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REVIEW



Recent perspective on cow's milk allergy and dairy nutrition

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ABSTRACT

Cow's milk is a highly nutritious biological fluid that provides nourishment and immunity to infants when breastfeeding declines. However, some infants, children, and adults are allergic to cow's milk because milk contains potential allergens in the form of proteins. Casein and whey proteins and their coagulated sub-fractions in the milk such as α S₁-casein, α S₂-casein, β -casein, κ -casein and α -lactalbumin, β -lactoglobulin, bovine serum albumin, immunoglobulins, lactoferrin, respectively are the major etiological determinant of cow's milk allergy (CMA). Moreover, milk processing techniques such as homogenization and pasteurization alter the milk fat and whey protein's molecular structure and serve them as allergens to the immune system of allergic individuals. Strict exclusion of nutrient-rich milk and other dairy products from diet puts children with CMA at higher nutritional risk. Thus, regular nutritional monitoring, the inclusion of protein and mineral-rich supplements as a substitute for cow's milk, management of animal genetics (sheep, goats, buffaloes, camel, mare, donkey, yak), and milk processing to produce non-allergenic milk by inactivating allergic proteins for designer nutrition is essentially required. This review paper details the prevalence, molecular profiling of milk allergens (proteins), body immune response against CMA, consequences of milk processing, treatment, and novel role of galectins as potentially allergy suppressors.

KEYWORDS

Cow's milk allergy; caseins; whey proteins; galectin; pasteurization; dairy cow nutrition

Introduction

The exceptional feature that differentiates mammals from other animals in the world is to synthesize and secrete milk from mammary glands. Milk is a nutritious biological fluid that is rich in high-quality proteins, lipids, minerals, (calcium, magnesium, selenium) and vitamins (riboflavin, vitamin B12, pantothenic acid). The primary biological function of milk is to provide nourishment and immunity to infant mammals (Bhat, Dar, and Singh 2016). Consequently, milk is nutritionally considered to be a complete food. Colostrum, the very first milk produced after parturition, contains the mother's immunoglobulins and either the same or higher protein and lactose concentration as milk without the fat (Alhussien, Manjari, Mohammed, et al. 2016). Infants are highly susceptible to infections because they do not have well-developed innate and adaptive immunity. However, through milk (colostrum) immunoglobulins that help provide passive immunity for fighting diseases are passed down to the infants (Alhussien, Manjari, Sheikh, et al. 2016). In addition to nutrition, milk provides several biological attributes such as antimicrobial properties, immune stimulants, enzymes, and antibodies (Park 2009). Moreover, due to neutrophils and macrophages as a part of innate immunity, milk protects the mammary glands from bacterial invasion (Haug, Høstmark, and Harstad 2007).

Milk from domestic dairy mammals has been used in the human diet for thousands of years except for some ancient tribes who grew up their children only on mother's milk without milk from any mammal, for example, the South American Indians. Around the world, cows (82.4%) and buffaloes (13.6%) contribute significantly to the world's fresh milk production while the remaining percentage is shared by goats, sheep, camels (Villa et al. 2018) and others like the Tibetan Yak, the North Country reindeer, even horses and donkeys (Gall 2013; Park, Haenlein, and Wendorff 2017). However, the breed, age, species, diet, lactation stage, season, and the number of parturitions profoundly affect milk composition and production. Human milk is the most appropriate food for infants because of its unique composition for their growth and development especially, bones, teeth, hair, and skin (Do, Williams, and Toomer 2016). However, cow's milk and other mammal milk are substituted for human milk when breastfeeding is discontinued, although some individuals, especially infants, can be allergic to milk. Most of the affected children outgrow milk allergy by four years of age; some retain it lifelong, possess allergies to milk and exhibit an immediate allergic reaction when consumed (El-Agamy 2007). This review paper details the role of cow's milk proteins (CMPs) in cow's milk allergy (CMA), the molecular architecture of major milk proteins, CMPs mediated immediate and delayed immune response, the effect of processed and unprocessed milk on CMA, CMPs cross-

Table 1. List of cow's milk bioactive components (Park 2009; Villa et al. 2018).

Major milk protein fractions	Milk protein subfractions	Bioactive compounds	Biological function
Caseins	α S ₁ -Casein	Isracidin	Calcium binding protein, antimicrobial
	α S ₂ -Casein	Casocidin	Calcium binding protein, antimicrobial
	α -, β Casein	Casomorphins	Opioids agonist
	α -, β Casein	Casokinins	Ace inhibitors
	α -, β Casein	Phosphopeptides	Calcium binding protein, increase Ca, P, Zn absorption
Whey proteins	α -, β Casein	Immunopeptides Casomorphins Casokinins	Increase immune response, phagocytic activity, milk stabilization, and coagulation
	κ -Casein	Casoxins	Opioid antagonist
	κ -Casein	Casoplatelins	Antithrombotic
	κ -Casein	κ -Casein glycol-macropptide	Probiotic (bifidobacteria) growth in GI tract
	α -Lactalbumin	Lactorphins	Opioid agonist
	β -Lactoglobulin	Lactorphins	Opioids agonist
	Serum albumin	Serorphins	Opioids agonist
	Immunoglobulins	IgA, IgE	Boost passive immunity
	Lactoferrin	Lactoferrin	Augment humoral immune response, natural killer cells, IL-6, thymocyte trafficking, antimicrobial activity, Probiotic (bifidobacteria) growth promoter in GI tract Decrease TNF- α , reduce viral attachment
	Lactoferrin	Lactoferroxins	Opioid antagonist
Other constituents	Oligosaccharides	Oligosaccharides	Probiotic (bifidobacteria) growth promoter in GI tract
	Glycolipids	Glycolipids	Antimicrobial function
	Prolactin	Prolactin	Augment lymphocytes, thymocyte trafficking
	Cytokines	IL-1, IL-2, IL-6, IL-10, TNF- α , IFN- γ , leukotriene,	Immune response development
	Growth factors Parathromone-P	TGF- α , TGF- β , IGF-1, EGF PTHrP	Organ growth and function Augment calcium metabolism and uptake

reactivity, the role of galectins as allergy suppressor, and dairy nutrition.

The role of cow's milk proteins in cow's milk allergy

Although there are some similarities in the composition of cow's and human milk proteins, the differences in the type of proteins and their concentration in cow's milk is sufficient to elicit an immune response in humans (Crittenden and Bennett 2005). It has been observed that CMPs are the most common cause of food allergy in infants (< two years). In healthy individuals, the immune system recognizes milk proteins as innocuous substances, while CMP allergic individuals are highly sensitive to milk proteins that initiate inflammatory responses that are characteristic of allergies. Epitope mapping of many CMPs, including caseins and whey proteins, demonstrated that many proteins bear multiple allergenic epitopes that have been implicated in allergic reactions (Crittenden and Bennett 2005). These epitopes are sensed by B and T lymphocytes that produce antibodies and cell-mediated immune responses, respectively (Crittenden and Bennett 2005). Milk allergy is often misdiagnosed as lactose intolerance, but these two phenomena are not the same. Many adults experience lactose intolerance, which is mainly caused by a deficiency of lactase enzymes in the intestine (Haug, Høstmark, and Harstad 2007).

Composition of unprocessed cow milk

Unprocessed cow milk contains a protein concentration three times higher than that of human milk (Savilahti and

Kuitunen 1992). CMP contains 20% whey proteins (β -lactoglobulin, α -lactalbumin, bovine serum albumin, lactoferrins, transferrins, immunoglobulins) and 80% casein proteins (α -s1-casein, α -s2-casein, β -casein, κ -casein) shown in Table 1 (Park 2009; Villa et al. 2018).

Molecular architecture of whey proteins

Whey contains primarily a globular protein, β -lactoglobulin (10%) is a retinol-binding protein that possesses six genetic variants and naturally occurs as a dimer of two monomeric subunits. β -lactoglobulin is a major allergen in milk, and it has a well-defined globular tertiary structure formed by eight-stranded antiparallel β -barrel and three turn α -helices. Furthermore, β -lactoglobulin has a high resistance to protease and acid hydrolysis that protects its structural integrity by permitting β -lactoglobulin to be absorbed through the intestinal mucosa, causing allergenicity (Fox 2001). Several reports have indicated that IgE binding epitopes are located at the protein surface as a hot spot to react with IgE antibodies that fall mostly at 121 to 135 AA residues (Miciński et al. 2013). α -lactalbumin (4%) is a calcium-binding metalloprotein that bears two genetic variants, is classified as a major allergen in cow's milk, and accounts for the second copious protein in whey that aids in lactose synthesis via the transference of galactose to glucose. α -lactalbumin consists of 4 disulfide bridges and has a high calcium-binding ability that fortifies its secondary structure.

