



## Prevalence, Risk Factors, Clinical Manifestation, Diagnosis Aspects and Nutrition Therapy In Relation to Both IgE and IgG Cow's Milk Protein Allergies among A Population of Saudi Arabia: A Literature Review

MASHAIL A BAGHLAF<sup>1\*</sup> and NOURA M S EID<sup>2</sup>

<sup>1</sup>Faculty of Applied Medical Sciences, Department of Medical Laboratory Technology, King Abdulaziz University, Jeddah, Saudi Arabia.

<sup>2</sup>Faculty of Applied Medical Sciences, Department of Clinical Nutrition, King Abdulaziz University, Jeddah, Saudi Arabia.

### Abstract

Cow milk protein allergy (CMPA) becoming a major public health issue that has attracted the attention of health professionals and researchers. This paper aimed to review the important aspects of both IgE and IgG types of cow's milk protein allergy in terms of prevalence, clinical manifestation, risk factors, other health-related issues and nutritional therapy proposed for such allergies in the adult and pediatric population in Saudi Arabia. A search on "cow's milk allergy" was done using PubMed, Google Scholar and Scopus Engine for published papers between 1993 and 2020 to find studies yielding knowledge on that context. The prevalence of cow's milk protein allergy (CMPA) among infants is now in the range of 2–3%. This type of allergy is also detected in adulthood but less frequently. CMPA is defined as an immunological reaction to specific proteins in milk. CMPA is classified based on its type as an immunoglobulin E (IgE)-mediated form and an immunoglobulin G (IgG)-mediated form, each type representing different immunological pathways. The presence of Genetic aspects, family history and short duration of breastfeeding in the infant are among the risk factors contributing to this form of allergy. Its manifestations mainly present as skin presentation, followed by the gastrointestinal and respiratory presentation in most cases in addition to a life-threatening anaphylactic reaction that may occur in 12% of cases. food allergy committees have



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**CONTACT** Mashail ABaghlaf ✉ mshbag5@gmail.com 📍 Faculty of Applied Medical Sciences, Department of Medical Laboratory Technology, King Abdulaziz University, Jeddah, Saudi Arabia.



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developed strict diagnosis criteria, including blood testing for food-specific immunoglobulin E (sIgE), a skin prick test and double-blind placebo-controlled food challenges (DBPCFC) as the gold standard. A diet free of cow's milk protein (CMP) allergen and including the appropriate alternative milk formula is the first line of prevention recommended by many organizations and food allergy experts. As for Saudi Arabia, more research and clinical trials are required to discuss the various aspects of adult and pediatric CMPA and to provide a better understanding along with good control strategies implementation.

## Introduction

Food allergies are on the rise and have become a major public health issue that has attracted the attention of many health professionals and researchers in the field of medical sciences and nutrition.<sup>1</sup> This trend has been observed in Westernized and other developed countries,<sup>2</sup> where guidelines and policies are in place. The Saudi Food and Drug Administration imposes regulations to protect people with allergies, such as ensuring appropriate and clear labelling of allergenic ingredients of food products and the raw materials used in these products.<sup>3</sup> However, a number of types of allergies or so-called "sensitivities" have been detected recently among infants, children and adults,<sup>1</sup> including cow's milk protein allergy (CMPA).<sup>2</sup> In identifying the reasons behind this persistent rise in allergies, immunological, genetic and risk factors, as well as other related health and dietary issues, need to be looked at.

CMPA can be provoked by different immunological pathways, the IgE-mediated type being elicited by IgE immunoglobulins and responsible for about 60% of cases. This type of allergy is characterized by manifestations that appear within two hours of exposure to allergenic proteins. In the other type of CMPA, the non-IgE-mediated reaction type, manifestations could occur between three hours and one week post ingestion of the allergenic proteins, mostly involve gastrointestinal symptoms.<sup>4,5</sup> The reactions involve several immunological mechanisms such as antibody-mediated responses, including type II and type III hypersensitivity reactions and the production of IgA and IgG immunoglobulins.<sup>1,4,6</sup> IgG-mediated food allergies occur when increased gut permeability enables particles of food allergens to gain access to the blood circulation, there by stimulating the development of

IgG immunoglobulins.<sup>7-9</sup> However, the mechanism of IgE-mediated reaction has been well discussed in many studies, whereas the IgG-mediated type is still not fully understood, though mentioned in a few studies that identified specific IgG subclasses, namely IgG1 and IgG4, which produce reactions to  $\alpha$ -lactalbumin and  $\beta$ -lactoglobulin milk protein.<sup>10-12</sup>

