

Review

The role of early programming and early nutrition on the development and progression of celiac disease: a review.

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Abstract: Experimental and epidemiological evidence has shown that modifications of the intrauterine environment can have deleterious consequences for individuals, expressed as an increased risk of suffering non-communicable pathologies in adult life, which is known as the hypothesis of the early origin of diseases or programming fetal. On the other hand, changes in gene expression patterns through epigenetic modifications can be the basis for long-term maintenance of the effects of fetal programming. In this sense, epigenetics comprises the study of intrauterine disturbances, which develop diseases in the adult, including Celiac Disease (CD). In addition, early feeding practices could influence the risk of CD development, such as breastfeeding timing and duration and age at gluten introduction in the diet. Gluten acts as a trigger for CD in genetically predisposed subjects, although approximately 30% of the world population has HLA DQ2 or DQ8, the prevalence of the disease is only 1-3%. It is not known what factors act to modify the risk of disease in genetically at risk subjects. Taking into account all these considerations, the aim of the current review is to elucidate the role of early programming and the effect of early nutrition on the development and progression of CD.

Keywords: Celiac disease, Early programming, Perinatal nutrition.

1. Introduction

The term early programming postulates that stimuli, environment or insults during critical developmental periods can have an impact in human lifespan [1]. In this sense, fetal life is one of the stages of greater plasticity, since at this stage, most of the organs and tissues are formed and developed. Experimental and epidemiological evidence has shown that modifications of the intrauterine environment can have deleterious consequences for individuals, expressed as an increased risk of suffering non-communicable pathologies in adult life, which is known as the hypothesis of the early origin of diseases or fetal programming [2].

Observational and cohort studies in England, Scandinavia and India were the first to show the close association between low birth weight and the subsequent development of chronic diseases [3]. Barker et al. [4] described, in 16,000 subjects in England, that death rates from cardiovascular disease were halved in those who were born at normal weight compared to those who were small for gestational age. Furthermore, this association was maintained after adjusting for multiple variables such as socioeconomic level, family history and weight at the time of the study. Interestingly, a higher body mass index in adult life increased the strength of this association [5]. Other anthropometric indicators of impaired fetal growth, for example, weight, height, low abdominal circumference and a high fetus-placental relationship, have been associated with the development of chronic disease in adult life [4,6].

In general, there are multiple factors that can alter birth weight, including maternal, placental and fetal factors [7]. The main causes of fetal macrosomia include gestational diabetes, obesity, and maternal overnutrition [8]. The placenta is a fundamental organ during pregnancy since it participates in the transport of nutrients, in the immune response, in the synthesis of steroid and peptide hormones and in the detoxification of substances harmful to the fetus. Therefore, an altered or poor placental function could be a central element in establishing an altered pattern of fetal development [9].

The concept of fetal programming involves a series of modifications in the structure and function of different tissues and organs, among which are a reduction or redistribution of different cell populations or an abnormal sensitivity of tissues to hormonal regulation [10]. On the other hand, changes in gene expression patterns through epigenetic modifications, such as DNA methylations, post-translational modifications in histones and microRNAs, can be the basis for long-term maintenance of the effects of fetal programming [11]. Given the complexity of these processes, it is highly probable that there are multiple variables that affect the final result of fetal programming. Sexual dimorphism could be one of its main modifiers because male fetuses adapt differently to female fetuses in the face of unfavorable conditions during pregnancy.

