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Bovine Milk Proteins as a Trigger for Autoimmune Diseases: Myth or Reality?

Vânia Vieira Borba[1,2,3], Aaron Lerner[4,*], Torsten Matthias[4], Yehuda Shoenfeld[3,5]

[1]Department 'A' of Internal Medicine, Coimbra University Hospital Centre, Coimbra, Portugal
[2]Faculty of Medicine, University of Coimbra, Coimbra, Portugal
[3]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel
[4]Aesku.KIPP Institute, Wendelsheim, Germany
[5]ackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
*Corresponding author: Aaronlerner1948@gmail.com

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Abstract Humans started to drinkmammal's milk 11,000 years ago. Nowadays, cow, goat and sheep milks account for about 87% of the world milk production. The high incidence of allergies to cow's milk components and autoimmune diseases is rising in the Western industrialized countries, where milk is a major dietary component, especially in processed foods. When allergenic milk proteins face immature and susceptible immune system in children it might represent a threat for future health. Several studies support strong evidences that exposure to dietary allergens during childhood can increase the risk of developing autoimmune diseases, such as type 1 diabetes, celiac disease, inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, neuropsychiatric disorders, among others. The *"Mosaic of Autoimmunity"* elucidates the diversity and multifactorial origin of autoimmune disease expression in humans. Growing evidence suggests a large overlap between oral tolerance, food antigens and autoimmune diseases. Assorted mechanisms have been hypothesized to explain the connection between these entities, mainly involving molecular mimicry, shared epitopes, cross-reactivity phenomena, enhanced hosts gut permeability, change in microbiome/ dysbiome ratio and even involving Mycobacterium avium subspecies paratuberculosis infection. Nowadays, different kinds of milk and dairy products are being evaluated for a potential benefit in human health. Likewise, milk derived nutraceutical products, such as bovine colostrum, claim many clinical advantages especially for its immune modulatory capabilities. The aim of this review is to explore the impact of cow's milk protein son human health, emphasizing its relationship with immune mediated and autoimmune diseases.

Keywords: *milk, autoimmune diseases, autoimmunity, food allergy, immune tolerance, type 1 diabetes, rheumatoid arthritis, multiple sclerosis*

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1. Introduction

The most recent Ice Age is defined as the period that began about 2.6 million years ago and it lasted around 11,700 years, with glaciers covering huge parts of planet Earth. In that time, bovine milk was mainly detrimental for humans due to the absence of lactase, an enzyme required to digest the milk principal sugar, lactose. Around 11,000 years ago, humans learned how to reduce lactose levels by fermenting milk, while farming started to replace gathering and hunting. Cow's domestication revolutionized human nutritional habits. Thousands of years later, a genetic mutation allowed man to produce lactase, tailoring the species for a new way of survival [1]. Cow, goat and sheep milk account for about 87% of the world milk production nowadays. However, Western societies have decreased its consumption in the last few decades, partly due to its claimed negative health effects [2]. The criticism emerged, associating non-human milk composition to heart diseases, hypertension, metabolic syndrome, diabetes mellitus type 2, overweight and obesity and multiple autoimmune conditions. The vulnerable period was suggested toward infancy. Whether diet may play a crucial role in autoimmunity initiation and progression has been the source for many unanswered questions and unresolved debates. *Shoenfeld et al.* described the *"Mosaic of Autoimmunity"*, which elucidates the diversity and multifactorial origin of autoimmune disease expression in humans [3,4,5]. Accumulating evidence indicates a large overlap between oral tolerance, nutrients and autoimmune diseases [6]. Recently, genome studies demonstrated that the most divergent proteins in the lactome are those with nutritional and immunological features. Employing food processing technologies and manipulations attempts were made to eliminate dietary allergenic compounds and reduce diet related disorders [7]. Moreover, nutraceuticals involving milk-derived products, such as colostrum, has been shown to provide numerous health benefits [8]. The aim of this review is to explore the impact of milk and dairy products consumption on human health, emphasizing its relationship with immune mediated and autoimmune diseases.

2. Milk and Human Nutrition

Lactation is unique to mammals. In 1758, the famous taxonomist *Carolus Linnaeus*, named terrestrial quadrupeds, whales and dolphinsas *"Mammalia"*, considering the fact that females bear mammary glands. Later in 1872, *Charles Darwin* devoted a substantial part of a chapter, in his book *"On the Origin of Species"*, to the discussion on evolutionary novelty, such as the origin of the mammary gland [9]. Milk represents an exquisite resource for translational medicine, containing a wide diversity of bioactive molecules with demonstrated clinical benefits. The lack of techniques to produce specific human milk compounds has limited its evaluation. Alternate production mechanisms include the isolation and analysis of specific molecules from bovine milk and other dairy products [10]. Despite having a biological and immune activities which is unique to human biology, cow milk structure has exhibited several advantages, based onimmunomodulatory, anti-inflammatory, anti-microbial, anti-cancerous, osteo protective, anti-lipemic, opiate, anti-oxidative and anti-hypertensive properties (Figure 1) [11].

