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Review article

OVOMUCOID (THE MOST IMPORTANT EGG WHITE ALLERGEN) AS A CAUSE OF SEVERE EGG ALLERGY: A REVIEW

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Abstract: Hypersensitivity, or an allergy to highly valuable chicken egg proteins, is a prevalent symptomatic condition. It occurs when the immune system of a hypersensitive or allergic individual overreacts upon contact with egg allergens (egg proteins), triggering a complex immune response. Among these allergens, ovomucoid is the most allergenic, making up 11% of egg white. Ovomucoid is both thermostable and resistant to digestion, distinguishing it from other egg white proteins. While ovalbumin is the most abundant protein in egg white, ovomucoid is responsible for the majority of its allergic properties. Humans generally lack tolerance to both raw and cooked eggs due to the presence of this allergenic protein.

Given the significance of ovomucoid in egg allergy, it has a direct impact on the quality of life of affected individuals. A better understanding of the role of various drug classes is essential for managing and treating egg allergy. Additionally, insights into embryogenesis may be critical in understanding the efficacy of these treatments in alleviating egg allergies. This knowledge could not only benefit individuals with egg allergies but also the egg production industry and society as a whole. Maintaining good health is one of the most crucial factors in serving our community, and addressing egg allergy is an important part of that.

Keywords: Egg allergy, ovomucoid, IgE-mediated food allergies, epidemic, embryogenesis, management, florfenicol, immunotherapies.

INTRODUCTION

The term “allergy” refers to an abnormal or hypersensitive reaction of the human body’s immune system to environmental stimuli or substances. One of the major challenges in today’s society is food allergies, which are increasingly prevalent (1). Among these, egg allergy is one of the most common allergic conditions affecting infants and children worldwide (2). Chicken egg allergy is a global health issue, impacting 1–2% of children globally. Four major allergens are found in egg white: ovotransferrin, ovalbumin, ovomucoid, and lysozyme. These proteins are the primary culprits behind egg allergy (hypersensitivity), while egg yolk allergens, including chicken serum albumin and YGP42, also play a role (1).

These egg allergens—ovotransferrin, ovalbumin, ovomucoid, and lysozyme—can cause serious medical conditions such as rhinitis, conjunctivitis, laryngeal edema, anaphylaxis, and chronic urticaria (3). Egg white consists of the following protein composition: ovomucin (4%), ovalbumin or conalbumin (Gal d 2, 55%), ovotransferrin (Gal d 3, 12%), lysozyme (Gal d 4, 3%), and ovomucoid (Gal d 1, 11%) (4).

Previous studies have shown that ovomucoid’s allergenicity is not affected by enzymatic proteinase activity (5, 6). The linear IgE binding epitopes on ovomucoid’s structure align with conformational epitopes across all domains, making cooking ineffective at reducing the allergic properties of ovomucoid. Targeted immunotherapies, such as producing hypoallergenic variants of ovomucoid, are under investigation as potential treatment options. Ovalbumin is the second most significant allergen in egg white. However, treatments like urea, carboxymethylation, or heating at 95°C have little effect on its allergenic potential, as reported by Mine and Zhang et al (7). Still, ovalbumin’s IgE-binding capacity can be altered by digestive enzymes in the gut. Its exact biological function remains unclear, though it is believed to resist protease activity. The third allergen, ovotransferrin, has also been extensively studied for its allergenicity and conformational changes during cooking. Tong et al. reported a critical link between these structural changes and increased allergenicity (8). Finally, lysozyme, which provides antimicrobial protection to the egg, has multiple sequential conformational epitopes. Though it causes fewer allergies compared to ovomucoid and ovalbumin, it still poses some allergenic risk (3).

Egg allergy in infants is closely associated with atopic dermatitis and significantly increases the risk of sensitization to aeroallergens and respiratory conditions like asthma. Influenza vaccination can also pose risks for individuals with severe egg allergies. Anaphylaxis further complicates immunization in children with egg allergies, making this a major health concern (9). Egg-associated allergies primarily trigger immune responses via food proteins, manifested by the presence of immunoglobulin E (IgE), a key biomarker for antibody-mediated allergies. Other conditions, such as eosinophilic esophagitis (EOE) and atopic dermatitis, are also linked to egg allergies (10).