However, the effect of early nutrition on long-term health variables does not occur only during the embryonic-fetal period, but is prolonged in the first years of life. CD is a systemic disorder, caused by an immune reaction triggered by the ingestion of gluten and related proteins, which occurs in people who carry the DQ2 and/or DQ8 Human Leukocyte Antigen (HLA) class II haplotypes, and it is characterized by a variable combination of high celiac disease-specific antibody titers, an inflammatory enteropathy with degrees of variables of severity and a wide range of digestive and/or systemic symptoms [12–14]. CD is due to permanent intolerance to some proteins found in cereals, mainly gliadin and other related proteins, present in cereals such as wheat, oats, barley and rye or any of its varieties and hybrids (spelled, kamut and triticale, among others) and derived products [15]. This intolerance generates atrophy severe intestinal villi, which in turn produces severe malabsorption of the nutrients in the intestine, even though CD is not only a food intolerance, it is a systemic disease [16]. Gluten causes an abnormal immune response in patients, generating autoantibodies [17] that can affect the entire organism, not only the intestine. As with any other autoimmune diseases, CD has a strong hereditary genetic component as testified by its high familial recurrence (~10–15%) and the high concordance of the disease among monozygotic twins (75–80%) [16]. In this sense, epigenetics comprises the study of intrauterine disturbances, which develop diseases in the adult, marking a process repeatable within the inheritance mechanism, which have been able to discern a wide variety of physiological and pathological events such as cancer, cardiovascular and metabolic diseases, neurological, reproductive and immunological disorders [18], including therefore, CD. In addition, early feeding practices could influence the risk of CD development. In Sweden, a high increase of typical cases of CD, was observed between 1984 and 1996. The increased incidence rate of CD in infants younger than 2 years of age increased 4-fold and it was hypothesized that it was due to changes induced in infant feeding [19,20] such as breastfeeding timing and duration and age at gluten introduction in the diet. Therefore, it is biologically likely that breastfeeding at the time of gluten introduction in the diet increases the chance of developing oral tolerance for the major gluten antigens. Taking into account all these considerations, the aim of the current review is to elucidate the role of early programming on the development and progression of CD..

2. Metabolic programming in autoimmune diseases

Genome-wide association studies (GWAS) have revolutionized the study of the genetic role of diseases, although the mechanisms are still not completely elucidated due to the difficulty of assigning the biological meaning of many genetic variants [21]. Autoimmune inflammatory diseases, which reflect complex interactions between genetic variants and the environment, are important systems for the investigation of genetic diseases in humans [22]. The grouping of different autoimmune diseases in families (familial clustering) suggests the existence of hereditary factors

underlying common pathways of the disease, although the different clinical presentation and response to drugs differentiates them [23]. GWAS have discovered hundreds of risk loci for autoimmunity. In 2015, Kai et al. [24] designed an algorithm, based on the union of genetics and epigenetics, to predict the association between a genetic variant and an autoimmune disease, publishing the map of the causal genetic variants of 21 autoimmune diseases, concluding that most of the risk variants alter gene expression.

Thus, the prevalence of CD is higher in subjects suffering from other autoimmune diseases: (10 to 15%), type 1 diabetes (3 to 16%), Hashimoto's thyroiditis (5%) or other autoimmune diseases (including autoimmune liver diseases, Sjögren's syndrome, and IgA nephropathy), Down's syndrome (5%), Turner's syndrome (3%), and IgA deficiency (9%) [25–30]. Reasons for the concurrence among these autoimmune diseases include shared HLA genetic risk [31–33]. It is well known that the level of expression and, therefore, the density of HLA molecules on the cell surface are associated with the pathophysiology of autoimmune diseases and, currently, the focus of research is on studying the personalized prevention of autoimmune diseases modulating the HLA-ligand relationship [34].

The first 1,000 days of life (from conception, during pregnancy and in the first two years) are essential in the prevention of future diseases, because throughout this period the "metabolic programming" is established, that is, conditioning the metabolism of the subject. The possible roles that prenatal and perinatal life events may play in disease development are well known, and the fetal origin of immune-mediated diseases has also been investigated [35]. For some autoimmune diseases, such as type 1 diabetes, the importance of the intrauterine environment has been studied by comparing concordance rates in dizygotic siblings and monozygotic siblings [36]. Higher concordance rates between twins sharing the same proportion of genes as siblings could support mechanisms that operate in the uterus, but there are also more similarities in twins than siblings in the postnatal life. However, this approach has not been tested for CDs, as far as we know.