2.1. Principal Differences between Human and Bovine's Milk

Mankind is the only species on hearth that consumes milk all along its life cycle. Each mammal produces a unique milk composition, in adapted to the offspring necessities (Table 1) [12]. Indeed, there is an inverse relationship between the different amounts of energy and nutrients in the milk and the time it takes for the newborn to double its birth weight [13]. Human milk contains 1.3g in comparison with 3.3g proteins per 100grof cow milk. Casein fraction dominates the bovine milk (80%), while whey protein constitutes only 20%. In human milk the amounts are 40% and 60% respectively. Regarding casein subclasses, ß-caseins dominate in human milk and α-S1 caseins constitutes the largest fraction in cow´s milk. The α-lactalbumin and the iron binding protein lactoferrin constitute a major fraction in human milk, while ß-lactoglobulin is the predominant whey protein in cow milk (which is completely absent in human milk).When analyzing immunoglobulins, IgA is the most dominant in human milk, while in bovine milk IgG has a 10-fold higher concentration in comparison to IgA. Concerning lactose, the difference is smaller (5.3gin cow and 7 per 100gr in human milk).Fat content is similar in both milks [12,14]. The diversity in milk composition is influenced by several different factors in both species (Table 2) [15,16,17,18]. Despite comparable values of iron, in the pediatric population, cow milk consumption is associated with iron deficiency and anemia, most probably, due to decreased bioavailability. Besides, its high protein content not only stimulates a rapid growth in bodyweight, but alsorepresents a high renal solute load for the newborn [19]. Significant differences between breastfeed and formula-feed infants fecal microbiota has been reported (Figure 2) [20]. Allergy to cow's milk proteins has a debatable prevalence in childhood, ranging between 1-5%, considered one of the first indications of an aberrant inflammatory response in early life. When allergenic proteins are facing an immature and susceptible immune system it presents a threat to the infant future health [21].

Table 1. Nutritional mean values of human and bovine milks.

Milk compounds	Human milk (mature) per 100gr	Bovine milk (whole, pasteurized) per 100gr
Calories (Kcal)	70	60
From protein (Kcal)	4.4	12.9
From carbohydrate (Kcal)	27.1	17.9
From fat (Kcal)	38.5	29.2
Water (g)	87.5	88.3
Protein (g)	1.3	3.3
Caseins, total (g)	0.4	2.6
Whey protein, total (g)	0.61	0.7
Lactoglobulins (g)	0.23	0.38
Immunoglobulins (g)	0.13	0.07
Lactoferrin (g)	0.14	0.22
Serum albumin (g)	0.04	0.03
Lysosyme (g)	0.07	0.00003
Carbohydrate (g)	7	5.3
Sugars, total (g)	7	5.3
Fat, total (g)	4.4	3.25
Saturated fatty acids total (g)	2	1.86
Monounsaturated fatty acids (g)	0.5	0.81
Polyunsaturated fatty acids (g)	1.7	0.19
Vitamins and Minerals		
Calcium (mg)	32	113
Iron (mg)	0.07	0.03
Sodium (mg)	15	43
Potassium (mg)	51	143
Magnesium (mg)	3	11
Phosphorus (mg)	15	94
Vitamin A (IU)	212	102
Vitamin C (mg)	5.0	0.0
Vitamin D (IU)	4.0	40
Vitamin E (mg)	0.1	0.1
Vitamin K (mcg)	0.3	0.2
Thiamin (mg)	0.0	0.0
Riboflavin (mg)	0.0	0.2
Niacin (mg)	0.2	0.1
Vitamin B6 (mg)	0.0	0.0
Folate (mcg)	5.0	5.0
Vitamin B12 (mcg)	0.1	0.4
Pantothenic acid (mg)	0.2	0.4
Choline (mg)	16	14.3