To prevent such types of allergies, a limitation diet is suggested by specialist organizations and guidelines, which prescribes the total avoidance of cow's milk from the patient's or child's and mother's diet, along with the use of appropriate cow's milk substitute formulas such as extensive hydrolyzed formula (EHF) and amino acid formula (AAF).<sup>13,14</sup> Guidelines also recommend breastfeeding an infant solely for 4-6 months and delaying the introduction of exogenous proteins and solid foods.<sup>9,15,16</sup> Recent studies showed that the addition of probiotics and prebiotics to a patient's diet helps to prevent food allergies, but supporting studies are few, as the World Allergy Organization attests.<sup>9,17,18</sup>

This paper aims to review the important aspects of both IgE and IgG types of cow's milk protein allergy in Saudi Arabia in terms of prevalence, clinical manifestation, risk factors, other health-related issues and protocols of nutritional therapy proposed for such allergies in the affected population.

## Literature Search

A literature search on "cow's milk allergy" was done using PubMed, Google Scholar and Scopus Engine for published papers between 1993 and 2020 to find studies yielding both knowledge and critical appraisal on the definition, epidemiology, types, risk factors, clinical presentation, diagnosis, prevention criteria and nutritional therapy strategies suggested for managing CMPA.

**Definition of Cow's Milk Allergy**

CMP allergies occur particularly in infancy and early childhood, owing to an immunological allergic reaction to proteins found in milk.<sup>5</sup> Studies have shown that most cases of CMP sensitivity belong to the IgE-mediated type, a smaller number to the non-IgE-mediated type. Reactions to both involve immunological mechanisms such as the T-cell response, complement activation and production of immunoglobulins such as IgG.<sup>4,7,9</sup> Although CMP allergies of the IgG type have been increasing in the past decades, the scientific evidence about this allergy is still sparse. The majority of allergic reactions in patients are linked to the identification of food-specific IgE in their blood, but IgG-mediated CMPA patients showed mostly negative results to that food-specific IgE identification.<sup>19</sup> As IgG typically takes time to produce, there is a possibility

that IgG-mediated CMPA patients may remain undiagnosed, even though they may have allergic symptoms.<sup>4,5,13</sup> However, studies about specific IgG-mediated CMPA are very limited. Although some studies have shown a correlation between urticaria and asthma and the existence of specific CMP-IgG levels in allergic patients' blood, CMPA has received less attention.<sup>20,21</sup> A study on the effect of early CMP intake on infants indicated that a pattern of early feeding with CMP helped promote the development of IgGs, which remained detectable until two years of age.<sup>22</sup> Other authors revealed the existence of IgG levels along with IgEs in the blood of IgE-mediated CMPA patients. IgG production is reportedly a physiological phenomenon that has a non-pathogenic impact and further clinical trials have been recommended to investigate the exact role of IgGs in CMPA pathogenesis.<sup>7,10,20</sup>

**Table1: Composition of cow's milk protein on the international list of allergens, adapted from IUIS allergen nomenclature<sup>25</sup>**

Fraction	Protein	Allergen name	g/L	% Total protein	Molecular weight (kDa)
<b>Caseins</b>			~30	80	
	$\alpha_{s1}$ -casein	Bos d 8*	12-15	29	23.6
	$\alpha_{s2}$ - casein		3-4	8	25.2
	$\beta$ - casein		9-11	27	24.0
	$\kappa$ -casein		3-4	10	19.0
	$\gamma_1$ -casein		1-2	6	20.6
	$\gamma_2$ -casein				11.8
	$\gamma_3$ -casein				11.6
<b>Whey proteins</b>			~5.0	20	
	$\alpha$ -lactalbumin	Bos d 4	1-1.5	5	14.2
	$\beta$ -lactoglobulin	Bos d 5	3-4	10	18.3
	Bovine serum albumin	Bos d 6	0.1-0.4	1	67.0
	Immunoglobulins	Bos d 7	0.6-1.0	3	160.0
	Lactoferrin	----	0.09	Traces	800.0

\*Bos d: The international code of taxonomic nomenclature identifies animals by genus with the first three letters, by species by initial letter (Bos d is Bosdomesticus) and by a number showing the chronological order in which the allergens were defined.