Early nutrition can potentially alter future metabolic programming [37]. The development of non-communicable diseases in adult life is marked both by the quality and quantity of nutrients consumed by the pregnant woman, and by the type and duration of breastfeeding and complementary feeding. The available literature data show a growing interest and concern about the impact of both the timing and the modality of complementary feeding on the appearance of subsequent non-communicable diseases, including CD. The most plausible explanation is that these factors modify the expressiveness of certain genes, modifying the response of certain organs and tissues, remodeling their structure and function. These epigenetic changes can be transmitted from one generation to the next, further highlighting the importance of the phenomenon of early metabolic programming.

The long-term health effects of breastfeeding, on both the prevention of autoimmune and metabolic diseases, are well known [38] and they are classified into the early metabolic programming. Not only the type and duration of breastfeeding are important, but also the timing of the introduction of complementary feeding and its characteristics, although most studies have focused on the period of breastfeeding, with complementary feeding receiving less attention, when its time and composition can have similar subsequent effects, since it is incorporated in a stage of rapid growth in which the body is susceptible to nutritional imbalances and there are rapid and marked changes in diet with exposure to many new foods that could influence disease development through various mechanisms including the effects of metabolic programming. Current evidence recommends avoiding the introduction of solid foods before 4 months to avoid obesity and certain allergies [39].

High body mass index is also a risk factor. Current evidence shows that not only low birth weight predisposes infants to a higher risk of developing chronic diseases in adult life, but also excessive fetal growth (macrosomia), as occurs in the offspring of obese or diabetic pregnant women [40,41].

3. Prenatal conditions associated with Celiac Disease

Maternal nutrition, together with environmental exposure, can permanently affect fetal and neonatal gene expression through epigenetic mechanisms that lead to metabolic abnormalities. An unfavorable nutritional environment during fetal development causes molecular, cellular, metabolic, neuroendocrine and physiological changes, therefore, inadequate nutrition of the pregnant mother has important long-term effects on the health of the child [42].

Maternal obesity and maternal overnutrition can cause epigenetic alterations during pregnancy and these alterations can influence the fetal and neonatal phenotype increasing the risk of metabolic disorders in later stages of life [43]. The maternal body mass index is positively correlates with systemic inflammation, including high levels of pro-inflammatory cytokines. Furthermore, an increase in these cytokines in the placenta has been shown to occur as a result of a high-fat diet. The high-fat maternal diet also causes insulin resistance through inflammatory changes in fetal adipose tissue. As a result of all these metabolic disturbances, excessive exposure to fetal lipids can affect fetal growth and development. Increased inflammation and blood lipids can have detrimental effects on the development of the liver, adipose tissue, brain, skeletal muscle, and pancreas, increasing the risk of metabolic disorders. Dietary factors can affect genome function and gene expression during early life through folate-mediated single-carbon metabolism or transmethylation pathways. Alterations in gene expression during pregnancy can influence the fetal and neonatal phenotype [44].

In this sense, pregnancy is considered as a factor that can unmask latent CD [45]. The gynecological and obstetric manifestations of CD are very varied. When obstetric outcomes were compared between women with and without CD, significant differences were found in infertility and vascular disorders and obstetric complications during pregnancy in celiac patients [46]. In active CD, malabsorption can lead to a deficit of different nutrients such as zinc, selenium, folic acid or iron, among others. Zinc and selenium deficiency affect gonadotropin synthesis, so the gonadal axis can be disrupted, and folic acid deficiency can affect neural tube development in the fetus [47]. The severity of malnutrition is directly correlated with the frequency and severity of gynecological-obstetric disorders, and a gluten-free diet has shown similar results in women with CD as in the general population [48]. The presence of transglutaminase (TG) has been demonstrated in endometrial cells, as well as in stroma and trophoblastic cells [49]. It has been postulated that the binding of TG and anti-TG may affect endometrial angiogenesis and decidualization, and thus affect implantation [50].

Several studies reveal that women with CD have a shortening of their fertile life with a delay in menarche and an earlier menopause compared to healthy women. Additionally, fertility problems are common in both men and women with CD and can be the first symptom of the disease. Other studies have indicated that there is a higher frequency of perinatal mortality and abortions among undiagnosed celiac women. These undiagnosed and untreated women are at higher risk of having low birth weight children than the general population [51,52].

