

INVITED REVIEW

Alcohol, IgE and allergy

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Abstract

Alcoholic drinks are involved in a variety of hypersensitivity reactions. These include flushing syndrome, anaphylactoid reactions (urticaria/angioedema and even shock), as well as the triggering of asthma, food allergy or exercise-induced anaphylaxis in susceptible subjects. In addition, there is increasing evidence that alcohol intake may play a role as a promoter of the development of immunoglobulin-E (IgE)-mediated hypersensitivity to different allergens. It seems clear that alcohol intake (alcohol abuse and even moderate alcohol consumption) is associated with increased total serum IgE levels. Similarly, alcohol intake may be associated with allergic (IgE-mediated) sensitization to environmental allergens. The clinical significance of these facts is probably moderate. The mechanisms by which alcohol can influence IgE responses are not entirely known, but further developments in this area could increase the understanding of both allergic diseases and alcohol-induced alterations in the immune system.

Introduction

Hypersensitivity can be defined as the presence of objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects.¹ In such a broad sense, hypersensitivity may or may not be immunologically mediated.¹ Classification of hypersensitivity reactions is difficult and more complicated due to the confusing and ever-changing nomenclature^{1–3} (Table 1).

Hypersensitivity reactions to alcoholic drinks are common, as reviewed recently.^{4,5} Manifestations and mechanisms of these reactions are heterogeneous (Table 2). Immunologically mediated hypersensitivity to ethanol itself (referred to henceforth as alcohol) is unlikely. Hypersensitivity reactions that appear immediately after drinking alcoholic beverages undoubtedly exist. Alcohol itself is clearly the cause of

some of them, such as the flushing syndrome, but this represents a metabolically based intolerance and not a true immunological hypersensitivity.^{6–12}

Some other reactions, such as exacerbation of bronchial asthma, can be due to non-alcohol components in the drinks.^{4,5,13–18} Alcoholic drinks may facilitate or trigger symptoms in patients with different allergies, particularly to foods,^{19–21} but this does not represent a true alcohol allergy. Finally, rare immediate manifestations such as urticaria/angioedema and even shock^{22–33} may be related to alcohol itself because, in some cases, they can be reproduced consistently after alcohol challenge.^{22–27} These manifestations closely resemble systemic (anaphylactic) manifestations of immunoglobulin-E (IgE)-mediated allergy, but they are commonly termed *anaphylactoid* because an IgE-mediated mechanism is unlikely in these cases. Ethanol is a

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Table 1. Glossary of hypersensitivity-related terms as employed in the present review¹⁻³

Term	Definition
Hypersensitivity	Presence of objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects. Includes both immunologically and non-immunologically mediated mechanisms.
Intolerance	Commonly applied to non-immunologically mediated hypersensitivity.
Allergy	In its broadest sense, it is applied to all types of immunologically mediated hypersensitivity. However, the term is preferably restricted to IgE-mediated hypersensitivity.
IgE-mediated hypersensitivity	Immunological hypersensitivity due to excessive formation of immunoglobulin-E (IgE) to otherwise innocuous environmental antigens (allergens). Immediate-type hypersensitivity, type-1 hypersensitivity and allergic sensitivity can be synonymous.
Allergic sensitization	Presence of IgE antibodies against environmental allergens. These IgE antibodies can be detected: (a) <i>in vivo</i> by means of skin prick tests (immediate wheal-and-flare skin reaction to the specific allergen), or (b) <i>in vitro</i> by means of commercial methods that detect serum-specific IgE.
Allergic diseases	Disorders caused by exposure to specific allergens in IgE-sensitized patients. Includes allergic asthma, allergic rhinoconjunctivitis, atopic eczema/dermatitis, food allergy and some reactions to drugs.
Atopy	Genetic predisposition to develop IgE antibodies to low doses of common airborne antigens (aeroallergens). Traditionally, it was diagnosed when allergic sensitization to these allergens could be demonstrated. Recent consensus suggests that symptoms of allergic diseases (asthma, rhinoconjunctivitis or eczema/dermatitis) should also be present before a diagnosis of atopy can be established. The term atopic is commonly applied to these patients and these diseases.
Anaphylaxis	May be employed as synonymous of allergy. However, it is usually restricted to the presence of systemic allergic symptoms such as urticaria, angioedema and, particularly, arterial hypotension (anaphylactic shock). Similar manifestations are termed as anaphylactoid when no IgE-mediated mechanism can be demonstrated.