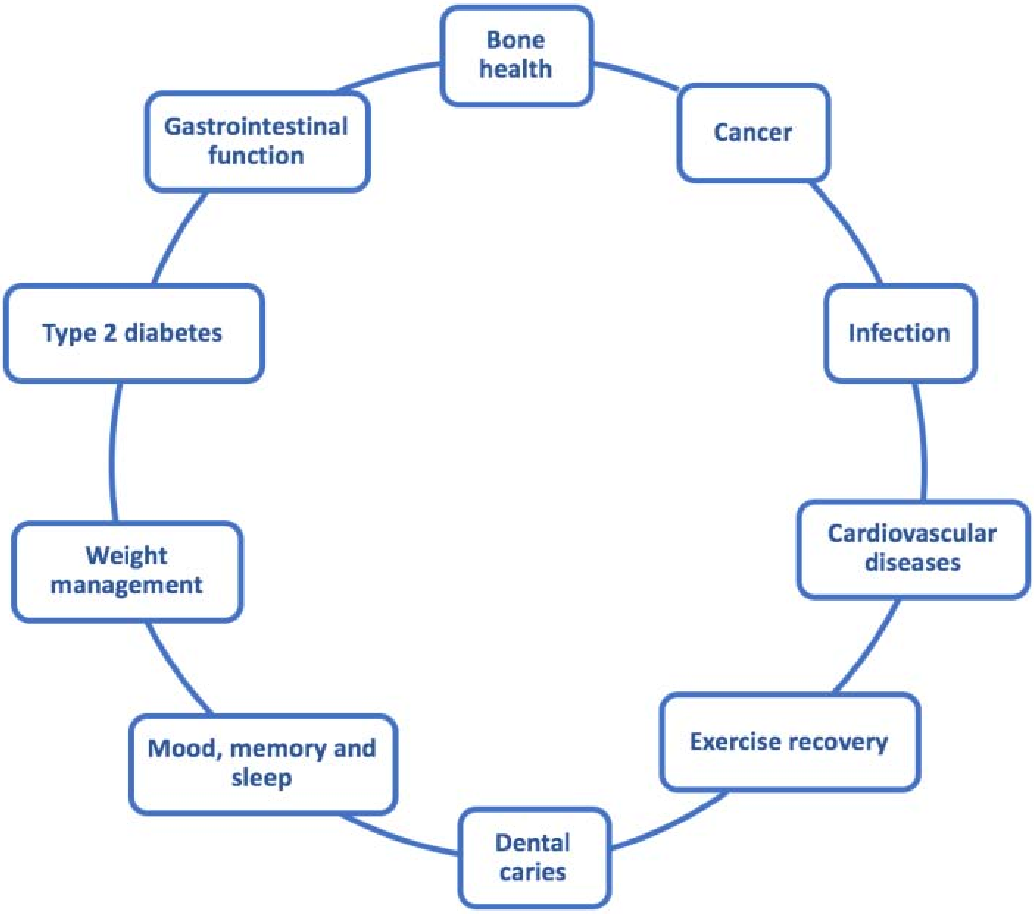

Figure 1. Benefits of bovine milk consumption in human health.

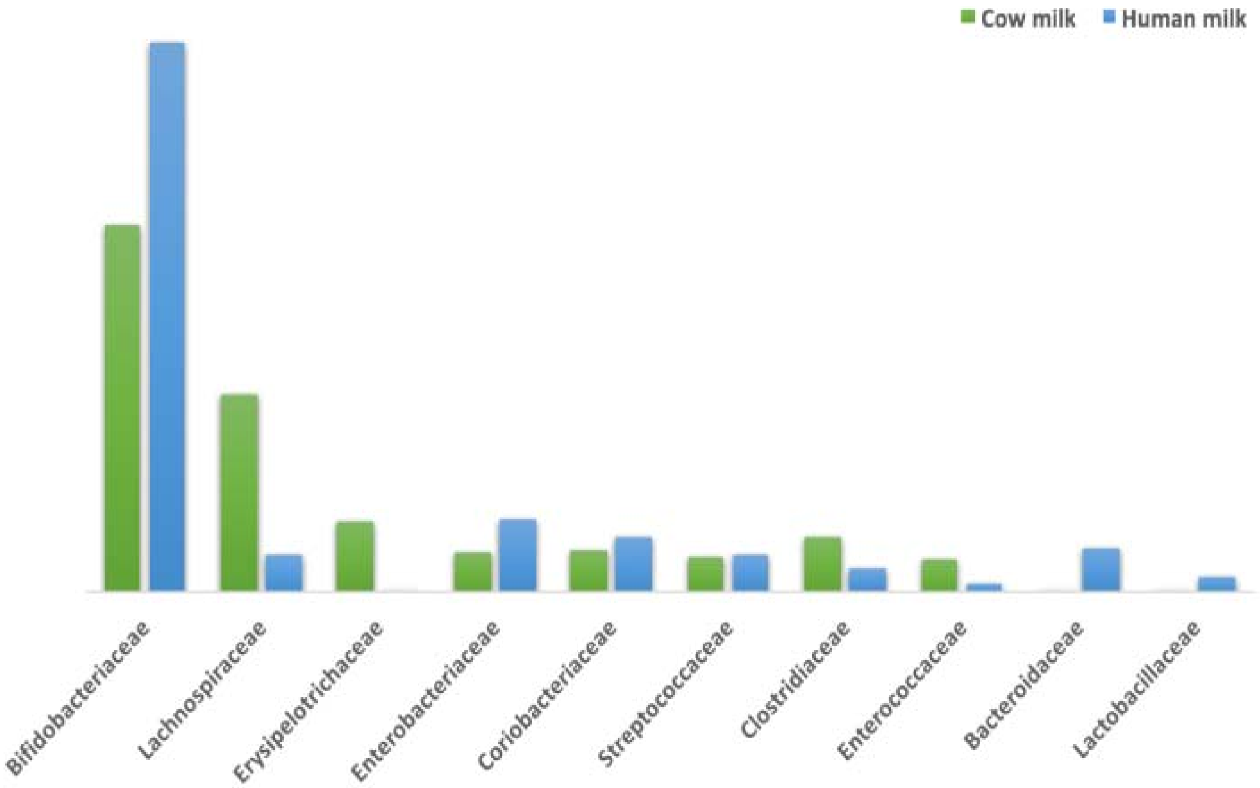

Figure 2. Differences in fecal microbiota composition between infant´s fed with cow milk formula and human milk.