In addition, as a consequence of the CD, a deficit of fat-soluble vitamins, such as vitamin K, can occur, which determine a deficit of all the factors dependent on this vitamin (factors II, VII, IX and X; protein C and S), inducing hemorrhagic manifestations or determining excessive vascular coagulation states. There are various gynecological and obstetric complications in this pathology fundamentally linked to all nutrient absorption disorders in the intestine: anemia due to iron deficiency or folic acid deficiency, hypoalbuminemia or hypocalcemia, with the pertinent consequences such as amenorrhea, infertility, early menopause, spontaneous abortions and delay in intrauterine growth, taking into account that folic acid, iron, and vitamin K are also essential for fetal organogenesis [53]. The development of arterial and/or venous thrombotic disease and its repercussion at the obstetric level has been linked in celiac disease in most cases to the presence of anticardiolipin and antiphospholipid antibodies as an associated autoimmune pathology [54]. Proteins C and S are vitamin K-dependent factors, physiological coagulation inhibitors that have a short half-life in relation to the other vitamin K-dependent factors, which is associated with their physiological decrease during pregnancy. Thus, an imbalance between procoagulant and

physiological anticoagulant factors may occur due to their premature decrease, favoring maternal thrombotic events with important repercussions on fetal development [54].

4. Early gluten consumption and development of celiac disease

Gluten acts as a trigger for CD in genetically predisposed subjects, but although approximately 30% [55] of the world population have HLA DQ2 or DQ8, the prevalence of the disease is only 1–3% [56]. It is not known what factors act to modify the risk of disease in genetically predisposed subjects. The so-called Swedish epidemic of the 1980s, when there was an increase in EC of up to 4 times greater than expected between 1985 and 1987, set off alarms. The changes in the amount of gluten that infants ingested, as well as the moment in which it occurred, suggested that the time of introduction of gluten or the amount of gluten could act as factors that modified the probability of developing CD. The increase in incidence in Sweden was justified due to the increase in the amount of gluten in malted beverages and cereals and the fact that it was administered after 6 months of age, in addition to being related to the introduction of gluten based on whether or not they were breastfed. [19]. The mechanisms by which gluten could act as a risk factor were explained by the possibility of gluten intake and the maturation of the intestinal barrier and by the gluten load and its relationship with the immune system [57]. It was thus, and together with other studies, that the window of opportunity with gluten intake arose, between 4 and 6 months of age, and that it has conditioned the feeding calendar of infants for years.

In the last 30 years, a multitude of studies have been carried out to determine if there is an optimal time for the introduction of gluten. In 2016, a systematic review with meta-analysis [58] concluded that there is an optimal window for the introduction of gluten, between 4 and 6 months of age, based on the analysis of fifteen studies [20,57,67–71,59–66]. Likewise, after analyzing various studies [20,57,65,68] a gradual introduction of the amount of gluten from 4 months was proposed to reduce the risk of developing CD. However, this work does not include two randomized clinical trials [72,73], which does include the systematic review with meta-analysis by Szajewska et al. [74]. In the study by Lionetti et al., [72] there were no differences in CD diagnoses at age 5 years between the group that received gluten at 6 months and those that received gluten at 12 months. Similarly, in the study by Vriezinga et al. [73] there were no differences in CD diagnoses at 3 years between the group receiving gluten between the group receiving placebo (during 4 and 6 months). Taking into account this, the conclusions of this systematic review with meta-analysis are very different. The authors do not corroborate the previous results, on the contrary, they point out that gluten can be introduced from 4 to 12 months regardless of the risk of developing CD before 5 years, and these results were similar to those of other subsequent systematic reviews [75,76].

After the publication of the previously cited studies [74] and especially after the publication of the two randomized and controlled clinical trials already discussed [72,73], the European Society of Gastroenterology, Hepatology and Nutrition (ESPGHAN) published an update in 2016 of its recommendations [77]. The most important novelties reported were: a recommendation on the type of gluten that cannot be made to modify the risk of developing CD; additionally, although there is no important evidence to support this recommendation, the intake of large amounts of gluten is not recommended during the first months after the introduction of gluten; and, most importantly, they recommend that gluten should be introduced between 4 and 12 months of age of the child, omitting the “window of opportunity” previously indicated [78], to prevent the development of CD.