Moreover, α -lactalbumin exhibits high thermal stability, refolding efficiency, and a compact tertiary structure (Villa et al. 2018). The prevalence of the IgE binding epitope sensitization in allergic patients with α -lactalbumin varies from

27.6% to 62.8%, and the major allergenic site is located at 124 to 135 AA residues. β -lactoglobulin and α -lactalbumin are primarily synthesized in mammary glands, while bovine serum albumin (1.2%) enters milk through secretory cells from the blood. There are various other fractions present in small quantities in whey, such as bovine serum albumin (BSA), orosomucoid, folate binding proteins, fat globules (1%), β -microglobulin, and iron-binding proteins (transferrin & lactoferrin). In contrast to human milk, cow milk possesses IgG1 immunoglobulin (2.1%) that is passed on to the colostrum in a greater amount than in human milk. Moreover, immunoglobulins IgA (2 monomers) and IgM (pentamers) exist in secretory forms in cow's milk (Savilahti and Kuitunen 1992). BSA is a major allergen in the milk. The allergenicity of BSA is mainly attributed to its surface IgE binding epitopes that can easily react with the circulating IgE and starts an allergic reaction in the patient. Even though the amount of BSA is low in the cow's milk, this small amount has binding efficiency up to 50% of the patient's serum samples to start a severe allergic response. BSA has a stable tertiary structure, and the disulfide bond stabilizes BSA's major antigenic site (524–598) that is exposed for binding (Hochwallner et al. 2014).

Molecular profile of casein proteins

Casein represents the major portion of cow's milk that upon fractionation forms α_{s1} (40%), α_{s2} (12.5%), β (35%), and κ -casein (12.5%) (Demeulemester, Giovannacci, and Leduc 2006). Casein proteins are a large family that has a hydrated structure of calcium-binding phosphoproteins whose negatively charged phosphate groups bind firmly with positively charged divalent calcium ions. Consequently, charge neutralization causes precipitation of the major subfractions of caseins (α_{s1} , α_{s2} , β) except κ -casein. In contrast, κ -casein has a low concentration of phosphate groups; thus, fewer calcium ions bind to it. As a result, κ -casein is unable to precipitate calcium ions. When the calcium concentration in milk is high, casein forms a quaternary structure in the form of micelles where lactoserum whey and κ -casein exist in the peripheral hydrophilic phase while fat globules, calcium, and α_{s1} , α_{s2} , β form a hydrophobic core (Fox 2001). The principal biological job of casein micelles is the transportation and the retention of a considerable amount of calcium and phosphate in the stomach to be assimilated into the body. Casein micelles are highly susceptible to proteinases and exopeptidases, but they are insignificantly affected by urea (denaturing agent) or heating. Casein forms a loose tertiary and flexible structure, and when it does not form a tertiary structure, it exhibits high surface hydrophobicity and is hence less immunogenic. Due to different proportions of hydrophobic, polar, and charged residues, the molecular structure of casein is not consistent. As a result, uneven hydrophilic and hydrophobic patches distributed throughout make it water-insoluble (Goff 2016). The genetic polymorphism of casein that is responsible for its high heterogeneity and the degree of glycosylation, phosphorylation, and partial hydrolysis greatly affects the allergenic properties of caseins (Fox 2001).

Alpha casein 1 (α_{s1} -casein) occurs in a single chain phosphoprotein containing 199 amino acids (AA) rich in proline residues. There are seven genetic variants of α_{s1} -casein. Due to the lack of disulfide bonds, α_{s1} -casein loosely forms tertiary structures. In addition, α_{s1} -casein has a small percentage of secondary structure with α -helix and β -sheets; as a result, the majority of molecular structures are unorganized (Goff 2016). The deficiency of conspicuous tertiary structure on α_{s1} -casein requires that potential epitopes must be present linearly, and their recognition could be a viable target for developing therapeutics and diagnostic tools (Matsuo, Yokooji, and Taogoshi 2015). It has been estimated that in cow's milk allergic patients, nearly 50% of serum samples react with α_{s1} -casein (Natale et al. 2004). There is a difference in opinion among the researchers regarding IgE binding epitopes on α_{s1} -casein. Some suggest IgE binding epitopes are located at 181–199 AA residues on C-terminal (Nakajima-Adachi et al. 1998), some in the hydrophobic region (Spuerger et al. 1996), while others at 28–50 residues (Cerecedo et al. 2008; Cong and Li 2012).

Alpha casein 2 (α_{s2} -casein), another family of casein, consists of 207 AA, per molecule one disulfide bond, and four genetic variants (A, B, C, and D). It has been found that 90% of serum samples react with α_{s2} -casein with six minor and four major IgE binding epitopes (Cerecedo et al. 2008). In terms of α_{s1} -casein and α_{s2} -casein levels, goat's milk is different from cow's milk. Goat's milk has remarkably less α_{s1} -casein and much higher α_{s2} -casein content compared to cow's milk. Moreover, goat's milk possesses β -casein as the major casein fractions, while in the case of cow's milk, it is α_{s1} -casein. It has been reported that the high digestibility of goat's milk is attributed to higher α_{s2} -casein content that in turn governs micelle conformation and apparently calcium availability, hence considered to be less allergenic than cow's milk (Haenlein 2004).

Beta casein (β -casein) has a primary sequence of 209 AA, five phosphate groups, and 12 genetic variants. The second major fraction in cow's milk is β -casein which has 12 genetic variants, including A1, A2, A3, B, C, D, E, F, G, H1, H2, and I (Kamiński, Cieślińska, and Kostyra 2007). A1 and A2 are widespread variants, differs in amino-acid composition particularly at 67 position, which is occupied by histidine in A1 while proline in A2 variants (Truswell 2005). B β -casein also has histidine at 67 position and is less frequent than A1 and A2 variants. Due to histidine at 67 position in A1 variant, β -casein becomes susceptible to enzymatic cleavage while proline at 76 position in A2 variants protects it from enzymatic cleavage (Elliott et al. 1999). In the small intestine, under the action of enzymes such as pepsin, elastase and leucine aminopeptidase, A1 β -casein is cleaved into a seven amino-acid peptide namely β -casomorphin-7 (BCM-7). In addition, BCM-4, BCM-5, BCM-6, BCM-8, and BCM-11 are also formed (Kamiński, Cieślińska, and Kostyra 2007). The opioid BCM-7 has agonist activity on μ -receptors and may be implicated as a risk factor in type 1 diabetes, arteriosclerosis, human ischemic heart disease, and known to affect gastrointestinal function in milk or lactose intolerant people (Elliott et al. 1999; He et al. 2017). However, the

other bioactive peptides from bovine β -casein exhibits several attributes such as immunomodulatory, antihypertensive, antimicrobial, antithrombotic, and mineral binding activities (Cieřlińska et al. 2012). β -casein possesses high similarity with α_{s1} -casein in terms of loose tertiary and reduced secondary structure-forming globular hydrophobic domain at C-terminal and hydrophilic (charged) structure at N-terminal with high proline content and no disulfide bond. Thus, the molecular structural architecture of β -casein advocates that IgE binding epitopes (6 major & 3 minor) on them are linear. Upon cleavage by milk plasmin protease, β -casein forms a non-immunogenic family of casein such as $\gamma 1$ -, $\gamma 2$ -, and $\gamma 3$ casein (Goff 2016).

Kappa casein (κ -casein) is composed of 169 AA, has a highly hydrophobic N-terminal, and strongly hydrophilic C-terminal. κ -casein possesses eleven genetic variants, and the variation arises as a result of the difference in the number of the oligosaccharides attached to κ -casein. The opposite charges on κ -casein creates electrostatic repulsive forces that prevent micelles aggregation. κ -casein is the only glycosylated casein that consists of galactose, sialic acid, and galactosamine. Depending on glycosylation, κ -casein forms 11 isoforms in the milk (Fox 2001). κ -casein is unable to precipitate calcium cations because it consists of a low concentration of anionic phosphate groups; as a result, κ -casein provides stability to other proteins. However, this stability is eliminated upon rennet cleavage that forms para- κ -casein (hydrophobic) and caseinomacropptide (CMP) (hydrophilic). CMP plays a crucial role in the overall digestion in individuals by augmenting serum gastrin secretion, decreasing gastric acid, serotonin secretion, showing anticoagulant properties, minimizes platelet agglomeration (Goff 2016). It has been stated that CMP's glycosylated form is digested in a smaller amount and may be responsible for immunoreactivity than nonglycosylated forms (Cieřlińska et al. 2012). κ -casein bears eight dominant IgE binding epitopes, and three of them are implicated with CMA by reacting 93% serum samples of patients. The majority of IgE binding epitopes fall at 9 to 68 AA residues, which cause allergenicity (Chatchatee et al. 2001; Han et al. 2008).