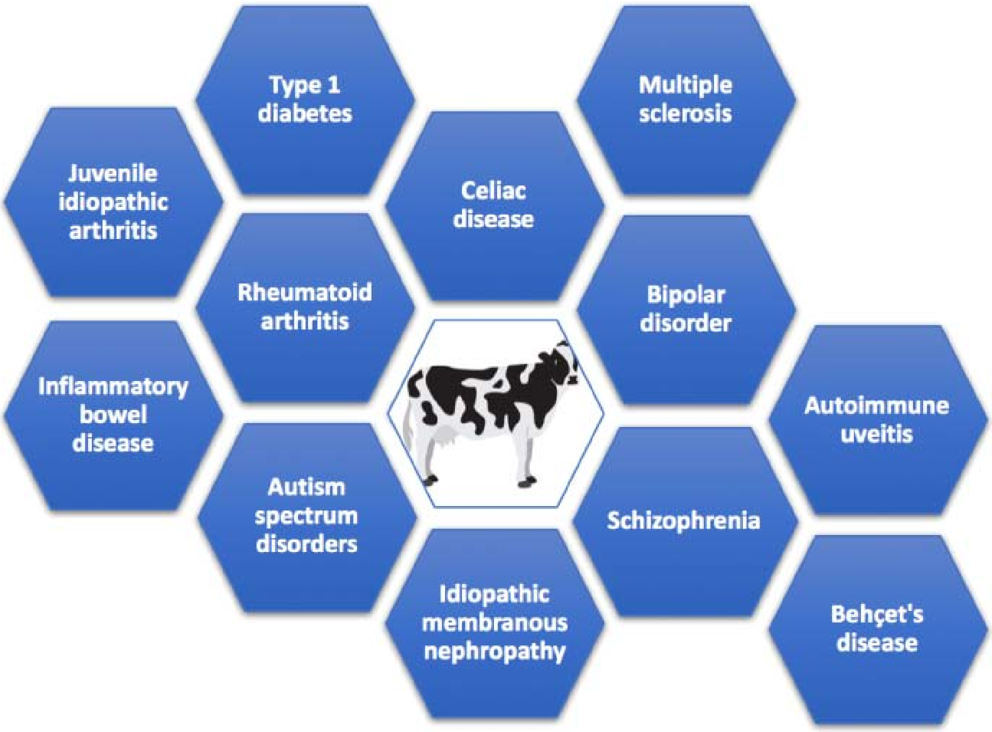

Figure 3. Autoimmune and immune mediated diseases associated with bovine milk consumption.

Table 2. Influencing factors in milk compositions.

Bovine Milk	Human Milk
Genetics (protein polymorphisms)	Mother´s diet
Lactation stage	Lactation stage
Type of feed	Gestational length
Seasonality	During a feed
Over time	During the day

3. Milk Consumption and Autoimmune Diseases

The *"Mosaic of Autoimmunity"* elucidates the diversity and multifactorial origin of autoimmune diseases expression in humans [4,5,22]. The main factors involved in autoimmunity can be categorized into four groups: immune defects, genetic, hormonal and environmental factors [4]. The incidence of allergies to cow milk and autoimmune diseases has risen in the Western industrialized countries, where milk is a frequent component of processed food. Several studies showed strong evidence that dietary allergens in childhood can influence the risk of future disease, with special emphasis on the early exposure to cow milk proteins [23,24]. Furthermore, there is no consistent evidence revealing disease prevention by the utilization of hydrolyzed cow milk-based formulas on the newborn diet [25]. Following are some examples of autoimmune diseases that were associated with dairy food consumption.

3.1. Milk and Type 1 Diabetes

Type 1 diabetes is an autoimmune disease which results from a complex interplay of environmental triggers and genetic susceptibility. It is characterized by the development of antibodies against pancreatic islet β-cells, often in the first years of life. These aspects suggest that an early shaping of the infant immune system might be crucial for the development of autoimmunity [26,27]. Ecological studies found a temporal and geographical relation between type 1 diabetes and cow milk consumptions. T-cell and humoral responses related to bovine milk proteins were suggested to trigger type 1 diabetes [28]. In addition, the development of type 1 diabetes associated antibodies might be induced by β-lactoglobulin, lacto-albumin, casein, bovine serum albumin and γ-globulin [29]. Several investigations reveal a link between the early exposure to cow milk proteins and an increased risk of type 1 diabetes [30,31,32]. Interestingly, a recent study demonstrated that the introduction of bovine milk in early infancy on children with enter ovirus infection could stimulate the appearance of type 1 diabetes associated autoimmunity [33]. Novel techniques allowed the analysis of the microbiota and a great number of studies connected the gut microbiome with the development of autoimmune diseases [31,34,35,36,37,38,39]. Diet represents an important factor influencing the microbiome since birth [40,41]. In murine models, the association between gut microbiome and type 1 diabetes was reported [42]. Between 2006-2014, a large study was performed which analyzed the microbiome of 298 stool samples taken up to the age of 3 years old, from 44 children (22 with anti-islet cell antibodies). The authors demonstrated that the microbiome changed markedly during the first year of life [43] and was greatly influenced by the infant diet, duration of breastfeeding and introduction of complementary food [44]. Likewise, a study from Finland found a lower bacterial diversity and differences in the abundance of the phyla Bacteroidetes and Firmicutes in children before the development of antibodies and during the evolvement of the disease [45]. In accordance, *Endesfelder et al.*