Immunological reactions to proteins in cow's milk have been found in both types. Cow's milk is composed of 20 different type of proteins, with two major fractions known to be major inducers of sensitization.<sup>23</sup> The predominant protein fractions are caseins, which account for about 80% of total

milk proteins, while whey proteins account for the remaining 20%. The composition of CMPs and their names as listed in international allergen nomenclature are shown in Table1.<sup>23-25</sup> Numerous cases of CMP sensitivity have been reported to be induced by casein proteins, in particular by  $\alpha$

S1-casein, although many other cases were also induced by  $\beta$ -lactoglobulin.  $\beta$ -lactoglobulin is the part of whey protein that appears not to be found in human milk, whereas it is believed to be the most important cow's milk allergen, responsible for 60–80% of CMP sensitivity cases.<sup>24</sup> As symptoms overlap, lactose intolerance may always be confused with CMPA. However, milk intolerance is characterized by a non-immunological reaction to milk elements that induce absorption, metabolism or digestion disorders due to an enzymatic defect, which is less dangerous than allergies.<sup>9,13,15</sup>

### Epidemiology of CMP Allergies Worldwide

Food allergies have been known for centuries. Hippocrates (460–375 BC) recorded the first food allergy: a gastric upset that occurred after eating cheese.<sup>26</sup> According to a World Health Organization (WHO) report in 2006, the prevalence of food allergies was estimated to be 1–3% in adults and 4–6% in children.<sup>27</sup> Regarding CMPA, 2–3% of infants and children were affected based on strict diagnostic criteria, and a 7.5% incidence rate has

been reported, especially during the first year of life.<sup>2,5,28</sup> European prospective cohort studies in the past years showed that the prevalence of CMP sensitivities ranged from 1.9% to 4.9% in children, especially in the first year of life.<sup>29</sup> A systematic review published in Europe between 2002 and 2012 used an oral food challenge test to demonstrate that cow's milk was the most common form of allergy inducer among studied children, with a 0.6% prevalence rate.<sup>30</sup> In the case of exclusively breastfed infants, the prevalence was estimated to be 0.5%, lower than the prevalence reported in infants fed with cow's milk. This is believed to be because dairy foods eaten by the mother are retained in her breast milk and transmitted to the infant through lactation.<sup>13</sup> Although little research has been done on CMPA in adulthood, CMPA was reported to have a 1.9% prevalence rate in a cross-sectional analysis on food allergies in US adults from 2015 to 2016.<sup>31</sup> Another cross-sectional analysis using skin prick tests on subjects aged 20–45 years found that milk allergy accounted for 0.09% of the overall 1.3% allergic study population.<sup>32</sup>

**Table 2: Summary of epidemiological studies carried on cow's milk protein in Saudi Arabia in both IgE and IgG variants**

Study and year	Data source	Study group	Outcomes measured	Findings	Method of diagnosis	Ref.
El-Rab, 1998	King Khalid University Hospital, Riyadh, Saudi Arabia	n=217 Adult patients	The prevalence of sensitivity to food allergens in Saudi patients	Food allergy prevalence: 17.5%  CMP sensitivity prevalence: 12.9%	Measuring specific IgE in food allergens, using Pharmacia CAP radioallergo-sorbent (RAST) fluoroimmunoassay (FEIA) test	33
Aba-alkhail, 2000	King Abdulaziz University Hospital, Jeddah, Saudi Arabia	n=392 Asthmatic patients	The prevalence of food sensitivity in asthmatic patients, longitudinally for three years	Food allergy prevalence: 29%  CMP sensitivity prevalence: 17%	Measuring specific IgE in food allergens, using Phadebase IgE PRISTR (Pharmacia Diagnostic Uppsala)	35
Sheikh <i>et al.</i> , 2015	Large tertiary care hospital, Riyadh, Saudi Arabia	n=238 Patients prescribed new adrenaline auto-injectors	Most common triggers among patients treated for anaphylaxis, by patients' records, reviewed	Food allergy prevalence: Adults: 46.09% Children: 77.27%  CMP sensitivity	Measuring specific IgE antibodies to food allergens	34

		>18 (adult)=110 ≤18 (paediatric) =128	retrospectively	prevalence: Adults:3.90% Children:20%		
Shakoor, Alfaif, Walamro, Tawil, & Ohaly, 2016	King Khalid University Hospital, allergic clinic Riyadh, Saudi Arabia	n= 71 Patients presenting allergic symptoms without laboratory - confirmed tests	The prevalence of food- specific IgGs among patients with clinically allergic symptoms with undetectable level of IgE	CMP sensitivity prevalence: 56.3%	Measuring food-specific IgG, using microarray assay	19
Tayeb, Alhussaini & Waked, 2020	Allergy clinics of Laluna, a private medical centre in Jeddah, Saudi Arabia	n=83 CMP sensitivity positive patients  >18 (adult)=52 ≤18 (paediatric)=31	Common allergic diseases associated with CMP sensitization, reviewed retrospectively	Frequency of positive sensitization to CMPs: α-lactalbumin 71% casein 58% milk 46% β-lactoglobulin 35% cheese mix 16%	Measuring food specific IgE, using the list panel of the RIDA® system	36
Alkhateeb, 2020	Database of patients who under went food-specific IgG tests with a standardized panel of 268 foods in Saudi Arabia	n=1644 Using a preexisting database for patients in Saudi Arabia who took the ImuPro™ food allergy test between 2011 and 2016	Most common food allergens causing IgG immune reaction across patients in Saudi Arabia and the effects by age or gender	CMP sensitivity prevalence: 75%  Males and females had equal response to food IgG-mediated reactions  IgG-mediated CMP higher among children <5 years (95.74%) than among adults	Measuring food-specific IgG, using ELISA-based IgG ImuPro™ test	37

