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# The Jigsaw Puzzle of Breast Feeding and Celiac Disease

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**Abstract** The puzzle of breast feeding effects on celiac disease development is complicated and despite numerous studies, remains unresolved. Several prospective or retrospective observational studies on the topic were reported, with contradictory results. The geoepidemiology teaches us that celiac disease incidence, in the west, is increasing, while breast feeding is decreasing, going along with the protective effect of mother's milk. But, human milk and gluten are only two in the growing list of environmental factors that affect celiac disease induction or behavior. The recent increased knowledge on gluten side effects in non-celiac populations and the fact that human milk contains gluten peptides, further complicate the breast milk-gluten-celiac disease cross-talks. Latest studies revealed that breast feeding, whether exclusive or in combination with formula intake, did not reduce the risk of CD development. More so, recent publications concluded that timing of introduction of gluten to infant diet did not influenced the risk of development of CD. It is hypothesized that local environments, nutritional habits, intestinal ecosystems or genetic background might have influenced the published results. Much more epidemiological and prospective investigational studies might clarify the jigsaw puzzle of breast feeding and celiac disease behavior.

***Keywords:*** *celiac disease, breast feeding, protective, infant, onset, gluten, timing*

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## 1. Introduction

The hypothesis of primary prevention of celiac disease (CD) by human breast milk or inducing oral tolerance, via early feeding of gluten, has been long investigated. The rationale for the protective effects of breast feeding (BF) is based on the following breast milk advantages: 1. Passive immunity conferred by the IgA antibodies, lactoferrin, lysozyme etc. 2. Reduction of gastrointestinal infections, 3. Regulation of gut permeability.4. Anti-inflammatory cytokines. 5. Induction of beneficial microbiome. 6. Diminished gut infections prevent tissue transglutaminase intestinal expression.7. Immune regulatory property exerted through suppression of autoimmunogenic T-cell. 8. Bioactive antimicrobial and anti-inflammatory agents, enzymes, hormones and growth factors involved in gut maturation and infant's innate and adaptive immunity development.

On the contrary, introducing gluten early in life or during a precise period, presenting a window of opportunity for tolerance induction, has logical background. In addition, human milk contains gluten in small quantities. This can induce tolerance to gluten as it has been suggested for other antigens [1].

Breast feeding as a protector from CD is a controversial topic. Several studies reported protective effect of BF on the risk of developing CD, while others, on the opposite side, reported no effects. The latter are the most recent ones and have the highest GRADE score and the lowest bias risk [2]. Maternal BF was once thought to be protective against the development of CD, to date evidence is inconsistent. Silano M et al, summarized most recently the effects of infant feeding on CD risk of development. The studies exploring BF effects and BF duration on CD development were positively protective in 5 and not effective in 9. When the BF effect at the time of gluten introduction on CD development was reviewed, 3 studies were protective, while 5 had no effects [2].

Several aspects are worthwhile to expand on.

## 2. CD Incidence in the West is Increasing, while Breast Feeding is Decreasing

The prevalence of early cessation of exclusive breast feeding is alarmingly high with 50% of infants no longer exclusively breast fed by age 2 months in Australia [3]. But also in developing countries, like India, low rates of breast feeding is observed to the point that it requires national action [4]. This trend is reinforced by the availability and commercial advertising of infant formulas. This is the reason that the current WHO recommendations on infant feeding stress the importance of exclusive BF worldwide [5]. The described drop of BF is epidemiologically followed by an increase incidence of CD, in the wheat consuming populations [6]. In fact, when reviewed by follow-up, long-term studies, CD incidence surged substantially. The mean ± s.d. of the net increase in %/year incidence of CD worldwide is 9.77±8.27. In all of these studies, differences between old vs new frequencies were highly significant ($p<0.0001$). Geoepidemiologically, Netherland/USA had the highest/lowest net %/year CD incidence increases:

9.23±9.64, 5.0±2.09 respectively. The increases were higher in northern/western countries than in southern/eastern countries [6]. Those relationship between the drop of BF and the surge in CD incidence are associative, but no causative connection, as yet, has been established.

## 3. Environment and CD Induction/prevention

Gluten and BF are not the only environmental factors that affect CD. Except for the major role of prolamines in CD induction, multiple environmental factors have been reported as enhancers of the disease. Infections like Rota virus in infants and Campylobacter jejuni in adults are associated with an increased risk of CD [7,8]. The infectome-autoimmune diseases relationship is congruent with the hygiene hypothesis, which states that decreased exposure to microbes may be driving the rise of autoimmune diseases. Additional environmental factors that have been associated with increased risk for celiac disease include: increased amount of gluten ingestion, prescription of antibiotics and proton pump inhibitors, elective cesarean section, socioeconomic factors and most recently, maternal iron supplementation to pregnant woman [8]. Lately, seven industrial food additives were described to abrogate human epithelial barrier function and increase intestinal permeability through the opened tight junction, enhancing the entry of foreign immunogenic antigens and activation of the sub-epithelial immune cascade [9,10,11]. The most relevant for CD is the microbial transglutaminase that imitate functionally the tissue transglutaminase, in cross-linking gliadin, thus creating a neo-epitope microbial transglutaminase-gliadin complex. This food additive, heavily used in the processed food industry as a “glue of protein” that are rich in glutamine and lysine residue, was found recently to be immunogenic in CD patients [9,10,12,13]. Given the uncertainty regarding causality, these associations between CD and environment mandate further investigations to test the mechanistic pathways by which modern exposures contribute to the induction of CD.

The other aspect of BF/gluten intake and CD is the growing knowledge of the side effects of gluten in non-celiac or normal populations. In the intestinal ecosystem it impacts the microbiome and increases intestinal permeability. Gluten is immunogenic and cytotoxic, pro-inflammatory, activates the innate and adaptive immune systems and alters regulatory functions. On the cellular level it increases apoptosis, decreasing viability and differentiation and impacts nucleic acids and glycoproteins synthesis. It has multiple systemic effects as inflammation inducer, enhancer of oxidative stress and impacts epigenetic processes. Finally, animal model’s consumption or in vitro application of gluten increases our understanding on those toxic or mal- effects of gluten. (Unpublished data). One wonders if BF alleviates some of those gluten associated side effects.

## 4. What is Known in the Recent Literature?

A recent meta-analysis by Szajewska et al., evaluating 21 studies, revealed that BF, whether exclusive or in combination with formula intake, did not reduce the risk of CD development [14]. A recent meta-analysis concluded that BF vs no BF does not affect CD risk, however, late (>6 months) introduction of gluten may be associated with increased risk of CD [15].Three recent publications concluded that timing of introduction of gluten to infant diet did not influenced the risk of development of CD by age 3-5 years [14,16,17]. On the contrary, the TEDDY study showed that the amount of gluten consumed until 2 years of age increases the risk of CD in genetically susceptible children [18]. Those topics were discussed extensively in recent editorials and reviews [19,20,21]. Interestingly, taking an example from an animal model, human colostrum and BF had an ameliorative effect against CD in autistic rats [22].

At the end of the day, the jigsaw puzzle of breast feeding and celiac disease is far from being resolved. It seems that, for now, the no effect reports are dominating and add an additional weight to the none-protective wing of the balance of BF and CD interplay. It is suggested that local environments, nutritional habits, intestinal ecosystems or genetic background might have influenced the study’s results and conclusions. Much more world-wide epidemiological and prospective investigational studies might clarify the puzzle.

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