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The Salutogenic Effects of Cow's Milk and Dairy Products in Celiac Disease

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Abstract

For the last 10,000 years human beings consume cow's milk. Along the evolution, human gut adapted to consume animals' milks for man benefits. Poured cow's milk, dairy food and bacterial fermented dairy products contain multiple health promoting and therapeutic factors that might help in multiple autoimmune diseases, including celiac disease. The present review summarizes the celiac disease pathophysiology and dysfunctions that can benefit from cow's milk and dairy food health promoters, on the preventive as well as on the therapeutic levels. The extended list of milk originated, bio-reactive agents forms a basis, and hopefully the drive for further studies in order to explore the beneficial compound buried in this biologically active and natural fluid and dairy products.

Keywords: Cow's milk; Dairy products; Bacterially fermented milk products; Bioactive compounds; Health-promotion; Celiac disease

Abbreviations: CD: Celiac Disease; GFD: Gluten Free Diet

Introduction

Human beings are consuming cow's milk since cattle were domesticated in the early Neolithic age, around more than 10,000 years ago. Along the evolution, human gastrointestinal tract adapted to consume animal milks, cow's milk being the major one. During thousands of years humanity benefited from cow's milk drinking and dairy products consumption as health promoters. It is only in the last decades that critics and drawbacks were related to its consumption and mainly popular reports categorized it to be detrimental to human health. It has been related to various conditions like cancers, autoimmune diseases, atherosclerosis, hypercholesterolemia, aging, acne and constipation [1]. Most of those publications are associative, where no cause and effects were demonstrated. On the contrary, the last years brought us huge amount of scientific observations on the cow's milk content, harboring multiple bio-active factors in the whey and the Casein compartments or were produced during bacterial fermentation. Cow's milk and dairy products are considered nowadays as health-promoting foods, some of them even as beneficial functional nutrients [2-6]. The aim of the present review is to update on those health-promoting compounds in relation to the potential beneficial effects they can offer as an adjuvant therapy, to Celiac Disease (CD)

Cow's milk and dairy products contents

Raw cow's milk contains 30-35 g of protein per litre; about 80% is arranged in casein micelles. Total proteins in milk represent 3.2% of its composition and are divided to whey and casein portions. Milk contains various carbohydrates including mono-, di-, oligosaccharides, whereas the main one is lactose which gives milk its sweetness and contributes approximately 40% of whole cow's milk's calories. Milk fat is secreted in form of a fat globule surrounded by a membrane. The fat-soluble vitamins A, D, E, and K along with essential fatty acids such as linoleic and linolenic acid are found within the milk fat portion of the milk. In addition, milk contains multiple minerals: calcium, phosphate, magnesium, sodium, potassium, citrate, and chlorine, salts of calcium and phosphates, vitamins: A, B6, B12, C, D, K, E, thiamine, niacin, biotin, riboflavin, folates, and pantothenic acid, and immunoglobulins, living white blood cells, mammary gland cells, various bacteria, and numerous active enzymes [5,6]. During processing, bacterial fermentation and by supplementing food additives, additional bioactive compounds appear that will be reviewed below.

Celiac disease

Celiac disease is an autoimmune inflammatory condition of the small intestine, triggered by the ingestion of prolamins contained in wheat, barley, rye or oat, in genetically susceptible individuals. The accepted incidence of CD averages 1-2% in the Western world, the majority of patients being undiagnosed [7]. Comparable to the predominance of the female gender in many other autoimmune diseases, the male/female ratio in CD is 1:2-3.

The epidemiology and phenotype of CD are constantly evolving. The classic intestinal clinical picture of malnutrition, chronic diarrhea and nutritional deficiencies are disappearing and extraintestinal presentations are emerging. Skin, endocrine, skeletal, hepatic, hematological, thrombophilic, gynecological, fertility, dental, psychiatric and behavioral abnormalities are increasingly described [7]. An epidemiological shift in the disease phenotype toward a more advanced age, and increased prevalence of latent, hyposymptomatic or asymptomatic behavior is observed. Increased risk of complications such as hematological and gastrointestinal malignancies, osteoporosis/penia and other extraintestinal manifestations like hepatitis, decreased height, malnutrition, nutritional deficiencies, fertility impairment, stillbirth, dysmaturity, psychosocial deterioration, impairment of quality of life, increased mortality and additional autoimmune conditions, if left untreated, are faced by the patients. Thus, early

diagnosis and subsequent adherence to a gluten-free diet (GFD) is highly recommended [8-11].