Since then, different studies have been carried out. The TEDDY Study Group published a study in 2016 [79] referring to a case-control study on 2,062 births in the study cohort. They observed that gluten intake at the age of 12 months behaved as a risk factor for the development of CD, with CD developing earlier in patients with higher genetic risk, although the amount of gluten was a factor independent risk for the development of CD. The children who consumed more gluten, likewise, had a higher risk than those with the lowest intake (OR: 2.65; 95% CI: 1.70 to 4.13). Subsequently, in 2019 the same group published a new study [80]. They analyzed gluten intake in 6,605 children at 6, 9, 12 months and biannually up to 5 years. Although the increased risk was small, they observed that

for every gram of daily gluten added to the diet there was an increase in CE (HR: 1.50; 95% CI: 1.35 to 1.66).

Recently, Lund-Blix et al., [81] in the Norwegian Mother and Child Cohort Study (MoBa), which included approximately 67,000 children and a mean follow-up time of 11 years, analyzed whether the amount of gluten ingested at age 18 months influenced the development of CD. They observed that the amount of gluten ingested by the children who subsequently presented CD was significantly higher than that of the controls, although an active search for CD was not carried out by analytical determination, but only patients diagnosed after review of the clinical history were included. Although the increased adjusted relative risk (RRa) among those who ate more and less gluten was minimal (1.29, 95% CI, 1.06 to 1.58), the data from this study suggest that the amount of gluten ingested is a factor to consider in the later development of CD.

Likewise, Marild et. al, [82] published data from the DAISY study, and 1875 children at risk of CD followed. They observed that for every gram of extra gluten intake, there was an increased risk of CD, although the results were not significant: (HR: 1.04; 95% CI: 0.98 to 1.10). This study, like this published by Aronsson [80], is limited to a population genetically at risk, unlike the study by Lund-Blix [81] which included children without genetic predisposition.

Unlike previous studies, the study published by Crespo-Escobar et al., [83] from the PreventCD cohort, showed that the amount of gluten consumed between 11 and 36 months of age was independent on the development of CD at 6 years old, in contrast with the previous results. However, in this multicenter study, which included several European countries, they did find differences for the HLA-DQ2.2/-DQ7 risk group, observing that a gradual increase in the amount of gluten between 11 and 18 months can act as a modulating factor for this specific group. Later, the data from this cohort in Spain was analyzed [84], concluding that the consumption of gluten during the first 3 years of life does not influence the risk of developing CD before 6 years of age.

5. Breastfeeding vs. infant formula and Celiac Disease

In recent years, attention has also been paid to the role that exclusive or mixed breastfeeding may play and its role in the prevention of CD. A window of opportunity has been hypothesized in which the mucosal immune response can be modulated, thereby causing different foods to change the probability of developing CD [85].

Human milk is not only a fully adapted source of nutrition for the newborn, but also a matrix of immunologically active molecules that modulate the immune response and the susceptibility to develop autoimmune diseases [86].

The World Health Organization (WHO) recommends breast milk as the ideal food for the newborn and infant during the first six months of life, due to its ability to achieve adequate post-statutory growth and maturational development [87].

One of the most important factors in the composition of breast milk are its bioactive agents, which make it have an important immunological effect, as well as nutritional, being considered a "functional" food, due to the presence of anti-infective agents (lysozyme, lactoferrin and immunoglobulin A), oligosaccharides, anti-inflammatories (polyamines, lactoferrin, epithelial growth factor, prostaglandins ...) and probiotics, among others.

Other important components include human milk oligosaccharides (HMOs), which are 10% of the carbohydrates present in human milk and which are practically absent in cow milk. They present a multitude of functions, the main ones being to nourish the infant's gastrointestinal tract with bacteria [88], since most are not digested and reach the colon, where they compete with pathogenic bacteria and viruses for the receptors of the intestinal epithelium, avoiding the adhesion of pathogens, promote the growth of *bifidobacteria* and *lactobacilli* [89,90] and stimulate the infant's immune system, thus being considered prebiotic agents that modify the infant's intestinal microbiome [91] (a situation studied in genetically at risk of CD [92]) and limiting the growth of potentially pathogenic bacteria [93,94]. For all these functions, some studies have linked the ability of HMOs to prevent the acquisition of viral diseases in infants [95].