In Saudi Arabia, a study of 217 adult patients in an allergy clinic in 1998 revealed a food allergy prevalence rate of 17.5%, identifying specific IgE antibodies towards eggs, peanuts, wheat and cow's milk as major triggers.<sup>33</sup> An additional study in a large tertiary care hospital in Riyadh showed that food was the biggest trigger for anaphylactic reactions among adults and children, CMP being an anaphylactic trigger with a 27% positive reaction rate.<sup>34</sup> A study in an asthma clinic in Jeddah registered a 29% food sensitivity rate among asthmatic patients, 17% being sensitized to milk protein from cows.<sup>35</sup> Research

on CMPA patients conducted at an allergy clinic in a medical centre in Jeddah in 2020, found that, among 83 positively confirmed CMPA patients, 62.6% adults and 37.4% pediatric, all of them reported sensitization to CMP with different degrees of severity.<sup>36</sup> Most epidemiological studies carried out on food allergies in Saudi Arabia, including CMPA prevalence, have been based on the quantification of IgE antibodies, while epidemiological studies on IgG-mediated CMPA are scarce and most have been carried out to determine the level of IgGs in food allergies in general, not specifically in CMPA

cases. A study in 2016 to assess the prevalence of food-specific IgG among allergic patients found that 56.3% out of 71 patients showed specific IgGs to CMP.<sup>19</sup> Research in 2020 aimed at determining the most important food triggers for IgG-mediated allergy showed that CMP was among the highest, ranking 75%, and the highest level of CMP-specific IgGs were identified in children under 5 years of age.<sup>37</sup> A summary of these studies is provided in Table 2.

Obviously, the wide variations in the estimated prevalence of CMPA between studies can be due to differences in the diagnostic criteria used, for example, whether diagnostically confirmed cases or self-reported cases, the nature and age of the population, the length of observation and the pattern of feeding.<sup>6</sup> However, the level of self-reported adverse reactions to CMPA is much higher than that of clinically confirmed diagnostic cases.<sup>38</sup> while epidemiological studies on IgG-mediated CMPA are scarce and most have been carried out to determine the level of IgGs in food allergies in general, not specifically in CMPA cases. A study in 2016 to assess the prevalence of food-specific IgG among allergic patients found that 56.3% out of 71 patients showed specific IgGs to CMP.<sup>19</sup> Research in 2020 aimed at determining the most important food triggers for IgG-mediated allergy showed that CMP was among the highest, ranking 75%, and the highest level of CMP-specific IgGs were identified in children under 5 years of age.<sup>37</sup> A summary of these studies is provided in Table 2.

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#### **Genetic and Environmental Risk Factors**

CMP allergies occur as a result of many contributory factors, which include genetic background and ethnicity.<sup>30</sup> With regard to ethnicity, many studies in the literature have elaborated the effects of ethnicity on the development of CMPA. AUS survey in The National Health and Nutrition Examination Survey (NHANES) on the paediatric population from 1991

to 1994 to measure the prevalence of sensitization to cow's milk protein by race tested sIgE in the blood and found that the lowest prevalence of sensitization was reported in non-Hispanic White children (5.6%) compared to non-Hispanic Black and Mexican American children, in whom the prevalence was 12.8% and 12.2%, respectively.<sup>39</sup> However, a study that analysed the clinical data of the population in New York City from 1997 to 2007 showed that the prevalence of CMPA did not differ by race and ethnicity.<sup>40</sup>