hypothesized a protective effect of butyrate in the development of anti-islet cell antibodies, based on lower levels of mucin-degrading and butyrate-producing bacteria like Bacteroides and Akkermansia [46]. Mycobacterium avium subspecies paratuberculosis (MAP) infection has also been associated with the development of type 1 diabetes, as a putative environmental trigger in Sardinian subjects [47,48]. *Niegowska et al.* reported high levels of antibodies against MAP-derived epitopes and their human homologs on β-cell antigen zinc transporter 8 in children and proinsulin, via cross-reactivity pathways, in children prone to type 1 diabetes [49]. Notably, the environmental factors that trigger islet autoimmunity might not be the same as the ones which promote progression from latent autoimmunity to overt disease. Avoiding cow milk based formulas in children with HLA-conferred risk for type 1 diabetes was associated with a reduction on cumulative incidence of diabetes-associated autoantibodies by the age of 10 years in a pilot study [50]. On the other hand, a recent systematic review and meta-analysis performed by *Garcia-Larsen e al.* found weaker support for the hypotheses that breastfeeding promotion reduces risk of eczema during infancy, that longer exclusive breastfeeding is associated with reduced type 1 diabetes mellitus, and that probiotics reduce risk of allergic sensitization to cow's milk, where grade certainty of findings was low [51].

3.2. Milk and Celiac Disease

Celiac disease is an autoimmune enteropathy induced by prolamins, mainly by wheat gluten proteins, leading to chronic inflammation of the small intestine resulting in mucosal lesions. The diagnosis is based on positive serology (mainly anti-endomysial and anti-tissue transglutaminase), histologic confirmation of duodenal villous atrophyas well as normalization of those findings after following a gluten-free diet [52]. Recent reports show a growing incidence of the disease in the last decades [53], paralleling the general increase in autoimmune diseases incidences and prevalences [54].

Although genetics represent an important risk factor for these patients, since most of them carry DQA1 *05, DQB1 *02 (DQ2) and DQB1*03: 02 (DQ8) alleles, environmental triggers are also suspected to play an important role [55,56]. The optimal time and dosage for gluten introduction is unknown, even though exposure before the age of 3 months or after the age of 7 months was suggested to be associated with a higher risk for celiac disease development [57,58]. Interestingly, the gut permeability is increased in recently diagnosed celiac patients [59], predisposing them to immune reactive responses towards dietary proteins [60]. Of note is the microbial transglutaminase as a new potential environmental factor of celiac disease induction [61,62]. Not surprising is the detrimental effects of gluten, heavily used as food additive in the processed food industries, in non-celiac autoimmune disease. In fact, its with drawal might be beneficial to some non-celiac autoimmune conditions [63,64]. The intolerance to bovine milk present in some celiac patients [65] is not related to the gluten proteins in the milk of wheat-fed cows [66]. Most naïve celiac patients don't tolerate cow's milk due to transient lactose intolerance that ameliorates on gluten free diet. A recent double-blind controlled trial performed by *Hytinen at al.* involving 230 infants with HLA defined predisposition, successfully demonstrated high titers of bovine milk antibodies in children who developed celiac disease, when compared to a healthy group [67]. These subjects show an increased anti-casein antibodies already at the age of 3 months (before being exposed to gluten), suggesting that the intestinal immune system may be compromised before gluten introduction [68]. Even during disease remission, celiac patients show mucosal inflammatory responses to bovine milk proteins [69]. Furthermore, *Saccharomyces cerevisiae* which is known to be a yeast that might be used in some fermentation processes, including in bakeries, was retrospectively detected among the preserved blood samples of the Israeli Defense Forces soldiers, years before celiac disease onset [70]. It appears that antibodies against *Saccharomyces cerevisiae*, are prevalent in celiac populations. Different pathways involving shared epitopes, autoantigens that might cross-react with antibodies against mannan of *S. cerevisiae* have been described which confer an association between this yeast and several autoimmune disorders [71,72,73]. In summary, most of treated celiac patients tolerate milk products, while naïve ones may not tolerate cow's milk due to lactase deficiency. Most recently, the beneficial cow's milk and dairy products' factors to celiac patients, were summarized [74]. At the end of the day, milk and celiac disease enigma is far from being elucidated.