Bioactive Compounds in Cow's Milk and Dairy Products with Potential Benefits in Celiac Disease

Celiac disease is an inflammatory, oxidative, apoptotic, tissue destructive and a dysbiotic condition. It is characterized by activation of the innate and reactive immune systems, surge in pro-inflammatory cytokines and activation of the autoimmune cascade. Being associated with increased incidence of type 1 diabetes, failure of the mucosal immune network and tolerance break toward gluten, hypercoagulability and nutritional insufficiencies, CD patients can benefit from numerous bio-active components which raw cow's milk, dairy products and bacterially fermented milk can offer. (Table 1) summarizes those compounds in relation to CD pathophysiological abnormalities.

Table 1A			
Cow's milk and dairy components	**Compound activity**	**Celiac disease abnormalities**	**References**
Casein proteins			
α-, β	Casomorphins: ↗AA, electrolyte absorption	↘absorption	[12,13]
	Casokinins: ↗intestinal blood supply	Intestinal damage	[12]
	Phospholipids: electrolyte binding+ absorption		[12,13]
	Immunopeptides, Casomorphins, Casokinins: ↗immune+phagocytic activities	Immune+phagocytic insufficiencies	[12]
κ	Casoplatelins: anti-thrombotic, coagulability	hypercoagulability	[12,14]
	ê-caseinglyco: probiotic, ↗*bifidobacteria*	Dysbiosis, ↘*bifidobacteria*	[12]
αs1	Isracidin: Antimicrobial, antioxidative		[12,15]
αs2	Casocidin: antimicrobial	Microbial induced	[12,15]
Table 1B			
Whey factors			
Immunoglobulins: IgG, IgA	Immunomodulators	IgA deficiency, immune deficiency	[12,15]
Lactoferrin	Anti-microbial,-inflammatory, Probiotic, ↗*bifidobacteria*	Dysbiosis, ↘*bifidobacteria*, microbial induced	[12,15-17]
Oligosaccharides	Probiotic, ↗*bifidobacteria*	Dysbiosis, ↘*bifidobacteria*	[12,16,17]
Glycolipids	Antimicrobial	prokaryotic epithelial attachment	[12,15]
Cytokines: IL-1, 2, 6, 10, TNF α, INF γ, TGF α, leukotriene B4, prostaglandin E2	Immunomodulation Cellular trafficking	Hyperactivity of innate+ reactive systems leading to intestinal damage	[12,18]
Growth factors: IGF 1, TGF α, EGF, TGF β	Organ development, growth and functions	Intestinal destruction,↘rehabilitation, dysfunction	[12,19]
β lactoglobuline	Rich in branched AA	↘absorption, nutritional deficiencies	[12,13]
α lactalbumin	Rich in tryptophan	↘absorption, nutritional deficiencies	[12,13]
Glycomacropeptides	Rich in essential AA	↘absorption, nutritional deficiencies	[12,13]
Albumin	High biological value, proteins and factors carrier	↘absorption, nutritional deficiencies	[12,13]
Parathormone-P	↗Ca absorption and metabolism	↘Ca absorption, osteopenia, osteoporosis	[12,20]

Prolactin	Immune modulation	immune destructive hyperactivity	[12,19,21]
Table 1C			
Bacterial dairy fermentation products			
Vitamins: B-1, 2, 7, 9, 12	Specific biological activities	↘absorption, nutritional deficiencies	[2-4,12,13]
Gamma-Aminobutyric Acid	Anti-diabetic	↗incidence of type 1 diabetes	[2,22]
Bacteriocins	Antimicrobial	Dysbiosis, microbial induced	[2,15,17]
exopolysaccharides	Antimicrobial, immunomodulator	Dysbiosis, microbial induced, immune destructive hyperactivity	[2,15,17,19]

Table 1: Health promoting compounds in cow's milk and dairy products, originated from: 1A-casein proteins, 1B- whey factors and 1C-bacterial fermentations induced compounds, having preventive and therapeutic potentials in celiac disease. [2-4,12]. AA-amino acids, Ca-calcium, ↗-increase, ↘-decrease