Genetic background is considered a main risk factor for IgE allergies, as found in many cohort studies. A Dutch study investigating the genetic background to CMP sensitization by analysing 30 DNA samples from children with confirmed CMPA found that two significant single nucleotide polymorphisms (SNP) were associated with this form of sensitization. This genetic variation was observed in TLR6 and IL2 genes and contributed to CMPA expression in young children.<sup>41</sup> Another study aimed to examine the relationship between sIgE level in children with CMPA and the genetic variants in the STAT6 gene, a gene that is associated with other food allergies, according to several previous studies.<sup>42,43</sup> The findings showed that the rs324015 GG genotype of the STAT6 gene was associated with a high level of sIgE in the serum of CMPA children and this variant could be an indicator of yet-undetected CMPA.<sup>44</sup> Epigenetic factors were also reported in a pilot study in 2016 into the role of epigenetic factors in CMPA expression, the results revealing a hypermethylation that was observed in the CMPA group of children relative to the control group. These hypermethylated genes were located in the DHX58, ZNF281, EIF42A and HTRA2 regions.<sup>45</sup> There are, however, no studies in the literature examining the genetic history of the IgG-mediated CMPA allergy group, which suggests the need for more research in this area.

Early exposure to and absorption of cow's milk protein in formulated milk and a shortened duration of breastfeeding are both considered factors that increase the risk of CMP sensitivity in infants.<sup>5,14</sup> Such factors seem to be associated with a history of allergies among parents or siblings.<sup>14</sup> A study in Poland in 2018, evaluating the effect of parental and environmental factors on CMP sensitivities on 138 confirmed affected infants, showed that the



prevalence was three times higher in the presence of a positive family history of allergy and twice as high in the presence of one affected sibling, in addition to a fourfold increase in the risk of CMP in infants exposed to formulated milk in the early months of life compared to breastfed infants. Such risk decreased the longer the breastfeeding period,<sup>46</sup> thanks to the essential beneficial functions of human milk, such as a balanced gut microbiome and anti-inflammatory properties.<sup>13,47</sup>

Moreover, several recent studies have highlighted the importance of the composition of gut microbiota in early infant life and its effect on food allergy development and as a predictor of food intolerance.<sup>17</sup> The composition of gut microbiota is thought to be influenced by factors such as diet, lifestyle, method of delivery and feeding habits. Studies to determine the effect of intestinal microbiota on CMPA found that altered gut microbiota were linked to atopic disorders such as CMPA.<sup>17,18</sup> Moreover, cases of CMPA showed a higher level of *Lactobacillus* bacteria and decreased in *Bifidobacterium* in the gut microbial community than healthy subject groups that showed increased in *Bacteroides* upon analysis of their fecal samples.<sup>48,49</sup>

A Chinese study showed that vitamin D plays a vital role in eosinophilic migration and in preventing the release of cytotoxic granules by those cells, concluding that the absence of vitamin D would lead to symptoms of blood eosinophilia and CMPA. The study observed that a decreased level of vitamin D in infants was due to the mother's inadequate level of vitamin D during pregnancy.<sup>50</sup>

No studies relating to Saudi Arabia appear to have been conducted on environmental contributors and risk factors for CMPA in both IgE- and IgG-mediated forms.

With regard to the duration of allergy, it has been found that IgE-mediated CMP allergy usually decreases after 12 months of age, and 80–90% of children with confirmed CMPA experienced a resolution of the problem by the age of five years. However, the remaining children reported with high sensitivity to milk, showing severe symptoms and an elevated level of milk-specific IgE in their blood up to the age of 12 months, are probably at high risk

of developing a food allergy at 18 years and even of becoming allergic to multiple food types. These findings were reported in a longitudinal study to examine the natural history of sensitization to cow's milk in the Royal Children's Hospital, Australia.<sup>2,51</sup> Non-IgE-mediated CMPA, on the other hand, is reported to occur in adulthood and its frequency is believed to increase with age.<sup>9</sup>

### Symptoms and Health Issues Associated with LGE- and LGG-Mediated Allergies

#### Symptoms

Among children, various clinical manifestations of differing intensity are observed, depending on the allergens to which they have been exposed, the time intervals between exposures and the types of immunological reaction involved.<sup>5</sup> Many signs appear within the first month of infancy or within one week of the initiation of processed cow's milk into the infant's diet.<sup>5,13</sup> Even breastfed babies may be exposed to allergens contained in the mother's diet and passed to the child in the breast milk.<sup>15</sup> Symptoms may be initiated at different times: IgE-induced immediate onset reactions occur within minutes or at any time up to two hours, whereas non-IgE delayed onset reactions typically occur between 48 hours and one week post exposure to cow's milk allergens.<sup>2,38</sup> Of these symptoms, 60-70% of children manifest these in the skin, followed by gastrointestinal presentation in 50-60% of children and respiratory presentation in 20-30% of affected children.<sup>5,6,13</sup> Cutaneous signs of CMPA are mostly manifested as atopic dermatitis, eczema and urticaria,<sup>2,4,9</sup> whereas gastrointestinal symptoms present as recurrent abdominal pain, vomiting or diarrhoea.<sup>15,52</sup> Respiratory symptoms manifest as asthma, wheezing, dry cough and rhino-conjunctivitis. Many other signs have also been documented in the literature, such as anaemia, night sweats and chronic pulmonary disease (Heiner's Syndrome) with pulmonary infiltration.<sup>13,23</sup> Most cases are deemed to be mild to moderate, but a life-threatening anaphylactic reaction may occur in approximately 12% of cases, leading to cardiovascular collapse and even death.<sup>5,6,9</sup> In fact, high-risk children with CMPA are more likely to experience multiple allergic reactions to foods, as well as allergic rhinitis, atopic dermatitis and asthma.<sup>26</sup> CMPA symptoms according to the immunological mechanism involved are shown in Table 3. However, the symptoms of CMPA may