Table 2. Hypersensitivity reactions to alcoholic drinks

Reaction	Frequency	Mechanisms	References
Flushing syndrome (facial redness, bronchoconstriction, tachycardia, abdominal discomfort)	~ 50% of individuals of Mongoloid origin.	Alterations in ethanol metabolism: increased acetaldehyde levels/	(6-12)
Exacerbation of asthma (triggering of bronchoconstriction in asthmatics)	Patients receiving disulfiram (Antabuse) or disulfiram-like drugs ~ 30% of Caucasian asthmatic subjects	sensitivity of genetic origin (alcohol dehydrogenase gene, Mongoloid origin) or drug-induced. Complex and not entirely known. Probably induced by non-ethanol components of drinks: sulphites, histamine (in wine, most common trigger) or cereals (in beer).	(4, 5, 13-18)
Facilitation of food allergy (manifestations of food allergy appear when alcoholic drinks are taken concomitantly)	~ 10% of patients with food allergy	Not known. Increased gut absorption of allergens due to increased ethanol-induced permeability may be involved.	(19, 20)
Facilitation of exercise-induced anaphylaxis (EIA) (manifestations of EIA appear when alcoholic drinks are taken concomitantly)	~ 10% of patients with EIA	Not known. Food allergy and other allergies may be associated.	(21)
Urticaria-angioedema/Anaphylactoid shock	Rare/very rare (isolated case reports)	Heterogeneous and not entirely known. Causative factors include either non-ethanol components of drinks or ethanol <i>per se</i> (oral challenge may be positive and ethanol has histamine-liberating effect, but IgE-mediated mechanism is unlikely).	(22-33)

low-weight molecule and should act as a hapten after binding to a protein in order to induce a specific immune response.²⁸ However, ethanol-specific IgE was never demonstrated in cases of suspected ethanol allergy.^{22–33} Positive skin prick tests against acetic acid (an end-product of ethanol metabolism) have been observed in some cases of anaphylactoid reactions to alcoholic drinks.^{22,24,31} Circulating IgE antibodies to conjugates of acetaldehyde (an intermediate product of ethanol metabolism) and protein have been detected in subjects with alcohol hypersensitivity reactions.³³ These findings, however, are not consistent among different studies²⁷ and their significance is unknown.

A different but related question is whether or not alcohol may also play a role as a promoter of the development of IgE-mediated (allergic) sensitization to other antigens. IgE synthesis and the mechanisms of allergic sensitization have received considerable attention in recent years because allergic diseases have a high prevalence and an increasing incidence, particularly in economically developed countries.^{34–36} IgE synthesis and atopy (the predisposition to develop IgE antibodies after exposure to low doses of common airborne allergens) are under genetic control.^{37–39} IgE is synthesized by lymphocytes of B lineage (B cells) that need both contact with their specific allergen and stimulation by specific type 2 T helper lymphocytes (Th2 cells) via adhesion molecules and cytokines for IgE synthesis (reviewed in Bacharier & Geha⁴⁰). Th2-type cytokines [specifically interleukin (IL)-4 and IL-13] are particularly important for B cell switch to IgE synthesis.^{40,41} Most of the described genetic variations predisposing to atopy and subsequent allergic diseases involve genes of these cytokines or their receptors.^{37–39} Similarly, diseases and environmental factors are associated with high IgE levels via increased production of Th2 cytokines or decreased production of counterbalancing Th1 cytokines.⁴² The distribution of total serum IgE levels in the population is not normal (symmetric and bell-shaped), but skewed toward low values. Most subjects have total serum IgE levels below 100 IU/ml, therefore considered the 'normal' threshold. Higher total serum IgE levels suggest atopic status, but the diagnostic value of this test is limited.^{43–46}

Atopic diseases show familiar aggregation that further proves their genetic link. However, clinical conditions of rapidly increasing incidence

are likely to be influenced by environmental factors.⁴⁷ Recent studies have highlighted the possibility that chronic alcohol intake can be among these environmental factors. Potential interactions between two common conditions such as alcohol consumption and allergic diseases could be relevant. In Western countries, atopic diseases can affect as much as 40% of people throughout their life and the incidence is increasing.^{34–36} In the same countries, the majority of the adult population consume alcohol on a regular basis and consumption is increasing.⁴⁸ The possible role of alcohol intake as a promoter of IgE-mediated sensitization and allergic diseases is the focus of the present review.