3.3. Milk and Inflammatory Bowel Disease

Inflammatory bowel disease consists of two major phenotypes: ulcerative colitis and Crohn disease [75]. It is characterized by a chronic relapsing inflammation of the intestine, emerging from a complex interaction between genetic, environmental and microbial factors and the immune response [76,77]. Aberrant and persistent immune reactions due to antigens presented to the gut of a genetically susceptible individual are known to play an important role [75,78]. Furthermore, adysfunctional mucosal barrier will allow food antigens to cross and evoke further allergic reactions [76]. Allergy to cow milk is the most common type of food allergy in the pediatric population with inflammatory bowel disease [79,80], especially in patients with ulcerative colitis [81]. In accordance, a study performed by *Judaki et al.* successfully demonstrated a significant relationship between ulcerative colitis and cow milk proteins [82]. As in ulcerative colitis, a higher risk associated Crohn's disease with cow milk allergy, as demonstrated by a recent Finish study involving 595 children [83]. Intriguingly, in the last years, a new hypothesis has emerged relating Crohn disease and bovine milk consumption [84,85,86]. Some animals have a frequent form of inflammatory bowel disease, known as Johne´s disease, which is caused by an infection with *Mycobacterium avium ssp. paratuberculosis* (MAP) [87]. This agent might be present in bovine milk and is capable of surviving pasteurization processes [88]. It has been hypothesized that MAP infection during immediate neonatal periods, in absence of acquired immunity, alters the immunological memory [89]. More so, repetitive exposures to MAP antigens will force the immune system to respond with a pro-inflammatory array of cytokines, due to a loss of immune tolerance [90]. Besides, the molecular mimicry between mycobacterial and human heat shock proteins (50-80% amino acid homology) could also be involved in the pathogenesis of Crohn disease [91,92]. *Biet et al.* performed a study involving 272 individuals and successfully demonstrated a correlation between anti-*Saccharomyces cerevisiae* antibodies and anti-MAP antibodies with Crohn disease, mostly related to extra-intestinal manifestations [93]. Interestingly, one wonders if increased antibodies against cow's milk proteins in inflammatory bowel diseased patient present an epiphenomenon, as was shown in other non-autoimmune and autoimmune conditions [94]. Like in celiac disease, some Crohn's patients don't tolerate cow's milk, due to their intestinal proximal disease low lactase activity.

3.4. Milk and Rheumatoid Arthritis

Rheumatoid arthritis is the most common inflammatory arthritis, which primarily targets the small joints of the hands leading to deformities and impaired physical functioning [95]. It results from a complex interaction between genetics and environment, inducing a breakdown of immune tolerance and synovial inflammation [96]. Antigen similarity between foreign and human antigens has been proposed to explain the autoimmune response in this disease [97]. The relationship between rheumatoid arthritis and food allergy has been suspected since 1953 [98]. More than 30 years ago it was postulated that bovine milk proteins, such as bovine serum albumin, could be associated with polyarthrit is in mice [99] and rheumatoid like lesions in rabbits drinking bovine milk [100]. Later, *Pérez-Maceda et al.* reported specific reactivity for a synthetic peptide contained in bovine serum albumin residues on rheumatoid arthritis patients' sera, responsible for the molecular mimicry [101]. Probably, these residues were able to pass the gut barrier, cross the synovial membrane, interact with the synoviocytes and trigger an immune response leading to arthritis [102]. For decades, many controversial studies emerged. In 2006, *Hvatum* et al. investigated intestinal immunity in rheumatoid arthritis patients, and found a positive correlation between rheumatoid arthritis and food antibodies, especially in terms of immunoglobulin M class [103]. Recently, Li et al. successfully demonstrated enhanced concentrations of milk-specific immunoglobulin G and E in collagen-induced arthritic rats [104]. However, nowadays many benefits are recognized in milk compounds specially, for non-susceptible individual (63, 64).

Investigation trends emerged, with novel treatments for rheumatoid arthritis and other autoimmune diseases based on the induction of bystander tolerance and stimulation of anti-inflammatory cytokines, known as milk-based nutraceuticals [105,106]. Impressively, camel milk has shown beneficial anti-inflammatory actions, mainly by down regulation of the arthritic process, opening new doors on the management and treatment of these patients [107]. The emerging nutritional therapies in rheumatic diseases is based on the place of the enteric eco-events contributing to autoimmune diseases and rheumatoid arthritis pathogenesis [63,64,74,108]

3.5. Milk and Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis is a heterogeneous group of diseases, which represent the most common chronic rheumatic disease of childhood [109]. It is considered an autoimmune disease, caused by an unbalanced interaction between genes and the environment [110,111]. Gene expression profiling studies have identified different immune mechanisms in distinct subtypes of the disease [109]. Although available scientific data linking juvenile idiopathic arthritis is not extensive, a recent study performed by *Arvonen et al.* involving 1298 infants with juvenile idiopathic arthritis has shown that boys with cow milk allergy had a twofold higher risk of developing the disease [112]. Interestingly, this risk was more significant in those who had gastrointestinal symptoms from cow milk allergy [113,114] and after being exposed to antibiotics [115,116], suggesting a crucial role of the gut mucosal integrity on the development of the disease [113,117]. In accordance, *Kindgren et al.* demonstrated in a large prospective cohort study that the introduction of cow milk formula before the age of 4 months was associated with an increased risk of developing juvenile idiopathic arthritis (OR 2.49, 95% CI 1.19-5.21; $p = 0.015$) [118]. The elimination of cow milk proteins from diet was associated with an improvement of the disease [119,120].