In context to CMA, epitope mapping of many CMPs, including caseins and whey proteins, demonstrated that many proteins bear multiple allergenic epitopes that have been implicated in allergic reactions (Crittenden and Bennett 2005). In particular, the amino acid sequence alignment of bovine and human milk containing α -lactalbumin, β -casein, and κ -casein is 78%, 49%, and 52% analogous and exhibits 81%, 63%, and 58% homology, respectively (Chatchatee et al. 2001 and Järvinen et al. 2011) (Figures 1 and 2A and B). Therefore, it is significantly evident that reported IgE binding epitopes on bovine milk show high resemblances with endogenous human milk proteins. As a result, endogenous human milk epitopes are identified by cross-reactive IgE antibodies of infants with CMA causing allergic symptoms.

In addition to cow's milk, there are a number of foods accountable for 90% of food allergies, such as peanuts, soybeans, tree nuts, crustacean shellfish, eggs, fishes, and wheat

(Table 2). As food allergy has severe health consequences, regulatory bodies in the USA, Canada, European Union, Australia, and New Zealand ask food manufacturers to give a piece of precise information about food ingredients to assure food-allergic consumers (Downs et al. 2013).

CMPs and immune response

It has been observed that when CMP passes through the gastrointestinal epithelium, it triggers either cell-mediated or humoral or both immune responses. Infants ingesting cow's milk always exhibit an immune response to proteins that can be evidenced with the presence of antibodies such as IgG and IgA isotypes in blood circulation and mucosal layers, respectively. The development of the above-mentioned immune response may be accountable for defensive anti-inflammatory function and enable the infants to digest CMP smoothly. In contrast, upon CMP ingestion, if the infant shows any adverse clinical sign and undesirable immune response, the sign represents an allergic reaction to milk.

As stated above, whey proteins, caseins, and their sub-fractions are the chief allergens responsible for milk allergy. However, in allergic individuals, the pathogenesis of allergic reactions is chiefly manifested by an imbalance between the expressions of T helper type (Th1) and type 2 (Th2) cells. Th2 mediated response is allergen-specific, while Th1 mediated immunity is protective. The therapeutic measure to curb CMA focuses mainly on the immune response modulation of the patients by mitigating allergen-specific Th2 response with simultaneous activation of protective Th1 immunity (Sziksz, Vannay, and Haczku 2012). Even though in the chronic phase, IgE antibodies initiate and mediate allergic inflammation, the clinical symptoms of pathogenesis are governed primarily by allergen-specific T lymphocytes. This phenomenon evidently reflects that Th2 (allergen-specific) cells are central to allergic inflammatory reaction maintenance while IgE-independent cell-mediated immunity is related to gastrointestinal food allergy (Mercer et al. 2009). In addition, the different genetic variants form different CMP with different nutritional properties, which in turn have different consequences in human health.

IgE mediated immediate hypersensitivity to CMPs

IgE-mediated sensitivity to CMPs is well-understood and easily diagnosed that consists of two crucial phases: sensitization and reaction elicitation (Table 3). Because the symptoms appear quickly upon allergen's exposure, the immune system of an individual responds rapidly; thus, the response is termed as immediate hypersensitivity. It is imperative to have a proper cross-talk between T helper cells and B cells to begin immune response for protein antigen (Savilahti and Kuitunen 1992). In particular, T helper cells such as Th1 and Th2 cells are major determinants of whether the immune response would be defensive or allergic. In addition, T cells are involved in different secretory roles for lymphokines secretion. When protein antigen/allergen

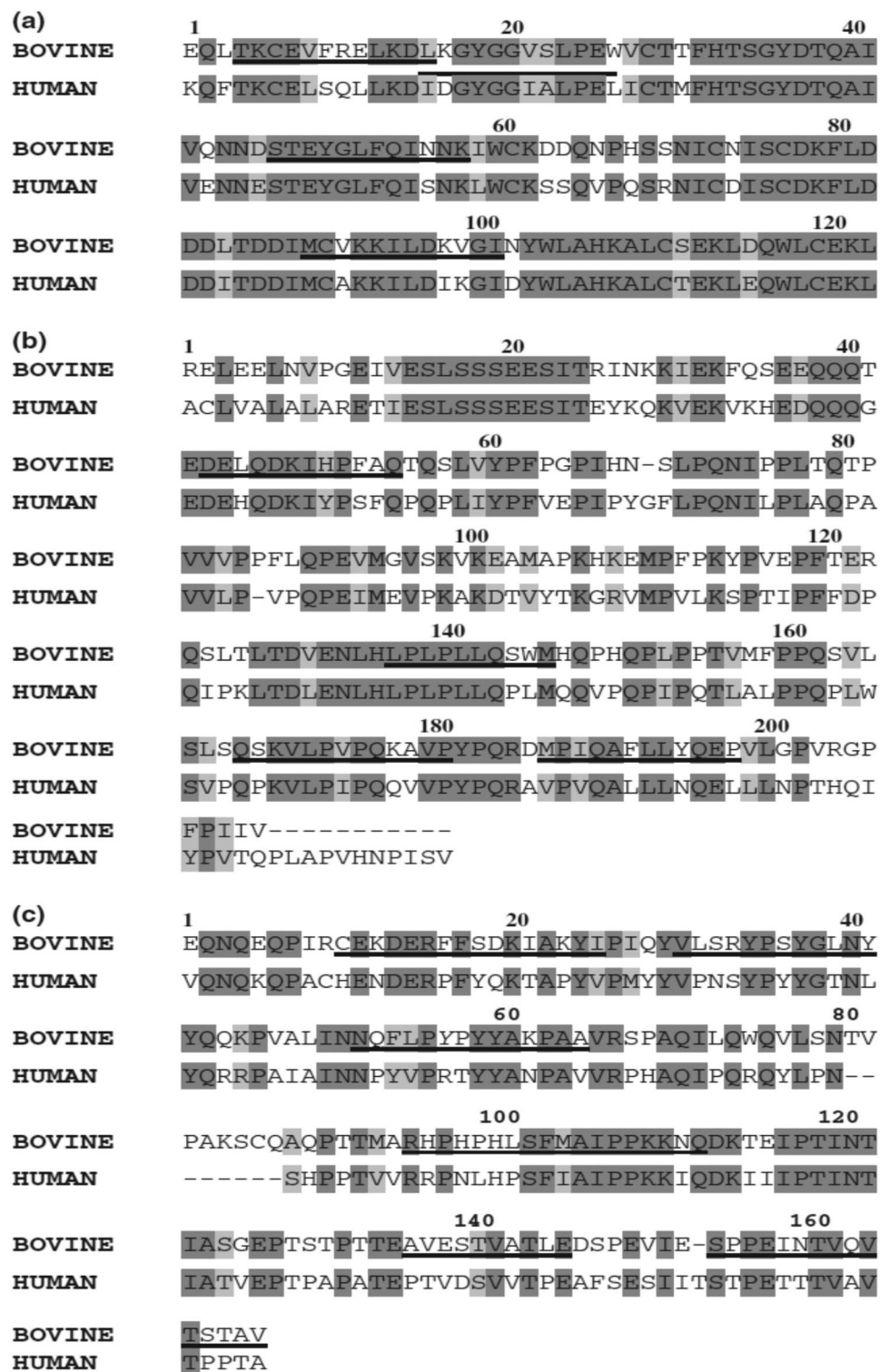


Figure 1. Amino acid sequence alignment of bovine and human (a) α -lactalbumin, (b) β -casein, and (c) κ -casein. Dark gray highlighted sequence represents identical amino acids, light gray for homologous amino acids and underlined for bovine protein bearing known IgE binding epitopes (Järvinen et al. 2011).

activates Th2 cells, interleukin-4 is produced without interferon-gamma; as a result, B lymphocytes abruptly secrete IgE antibodies (Figure 3). In mice, IgE has been implicated in atopic dermatitis and allergic reactions by cell-mediated immunity. Th2 secreting lymphokines trigger the proliferation of mast cells involved in various allergic reactions. IgE antibodies are attached to the surface of mast cells and basophils and fortified them with the allergen-specific trigger.

