, lipopolysaccharides, peptidoglycans, and nucleic acids. The reorganization of these patterns depends on recognition receptors in the host, especially toll-like receptors (TLRs). The TLRs had a protective effect on the host against infections by recognizing Pathogen-associated molecular pattern molecules (PAMPs) derived from gut microbiota **(Li et al., 2013).** Microbiomes trigger TLR to induce diabetogenic and antidiabetogenic signals. Such signals are mediated by myeloid differentiation response 88 protein (MYD88) protein (protein adaptor for multiple immune receptors that recognize microbial stimuli) to promote cellular response to lipopolysaccharides (LPS) **(Kieser and Kagan, 2017)**. LPS acts as a molecular link between GM and T1D development via increasing the pro-inflammatory cytokines

with secondary impairment of B cell function **(Ghosh et al., 2020).**

In a study conducted to demonstrate the pro-inflammatory state of T1D, T1D was found to have higher levels of TLR2, TLR4, and endotoxin than controls, **(Devaraj et al., 2009). Gulden et al., (2013)** demonstrated that TLR4 deficiency results in an acceleration of diabetes development and immune cell infiltration of islets in NOD mice. They concluded that TLR4 is involved in the progression of the insulitis process. In a study conducted by **Calcinaro and colleagues (2005)**, they found that early oral administration of probiotics could prevent diabetes development in non-obese diabetic (NOD) mice. Protected mice showed reduced insulitis and a decreased rate of beta cell destruction. Prevention was associated with increased production of IL-10 from Peyer's patches and the spleen and with increased IL-10 expression in the pancreas**.** Regulatory T cells (TREG) have a protective role against T1D development. Treatment with a low dose of IL2 could increase TREG cell number decrease the inflammatory response, and protect NOD mice from diabetes. TREG cells were found to be linked to an increase in Bifidobacterium and decreased numbers of Bacteroidetes, oscillospira, and Clostridial families. So gut microbial alteration could stimulate immune response and increase susceptibility to T1D **(Zoka et al., 2015).**

- **Mucosal barrier disruption**

The intestinal epithelium acts as a barrier against the passage of harmful intraluminal foreign elements, and a selective filter allowing the translocation of essential dietary nutrients, electrolytes, and water from the intestinal lumen into the circulation **(Blikslager et al., 2007)**. Disruption of intestinal mucosa increases the permeability of toxins, food antigens, and other infectious agents. The leaked factors reach the pancreatic lymph nodes and damage β-cells with secondary T1D development **(Stefano et al., 2017).**

Maffeis et al., 2016 assessed the intestinal permeability and gut microbial composition, using PCR 16S rRNA gene technique, in 10 children with β cell autoimmunity at risk of diabetes and another 10 healthy controls. They found altered

permeability in patients and three micro-organisms (Dialister invisus, Gemella sanguinis, and Bifidobacterium longum) were detected in association with the pre-pathologic state **(Maffeis et al., 2016).**

All the previous studies support that GM alteration either compositionally and /or functionally is strongly associated with B-cell autoimmunity and destruction with secondary T1D development. So healthy microbiome promotes adequate barrier function

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- **GM, Hormones, and T1D**

Hormones are included in the several mechanisms by which microbiota affect the host. The precise pathways of microbiota hormonal signaling haven't been yet established, meanwhile, hormonal level changes correlate with the presence of gut microbiota **(Neuman et al., 2015).** T1D is more in female NOD mice than in males on feeding under specific pathogen-free (SPF) conditions but under germ-free (GF) conditions, no gender bias was found **(Yurkovetskiy et al., 2013).** Microbial transplantation from adult male NOD rats into immature NOD females' gut could change GM composition and testosterone levels and protect them from diabetes **(Yurkovetskiy et al., 2013).**

- **Gut-brain axis**

Bidirectional communication channels involving inflammatory and neuro-endocrinal mechanisms exist between gut microbiota and the brain. These channels are influenced by the permeability of intestinal mucosa and the blood-brain barrier **(Sarkar et al., 2016).** Such interactions occur in the first 3 years of life. GM has an indirect role on the nervous system as a result of dysbiosis stress stimulates the hypothalamic pituitary adrenal axis. The increased cortisol level results in a breakdown of the extracellular matrix leading to barrier dysfunction **(Sarkar et al., 2016).** The relationships between GM and other organs especially the brain will be key to solving many mechanisms of diseases in the near future.