Results

Alcohol consumption increases total serum IgE

Alcohol consumption is associated with increased total serum IgE levels and evidence supporting that is as follows: (a) total serum IgE levels are increased in alcoholics,^{20,49–66} (b) total serum IgE levels decrease after alcohol abstinence in alcoholics,^{54,56,59} (c) total serum IgE levels are increased in moderate alcohol consumers,^{67–71} (d) total cord blood IgE levels are increased in offspring from mothers who used alcohol during pregnancy⁷² and (e) experimental administration of alcohol is followed by a total serum IgE increase in rodents.⁷³

In 1970, Heiner & Rose first described increased serum IgE levels in patients with alcoholic cirrhosis.⁴⁹ From that moment onwards, at least 18 cross-sectional studies from a variety of settings have shown uniformly that a sizeable proportion of alcoholics have increased serum IgE levels.^{20,50–66} These studies included patients with alcoholic liver disease^{49–55,57–59,63} and patients with other complications of alcoholism.^{20,56,60–62,64} Studies were performed in Europe,^{20,52,55,56,58–62,64,65} North America,^{49,50,54,57} South America^{64,66} and Australia.^{51,53} Statistically significant differences in IgE levels were demonstrated in studies including non-alcoholic controls.^{51,53–55,58–64,66} The largest study was performed on 186 alcoholics admitted to a single internal medicine department in Spain⁵⁹ (Fig. 1). Median total serum IgE levels in alcoholics are five- to sevenfold higher than those of controls.^{59–61} Total serum IgE is increased (higher than 100 IU/ml) in most alcoholics.^{59–61} Extreme elevation of total serum

IgE levels (higher than 1000 IU/ml) after dismissing other causes of IgE increase is found in more than 10% of alcoholics.^{59–61} However, it is noteworthy that many alcoholics have 'normal' (lower than 100 IU/ml) total serum IgE levels (Fig. 1). Total serum IgE increase in alcoholics is independent of potentially confounding factors that can be associated with both alcohol intake and IgE increase such as age, gender, smoking, nutritional status, parasite infestation and atopy.^{56,58–61} Unlike total serum IgA, total serum IgE increase in alcoholics is not related to liver dysfunction.^{59–61} Serum IgE has a short half-life (2–7 days), and cohort studies in alcoholics have shown that total serum IgE levels decrease shortly after alcohol abstinence.^{54,56,59}

Three cross-sectional studies in selected non-alcoholic populations evaluated the effect of regular alcohol intake on serum IgE levels. These studies were performed in specific settings, namely a follow-up clinic of subjects with risk practices for HIV infection in the United States (including 83 adult subjects),⁶⁷ a lipid research clinic in Puerto Rico (including 621 adult subjects)⁶⁸ and an allergy clinic in Spain (including 460 adult subjects).⁶⁹ The first two studies were not focused specifically on the effect of alcohol on IgE levels, and the amount of alcohol intake on regular drinkers was not determined.^{67,68} In addition, two recent studies from Denmark (the Copenhagen Allergy Study, including 1112 adult subjects)⁷⁰ and from Spain (the A-Estrada Allergy Study, including 469 adult

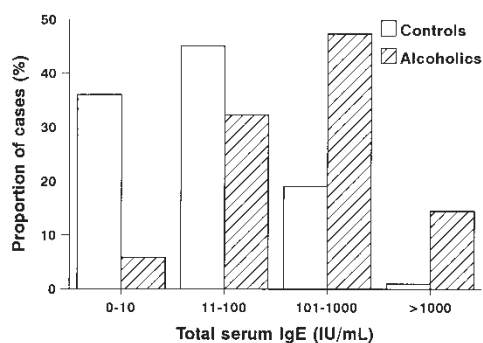


Figure 1. Distribution of total serum IgE concentrations in a group of 186 alcoholics and a group of 101 healthy controls. Both alcoholic and controls were clinically non-atopic (subjects without history of either rhinoconjunctivitis, asthma or atopic dermatitis). A *p*-value was obtained with the two-tailed Mann–Whitney test (modified from Gonzalez-Quintela et al.,⁵⁹ with permission from Blackwell Publishing).

subjects)⁷¹ have evaluated specifically the possible role of a regular alcohol intake on total serum IgE levels in general unselected adult populations. Again, all these studies show uniformly that regular alcohol consumers (as a group) have higher total serum IgE levels than abstainers.^{67–71} A representative example is given in Fig. 2. There is probably a threshold level for such effect. Total serum IgE increase is observed in those who regularly consume more than 70–140 g of alcohol every week (equivalent to 1–2 alcohol standard drinking units per day), but not for lower doses of alcohol intake.^{69–71} Total serum IgE increase in alcohol consumers is independent of potentially confounding factors such as age, gender, smoking, nutritional status and atopy.^{67–71} However, the effect of such alcohol intake is statistically significant but moderate, and it is either more evident^{69,71} or only present⁷⁰ in