Upon attachment of IgE antibodies to allergenic epitopes on the milk protein, immediately initiate a series of cascade reactions of hypersensitivity and inflammation leading to allergy (Crittenden and Bennett 2005). IgE-mediated immediate hypersensitivity to CMP affects the body at cutaneous (eczema, urticaria, angioderma), respiration (asthma, rhinoconjunctivitis), gastrointestinal level (oral allergy, vomiting, nausea, diarrhea), and generalized (anaphylactic shock)

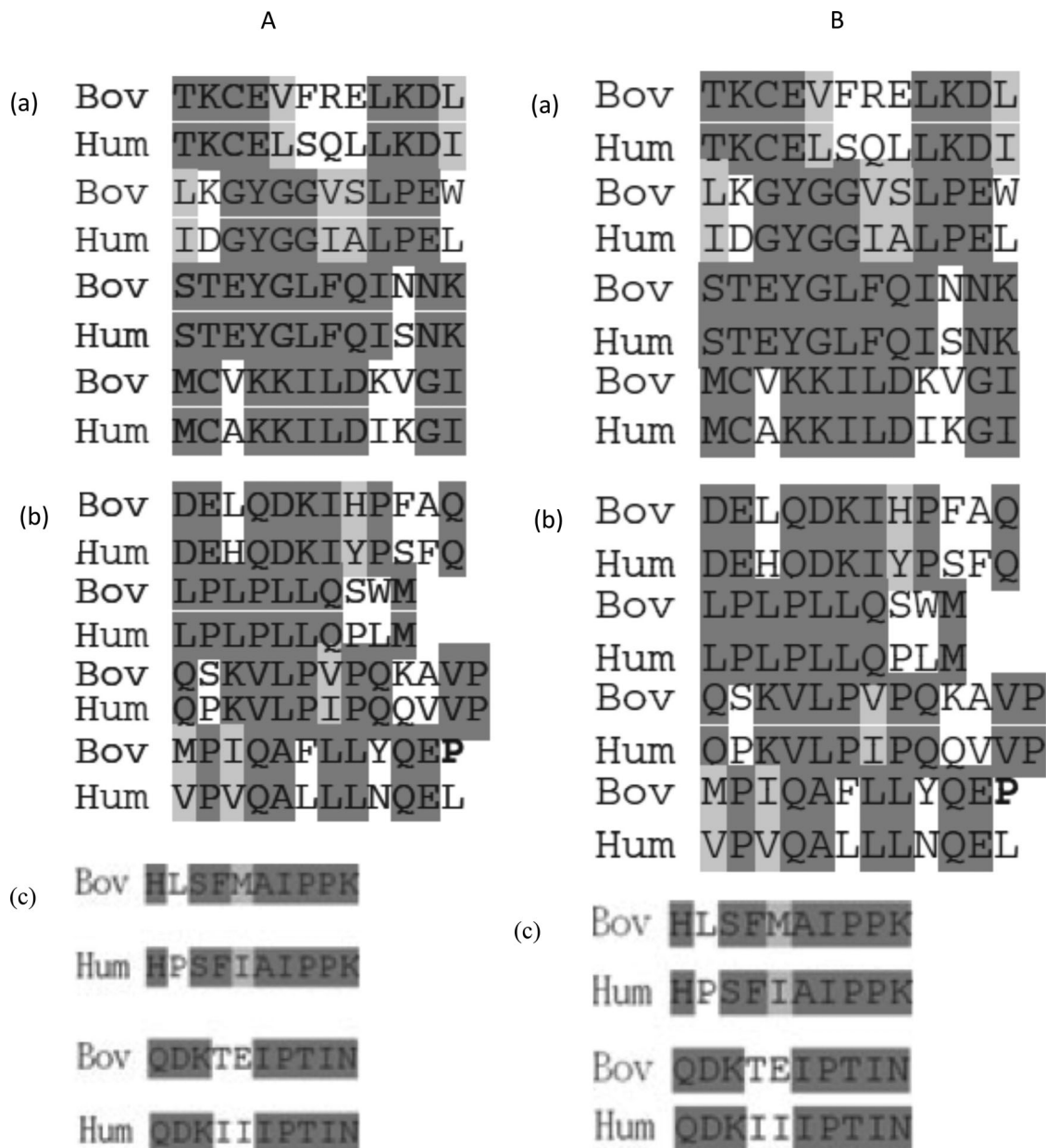


Figure 2. (A) Amino acid sequence alignment of known IgE epitopes on bovine milk (Bov) (a) α -lactalbumin, (b) β -casein, and (c) κ -casein and homologous peptides on human milk (Hum) of breastfeeding infants (Figure 3(B)). Amino acid sequence alignment of known IgE epitopes on bovine milk (Bov) (a) α -lactalbumin, (b) β -casein, and (c) κ -casein and homologous peptides on human milk (Hum) of older children (5-15 years). Dark gray highlighted sequence represents identical amino acids, light gray for homologous amino acids (Järvinen et al. 2011).

(Table 4). Sometimes CMA leads to a life-threatening condition, but its occurrence is infrequent. However, strategies are made focusing on mitigating CMP's allergenicity by ameliorating protein digestibility.

Non-IgE mediated delayed hypersensitivity to CMPs

Delayed hypersensitivity is linked to the absence of specific milk protein antibodies (IgE) in blood circulation in the majority of adults and infants. Therefore, non-IgE mediated allergic responses tend to be tardy and show symptoms from one hour to several days after milk ingestion. As delayed reactions are dependent on T-cell response, as a result, the response affects the body at the skin and intestinal level (El-Agamy 2007). Upon interaction with a protein

antigen, Th1 cells stimulate lymphokines mediated B lymphocytes activation to secrete IgG and IgA (Figure 3). Delayed allergies to CMP are manifested by crypt hyperplasia, villous atrophy, the augmented density of lymphocytes in the intestinal epithelium, and the infiltration of mononuclear cells.

Raw milk versus commercial/processed milk allergy

The history of cow's milk consumption by humans is thousands of years old. For many years, milk was consumed as raw milk until the technique of pasteurization was invented. It has been reported that raw milk poses a health risk due to its association with several bacterial pathogens that may threaten infants and pregnant women. Thus, to alleviate the

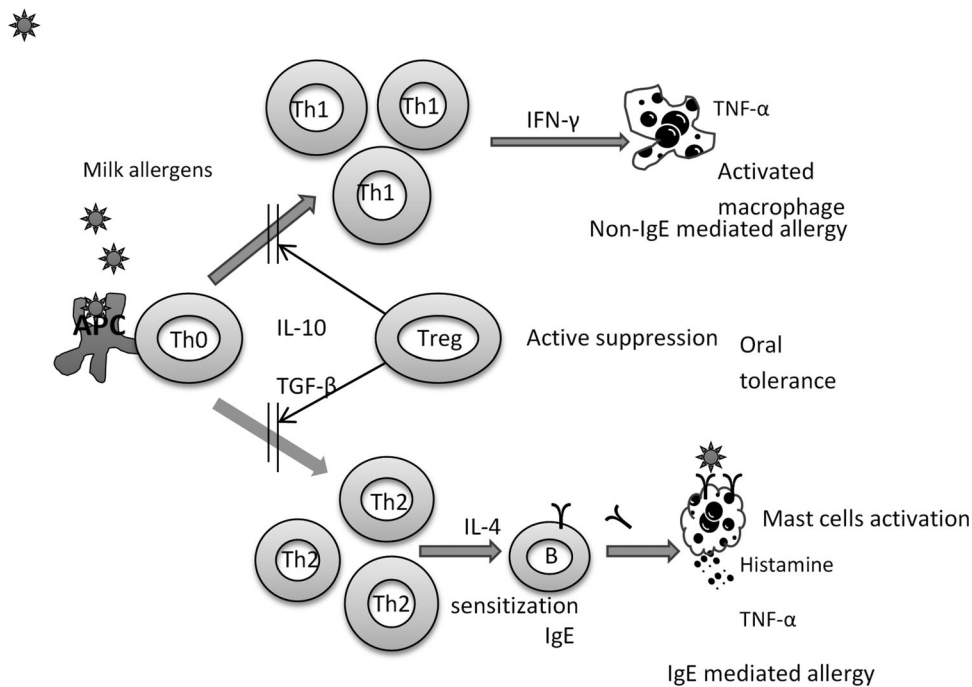


Figure 3. Schematic representation of IgE and non-IgE mediated allergy (Crittenden and Bennett 2005).

Table 2. Common allergenic foods for selected countries (Downs et al. 2013).