also occur in adulthood, even at a late age, and in such cases tend to persist longer and have with a higher degree of severity. Most cases report respiratory and skin symptoms.<sup>53,54</sup>

**Table 3: Summary of clinical symptoms related to Cow's milk protein allergy**

Symptoms	IgE-mediated CMPA symptoms	Non-IgE-mediated CMPA symptoms
<b>Cutaneous</b>	Angio-oedema Acute urticaria Atopic dermatitis	Local rash Atopic dermatitis
<b>Gastrointestinal</b>	Nausea Vomiting Diarrhoea Severe colic Oral allergy syndrome	Prolonged constipation Gastro-oesophageal reflux Rectal bleeding Infantile colic Transient enteropathy Protein-losing enteropathy
<b>Respiratory</b>	Coughing Wheezing Asthma Rhino-conjunctivitis Otitis media Laryngeal oedema	Chronic pulmonary disease (Heiner's Syndrome) with pulmonary infiltration
<b>Other</b>	Systemic anaphylaxis reactions	
<b>Uncommon symptoms with unknown immune mechanisms</b>	Anaemia Night sweats Food rejection Mouth ulcers Migraine	

#### Associated Health Issues

Other atopic disorders are also reported to be associated with the presence of CMPA. A study carried out in Jeddah on 83 patients diagnosed with CMP sensitivity showed that the most severe chronic allergic disorders associated with this sensitivity were atopic dermatitis and allergic rhinosinusitis, followed by asthma, allergic conjunctivitis and angio-oedema (see Table 4).<sup>36</sup> In addition, CMPA was investigated in relation to the presence of persistent gastrointestinal disease in patients suffering from functional abdominal pain disorders (FAPDs) which it is unusual gut disorder that characterized by persistent or recurring abdominal pain that rarely linked to gut function.<sup>52</sup> In a study conducted in 2018, IgG antibodies to milk were shown to be highly

elevated in patients with major depressive disorders (MDD) and those with irritable bowel syndrome (IBS) compared to healthy subjects.<sup>55</sup>

A further health issue associated with the presence of CMPA, reported in a number of studies, is obesity and overweight. Obesity often marked by low-grade inflammatory status, which can result from the release of cytokines and adipokines.<sup>56,57</sup> Several experiments on the correlation of body weight with atopic disorders such as atopic dermatitis and asthma have been performed, yet rarely studied in relation to food sensitization, especially in the paediatric population.<sup>57,58</sup> Research on American children in the National Health and Nutrition Examination (NHNE) survey investigating the



association between obesity and IgE levels and allergic symptoms showed that increased levels of total and allergen-specific IgE were identified in obese and overweight children compared to children of normal weight. The study concluded that obesity may contribute to increasing the prevalence of atopic

disease in children.<sup>59</sup> This may be attributed to the increased production of proinflammatory cytokines from adipose tissue in obese subjects, resulting in immune system deficits and thus the presence of allergic disorders such as food sensitization.<sup>60</sup>

**Table 4: Summary of health issues associated with cow's milk protein found among studies in Saudi Arabia in both IgE- and IgG-mediate allergy**

Study	Characteristics of the study	Other allergic disorders associated with CMPA confirmed cases	Ref.
Tayeb <i>et al.</i> , 2020	n=83 CMP sensitivity positive patients  >18 (adult)=52 ≤18 (paediatric)=31	Atopicdermatitis 48% Allergic rhino-sinusitis 43% Asthma 31% Allergic conjunctivitis 14% Urticaria and angio-oedema 12%	43