3.6. Milk and Idiopathic Membranous Nephropathy

Membranous nephropathy is an immune mediated disease caused by sub-epithelial immune deposits, resulting on a functional impairment of the glomerular capillary wall. It is the most common cause of nephrotic syndrome in adults, although it is rarely seen in children. Idiopathic membranous nephropathy has been related with antigens such as neutral end opeptidase and M-type phospholipase A_2 receptor (about 70% of patients), even though in the pediatric population it appears largely to be secondary to exogenous factors [121]. Distinct forms of membranous nephropathy have been reported in children with high levels of anti-bovine serum albumin antibodies and circulating cationic bovine serum albumin, associated to a predominance of the T-helper type 2 immune response, as it was described by *Debiec et al.* and *Mogues et al.* [122,123]. The circumstances leading to the originof this modified food-derived antigen are not known, although the author hypothesized that gastric pH associated with an immature gut barrier function could allow little fragments to be absorbed and finally planted in the anionic glomerular basement membrane [122,124,125]. It is not known whether the avoidance of cow milk and other dairy products would eliminate the offending antigen and induce remission of the disease [124,126]. Although, not in idiopathic membranous nephropathy, early introduction of cow's milk was associated with increased risk of future primary IgA nephropathy [127].

3.7. Milk and Multiple Sclerosis

Multiple sclerosis is a chronic, life-long neurological condition associated with inflammation and degeneration in the brain and spinal cord. It is considered an immune mediated disease, resulting from several genetic and early-life environmental trigger exposures which are believed to disrupt immunological self-tolerance to myelin in the central nervous system [128]. Various epidemiological studies associated the prevalence of multiple sclerosis with the consumption of milk and dairy products [129,130,131]. Observations speculated the existence of a link between multiple sclerosis and aberrant T cell immunity against common food antigens in cow milk. Mechanisms based on molecular mimicry and induction of autoimmune phenomena due to homologies are thought to play a crucial role [132]. The relevance of molecular mimicry in this disease was first recognized following the demonstration of immunological cross-reactivity between cow milk proteins and central nervous system myelin in animal models, involving epitopes from myelin basic protein and milk protein butyrophilin, myelin oligodendrocyte glycoprotein and bovine serum albumin [133,134]. *Guggenmos et al.* demonstrated a cross-reactivity reaction between the extracellular Ig-like domain of myelin oligodendrocyte glycoproteinand a homologous N-terminal domain of the bovine milk protein butyrophilin [135]. Furthermore, an increased production of milk-related transcripts in the lymph nodes and blood follows an inflammatory event in experimental multiple sclerosis mice, has shown by *Otaegui et al.* [136]. Interestingly, the immunological cross-reactivity of bovine milk butyrophilin with human oligodendrocyte glycoproteins may bring to light a potential novel therapeutic protein for multiple sclerosis immunotherapy by restoring immune tolerance to target self-antigens. *Mokarizadeh et al.* hypothesized that transdermal delivery of bovine milk vesicles, could be considered as an intriguing approach to induce human oligodendrocyte glycoprotein-specific tolerance in patients with multiple sclerosis, creating new strategies for antigen-specific immunotherapies [137].

3.8. Milk and Behçet Disease

Behçet disease is a chronicmulti-systemic inflammatory disorder with a genetic basis, characterized by oral and genital ulcers, uveitis, pustular erythematous cutaneous lesions, arthritis, central nervous system involvement and possible vascular manifestations [138]. Several immunological variables have been studied until now, suggesting a putative role of the immune system in the pathogenesis of the disease. Triolo et al, performed a study in 2002,involving 46 patients with Behçet disease, aiming to investigate their humoral and cellular immune response against cow milk proteins. The authors successfully demonstratedan enhanced frequency of antibodies directed against cow milk proteins (anti-β-lactoglobulin and anti-β-casein)in patients with active Behçet disease, but not against other dietary antigens [139]. It is known that upon digestion, several caseins may give rise to opioid peptides, which influence the modulation of T cells and macrophages by binding to their opioid receptors and promoting a breach in oral tolerance [140,141]. Furthermore, antigens found in milk exert detrimental effects on gut and systemic immunological reactivity. Hypothesis involving mimicry of peptides, gut flora and the microbialheat shock, have been postulated for the pathogenesis of Behçet disease [142].

3.9. Milk and Autoimmune Uveitis

Autoimmune uveitis is an inflammatory disease of the eye [143], where CD4+ Th1 cells recognize retinal autoantigens and destroy photoreceptors and neuronal cells, leading to blindness [144,145]. The interphotoreceptor retinoid-binding protein (IRBP) and S-antigen (S-Ag) are well recognized as autoantigens both for animal and human models, although they are normally invisible to the immune system (sequestered antigens).The αS2-casein, which is absent in human milk, and the peptide sequence of Cas(a cross-reactive epitope that mimics retinal peptide) are highly specific for cow milk. These molecules have been proven to be immunogenic in humans and uveitogenic in rats [146]. In 2003, *Wildner et al.* performed a study, where rats immunized with peptides and casein protein developed uveitis. Moreover, the peptides were also recognized by lymphocytes in sera from uveitis patients [147]. Breaking the oral tolerance to bovine casein could happen in any stage of life, while consuming cow milk under conditions that promote sensitization, like gastrointestinal infections, triggering Th1-driven aggressive immune responses [148]. Despite all, casein more often leads to an allergy than to uveitis, considering that this disease affects around 2% of the population in developed countries [149].