Ovomucoid is resistant to acid and heat, and individuals allergic to ovomucoid tend to have low tolerance for both raw and cooked eggs. While the allergenicity of ovalbumin may be reduced by high temperatures, allowing some allergic individuals to tolerate cooked eggs, this is not the case for ovomucoid (11). A key question remains: which egg protein is the most allergenic? Ovomucoid, despite being resistant to heat and not coagulable by it, is the most persistent allergen, while other egg proteins are disrupted by heat. A landmark study conducted in Japan by Urisu et al. (12) used a double-blind, placebo-controlled food challenge to establish ovomucoid as the primary allergen responsible for egg white-induced allergic conditions in humans. The study also highlighted the allergenic properties of ovalbumin and ovotransferrin, with lysozyme having the weakest allergenicity. These conclusions were based on the comparative levels of IgE antibodies for ovomucoid, ovalbumin, ovotransferrin, and lysozyme (12).

There are many commercially available drugs that increase chicken egg production (embryogenesis), which in turn has significant implications for human allergies, their diagnosis, and management (Table 1). While increased egg production can serve as a valuable revenue-generating tool globally, understanding how to minimize human allergies in relation to these drugs is equally important. This could be a game-changer for middle-class families involved in the egg production industry, as it can lead to greater prosperity and economic development in today's challenging financial climate.

On the other hand, there are also drugs that decrease chicken egg production (inhibit embryogenesis), and this, too, has serious implications for human allergies, their diagnosis, and management (Table 2). If the effects of these drugs on human populations are not well understood, the global egg production industry may suffer severe consequences. Communities involved in the egg industry must be informed about which drugs can negatively impact their income, both annually and periodically.

Moreover, this review establishes a link between the severity, consequences, management, and treatment of egg allergies in humans and the various drug classes used in egg production (Table 3). If further studies focus on the relationship between these drugs and the pattern of egg allergies, particularly in children, it may lead to the development of novel strategies to counteract egg allergies. This could answer more complex and multifaceted questions related to human allergic conditions.

The primary objective of this review is to explore the relationship between ovomucoid (egg allergy) and different classes of drugs, particularly those that either increase or decrease egg production. Understanding this association is essential for developing improved management and treatment strategies for human allergic conditions, especially those caused by eggs during infancy or early childhood. Therefore, it is crucial to develop a comprehensive understanding of egg allergens, their impact on allergic reactions, and their prevalence. This approach is key to improving the diagnosis and treatment of egg allergies, which will shape future healthcare strategies.

For this review, data from reputable and reliable sources such as Google Scholar, Cochrane Library, PubMed, and ScienceDirect have been utilized, covering research from the past 30 years. Keywords like "egg allergy," "ovomucoid allergy," and "human allergies" were extensively used to search for relevant studies. The focus of this review is on ovomucoid, the primary cause of egg allergy, which is heat-stable, acid-resistant, and not degraded by cooking. Other egg white allergens are generally excluded from the scope of this review.

Significance of Ovomucoid in egg allergy

Ovomucoid is the most significant egg white allergen, comprising about 11% of egg white. It is a trypsin-inhibitory glycoprotein with a molecular weight of 28 kDa, consisting of 186 amino acids arranged in three tandem domains. Each domain contains about 60 amino acids, five carbohydrate side chains, and nine intra-domain disulfide bonds.

Trypsin inhibition occurs through the second domain, which contains the reactive site for inhibitory activity. Ovomucoid's domain alignment is similar to that of pancreatic trypsin inhibitor activity. Its key characteristic is the ability to resist degradation by heat and proteinase activity. This is due to the linear trajectory of its IgE-binding epitopes, some of which have conformational features. Cooking does not reduce the allergenicity of ovomucoid, making it a prime candidate for exploration in targeted therapies and treatment strategies (3).