Allergenic food	USA	Canada	European Union	Australia/New Zealand
Celery			Y	
Cow's milk	Y	Y	Y	Y
Crustacean shellfish	Y	Y	Y	Y
Egg	Y	Y	Y	Y
Fish	Y	Y	Y	Y
Lupine			Y	
Molluscan shellfish		Y	Y	
Mustard		Y	Y	
Peanut	Y	Y	Y	Y
Sesame Seed		Y	Y	Y
Soybean	Y	Y	Y	Y
Tree nuts	Y	Y	Y	Y
Wheat	Y	Y	Y	Y

*Y stands for yes.

above-mentioned risks, industrial milk processing (pasteurization & homogenization) of raw milk started in the late 19th century. The main purpose of raw milk processing was to extend the shelf life and minimize the risk of milk-borne pathogens such as *Mycobacterium tuberculosis*, *Listeria*, *Salmonella*, *Escherichia coli*, *Campylobacter* (Abbring, Kusché et al. 2019). Homogenization works through centrifugation to remove milk fat globule from raw milk to form skimmed milk ($\leq 1\%$ fat), semi-skimmed milk (2% fat), and whole milk ($> 3.25\%$ fat). Although, this process makes milk emulsion more stable, which in turn increases the surface area of droplets to which casein micelles adsorb but augments allergenicity of the processed milk through disruption of fat globules and casein micelles (Braun-Fahrlander and Von Mutius 2011; Abbring, Hols et al. 2019). Heating is another procedure of milk processing that includes pasteurization for 15–40 seconds at 71 °C and the industrial heat treatment like sterilization for 10–20 min at 110–120 °C and ultra-high temperature (UHT) for 0.5–4 seconds at 135–145 °C (Verhoeckx et al. 2015). Although the sole

objective of processing was to reduce microbial pathogens from the raw milk, methods opted in the form of homogenization and pasteurization also alter the milk fat and whey protein molecular structure, respectively, and these potentially altered structures present themselves as allergens to the immune system (Braun-Fahrlander and Von Mutius 2011). Casein is a heat-stable protein; as a result, heating does not alter its conformational structure. In contrast, whey proteins, particularly β -lactoglobulin and α -lactalbumin are heat susceptible. Consequently, the biological functionality of the abovementioned protein subfractions is lost on heating and causes aggregation, denaturation, and insolubilization (Brick et al. 2017). Peyer's patches (PPs) are small groups of lymphoid follicles located in the mucosal membrane of the small intestine. During food allergy, PPs play a pivotal role in immune surveillance. Native whey proteins (unaggregated form) are usually taken up by enterocytes (intestinal epithelium), and this uptake is comparatively less immunogenic than that of PPs. In contrast, upon pasteurization, aggregation of whey proteins takes place that stimulates allergic sensitization because the normal intestinal uptake of whey proteins is skewed from enterocytes to PPs (allergic). This abnormal shift in whey protein's uptake via PPs is observed, particularly during food allergy, thereby provoking immunogenicity (Abbring, Hols et al. 2019). Existing epidemiological evidence has speculated that consumption of organic raw milk from the farm has beneficial and protective health effects compared to commercially processed milk because raw milk reduces the risk of asthma, atopic sensitization, and hay fever (Braun-Fahrlander and Von Mutius 2011). It has been found that pasteurization at 72 °C denatures part of raw cow's milk IgG and also changes the structure of lactoferrin. On the contrary, homogenization, and sterilization denature IgG fully and reduce lactoferrin content. In addition, the concentration of cow's transforming growth

Table 3. Classification of allergic reactions to milk (Downs et al. 2013).

1.	True food allergies
A.	Antibody mediated immediate hypersensitivity (milk allergies)
a.	IgE facilitated milk allergy including oral allergy syndrome
a.	Exercise-associated milk allergy (milk + exercise)
A.	Cell-mediated food allergies (Delayed hypersensitivity)
a.	Milk protein-induced enterocolitis
a.	Milk protein-induced enteropathy
a.	Milk protein-induced proctitis
A.	Either antibody-mediated and/or cell-mediated
a.	Allergic eosinophilic gastroenteritis
a.	Allergic eosinophilic esophagitis
2.	Food intolerances
A.	Lactose intolerance (a kind of metabolic disorder)

factor (TGF- β 1) was noticed to be drastically lower in commercially processed milk than that of raw milk (Sozańska 2019). Several epidemiological studies on the murine model have suggested that raw milk remarkably diminishes inflammatory cells count such as eosinophils, neutrophils, lymphocytes, and macrophages in bronchoalveolar lavage fluid as well as IL-5 and IL-13 in lung T cells, hence, the abovementioned attributes consider the raw milk as protective milk and is preferred over processed milk in allergic asthma. However, medical guidelines sharply discourage the consumption of raw milk as a therapeutic measure for allergic diseases because raw milk contains a significant amount of microbial pathogens that could lead to infection (Sozańska 2019).

Processed CMP in infant formulas

Infant formulas contain processed CMP whose casein proportion is reduced to 40% (6 gm/L), which is equivalent to human milk. However, the amount of casein in formulas varies from 18 to 20 gm/L for preterm infants to 15 gm/L for term infants. Commercial formulas are usually heat processed in which desired casein concentration is accomplished by mixing an equal proportion of skim milk and whey protein (Savilahti and Kuitunen 1992). Infant formula is classified into four formulas:

Partially hydrolyzed formula (PHF): PHF is a cow milk-based formula that has been partially hydrolyzed, containing larger peptides than EHF. The cow milk proteins are processed in such a way that processing techniques wipe out allergenic epitopes that can cause allergenicity (Crittenden and Bennett 2005).

Extensively hydrolyzed formula (EHF): EHF is a proteolytic enzyme-treated cow milk-based formula whose bitter taste makes EHF unpalatable to consume. The children diagnosed with CMA are highly recommended to use EHF as a milk substitute. In some countries like Italy, EHF is prepared using goat milk (Braun-Fahrlander and Von Mutius 2011).

Soy formula (SF): SF is a soy protein-based formula whose nutritional value is analogous to EHF, and SF formula is found more palatable. Fifty-three to eighty-three percent of children with CMA can well tolerate SF, while 17–47% shows SF allergenicity (El-Agamy 2016).

Amino acid-based formula (AAF): AAF is also a cow milk-based formula and considered to be less allergic. Nearly 10% of children who fail to tolerate EHF, comparatively show clinical benefits against CMA when supplemented with AAF (Hill et al. 2007).

Table 4. IgE mediated milk allergy symptoms (Downs et al. 2013).

1.	Gastrointestinal
	Abdominal cramps
	Diarrhea
	Nausea
	Oral allergy symptoms
	Vomiting
2.	Cutaneous
	Angioedema
	Dermatitis
	Pruritis
	Urticaria
3.	Respiratory
	Asthma
	Heiner's syndrome
	Laryngeal edema
	Rhinitis
	Rhinoconjunctivitis
4.	Generalized
	Anaphylactic shock

Allergic cross-reactivity to cow's milk

Allergic cross-reactivity to Cow's milk is observed in children with an inability to tolerate goat's or sheep's milk (Ah-Leung et al. 2006). Protein mapping revealed that allergic cross-reactivity between milk proteins, namely caseins and whey proteins from different dairy species such as goat, sheep, camel, buffalo, donkey, and mare is mainly attributed to their common amino-acid sequences and analogous ability to bind specific IgE immunoglobulins (García and Lizaso 2011). Cow and goat milk have a similar composition (87% water, 3–4% fat, 3.2% protein, lactose 4.8%, micronutrients), while sheep milk accounts for a significantly higher fat, protein, and lactose contents. It suggests that sheep and goat, particularly due to α -casein, have a high allergic potential. However, camel milk also shows high similarity with cow milk but is slightly salty, three times more vitamin C content, unsaturated fatty acids, and vitamin B than cow milk. Camel and goat milk are mostly consumed raw, while due to overall solid content, sheep milk is appropriate for the cheese industry (FAO, 2021). It has been reported that 92% and 4% of CMA patients demonstrated clinical allergy to goat milk and mare milk, respectively (Bellioni-Businco et al. 1999; Businco et al. 2000). Donkey and camel milk is considered to be hypoallergenic compared to cow milk (El-Agamy 2016). The sera of CMA children are highly likely to identify major parts of casein and whey proteins of goat, sheep, and buffalo, while feeble cross-reactivity was observed from donkey and mare and almost no reactivity with camel milk. β -lactoglobulin is the main whey protein allergen in cow, goat, buffalo, sheep, mare, donkey milk, while human and camel milk is devoid of β -lactoglobulin (El-Agamy, Abou-Shloue, and Abdel-Kader 1997). This clearly demonstrated that the low allergenicity of human and camel milk is ascribed to the absence of β -lactoglobulin (Kappeler 1998). Due to the absence of β -lactoglobulin and human milk protein similarity, camel milk has emerged as hypoallergenic milk.

Diagnosis of CMA

Owing to the multiplicity of allergic symptoms, the clinical diagnosis of CMA varies greatly. The diagnosis can be

performed by testing either skin or blood or both. Due to the involvement of IgE antibodies in immediate hypersensitivity, the diagnosis in blood or skin test comes promptly. There are 60% cases of CMA in children where the symptoms are delayed; thus, their instantaneous clinical outcome is highly unlikely (El-Agamy 2007). The four reliable clinical diagnostic tests are as follows.

Skin prick test (SPT)

SPT is considered to be the most precise test in young kids; however, there is no specific age limit for this test. In addition, a strong allergic reaction is a prerequisite for the clinical reliability of SPT (Majamaa et al. 1999). SPT is a qualitative test that detects IgE antibodies located on the surface of mast cells that reacts with drops of milk proteins allergen placed on the forearm of patients. After a few minutes, wheal and flare reaction start to allergic patients that witness CMA.