3.10. Milk, Schizophrenia and Bipolar Disorder

Schizophrenia is a complex brain disorder, characterized by psychotic symptoms, such as hallucinations, as well as cognitive disorganization, withdrawal and apathy. On the other spectrum, bipolar disorder is a devastating disease, represented by periods of depression and mania. Although the causes of this diseases have not been fully defined, their relationship with autoimmune diseases have been hypothesized for more than 50 years [150]. Dohan et al. (1988) suggested that peptides (exorphins) could bind to opioid receptors, particularly in the brain [151], based on earlier studies documenting increased levels of neuroactive food antigen peptides in the urine, blood and cerebrospinal fluid of schizophrenia patients [152,153,154,155,156]. This exorphins result from the digestion of gluten and bovine milk casein [157] and are able to extend their range beyond the gut wall. Recently, increased antibodies against bovine milk casein have been reported in schizophrenia [158,159,160] and bipolar patients [161], which can be found as early as two years prior to the disease onset [162].

4. Impact of other Milks in Human Health

Nowadays, different species milk is being evaluated for potential benefits in human health [163]. Donkey milk, due to a great similarity with human milk, represents a good alternative for infant´s with allergic or immunologic disorders. It is capable of influence the release of inflammatory and anti-inflammatory cytokines, maintaining a state of immune homeostasis, including the intestinal mucosal immune response in children and the elderly [164]. More so, goat milk is easily digestible due to a medium chain fatty acids composition. Besides, it triggers innate and adaptive immune responses, inhibiting monocyte endotoxin-induced activation [165]. Furthermore, camel milk has shown great benefits for human health being closest to human milk. Studies have show nadvantages in type 1 diabetic mice by decreasing free radicals and modulating immune functions [166], such as stimulation of B cells and suppression of T cells during disease states [167]. It was proven to decrease and orchestrate the redox status and subsequently rescue the immune cells from exhaustion [168]. Al-Ayadhi et al.(2015) successfully demonstrated promising benefits with camel milk as a therapeutic intervention in children with neuropsychiatric disorders [169]. Finally, Buffalo milk is frequently used in some countries as Nepal, although its characteristics are similar to bovine milk [170].

5. Milk-Derived Nutraceuticals

Nutraceutical derives from a combination of two words: nutrition and pharmaceuticals. It relates to a food, or a food derived product that provides health benefits, representing an emerging trend nowadays. Bovine colostrum is thought to be a promising nutraceutical due to its rich immune, growth and antimicrobial properties [171]. Several studies support an active participation in promotion of normal gut microbiome and support healing of damaged mucosa. It has also been suggested that colostrum may reduce the hypersensitivity associated with allergies and autoimmunity [172]. Besides, the proline-rich polypeptide present in colostrum exerts a regulatory function over the thymus gland. Recent data showed clinical benefits, improving autoimmune disease symptomsin multiple sclerosis, lupus and rheumatoid arthritispatients [8,173]. As mentioned before, even in celiac disease, bovine milk and dairy product can exert beneficial effects [74].

6. Conclusion

The "mosaic of autoimmunity" elucidates the diversity and multifactorial origin of autoimmune disease expression in humans. Several studies have shown strong evidence that dietary exposure during childhood can influence the risk of developing various autoimmune diseases, such as type 1 diabetes, celiac disease, inflammatory bowel disease, rheumatoid arthritis, juvenile idiopathic arthritis, idiopathic membranous nephropathy, multiple sclerosis, Behçet's disease, autoimmune uveitis, schizophrenia and bipolar disease. Assorted mechanisms have been hypothesized to explain the connection between these entities, mainly involving molecular mimicry, shared epitopes, cross-reactivity phenomena, changes in host gut permeability, microbiome and even through chronic infections. The consumption of cow milk and dairy products by susceptible populations to develop autoimmune conditions should be further investigated, since most of the studies alluded for associative, but not causative relationship. Before declaration of cow's milk proteins as playing a role in auto-immunogenesis, the clinical and research community should investigate thoroughly the cause and effect re lation.Nowadays, different kinds of milk are being evaluated for potential benefits in human health. Likewise, clinical advantages of milk-derived nutraceutical consumption have been reported by improving autoimmune disease symptoms. It is hoped that the present review will encourage and stimulate such investigations.

7. Highlights

- The "mosaic of autoimmunity" elucidates the diversity and multifactorial origin of autoimmune disease expression in humans.
- Milk consumption has been associated with the development of several autoimmune diseases, such as type 1 diabetes, celiac disease, inflammatory bowel disease, rheumatoid arthritis, juvenile idiopathic arthritis, idiopathic membranous nephropathy, multiple sclerosis, Behçet disease, autoimmune uveitis, schizophrenia and bipolar disorder, but not cause and effect relationship was established.
- The link between milk and autoimmunity might be explained by different mechanisms involving molecular mimicry, shared epitopes, cross-reactivity phenomena, changes in hosts gut permeability, microbiome and even through chronic infections.
- Nowadays, different kinds of milk and milk-derived nutraceuticals are being evaluated for potential benefit´s in human health.

Conflict of Interest

Professor Yehuda Shoenfeld is chairperson of the Scientific Council of the Milk Society in Israel. The other authors have no potential conflicts of interest in authorship or publication.

Financial Declaration

The authors have no relevant financial disclosures.

Abbreviations List

MAP: Mycobacterium avium ssp. paratuberculosis; IRBP: interphotoreceptor retinoid-binding protein; S-Ag: S-antigen.

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