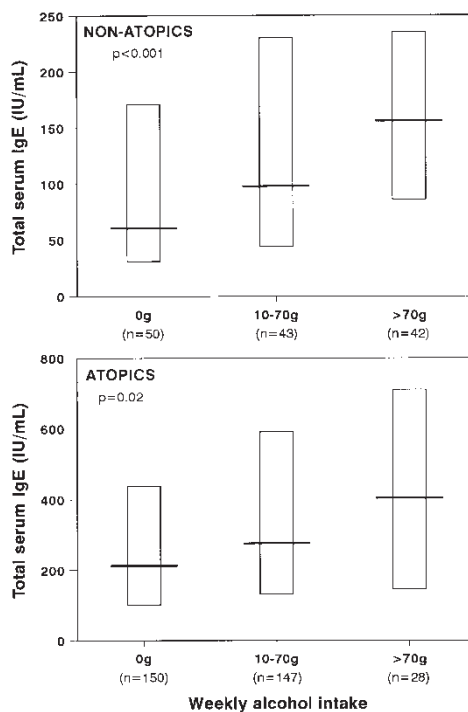


Figure 2. Total serum IgE concentrations in a series of 460 patients studied in an allergy clinic. Atopics are patients with allergic symptoms and positive skin prick tests. Non-atopics are patients with no allergic disease and negative skin prick tests. Bars represent interquartile ranges (25th percentile–75th percentile). Horizontal lines represent median values; *p*-values were obtained with the two-tailed Jonckheere–Terpsstra test (reproduced from Vidal et al.,⁶⁹ with permission from Lippincott, Williams and Wilkins Publications).

non-atopic individuals (Fig. 2). Similarly, a large birth cohort study including 2631 infants in Denmark showed that newborns from mothers who drank more than 30 g of alcohol per week during pregnancy have higher cord blood total IgE levels than newborns from abstainer mothers, even after adjusting for potential confounders.⁷²

In summary, observational studies in humans demonstrate that chronic alcohol intake is associated with an increase in total serum IgE levels. Several criteria support that alcohol is the cause of such IgE increase:⁷⁴ (a) strength of the association; (b) consistency among studies from different groups and in different settings; (c) presence of a biological gradient (dose-response effect); and (d) partial disappearance of the effect when alcohol intake is withdrawn. In addition, there is some biological plausibility (see below). It is also noteworthy that the association between alcohol consumption and increased serum IgE values was found not only in studies focused specifically but also in studies not focused specifically on that question. There is no reason to think that such consistency derives from publication bias. For ethical reasons, there are no experimental studies in humans that can obviate potential bias inherent to observational studies. However, experimental studies in rodents strongly support that alcohol intake *per se* causes serum IgE increase. In mice, alcohol administration is followed shortly by a significant increase in total serum IgE levels.⁷³

The relevance of this phenomenon is moderate. From a physiological point of view, it gives an insight into the mechanisms of IgE production. From a diagnostic point of view, alcohol intake should be taken into account when total serum IgE is employed as a diagnostic tool. Finally, from a clinical point of view, it should be noted that total serum IgE increase *per se* is neither a disease nor causes clinical manifestations. IgE increase may be associated with allergic sensitizations and allergic disease, but not as a rule. In fact, worm infestation is associated characteristically with increased total serum IgE levels but it may also even protect from allergic disease.⁷⁵ The possible implications of alcohol consumption on allergic sensitization are discussed below.

Alcohol consumption can induce allergic sensitization
The following evidence supports that alcohol consumption is associated with IgE-mediated

allergen sensitization: (a) the prevalence of allergen sensitization is different in regular alcohol consumers than in abstainers,^{47,71} (b) among allergic subjects, serum-specific IgE levels to some allergens are higher in regular alcohol consumers than in abstainers⁶⁹ and (c) the incidence of allergen sensitization tends to be higher in regular alcohol consumers than in abstainers.⁷⁰