Blood tests

RAST and enzyme-linked immunosorbent assays (ELISA) are the two tests that frequently diagnose the level of IgE in the blood serum of the patients (Garcia-Ara et al. 2004). In RAST, the serum sample of the patient is incubated with milk allergen, and the latter is already fixed on a solid phase, namely a cellulose disk. This is followed by further incubation with radiolabelled anti-IgE. The antigen-specific binding between anti-IgE and IgE finally corresponds to the amount of IgE in the blood. In the ELISA test, all steps are followed as RAST, but instead of radiolabelled anti-IgE, the enzyme is linked to anti-IgE to determine the amount of antigen-specific IgE (Ghosh, Malhotra, and Mathur 1989).

Elimination-challenge test

In this test, milk allergy is confirmed in two steps (a) exclusion of cow milk and its product from the daily diet and observation of clinical symptoms and improvements, and (b) re-inclusion of milk-based diet and reappearance of the allergic symptoms (El-Agamy 2007).

Treatment of CMA

To date, there is no generally valid proven cure and treatment for CMA. The only precautionary measure is avoiding the consumption of CMPs throughout the entire length of allergic disease. In addition, for managing CMA in breast-fed and formula-fed infants, some remarkable recommendations and guidelines have been established for general pediatricians and primary care physicians (Vandenplas et al. 2007). The above-mentioned recommendations also included prominence of breastfeeding in healthy infants, emphasis on far-reaching history checks of the family for allergy, meticulous physical examination to rule out other causes, ascertaining any existing health problems, and categorizing CMA into mild, moderate, or severe. The algorithms have been summarized exclusively based on the method of feeding in

Figures 4 and 5. Moreover, the infants with suspected or proven CMA should not be given unmodified cow's, sheep, buffalo, horse, or goat's milk because they not only pose a threat of allergenic cross-reactivity but also lack ample nutrients to nourish infants as a sole food source (Spuerger et al. 1997). It has been reported that allergy to milk from other species such as goat, sheep, or camel is less common (Cases et al. 2011). However, despite some dissimilarity between human milk proteins and milk from sheep, goat, camel, etc. they can allocate several allergenic epitopes with CMPs; as a result, they cannot be regarded as generally valid hypoallergenic candidates but only in individual cases as substitutes for cow milk (Crittenden and Bennett 2005). It has been observed that CMA patients are also susceptible to several foods such as soymilk, peanuts, fish, coconuts, etc.; hence, they are not always reliable substitute for cow milk in infants. Accidental exposure and adverse immunological reactions of CMA can be treated with H1- & H2 antihistamines, beta-2-agonists, or glucocorticosteroids; however, under life-threatening allergic condition, epinephrine is given to the allergic patients (Villa et al. 2018).

Role of galectins as allergy suppressor

The surface of all mammalian cells consists of glycan structures that, under several pathological and physiological body conditions, go through conformational changes and offer the best platform to monitor and identify molecular signatures. Galectins are a class of beta-galactoside binding lectins that bears highly conserved carbohydrate recognition domains (CRDs). Although galectins are known to bind specifically galactose, they also have a high affinity for oligosaccharides (Worku et al. 2018; Asiamah et al. 2017). Galectins and their particular glycan ligands are profusely situated in the gastrointestinal tract. Recently, galectins have emerged as novel regulators of several cellular functions such as inflammation, T-cell activation, cell growth, cell adhesion, migration, and apoptosis (Sziksz, Vannay, and Haczku 2012). Among all, migration, T-cell activation, and apoptosis are crucial immunological processes, and they are highly dependent on the glycosylation of cell surface proteins (Toscano et al. 2007). Of all, galectins-9 is 'tandem repeat type', which has two separate CRDs linked by non-conserved amino acid sequence, and galectin 3 is characterized to be a 'chimera type' bearing one CRDs and N-terminal, play a pivotal role in modulating allergic reactions (Mulakala et al. 2018). It has been reported in intraepithelial gut lymphocytes of CMA allergic children that the expression of galectin-3 augments dramatically during cow milk intake compared to non-allergic children signifying the potential role in modulating epithelial-immune cells interaction during an allergic reaction (Mercer et al. 2009).

In particular, galectin-9 has a specific role in immunoregulation involving suppression of allergic reactions. In the murine model of CMA, supplementation of galacto-fructooligosaccharides and *Bifidobacterium breve* advocated the suppressive role of galectin 9 in food-induced allergic inflammation by reducing IgE mediated mast cell

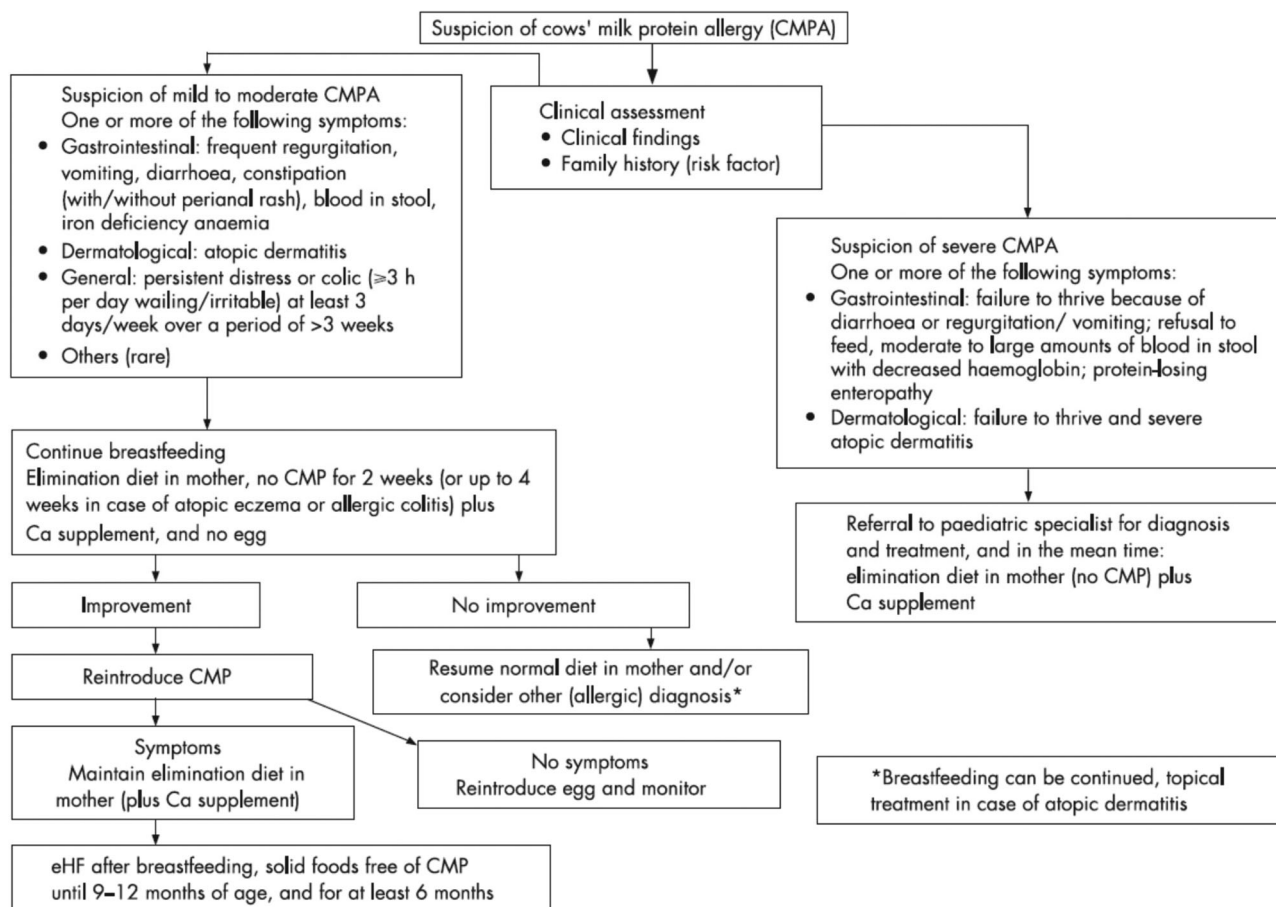


Figure 4. Algorithms showing diagnosis and management of CMA in specifically breast-fed infants (Vandenplas et al. 2007).

granulation (de Kivit et al. 2012). Recently, it has been found that galectins-9 binds firmly with IgE-mediated allergic reaction. Galectins-9, upon binding with highly glycosylated IgE antibodies (galectin9-IgE glycan) minimizes the chances of the formation of the protein antigen-IgE complex, which is responsible for initiating the allergic reaction, thereby exhibiting an anti-allergic effect (Niki et al. 2009). So, commercially available galectins could be a viable source to target glycosylated IgE antibodies to minimize allergic reaction.