Bone Health, Dairy Products and Celiac Disease

Most of CD patients today are diagnosed during adulthood and around half of them present decreased bone mineral density at diagnosis [23]. When a general CD US population was screened, children and men had reduced bone mineral density and men ≥ 40 years had increased risk of osteoporotic fractures [24]. Many conditions and circumstances can contribute to the skeletal alterations in CD. Hypocalcaemia of various etiologies, hypovitaminosis D, the inflammatory state of the small bowel, bone related hormones, associated autoimmune diseases, active or non-responsive disease, life factors like reduced physical activity and smoking and bone affecting drug intake, but above all is the calcium status, being the "common denominator of bone and intestine" [25]. Nutrition represents a major factor in proper bone mineralization and upon gluten withdrawal, calcium intake may be reduced. In fact, GFD is low in vitamin D and calcium, intake of milk and dairy products is reduced in order to avoid lactose and seldom gluten-free products are enriched with calcium and vitamin D. Thus, adherence to GFD, a well-balanced diet and adequate consumption of dairy products is highly recommended [25]. The highest calcium nutrients are represented by milk and dairy foods which provide also vitamin D, potassium, magnesium, proteins and other micro and macro compounds. Those products positively affect bone mass accretion and maintenance during the whole life cycle, thus lowering the risk of fractures later in life, including in CD [26-30].

Milk Products and the Dysbiosis of Celiac Disease

An intricate human-microbe symbiotic relation in the gut lumen has coevolved since the beginning of humanity, for the last two million years. The adaptation and fine-tuning of the two kingdoms benefit both to the degree that one cannot survive without the other [16,17]. The enteric bugs protect us from systemic diseases, intestinal infections, drive the gut immune systems and produce a mobilome, acting as metabolic organ that support the homeostasis of gut and systemic essential biological events [31-33]. The literature suggests that in CD, there are abnormalities in the composition and diversity of the microbiome [16,17] and its metabolic activity [32]. Zooming back on cow's milk and dairy products benefits, the two families of *bifidobacteria* and *lactococcus* are less abundant in CD intestinal lumen and stools, while multiple casein and whey compounds are inducing or maintaining their growth [1,4,34-38]. More specifically, κ-casein, Lactoferrin and Oligosaccharides, were shown to induce or maintain *bifidobacteria spp* (Table 1). Interestingly, *Bifidobacteria* and *lactobacilli* are capable to degrade immunotoxic gluten peptides, resulting in a new potential therapeutic modality for CD [19,39,40]. In a wider angle, those microbial components are associated with additional autoimmune diseases like type 1 diabetes, inflammatory bowel diseases and thyroid autoimmunity and with non-autoimmune conditions like irritable bowel syndrome [41-43].

Whey proteins can modulate gut microbiome, thus preserving intestinal health and by their probiotic functions, dairy products are potential drivers of a more physiological mobilome, whereby short chain fatty acids is a good example [32,35]. Interestingly, a recent study analyzing breast milks of CD mothers showed decreased numbers of *Bifidobacterium spp*, compared to control breast milk [44]. The impact of CD mother's milk microbiota on CD development of their offspring is still unknown.

Milk Products and Intestinal Permeability

Multiple intestinal luminal environmental factors and eco-events can perturb tight junction integrity, resulting in a leaky gut [33,45], thus breaking equilibrium between tolerance and immunity to non-self- antigens. Nutrients that are enhancing or breaching tight junction performance were summarized lately [33]. Many of the enhancers originate from cow's milk, dairy food, bacterially fermented milk products or supplementations. Short chain fatty acids like butyrate, polyunsaturated fatty acids, certain amino acids like glutamine, trace elements like zinc, vitamins like A and D, carotenoids, retinoids and proteases are some of them [33,46-49]. More so, in recent years, the fermented dairy industries are very productive in finding or adding health promoting factors to their products. Fruits to introduce fibers as prebiotics, polyphenols as a defence and antioxidant compounds, flavonoids, probiotics and other factors that protect the intestinal luminal compartment and the mucosal integrity, were recently described [50-54]. Finally, as increased intestinal permeability exists in CD patients, those dairy products can attenuate tight junction dysfunction for the benefit of the gluten sensitive populations.