- **GM, diet, and T1D**

GM and diet interrelationship and their effects on host metabolism and immunity were reported in many studies. Diet contributes to modulating GM composition and function and in

turn, hosts response and T1D development. **(Tremaroli and Backhed, 2012),** and includes multiple factors:

Early nutrition and breastfeeding

Autoimmunity against B cells starts in early life, as autoantibodies could be detectable in the first 2 years of life **(Knip et al., 2010)**. **Lund-Blix et al (2017)** found that children who did not breastfeed have a 2-fold increase in T1D risk compared with those who were breastfed irrespective of the duration of breastfeeding**.** Many hypotheses explain mechanisms by which breastfeeding protects from T1D and modulates microbiota and immunity. Breast milk contains many nutrients and substances such as cytokines, growth factors, immune modulators, and oligosaccharides **(Xiao et al., 2018).**

Lactobacilli in human breast milk (HBM) have antibacterial activity against staph aureus in vitro and inhibit the adhesion of salmonella enterica in infected mice **(Olivares et al., 2006).** The immune-modulatory activity of lactobacilli affects immune cells, cytokines, and chemokines **(Perez-Cano et al., 2010).** The microbiota of infants exclusively breastfed for 6 months is enriched with Bifidobacterium longum subsp. Infantis, which is involved in a child's immunity **(Insel et al., 2015).** It belongs to lactic acid bacteria, Bifido-bacterium and Lactobacillus, which can break down human milk oligosaccharides **(Dedrick et al., 2020).**

In breastfed infants, an abundance of Bifidobacterium was observed, which has been inversely correlated with T1D risk by a number of cross-sectional and longitudinal human studies **(Dedrick et al., 2020).** Lacto-bacillus and Bifidobacterium species in breast milk have a protective role in preserving gut integrity and stimulating the growth of the Firmicutes bacteria phylum that is found deficient in people with T1D **(Fassatoui et al., 2019).**

Formula milk composition was also investigated and it was concluded that infants fed with insulin-free formula had a lower incidence of beta-cell auto-immunity by 3 years of age **(Vaarala et al., 2012).** In addition, an increase in Bacteroides and a decrease in Bifidobacterium

amount were found in formula-fed infants who shifted to seroconversion **(de Goffau et al., 2013).** These studies support the protective effects of breastfeeding against T1D development.

Complementary Foods

Many systematic reviews reported that commencing complementary feeding before the 3rd – 4th months of life was associated with an increased risk of allergic conditions, meanwhile, gluten introduction before 4 months can be linked to the development of celiac disease and T1D **(Szajewska et al., 2015).**

Early introduction of cow milk has been associated with increased intestinal permeability and gut inflammation, Children with T1D express higher levels of antibodies against cow milk proteins (β-lactoglobulin, insulin, albumin); this could be the effect of a dysregulated immune response or an increased intestinal permeability **(Knip et al., 2010).**

A recent study showed that the early introduction (<3 months) of complementary food is associated with an altered microbial composition with higher diversity and an accelerated maturation pattern **(Differding et al., 2020).** Enhanced fecal excretion of butyrate and other SCFAs is a marker of reduced microbial diversity and increased gut barrier permeability. It is associated with systemic inflamemation, dyslipidemia, hyperglycemia, and an increased risk of obesity and hypertension **(de la Cuesta-Zuluaga et al., 2018).** Finally, the early introduction of food results in an increased fecal butyrate concentration **(Differding et al., 2020).**

Gluten-containing food

Resistance of gluten to digestion by enzymatic action is the principal mechanism by which gluten provokes immunological pathways in celiac disease and T1D **(Antvorskov et al., 2014).** Islet autoimmunity and diabetes progression were not affected by the cumulative amount of gluten in infancy, while the early introduction of gluten before 4 months was significantly associated with a higher risk of T1D development **(Lund-Blix et al., 2019). Hakola and colleagues (2019)** reported that a high intake of gluten-containing food was associated with islet B cell

autoimmunity. Children with celiac diseases (CD) had a microbiome characterized by a higher amount of Proteobacteria, Bacteroides, Actinobacteria, *Neisseria spp.,* and *Haemophilus spp.* and a lower abundance of *Lactobacillus* and *Bifidobacterium* **(Krishnareddy et al., 2019).**