Human milk also contains a large quantity of microRNAs [96], which are small non-coding RNA molecules that regulate gene expression at the post-transcriptional level, implicated in mechanisms of cell proliferation and also in apoptosis and developmental programming [97, 98]. Although its involvement in human milk is unclear, it appears to play an important role in the development of the immune system [99].

Other components such as lysozyme also seem to have an antimicrobial effect, thanks to their ability to destroy peptidoglycans of the bacterial wall [100]. Lactoferrin, on the other hand, acts as an iron chelator, and it has been described that part of the undigested lactoferrin that reaches the intestine inhibits the growth of pathogens such as *Escherichia coli*, thanks to its ability to compete with said bacteria for ferric iron [101]. Also, the milk fat globule membrane (MFGM) is related to the development of the immune system and the functionality of the gastrointestinal tract [102,103]. Different environmental triggers have been hypothesized, such as viral infections, intestinal dysbiosis, lifestyle, or eating in the early stages of life [104–107]. On this theoretical basis, breastfeeding could decrease the capacity of infectious triggers to promote the development of CD, due to its antimicrobial capacity.

On the other hand, concomitant elevation of anti-transglutaminase antibodies and elevation of antibodies against cow milk have also been observed in certain patients [108], being on many occasions not dependent on CD, due to states of increased intestinal permeability, such as in situations of allergy to cow milk proteins [109]. Despite this, some authors have hypothesized that cow's milk could act as a trigger for CD, due to the presence of advanced glycation end products (AGEs) that are the result of the join of powdered milk and other products, producing a pro-inflammatory effect with increased intestinal permeability, a situation observed in vitro [110], and an alteration of the intestinal microbiota [111].

Likewise, the presence of anti gliadin antibodies in breast milk has led some authors [112,113] to suggest that breastfeeding may have a protective effect on the development of CD due to its ability to modulate the infant's immune system. As we can see, there are various mechanisms that have been postulated to explain the relationship between breastfeeding and the development of CD.

From a practical point of view, breastfeeding has been related to the prevention of a multitude of pathologies, acting as a protective factor. Thus, it has been associated with a decrease in autoimmune diseases such as type 1 diabetes, multiple sclerosis or rheumatoid arthritis [86,113–116], and there is currently evidence of its role in the development of atopic eczema and wheezing in the first two years of life and in incidence of asthma in the first five years of life [117]. Furthermore, the beneficial effects of BF in the development of obesity have been demonstrated, both exclusively [118] and when compared with artificial formula [119], the effect being greater when it is administered exclusively [120,121] and observing a greater association if it is prolonged [120].

Other authors [122] have studied the relationship between the type of breastfeeding and its influence on inflammatory markers in subjects genetically predisposed to CD. In a sample of 170 children, a higher percentage of CD4+ CD25+ and a lower percentage of CD4+ CD38+ was found in children fed at the breast compared to children breastfed with artificial formula, the increase in CD4+ CD25+ being related to the decrease in development of autoimmune diseases through the differentiation of regulatory T cells [123], thus suggesting a beneficial profile related to breastfeeding, due to a more mature and more differentiated immune system towards regulatory T cells than in formula-fed infants, as a consequence of the beneficial properties of breast milk.

Several studies [20,63,64,71] have described a protective effect of breastfeeding on the development of CD, although most of the studies published to date have not been able to corroborate this protective effect. Other prospective studies [57,59,66,72,73,124–128] have not been able to demonstrate a beneficial effect of breastfeeding with respect to the development of the disease.

Regarding the duration of breastfeeding, four prospective studies [59,66,72,79] analyzed the influence of the duration of breastfeeding on the risk of developing CD, and five case-control studies [20,62–64,126] They also investigated whether breastfeeding for a longer time had an advantage over

a shorter time of breastfeeding. Of all of them, only two studies [63,64] found statistically significant differences between breastfed infants and infants fed with artificial formulas.