## Diagnosis and Immunological Testing

### Diagnosis

There is no clear, definitive test that by itself correctly detects CMPA.<sup>1</sup> Physical examination by an allergic specialist and an accurate patient history are the most reliable diagnostic pathway.<sup>2,5</sup> Diagnosis of CMPA becomes easier when the association between ingestion of CMP and the initiation of symptoms is documented and when these symptoms indicate immunological reactions.<sup>15</sup> Since patients experience diverse conditions based on the type of allergic reaction, the onset of allergy symptoms and age, the diagnosis of CMPA should follow strictly defined guidelines.<sup>9,15</sup> In the case of IgE-mediated food allergic reaction, the skin prick test and blood tests using IgE antibodies quantifications to the specific food allergen are routine laboratory protocols. sIgE quantification can be measured with aradioallergo-sorbent test (RAST) and enzyme linked immuno-sorbent assay (ELISA) methods in medical laboratories.<sup>5,13</sup> SPT and sIgE tests provide an indication of the state of sensitization, although they do not necessarily confirm allergy.<sup>14</sup> Since these tests are sensitive but not specific enough, the oral food challenge test with CMPs is the preferred method in such cases.<sup>14</sup> In the case of non-IgE mediated allergy, many reviews and committees of allergy experts have suggested that the preferred test consists of eliminating CMPs for a period of two to six weeks

and reintroducing the CMP to the patient, using one of the oral food challenge procedures suitable for the age and condition of the patient.<sup>9,13</sup> The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has developed a diagnostic algorithm for detecting and confirming CMPA, including testing the blood for sIgE and oral challenge test, the medical practice in which food is consumed to accurately diagnose food allergy in gradually increasing quantities under medical supervision.<sup>61</sup> In addition, based on the World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guidelines, the double-blind placebo-controlled food challenges (DBPCFC) that follow the diet elimination test are considered the gold standard method for confirming CMPA.<sup>62</sup> Since DBPCFC testing is intensive, time-consuming, and must be carried out under professional supervision, the British Society of Allergy and Clinical Immunology (BSACI) recommended the use of an open challenge test in which both doctor and patient realize what food allergens are consuming as an alternative to validate all forms of food allergy cases, either IgE-mediated or non-IgE-mediated, for clinical purposes by following the elimination diet.<sup>15</sup> On the other hand, the use of food-specific IgG identification test as a diagnostic tool for food allergy is still controversial. Many laboratories in the US and Europe, however, favour this test on the grounds that the presence of

food-specific IgG antibodies may explain symptoms that cannot be confirmed by routine food allergy diagnostic tests.<sup>8,63</sup> Recently, much effort has been devoted to creating a new detection approach using biosensors (immunosensors and aptasensors) along with novel nanomaterials to detect cow's milk allergens, thus creating a reliable alternative detection system.<sup>24</sup>

In Jeddah, Saudi Arabia, CMPA was tested using in-vitro sIgE panels containing 30 different and separate food allergens chosen based on the most common food sensitizers in the region. The results have identified sensitization to foods other than cow's milk in the study group, with different degrees of severity.<sup>36</sup> However, the study depended on detecting bloods IgE in the diagnosis without covering other immunological parameters such as CMP-IgG levels that might represent IgG-mediated CMPA cases. Moreover, the findings did not involve probable risk factors nor indicate any correlation with the demographic characteristics of the study population, such as age, gender and weight. There are no studies in the literature in Saudi Arabia using IgG as a tool for diagnosing CMPA, most of the studies instead investigating the level of IgG against food allergens in general, as shown in Table 2.

### **Nutrition Therapy and Prevention**

#### **Limitation Diet**

The current basic method of treating CMPA is the complete avoidance of milk and its elimination from the affected patient's diet in any form. In the case of an exclusively breastfed infant, the mother should avoid all dairy products in her own diet and consider adding calcium supplements as a replacement for milk.<sup>13,62</sup> Eliminating milk from the child's diet should be done under medical supervision, along with choosing the appropriate substitute diet or regimen. The type and severity of symptoms, patient's age, nutritional deficiencies, cost and time should all be kept in mind when choosing an alternative diet.<sup>9,62</sup> Based on BSACI recommendations, children should be tested for tolerance and the possibility of reintroduction of cow's milk every six to 12 months for children aged one year or more and every six months for children under one year of age.<sup>15</sup> Extensive hydrolyzed formula (EHF) is one of the first-line milk substitutes recommended for the treatment of CMPA during infancy and early childhood, particularly in infants less than six months