Eggonomics: impact and hazards of egg production

Egg production often fluctuates based on global demand and supply, leading to increased production in some cases and halting it in others. Certain drugs that boost egg production can also have serious side effects, spreading diseases and causing significant medical conditions in humans (Table 1). On the other hand, essential drugs like amphenicols, sulfonamides, and coccidiostats, which reduce egg production, can cause severe health issues such as mutagenicity, cancer, diabetes, neuropathy, and bone marrow toxicity (Table 2). The egg industry must adopt scientific approaches to mitigate these adverse health outcomes while improving the livelihood of poultry workers and others connected to the industry.

Role of drugs in managing human allergies

Many diverse classes of drugs, including nitrofurans, tetracyclines, imidazoles, beta-lactams, aminoglycosides, macrolides, amphenicols, ionophores, sulfonamides, and coccidiostats, can trigger severe allergic reactions (as outlined in Table 1 and Table 2). These drugs can also cause various conditions such as cancer, eye and skin allergies, nephropathy, hepatotoxicity, gastrointestinal disorders, and cardiac complications. To manage and alleviate human allergies, a thorough understanding of these drugs' side effects is necessary. The use of these drugs must be closely monitored to ensure a healthy poultry industry and improve human quality of life.

Biomarkers in clinico-commercial diagnostics

Biomarkers, or biological parameters, play a critical role in diagnosing and investigating allergic conditions. Many drug-induced disorders, linked to increased egg production, require biomarker testing for accurate clinical diagnosis and effective treatment initiation (Table 1). Similarly, drugs that significantly reduce egg production and cause severe side effects (Table 2) require proper diagnosis through validated biomarker identification**.** Failing to do so may lead to lethal consequences.

Future strategies for managing human allergies

Looking ahead, researchers have developed crucial strategies and therapies to improve allergy management and provide effective alleviation. These efforts include the following treatments (Table 3).

1. Oral Immunotherapy (OIT)
2. Monoclonal Anti-IgE Antibody Therapy
3. Allergen-Specific Immunotherapy
4. Chinese Herbal Formulations
5. Diets Containing Extensively Heated Eggs
6. Omalizumab
7. DNA Vaccines
8. Epicutaneous Immunotherapy (EPIT)
9. Subcutaneous Immunotherapy (SCIT)
10. Biologics have shown promising results in treating severe allergies, such as psoriasis, by providing a balance between safety and efficacy (13)
11. Additionally, breastfeeding has been found to help in reducing food allergies (14).

CONCLUSION

Egg allergy remains a significant challenge, both in the past and present. With advancing research, we now recognize that several proteins, most notably ovomucoid, play a pivotal role in this phenomenon. Ovomucoid offers valuable insights into the management, treatment, and future strategies for addressing egg allergies. Furthermore, understanding the impact of drugs on egg production is essential for shaping future strategies aimed at combating allergic conditions and improving public health.

Social welfare and well-being should be at the forefront, with particular attention given to the poultry industry and those involved. The concept of "eggonomics" emphasizes balancing commercial egg production with prioritizing human health and therapeutic needs. The use of specialized biomarkers can aid in the development of diagnostic and treatment strategies, addressing allergic conditions and disorders related to drugs influencing egg production.

Looking ahead, therapies should be designed to provide more effective treatments for human allergies. The egg and poultry industries must also acknowledge their responsibility to society, establishing robust research and development programs to better manage and prevent allergic conditions through innovative anti-allergy regimens and therapies.