The biological role of milk

Milk is considered to be a complete food as it is a rich source of all of the following: fats, saturated fatty acids, oleic acid, lauric acid, myristic acid, palmitic acid, linoleic acid, alpha-linolenic acid, essential amino acids, bioactive proteins and peptides, lactose, magnesium, zinc, selenium, vitamin A, vitamin E, folate, riboflavin, and vitamin B₁₂. Therefore, the daily intake of 500 ml of milk supplies an ample amount of nutrients to the body. The major biological attributes of milk constituents are described below.

Fats

Fats (33 g/l) supply the body with energy. Among the major saturated fatty acid (19 g/l), butyric acid helps prevent cancer, while caprylic acid delays tumor growth (Thormar et al.

1994). Capric and the lauric acid act as antiviral, antibacterial, and COX-I, COX-II inhibitors (Henry et al. 2002). By augmenting reverse cholesterol transport, lauric acid, palmitic acid, and myristic acid, which are saturated fatty acids, increase high-density lipoproteins (HDL) (Insel, Turner, and Ross 2004). Being a single unsaturated fatty acid, oleic acid (8 g/l) reduces plasma cholesterol, triglycerides, and LDL-cholesterol concentration (Kris-Etherton et al. 1999). Eicosapentaenoic acid (EPA), which is metabolically produced by linoleic acid (omega 6 fatty acid) and alpha-linolenic acid (omega 3 fatty acid), decrease cardiovascular risk, and tumor growth (Bagga et al. 2003). In addition, conjugated linoleic acid from bovine milk has been found to have anti-proliferative and pro-apoptotic effects that decrease the risk of colon cancer. Phospholipids and glycosphingolipids (1% of total milk lipids) present in milk lipids have a bioactive role in emulsion stabilization, cations binding, transmembrane signaling, some hormones, and growth factors receptors, cell-cell interaction, differentiation, proliferation, and immune recognition (Keenan and Patton 1995).

Proteins

Bovine milk proteins (32 g/l) are of high significance because of their prime role as antimicrobials, growth factors, enzymes, hormones, antibodies, calcium & phosphate carriers, and immune stimulants (Clare and Swaisgood 2000). Some milk peptides exhibit antihypertensive effects, while

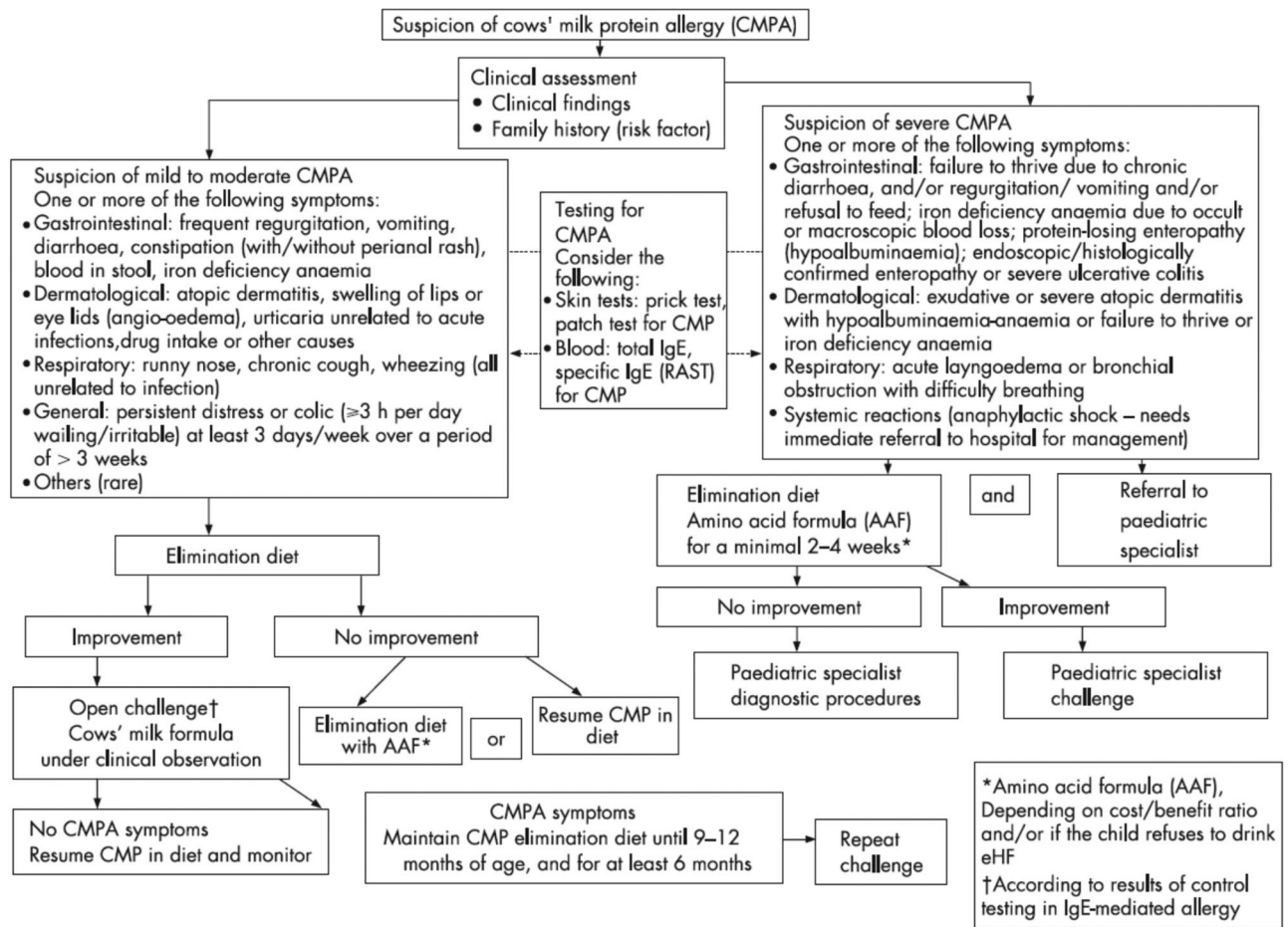


Figure 5. Algorithms showing diagnosis and management of CMA in specifically formula-fed infants (Vandenplas et al. 2007).

essential amino acids and branched-chain amino acids promote muscle protein synthesis. Cow's colostrum contains taurine (18 mg/l) whose physiological function is related to neuromodulation, bile acid conjugation, retinal development, parenteral nutrition, and anti-inflammation properties (Lourenco and Camilo 2002). Glutathione, an important blend of tripeptides such as sulfur-containing cysteine, glycine, and glutamic acid, is a master antioxidant that regulates hydrogen peroxides production by quenching reactive oxygen species (ROS) (Haug, Høstmark, and Harstad 2007). In addition, glutathione regulates pancreatic insulin production, protects the lungs, and lowers respiratory infections (Haug, Høstmark, and Harstad 2007). Glutathione is present in raw milk (9.3 mg), but upon high heat treatment during pasteurization, the level significantly reduced in pasteurized milk (4.5 mg). The conspicuous reduction in glutathione content in pasteurized milk is attributed to the breaking of glutamyl-cysteine bonds that itself represents two-third of glutathione molecule (Masterjohn 2010).

Antioxidants, vitamins, and minerals

In bovine milk, Vitamin E (0.6 mg/l) is present in the form of alpha-tocopherol and results in a strengthened immune system and a reduction in the risk of cancer and coronary heart disease (Haug, Høstmark, and Harstad 2007). Proper vision, reproduction, growth, and immunity are mainly

governed by Vitamin A (280 ug/l), and milk is a good source of this vitamin (Insel, Turner, and Ross 2004). Selenium (37 ug/l) is the mineral that serves as an antioxidant and is aiding in DNA synthesis, DNA repair, thyroid hormone metabolism, and prevention of cancer and asthma (Dodig and Čepelak 2004). Bovine milk is also a rich dietary source of calcium (1 g/l), which keeps bones and teeth healthy (Insel, Turner, and Ross 2004). In addition, milk helps to prevent hypertension, kidney stones, and colon cancer. An important element of the thyroid hormone is iodine (160 ug/l) in milk, which also regulates the metabolic rate and body temperature (Haug, Høstmark, and Harstad 2007). Milk is a good source of magnesium (100 mg/l), which has a significant role in reducing asthma and oxidative stress. Moreover, in conjugation with taurine, milk helps to regulate calcium release in the cells (Cheuk, Chau, and Lee 2005). Zinc (4 mg/l) is present in milk in an adequate amount to govern DNA repair, cell growth, gene expression, lipid metabolism, protein metabolism, immune function, and DNA replication (Insel, Turner, and Ross 2004). It is worth noting that even though cow's milk is a good source of vitamin D, very low iron (Fe) content leads to Fe deficiency in young children. In addition, daily intake of cow's milk depletes the Fe absorption from other food and causes gradual loss of Fe in the fecal matter through minor intestinal bleeding. Consuming 400 g/d of fortified milk, routinely supplemented with vitamin D and Fe, meets the daily

requirement of children (Sidnell et al. 2016). Folate concentration in bovine milk is 50ug/l, and folate's biological role is to protect the body from hypertension and coronary heart disease. Milk also contains riboflavin (1.83 mg/l) and vitamin B12 (4.4 ug/l), and these vitamins have major roles in metabolic pathways (Haug, Høstmark, and Harstad 2007).