Similarly, only retrospective or case studies have shown a protective factor of receiving BF at the time of gluten introduction [63,71], not being corroborated by the prospective studies carried out [57,66,72,73,125]. The meta-analysis performed by Akobeng et al., [129] reported that breastfeeding had a protective effect on the development of CD, although it must be taken into account that it is a study that includes studies up to 2004, and only 6 studies of low methodological quality, case-controls were included.

A meta-analysis by the PREVENTCD Study Group [130] determined in 2015 that there is no relationship between BF and the development of CD, nor between its duration and the appearance of disease, these recommendations being identical to those of ESPGHAN in 2016 [77]. These data have been corroborated more recently in a systematic review [131], in which the expert committee determines a very weak level of evidence for the claim that drinking breast milk at some point compared to artificial milk protects against development of CD. Likewise, it concludes with respect to the duration of breastfeeding that the evidence is insufficient to draw conclusions, because in many of the studies the disease developed before the lactation period had ended, and a clear causal relationship could not be established.

Due to the small number of studies and their methodological weaknesses, the majority being of the case-control type, with a small number of samples and without controlling for confounding factors, these results must be taken with caution.

On the other hand, several studies have analyzed the characteristics of powdered formulas and their relationship with the development of CD. Hyytinen et al., [132], analyzed whether there was a difference in genetically predisposed subjects in taking conventional artificial formula or extensively hydrolyzed formula during the first 6-8 months of life, finding no differences in this regard. Segerstad et al., [133], evaluated the risk of developing CD in relation to artificial feeding in genetically predisposed subjects. They analyzed the amounts of powdered milk that infants ingested and observed that there were no differences in the development of the disease depending on the amount of powdered milk they drank, although the follow-up was only 2 years, losing the diagnosis of those subjects who developed the disease years later.

The relationship between feeding in the early stages of life has also been studied according to the predisposition of the subject. Welander et al., [134] studied whether the type of diet influenced the development of CD in children of mothers with CD and mothers without the disease, finding no differences regarding the type of diet between the two groups and suggesting that the type of feeding contributes little to the risk of developing the disease in the offspring of celiac patients, being other factors that explain the increased risk of this group and not the type of breastfeeding or feeding in the first months.

6. Importance of the composition of the intestinal microbiota and Celiac Disease

The fetus does not reside in a sterile intrauterine environment and is exposed to commensal bacteria from the gut and/or maternal bloodstream, which crosses the placenta and colonize the amniotic fluid. Intestinal crosstalk with colonizing bacteria in the developing intestine affects the baby's adaptation to extrauterine life (immune homeostasis) and provides protection against the expression of diseases (allergy, autoimmune disease, obesity, etc.) later on. Colonizing gut bacteria are critical for the normal development of host defense [135]. In fact, over the past decade, both scientists and clinicians have recognized the importance of bacteria, particularly bacteria that colonize the gastrointestinal tract, in the metabolic and protective function of the host [136].

Taking into account that most of the population does not present any problem when consuming gluten, even for those with genetic susceptibility, it is clear that there may be factors other than gluten, which could be involved in the development of CD. The presence of anchored bacillary bacteria, not present in healthy individuals, has been observed in the duodenum of children with CD [137], which may indicate the importance of microorganisms in the pathogenesis of CD. There are studies that focus on evaluating the microbiota present in the intestine because CD is a disease that

affects this region. Through techniques such as fluorescent in situ hybridization (FISH), in duodenal biopsy samples, a reduction in the population of *Lactobacillus* and *Bifidobacterium* and an increase in *Bacteroides* and *Escherichia coli* in children with CD compared with healthy children [138]. In stool samples and duodenal biopsy from healthy celiac children, an increase in *Bacteroides sp.* was observed through real-time PCR. and *Clostridium leptum* in celiac children, while *Bifidobacterium longum* was decreased [139,140]. Likewise, the levels of *Escherichia coli* and *Staphylococcus* were higher both in the biopsies and in the stools of children with active CD compared to those who were treated and controls.