Two population-based studies have shown that regular alcohol consumption is associated with sensitization to inhalant allergens.^{47,71} In the nested case-control Copenhagen Allergy Study, alcohol consumption was associated with overall allergen sensitization as revealed by skin prick tests.⁴⁷ In the cross-sectional A-Estrada Allergy Study, alcohol consumption was not associated significantly with overall allergen sensitization, but a significant association with positive skin prick tests to pollens was observed.⁷¹ In both studies, there was still an association after adjusting for confounders, including age, gender and smoking.^{47,71} Similarly, the positive association between alcohol consumption and allergen sensitization appeared to increase along with the daily dose of alcohol intake.^{47,71} An additional cross-sectional survey in 325 atopic subjects studied in an allergy clinic in Spain showed that regular alcohol consumers have higher levels of serum-specific IgE to the inhalant allergen of

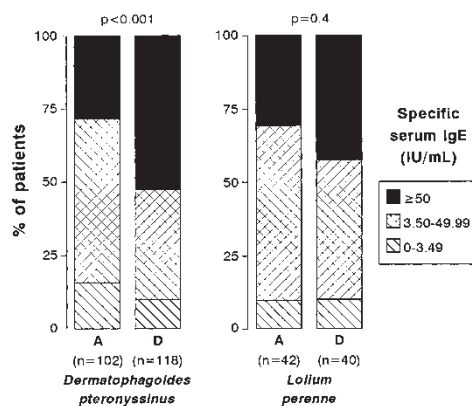


Figure 3. Serum-specific IgE concentrations in a series of patients allergic to *Dermatophagoides pteronyssinus* and/or *Lolium perenne* studied in an allergy clinic. A: Abstainers; D: regular alcohol drinkers; p-values were obtained with the Chi-square test for trend (reproduced from Vidal et al.,⁶⁹ with permission from Lippincott, Williams and Wilkins Publications).

house dust mites (*Dermatophagoides pteronyssinus*).⁶⁹ A similar non-significant trend was observed for serum-specific IgE to grass pollen (*L. perenne*) (Fig. 3).⁶⁹ A cross-sectional survey of 38 alcoholic patients admitted to a single hospital in France showed a high prevalence of sensitization to food allergens as revealed by skin prick tests.²⁰ These results, however, were not confirmed in a cross-sectional study performed in 27 alcoholic cirrhotics in Spain.⁵⁸

A longitudinal evaluation (cohort survey) of subjects included in the Copenhagen Allergy Study showed that the risk of developing skin prick test positivity to inhalant allergens tends to increase along with increasing consumption of alcohol.⁷⁰ In the same study, however, a similar trend was not observed for the association between alcohol consumption and the incidence of serum-specific IgE positivity.⁷⁰

In summary, observational studies in humans suggest that chronic alcohol intake can influence allergic sensitization. Criteria supporting that alcohol is the cause of such variation in allergic

sensitization include:⁷⁴ (a) consistency among studies from different groups and in different settings and (b) presence of a biological gradient (dose-response effect). The evidence, however, is not as strong as that supporting total serum IgE increase because: (a) the statistical association between alcohol consumption and allergic sensitization is weaker, (b) the association may be found for some groups of allergens but not for others and (c) the association may be found for skin prick test positivity but not for serum-specific IgE positivity.

The relevance of this phenomenon is unknown. From a pathophysiological point of view, further developments in this field could provide an insight into the complex mechanisms of allergic diseases. From a clinical point of view, alcohol intake probably explains little of the variation of the risk of allergic sensitization. Moreover, the presence of allergic sensitization is not always followed by the development of allergic disease.¹ However, as Linneberg *et al.* pointed out, the increase in atopic diseases