old. This formula has been treated with proteolytic enzymes and includes only protein oligopeptide, which is reportedly tolerated by 90% of allergic infants.<sup>13,62</sup> In extreme cases of CMPA or severe symptoms or in children refusing the EHF option, an amino acid formula (AAF), which provides protein in free amino acid form, could be prescribed based on BSACI guidelines.<sup>5,15</sup> Other mammalian milk such as sheep, goat and buffalo cannot be used as an alternative to CM, owing to homologues between their sequence of CMP allergens, which could cause unwanted allergic cross-reactivity.<sup>9</sup> Soy protein formula is another substitute used for CMPA patients, especially in infants over six months of age, with the proviso that a clinical soy protein tolerance test should be administered before prescribing it to the patient, owing to its high allergenic potential.<sup>13,61,62</sup> In some Middle Eastern institutions, a partially hydrolyzed whey formula (pHF-W) is used, which combines the properties of both EHF and AAF and intact cow milk.<sup>14</sup> Another strategy proposed for CMPA treatment is oral immune therapy (OIT), which is based on the principle of ingestion of small quantities of allergenic food, gradually increasing the amount daily. This results in desensitization and improved patient resistance to allergenic foods.<sup>5</sup> Several studies have shown that early introduction of allergenic products into infant diets has a positive impact on the effectiveness of that infant's CM tolerance.<sup>6</sup> Whichever diet is proposed for CMPA patients, whether involving the elimination of certain foods or building resistance to foods, the diet must be properly overseen by a consultant or dietitian and must supply necessary and sufficient growth elements such as proteins, vitamins and calories.<sup>9</sup>

#### **Prebiotics and Probiotics**

Some studies have suggested the addition of probiotics and prebiotics as an innovative strategy for preventing CMPA.<sup>64</sup> Probiotics are defined as living microorganisms that colonize the intestine when added to the diet, giving the host a health benefit,<sup>18,64</sup> while prebiotics are non-digestible food elements that are selectively utilized by host microorganisms to provide beneficial functions for their growth and activity.<sup>65</sup> These compounds are thought to be protective against immune reactions such as food allergies through their interactions with intestinal immune cells, breakdown of specific allergic proteins and through the development of specific cytokines, which in turn prevent allergic reactions.<sup>17</sup>

Pre-clinical trials on animal models revealed that the colonization of specific types of probiotics in germ-free mice helps to regulate the allergic reaction to CMP, with reported production of casein-specific IgG levels.<sup>66</sup> Further, the addition of probiotics helpsto reduce the concentration of IgE immunoglobulin in allergic patients and is associated with a higher probability of acquiring tolerance to CMPA.<sup>17,67</sup> On the other hand, someauthorshave concluded that further research is necessary to demonstrate the exact role of probiotics and prebiotics in preventing CMPA because of shortcomings in the studies conducted and inadequate experimental evidence to verify their role.<sup>9,13,64</sup>

### Breast Feeding

Experts suggest that, in addition to avoiding allergenic proteins, infants should be solely breastfed for the first four to six months of life and exogenous proteins and solid food in the infant's diet should be deferred until after that time. These recommendations were reported in the 2019 Middle East Step-Down Consensus for the management of CMPA and in many other guidelines.<sup>14,15</sup> Breast feeding is known to afford protection against CMPA in two ways, either passive protection by minimizing the infant's exposure to exogenous allergens that might be sensitizing inducers in early life, or active protection fromthe presence of functional substances that promote immunity, such as polyunsaturated fatty acids, immunomodulatory components, growth factors and antioxidants such as vitamin C, a-tocopherol and b-carotene. These factors influence the development of gastrointestinal mucosa and promote gut microbial resistance to sensitivity, which further strengthens the immune system.<sup>13,47,68</sup>

### Conclusion

CMPA consider the most common food allergy disorder, particularly in infants and children but less frequently among adults. The prevalence of CMPA differs between global studies due to differences in the design of studies, tools, and variations in the population of the study. However, the prevalence of cow's milk protein allergy (CMPA) among infants is now in the range of 2–3%. The manifestation of CMPA is primarily seen in children as cutaneous symptoms in 60-70%, while in adults manifests mainly as respiratory symptoms. Diagnosis of CMPA cases meets strict consideration with using DBPCFC as a gold standard approach in diagnosis under medical supervision. Total avoidance of cow's milk from the patient's or child's diet, along with the use of appropriate cow's milk substitute formulas such as extensive hydrolyzed formula (EHF) or a partially hydrolyzed whey formula that suggested by some Middle Eastern institutionsare among preferred therapeutic CMPA protocols. This (pHF-W) combines the properties of both EHF and AAF and intact cow milk. However, the studies on CMPA among the Saudi population are scarce and none appear to have been conducted on prevalence, environmental contributors and risk factors for CMPA in both IgE- and IgG-mediated forms. To increase knowledge in this allergy area, many scientific studies regarding CMPA in the Saudi population are required.

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### Conflict of Interest

The author(s) confirm that this article content has noconflict of interest.

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