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Table 1. *Drugs that increase egg production and their effects on humans*

CLASS	DRUGS	EFFECT ON EGG PRO-DUCTIONON	EFFECT ON HUMANS	TREATMENT / MANAGEMENT	BIO-MARKS
Nitrofurans (15)	Furazolidone	Increase	• Autoimmunity • Carcinogenicity • bone marrow toxicity • nephropathy • reproductive disorders • hepatic disorders • vaginal adenocarcinoma • neoplasia (15)	• Boiling (heat treatment) (15)	• C-reactive protein (CRP) • glomerular filtration rate • albumin, creatinine • blood urea nitrogen
Tetracyclines (15)	Oxytetracycline	Increase	• poor development of fetus • staining of teeth in children • immuno-pathological effects • gastrointestinal disorders • proinflammatory • cytotoxicity • allergic reactions (15)	• Thin layer chromatograph • Microbial inhibition tests • Boiling (15,16)	• placental growth factor (plgf) • (CRP) c-reactive protein • Insulin-like growth factor who are bindingprotein-1 & -3 • total IgE • specific IgE (sIgE) • IgG4
Imidazole	Methimazole	Increase	• Hives and itching • Hepatotoxicity • Teratogenicity • Hypothyroidism	• Heat treatment (microwaving) (15)	• alanine aminotransferase (ALT) • lipid profile test • thyroid profile test • cytokine test
Supplements	Vitamin A	Increase	• prevent any symptoms for the deficiency • hair loss • Problems of skin • an increased risk of infections and dry eyes	—	—
	Vitamin E	Increase	• promoting the avoidance of certain cancers • age related eye disorders gets very low • it also shows cognitive decline related with aging	—	—
	Vitamin C	Increase	• protective effect of higher intake from cardiovascular disease and certain cancers • protect from eye diseases like cataracts and macular degeneration	—	—
	Carotenoids	Increase	• macula is protected from deterioration by blue light • Decreases the risk of cataractsand age-related macular degeneration • Heart associated cardiovascular diseases • possibly different cancersand Alzheimer's • improve visual acuity (17)	—	—

Beta-lactams (15)	Penicillin	Increase	• Dermatitis • cutaneous eruptions • anaphylaxis • hemolytic anemia • vasculitis • acute interstitial nephritis (15)	• Refrigeration • microbiological inhibition assay (screening method) (15, 16)	• Tryptase • (ESR) Erythrocyte sedimentation rate • (CRP) C-reactive protein • blood urea nitrogen • serum creatinine
Amino-glycosides (15)	Streptomycin	Increase	• Allergic reactions (15)	• microbiological inhibition assay (screening method) • boiling • steaming • frying • microwaving (15, 16)	• total IgE • specific IgE(sIgE) • IgG4
Macrolides (15)	Erythromycin	Increase	• Carcinogenicity • Liver injury as an answerto macrolide metabolite-modified hepatic cells (15)	• microbiological inhibition assay (screening method) • boiling • steaming • frying • microwaving (15, 16)	• transaminases alanine aminotransferase (ALT) • aspartate aminotransferase (AST, or SGOT) • Cytokeratin 10 (CK18)

Table 2. *Drugs that decrease egg production and their effects on humans*

CLASS	DRUGS	EFFECT ON EGG PRO-DUCTIONON	EFFECT ON HUMANS	TREATMENT / MANAGEMENT	BIO-MARKS
Amphenicol (15)	Florfenicol	Decrease	• Hepatotoxicity • Mutagenicity • bone marrow toxicity (15)	• Heat treatment • Microbiological • Inhibition method • Boiling • Steaming • Frying • microwaving (15)	• (ALT) alanine aminotransferase • (AST) aspartate aminotrans-ferase • alkaline phosphatase (ALP) • (GGT) glutamyl transpeptidase • (TBIL) total bilirubin.
	Azasterol (18)	Decrease	• Heart diseases • Diabetes • Certain cancers		• Myoglobin • Cardiac Troponin • creatine kinase • increased blood pressure • decreased HDL cholesterol • increased triglycerides
Coccidiostat (Anticoccidial) (15)	Nicarbazin (19)	Decrease	• Toxic effects (if high dose)	• solid-phase extraction & purification (20)	
	Amprolium (21)	Decrease	—	—	
Ionophore (Anticoccidial) (15)	Monensin (19, 22)	Decrease	• Irritation • Allergic reactions (15)	• solid-phase extraction & purification (20)	• skin prick testing (SPT) • total IgE • specific IgE • IgG4
Sulfonamides (15)	Sulfanilamide (23)	Decrease	• Skin Allergic reactions • bone marrow toxicity • neuropathy • carcinogenicity (15)	• Thermal treatment • Vaccine • Application of probiotics • Agricultural management (15)	• skin prick testing (SPT) • total IgE • specific IgE (sIgE) • IgG4 • Rateof glomerular filtration • creatinine and albumin • blood urea nitrogen
	Sulfamerazine (24)	Decrease			
Coccidiostat (15)	Buquinolate	Decrease	• Toxic effects	• solid-phase extraction & purification (20)	