IgA Deficiency, Dairy Products and Celiac Disease

Selective IgA deficiency is a frequent genetic immunodeficiency state. IgA antibodies are responsible for combating pathobionts along mucus membranes that are constantly exposed to the environment and

are important in maintaining the physiological immune balance in the gut lumen. It is relative resistant to the intestinal proteases with a longer half-life. IgA deficient people should be tested for CD since they are 10-20 times more likely to develop the disease [55]. Unfortunately, IgA deficient people are in high risk for additional autoimmune diseases like rheumatoid arthritis and lupus. It is estimated that 2% of CD affected people have selective IgA deficiency. Cow's milk and mainly colostrum contain IgA and many dairy-based functional products are fortified with colostrum, thus rich in IgA [56]. The dairy IgA should be added to the multiple antimicrobial compounds embedded in cow's milk originated products to fight gastrointestinal infections (Table 1). Interestingly, IgA expressing food products are in process of being developed [57].

Secondary Lactose Intolerance and Celiac Disease

Lactose malabsorption occurs secondarily in CD. Patients, once on GFD, lactase activity will gradually return to normal, following the mucosal recovery [58].

Unabsorbed lactose is a driver of *bifidobacteria* proliferation and facilitates calcium absorption. Thus, it is presenting an additive effect to the other probiotic and bifidogenic factors and calcium absorption enhancers in dairy products (Table 1). So, in view of the modern trends and before a sweeping suggestion for long term lactose avoidance, which often goes with cow's milk and dairy food withdrawal, all the above mentioned health promoting features of the lactose should be taken in account when treating CD patients. More so, avoidance of milk-based formula in high-risk CD infants or bovine milk intolerance in CD patients does not reduce CD development nor T-cell stimulatory epitopes of gluten, respectively [59,60].

Discussion

A close evolutionary relationship between cow milk consumption and shaping of intestinal functions and the microbiota composition and diversity exist. However, the recent two centuries since the industrial revolution and the last decades of food processing industrialization and the global nutritional and life style Westernization has reshaped the dynamics of food consumption [33,45,61-64]. Even the celiac patient's genetic make-up was remodelled during evolution, where protective genes were accumulated for their last 2 millenniums survival [65]. Not less interesting is the external genetic cargo transmitted from the prokaryotes to the eukaryotes, including human cells, by the horizontal gene transfer, thus connecting environmental microbes to human genome [66]. Human immune systems are continuously facing foreign antigenic load and gluten is only one example [61]. In vast majority of the people, it is tolerated, in contrary to the case of gluten mediated condition, were tolerance is breached, resulting in CD and non-CD auto and non-autoimmune chronic diseases [67]. CD has genetic basis but the environmental alterations have created a maladapted state for the body, thus the genetic susceptibility gets uncovered.

For multiple millenniums, milk is a nutrient that human body evolved with. Right from birth, breast milk and then in childhood, adolescence and adulthood, milk from various animal sources was consumed. Our immune system is likely "learnt" to be tolerant to compounds present in milk. But genetic susceptibility factor combined with environmental trigger can unleash the immune system to break the tolerogenic checkpoint. Assessment of food quality by epithelial cells and enteric immune cells like gamma delta T cells, innate lymphoid cells and/or the glial enteric nervous system is constantly unravelled [33,68]. In this regard, cow's milk has many components that likely our immune system cares about and evaluates. Parallel to the evolutionary stress on the human body, its protective immune machinery, the enteric microbiome and natural foods, the milk producing animal kingdom also experienced evolutionary constrains. Recent changes in farming, use of pesticides, drugs like antibiotics and processed food has also altered cows' diet and potentially the milk it produces. Such altered cow milk when consumed by humans can impact immune monitoring and responses.

Those are several raisons why effort should be concentrated on food quality control. Safe food is the right of every citizen worldwide and the corresponding regulatory authorities should concentrate on safety of animal's milk and their products' manufacturing, processing and consumption to avoid any detrimental effects on public health. At least, the European commission and the American FDA have done some recent progress to protect citizens from those foods' side effects [69,70].

Conclusion

Cow's milk, dairy food and bacterial fermented dairy products contain multiple preventing, health promoting and therapeutic factors that might help in multiple chronic inflammatory and autoimmune conditions, CD included. The present review summarizes the CD abnormalities and dysfunctions that can benefit from cow's milk and dairy food health promoters, on the preventing, as well as, on the therapeutic aspects. It should be stressed that many of the beneficial effects of cow's milk and dairy products were shown on animal or cellular models and not directly on CD patients. The extended list of milk originated, bio-reactive agents forms a basis, and hopefully the drive to further study and explore the beneficial compounds buried in this biologically active and natural fluid and products, *in vivo*.

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