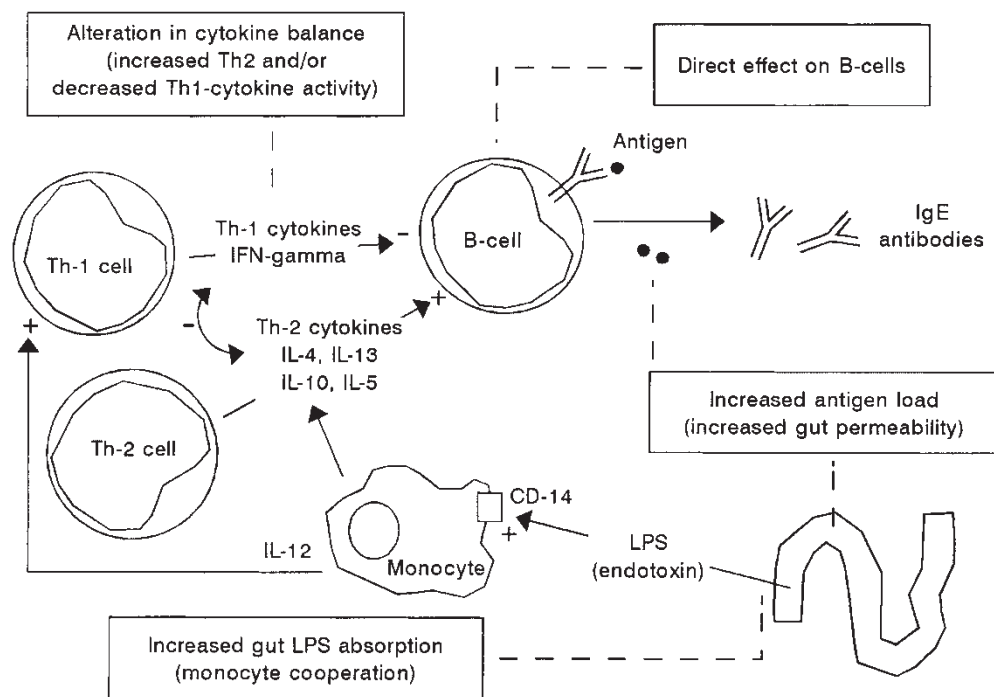


Figure 4. Schematic representation of factors involved in IgE synthesis and putative mechanisms of alcohol-induced promotion of IgE responses (within boxes).

IFN: interferon; Th: T helper cell; LPS: lipopolysaccharide; +: stimulatory action; -: inhibitory action.

coincides with recent increases in alcohol consumption in some countries, and this issue deserves further investigation in large-scale observational as well as, perhaps, experimental studies.⁷⁰

The mechanisms by which alcohol can induce IgE responses are not fully understood

Most probably, the effect of alcoholic drinks on IgE responses is due to ethanol itself and not to non-ethanol content of alcoholic drinks. First, the effect of alcoholic beverages on IgE levels in humans is independent of the type of beverage.⁷⁰ Secondly, experimental administration of ethanol to laboratory animals induces increasing IgE levels few days later, as already mentioned.⁷³ Alcohol is a powerful immunomodulatory drug^{76,77} and the IgE system is very sensitive to immunomodulatory actions. It is therefore not surprising that chronic alcohol intake can alter IgE responses. Figure 4 represents a schematic view of factors involved in IgE synthesis and putative mechanisms of alcohol influence. These mechanisms are not mutually exclusive. Theoretically, ethanol could have a direct effect on B cells favouring IgE switch. In fact, other alcohols such as salbutamol and terbutaline can increase IgE synthesis via interaction with the beta-2 receptor on B cells.^{78,79} This explanation, however, is speculative. Alternative hypotheses include an increased absorption of products from the gut lumen due to alcohol-induced increased permeability. Increased absorption of dietary antigens has been implicated in the triggering of symptoms in patients with food allergy (Table 2).^{19,20} In addition, such increased antigen load has been suggested as a cause of both increased serum IgE levels and sensitization to food allergens in alcoholics.^{20,62} Nevertheless, this probably could not explain the increased rate of sensitization to airborne allergens associated to chronic alcohol consumption.^{47,70,71} Increased gut permeability is also responsible for endotoxin (lipopolysaccharide) absorption after alcohol consumption.^{80,81} In turn, lipopolysaccharide mediates many of immunological alterations associated with chronic alcohol consumption.⁸² Interaction of lipopolysaccharide with the CD14 receptor of monocytes could indirectly favour IgE synthesis.^{83–85} Additional alterations in Th1/Th2 cytokine balance favouring Th2 cytokine predominance could also promote IgE synthesis.^{40,41}

There is substantial evidence that chronic alcohol intake induces significant alterations in cytokine balance.^{60,61,82,86–89} Serum levels of Th2 cytokines such as IL-13 and IL-10 are increased in alcoholics, and such an increase is correlated with a serum IgE increase in the same patients,⁶⁰ but results are somewhat conflicting.⁶¹

Conclusions

It is increasingly clear that alcohol consumption may play a role as a promoter of IgE responses in humans.^{90,91} Alcohol consumption increases total serum IgE levels and alcohol consumption could possibly modify the risk for IgE-mediated allergic sensitization. This illustrates the great variety of alcohol-induced effects on organ systems. The clinical relevance of this phenomenon is, at most, moderate. In addition, the exact mechanisms responsible for this phenomenon are not understood fully. However, further developments in this intriguing phenomenon could increase our understanding of the effects of alcohol on the immune system, as well as in the mechanisms of IgE production and allergic diseases.

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