Dairy nutrition and CMA

An adequate amount of nutrients in the diet not only maintains a functional immune system but also protects cows from metabolic disorders, inflammation, and diseases. However, the breed, age, species, diet, lactation stage, season, and the number of parturitions profoundly affect the milk compositions and production (Linn 1988). Genetic selection is an important tool through which milk protein percentage and composition can be altered (Linn 1988). However, dietary protein percentage has a less conspicuous effect on milk protein percentage. Milk immunoglobulins and albumins are not synthesized in the mammary gland; rather, they are transported to them from the blood (Larson 1979). On the other hand, most of the milk proteins are synthesized in the mammary gland; therefore, it is imperative to have a regular supply of essential and non-essential amino acids to the gland for protein synthesis through diet. Increased milk protein percentages have been reported in the cows grazing in early spring pastures (Linn 1988). It has been reported that milk protein percentage and propionic acid in the rumen are positively correlated with enhancing concentrate feeding and decreasing forage size in the diet because high propionic acid in the rumen augments milk protein synthesis (Thomas 1983).

The consumption of animal-derived fat and saturated fatty acids (SFA) raised concern because of their implication in the risk of cardiovascular diseases, obesity, and type-2 diabetes (Givens 2005). Fat is the most variable constituent in milk. The fatty acid composition of milk can be altered through enhanced dairy nutrition, especially introducing PUFA or MUFA enriched dairy diet. It has been reported that cow's milk quality changes remarkably upon changing the feed ingredients such as camelina meal, which is rich in PUFA (Toma et al. 2015). Camelina is a flowering plant which is also known as false flax. Camelina meal is obtained by cold pressing of camelina seed during oil extraction. It is rich in protein and oil and used as livestock feeding material (Korsrud, Keith, and Bell 1978). When sunflower meal was substituted with camelina meal (50 to 100%) in the compound feed (corn, wheat bran & sunflower meal), milk quality was changed with a higher concentration of polyunsaturated fatty acid (PUFA), n-6 PUFA, and conjugated linoleic acid (CLA) with significant decrease in saturated fatty acid (SFA) contents (Toma et al. 2015). The bovine mammary gland has the unique ability to secrete a large amount of short and medium-chain fatty acids from the synthetase complex. Under the microbial action, ruminants undergo extensive biohydrogenation; as a result, long-chain fatty acids are produced and absorbed in the mammary glands. The augmented long-chain fatty acids supply, in turn, obstructs the synthesis of SFA, and a high amount

of PUFA is being secreted in the milk (Givens 2005). Also, it has been reported that oral probiotic administration in lactating Holstein-Friesian cows boosted immunity and modulated the systemic effect on global gene expression by upregulating the expression of Toll-like receptor (TLR), inflammation response, and Wnt signaling pathways, which are involved in immunity and homeostasis (Adjei-Fremah et al. 2018). TLR are pathogens recognition receptors that have the ability to sense highly conserved structural motifs of invading pathogens. These motifs are known as the pathogen-associated microbial pattern (PAMP) and are recognized efficiently by TLR that triggers a local and systemic immune response to combat infection (Jaiswal, Ismail, and Worku 2020). Wnt signaling pathways have been linked with signal transduction of cellular and biological processes responsible for maintaining homeostasis. In particular, probiotic supplements upregulated the genes for cytokines (IL-1R1, IL-65T, IL-12b, IL-6, IL-12A, IL-13, IL-10), chemokines (CXCR1, CXCL8, CXCL2), Toll-like receptors (TLR1, TLR2, TLR3, TLR9), Wnt signaling (WNT6, WNT2B, WNT5B, WNT3, WNT9A, WNT1) and transcription regulators (NFKBIL1) (Adjei-Fremah et al. 2018). The level of lactose, mineral, and vitamin in the milk is almost constant, and they get hardly affected through genetic and nutritional manipulation unless there are mastitic conditions (Linn 1988).

Several epidemiological evidence has shown that due to the exclusion of milk and dairy products, children suffering from CMA are usually short statured with lower calcium and fat consumption than healthy control groups (Boaventura et al. 2019). In addition, a high prevalence of micronutrient deficiencies of vitamin A and D was noticed in CMA patients. Such deficiencies are possibly linked to the development of food allergies and intolerance to dietary proteins such as casein, whey, and soy protein (Boaventura et al. 2019). During the growth and development of children, an adequate supply of dietary calcium is imperative because calcium is an important element of bones. Ample dietary calcium intake not only ensures strong and healthy bones but also augments bone mineral density (BMD) (Jensen et al. 2004). Some ancient tribes grew up their children only on mother's milk without milk from any mammal, e.g., the South American Indians did not have any milk-producing animals before the arrival of the Spanish conquistadores. Because these tribal populations never drank milk in history and presently, so tribal babies profoundly depend on mothers' milk for all nutrition. It has been reported the breast milk produced by women who are at a low nutritional level produces milk with a consistent level of lactose and protein content, but fat contents vary drastically in the milk that dependent on nutritious food intake (Wray 1978). For kids below three years, 700 mg (2–3 servings) of dietary calcium intake is recommended require for proper bone development while one cup of mother's milk provides 79 mg of calcium that is too low than the recommended level. Malnutrition and early nutritional deficits are associated with long-term impairment in overall growth and development. BMD is an important criterion to identify bone health, and a low level of bone health indirectly reflects

low calcium dietary intake. Milk is a rich source of calcium and other nutrients. Due to CMA and lactose intolerance, many children either avoid or limit their milk intake, and this adversely affects bone health and attainment of height (Black et al. 2002). As a result, children with CMA are at greater nutritional risk because, as a crucial part of treatment, they are advised to strictly exclude milk and other dairy products from the diet (Boaventura et al. 2019). A dairy product such as cheese, yogurt, and butter is basically made of milk from the cows, buffaloes, goats, sheep, yak, zebu, camel, and reindeer. In addition to milk, cheese, and yogurt in the diet reduce the cardiometabolic risk in youths. Thus, the inclusion of these products in the daily diet is of paramount importance (Abreu et al. 2014). However, it has been found that some CMA patients are not allergic to cheese produced from cow's milk but show allergenicity to cheese made from goat's or sheep's milk (Wüthrich and Johansson 1995).

Moreover, most children with IgE-mediated CMA can tolerate yogurt well (Monaco et al. 2019). These findings demonstrate that CMA patients may or may not be allergic to cheese or yogurt or other milk products, and the degree of allergenicity or tolerance vary from cases to cases. Consequently, regular nutritional monitoring is imperative to children with CMA in order to ensure sufficient nutrient intake for normal growth.

Conclusions

Casein, whey protein, and some of their sub-fractions in cow's milk cause allergies in some infants, children, and adults. Even though pasteurization reduces the risk of microbial pathogens from raw milk, homogenization, and other processing techniques alter milk proteins and fat molecular structure and makes them more vulnerable to allergies. Although, there are many different but no available treatments for CMA. For managing CMA in breast-fed and formula-fed infants, some great recommendations and guidelines have been established, including the prominence of breastfeeding in healthy infants, emphasis on far-reaching history checks of the family for allergy, meticulous physical examination to rule out other causes, ascertaining any existing health problems and categorizing CMA into mild, moderate or severe for general pediatricians and primary care physicians. Recently, galectins have emerged as a possible novel approach to suppress milk allergies that warrant an in-depth study. As a crucial part of treatment, strict exclusion of nutrient-rich milk and other dairy products from the diet puts children who have cow's milk allergy at greater nutritional risk; thus, regular nutritional monitoring and inclusion of additional nutrients supplement are imperative for their proper growth. Further investigation is needed on the use of appropriate nutrition and animal genetics that also looks at the glycome (breeds of sheep, goats, mares, donkeys, camels, Yak, buffaloes, Zebu, reindeer) as well as improved milk processing to produce non-allergenic milk by inactivating allergic proteins for designer nutrition.

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