The concomitant presence of celiac diseases and T1D is not rare (8% of coexistence) and is challenging. To date, the gluten-free diet (GFD) and insulin are the only recommended treatments for CD and T1D, respectively. However, such therapy carries challenges to both clinicians and patients, as GFD has a high glycemic index that affects glycemic control. Moreover, intermittent gluten intake by non-compliant patients stimulates the autoreactive immune cells with an enhanced immune response **(Kaur et al., 2018).**

A case-control study on T1D and GFD-treated celiac patients compared with T1D alone showed that a long-term GFD did not affect glycemic control, but it had a different impact on diabetes complications **(Creanza et al., 2018).** Conversely, an RCT adopting a GFD for 1 year on T1D and subclinical CD patients, showed better glycemic control and a decreased number of hypoglycemic episodes **(Kaur et al., 2020).**

The use of *Bifidobacterium* strains as probiotics were reported to reduce intestinal inflammation and proinflammatory cytokines production with the consecutive improvement of the gut barrier's function. *Bifidobacterium* strains were also effective in the reduction of gliadin toxicity by degrading the proinflammatory gluten peptides and reducing their immunogenicity **(Valitutti et al., 2019).**

Cow milk

Cow milk had been studied as a causative trigger for T1D. Different results, results were obtained. **Virtanen and colleagues (2012),** found T1D risk increased with cow milk consumption in susceptible children **(Virtanen et al., 2012).** IN an RCT study on T1D genetically susceptible children, hydrolyzed casein-based formula had no protective effect against the development of islet autoimmunity if compared to a standard formula **(Knip et al., 2018).**

Cross-immunity between beta cells' antigens and cow milk

proteins could represent a mechanism explaining the association between cow milk and T1D **(Vaarala et al., 1999).** Early exposure to cow's milk has been associated with enhanced intestinal permeability and alteration of the gut barrier, which predisposes to exogenous antigen reactivity and immunologic dysregulation **(Westerholm-Ormio et al., 2003).**

Micronutrients

The role of micronutrient intake and its relation to T1D had been studied. Vitamin D, E, zinc, and omega 3 many were the most studied factors **(Virtanen, 2012).** Vitamin D has several immunomodulatory effects on innate and adaptive immunity. Low serum vit D levels have been linked to a greater risk of several immune-related disorders, such as T1D **(Charoenngam and Holick, 2020).** The highest incidence of T1D in the world is present in Finland **(Harjutsaloet al., 2013).** One explanation is the lack of sunlight exposure resulting in vitamin D deficiency in the Finnish population, especially in northern Finland. Norwegians living in the far north, are unable to produce vitamin D_3 in their skin from sun exposure for more than half a year during the early spring and late autumn, and winter **(Wacker and Holick, 2013).** This is supported by a report that T1D is more common in high-latitude and short daytime period countries **(Chen et al., 2017).**

Norris and colleagues (2018) in their study showed that higher serum levels of vitamin D were associated with decreased risk of β cell autoimmunity in children with genetic susceptibility to T1D. But, in a cross-sectional study, Vitamin D levels were reported to be lower in children with multiple islet autoantibodies and in children with T1D than in autoantibody-negative children. However, in children with multiple islet autoantibodies, vitamin D deficiency was not associated with faster progression to T1D **(Raab et al., 2014).**

A systematic review of many trials revealed that vit D supplementation for adults and children resulted in the reduction of insulin doses and stimulation of β cells thus controlling diabetic activity **(Gregoriou et al., 2017)** Vitamin D plays a pivotal role in intestinal immunity, intestinal integrity, and microbiome modulation in the autoimmune

diseases **(Yamamoto and Jorgensen, 2020).**

Vitamin A regulates both adaptive and innate response through the regulation of transforming Th1 to Th2 lymphocytes. Vitamin A inhibits islet cell inflammation and progression to diabetes by induction of immune tolerance **(Yosaee et al., 2016).** Vitamin A deficiency contributed to alteration in GM composition and function **(Tian et al., 2017).** A study had been performed to investigate the effect of vitamin A on the infant microbiota and concluded that better Vit. A status in infancy might influence health both in infancy and later in life by enhancing the establishment of a healthy GM (*Bifidobacterium and Akkermansia*) ***(*Yamamoto and Jorgensen, 2020*).***