Table 3. *Management, treatment, and future therapy prospects for egg allergy (focusing on Ovomucoid)*

SEVERITY OF OVOMUCOID ALLERGY	CONSEQUENCES OF UNTREATED EGG ALLERGY	TRADITIONAL MANAGEMENT OF EGG ALLERGIES	FUTURE PERSPECT AND NOVEL THERAPIES FOR EGG ALLERGY
• Anaphylaxis • Severe eczema • Rhinitis • Skin rashes or hives • Mild to severe cutaneous reactions • severe vomiting or diarrhea • Respiratory symptoms (cough, wheeze or swelling of throat, choking, affect breathing) • cramps • nasal congestion • Asthma (25, 26)	• Scarring and thickening of the skin. • Irreversible lung damage. • Diarrhea • Abdominal pain • anaphylactic shock • Low blood pressure • Swelling (25, 26)	• Saline nasal irrigation • Acupuncture • Completely avoid food containing egg • Probiotics • Stinging nettle • Antihistamines • Epinephrine auto-injector • MSM Supplements (Methylsulfonylmethane) • Peppermint and eucalyptus essential oils • Food rich in Vitamin C • Ginger & Garlic (25-29)	• Oral immunotherapy (OIT) • monoclonal anti-IgE antibody therapy • Allergen-specific immunotherapy • Chinese herbal formulation • Diets containing extensively heated eggs • omalizumab • DNA vaccines • epicutaneous immunotherapy (EPIT) • subcutaneous immunotherapy (SCIT) (30-33)

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Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

OVOMUKOID (NAJVAŽNIJI ALERGEN BELANCA) KAO UZROK TEŠKE ALERGIJE NA JAJA

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Hipersenzitivnost, ili alergija na proteine iz kokošijih jaja, je rasprostranjeno simptomatsko stanje. Do nje dolazi kada imunološki sistem hipersenzitivne ili alergične osobe reaguje na kontakt sa alergenima iz jaja (proteini iz jaja), izazivajući složen imunološki odgovor. Među ovim alergenima, ovomukoid je najpotentniji, čineći 11% belanca. Ovomukoid je i termostabilan i otporan na varenje, što ga razlikuje od drugih proteina u belancetu. Dok je ovalbumin najzastupljeniji protein u belancetu, ovomukoid je odgovoran za većinu njegovih alergijskih svojstava. Ljudi generalno nemaju toleranciju ni na sirova ni na kuvana jaja zbog prisustva ovog alergenskog proteina.

S obzirom na značaj ovomukoida u alergiji na jaja, on direktno utiče na kvalitet života pogođenih pojedinaca. Bolje razumevanje uloge različitih klasa lekova je od suštinskog značaja za kontrolu i lečenje alergije na jaja. Pored toga, uvid u embriogenezu može biti ključan za razumevanje efikasnosti ovih tretmana u ublažavanju alergija na jaja. Ovo znanje može koristiti ne samo pojedincima sa alergijom na jaja, već i industriji proizvodnje jaja i društvu u celini. Održavanje dobrog zdravlja je jedan od najvažnijih faktora za služenje našoj zajednici, a rešavanje alergije na jaja je važan deo toga.

Ključne reči: Alergija na jaja, ovomukoid, IgE-posredovane alergije na hranu, epidemija, embriogeneza, kontrola, florfenikol, imunoterapije.

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