On the contrary, there are other studies that, using the Denaturing Gradient Gel Electrophoresis (DGGE) technique, indicate a reduction in the diversity of *Bacteroides* in the biopsies of celiac children regardless of the treatment, so that certain species such as *B. distasonis*, *B. fragilis*, *B. uniformis* and *B. ovatus* appeared more frequently in healthy controls than in active and treated celiacs, while *B. vulgatus* appeared increased only in healthy [141]. Schippa et al. [142] analyzed the composition of the microbiota of the duodenal mucosa of children with CD and healthy children using temporal temperature gradient electrophoresis (TTGE). A greater diversity was observed in the duodenal mucosa of children with CD, presenting a different electrophoretic profile by TTGE before and after treatment.

Sánchez et al. [143] cultured the microbiota present in duodenal biopsies of children with active celiac disease, treated and non-celiac controls. They concluded that children with an active form of the disease had a higher proportion of *proteobacteria*, while the opposite occurred with *firmitutes*. Specifically, *Klebsiella oxytoca*, *Staphylococcus epidermidis* and *Staphylococcus pasteurii* were more abundant in active celiac patients than in controls. On the contrary, in celiac children, species of the family *Streptococcaceae*, appeared in a lower proportion.

It should be noted that not all the studies analyzed indicated the existence of clear differences between the microbiota of celiac and healthy children. Ou et al. [144] carried out the characterization of the microbiota of the proximal part of the small intestine by sequencing a region of 16S rDNA and found no differences in bacterial populations between biopsies of children with CD and healthy children.

In addition, it is important to take into account not only the differences in the composition of the intestinal microbiota between healthy children and celiac disease, but also its activity, since it can also be altered. Thus, by means of zymography, it has been revealed that celiac patients present a profile of bacterial proteases capable of hydrolyzing gliadin that was absent in healthy ones. It is shown that in addition to the imbalance in the intestinal microbiota, children with CD present a proteolytic activity of different bacterial origin [145].

7. Conclusions

The increase in prevalence that is occurring in CD in recent years may not be due solely to the improvement in the diagnosis and the increase in the diagnostic of the disease, there are other factors that help to contribute to this increase. Given the strong environmental burden that seems to act as a modifying factor for the disease, it is logical that attention has been paid to gluten as a key element in preventing the disease. However, based on the studies published so far, it seems clear that there is strong evidence in favor of the fact that the time of introduction of gluten during lactation (between 4 and 12 months) does not seem to modify the risk of developing CD. , if anything, delay its appearance. It is unclear due to the lack of quality randomized clinical trials how the amount of gluten ingested influences and at what ages. To understand the keys to the Swedish epidemic, perhaps it is other triggers that could explain the differences in this population and, also, the different prevalence between countries.

Similarly, there is no strong evidence in favor of the protective factor of breastfeeding and the development of CD, although small studies have shown that there may be a relationship and others have shown immunological changes in genetically at risk subjects. Despite the different hypotheses proposed, it is not clear why the breastfeeding would act as a protective factor of the disease. It

seems that due to its anti-infective properties there could be a delay in diagnosis rather than true protection, it remains to discover its role in metabolic programming, which could act more in the long term.

Despite having recognized in recent years different mechanisms as possible disruptors in CD, there is no certainty about the mechanism that triggers the disease, and the evidence is very scarce on the role that diet plays in the early stages of life. More studies are needed to determine which factors may increase the risk of developing the disease in a genetically at-risk population, as well as studies that definitively clarify the role of gluten intake in the first year of life in this population at risk. The dramatic increase in the incidence of the disease makes it necessary to actively search for these factors even from prenatal stages, with fetal programming being a factor that can modulate risk. Diet, genetic risk, microbiota and environmental interaction are possible triggers of the change in tolerance to an immune response to gluten, and the greater knowledge of them will lead to an improvement in the diagnosis of the disease, and who knows if its prevention in early stages. That the perinatal environment influences the development of CD is still circumstantial evidence. Large-scale cohort studies and emerging scientific concepts, such as epigenetics, may help us establish the role of these factors.

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