Several types of research had been focused on the potential role of oxidative stress induced by free radicals in the development of T1D. Based on this assumption, micronutrients with antioxidant properties such as vitamin C (ascorbic acid), zinc (Zn), and selenium (Se) may play a role in the pathogenesis and exacerbation of T1D. Plasma ascorbic acid concentration was assessed in children at high genetic risk of T1D, initially at 6 and 12 months and then annually up to 6 years of age. The Authors found that higher plasma ascorbic acid levels were associated with decreased islet autoimmunity risk, but not with T1D risk progression **(Mattila et al., 2020).**

Animal studies revealed that selenium-dependent proteins (seleno-proteins) with redox properties were involved in glucose metabolism, given that insulin release and signaling were influenced by the cellular redox potential **(Jablonska et al., 2016).** Significantly lower levels of Se and Zn were found in children affected by T1D, and glycosylated hemoglobin (HbA1c) levels appeared inversely correlated with Se and Zn levels **(Özenç et al., 2015).** Zinc supplementation can increase bacterial diversity, richness, and activity in the ileum of piglets **(Zimmermann et al., 2010).** Moreover, zinc deficiency may promote the development of T1D by affecting the inflame-matory response and impacting metabolic control **(Xia et al., 2017).** Further studies are needed to investigate the effect of micronutrient deficiencies and potential supplementation during

the transition to solid foods to reduce the risk of T1D and its complications.

CONCLUSION

A strong relationship exists between the host's gut microbiota and health disorders especially those of autoimmune nature as T1D. The disturbed relationship between food, intestinal microbiota, and the beginning and advancement of T1DM may support the theory that diet can alter both the onset and progression of the condition by modifying the intestinal microflora and lowering the related pro-inflammatory profile.

Although there has been a lot of interest in the use of fibers, probiotics, prebiotics, and postbiotics in the prevention of T1D, more research is still needed to determine the precise microbial profiles of various patient types and to evaluate the effectiveness of various treatments for various T1D microbial profiles.

The major points from this study are that encouraging prolonged breastfeeding during the first six months of life, avoiding the introduction of complementary foods and gluten before four months of age, and delaying the introduction of cow's milk until 12 months of age may all lower the risk of developing T1D.

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دراسة العلاقة بين داء السكرى النوع الأول وماكروبيوم الجهاز الهضمى

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الملخص العربي

داء السكرهو إحدى أهم إضطربات التمثيل الغذائى على مستوى العالم. داء السكرى النوع الأول أحد انواع داء السكر العام، الذى يتميز بإضطراب المناعة الذاتية وإفساد خلايا بيتا بالبنكرياس. داء السكرى النوع الأول مرض أصوله متعددة جنبا إلى جنب التأثير الجينى والعوامل البيئية. العوامل البيئية متعددة, مشتملة على ماكروبيوتا الجهاز الهضمى. وهي أحد فصائل الميكروبات النشطة النافعة التى تسكن أمعائنا التى لها تأثير ملحوظ فى توازن أجسامنا من حيث أمراض التمثيل الغذائى. دراسات متعددة وجدت أن إضطراب الماكروبيوتا وتغيرصفاتها يلعب دورا مهما فى نشوء مرض السكرى النوع الأول. كان هدف الدراسة هو تحديد العلاقة بين داء السكرى النوع الأول وماكروبيوتا الجهاز الهضمى. وإرساء أفضل الأليات لتعاقب وتناوب الماكروبيوتا للمساعدة فى الوقاية من حدوث داء السكرى النوع الأول وضبط تركيز السكر بالدم فى المستقبل القريب. تم البحث لفهم ودراسة استفسارعن علاقة داء السكرى النوع الأول وماكروبيوتا الجهاز الهضمى. كل المعلومات المتاحة تم الحصول عليها من خلال بب مید/ ميدلاين, جوجل, رابط سبرنجر,القاعدةالطبية الالكترونية, تمت مراجعة مكتبة كوهران لإنجاز الأهداف المطلوبة. اخيرا نظام التغذية يستطيع تغيير بداية وسلوك أمراض المناعة الذاتية ومنها داء السكرى النوع الأول بتعديل ماكروبيوتا الجهاز الهضمى.

الكلمات المفتاحية: داء السكرى, داء السكرى النوع الأول, ماكروبيوتا الجهاز الهضمى.