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ALCOHOL-INDUCED ALTERATIONS IN SERUM IMMUNOGLOBULIN E (IGE) LEVELS IN HUMAN SUBJECTS

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1. ABSTRACT

The association of alcohol intake with total serum IgE concentrations in humans is discussed in the present review. The possible relationship of regular alcohol intake with both the risk of allergic sensitization and serum allergen-specific IgE values is also reviewed. Several studies consistently show that total serum IgE concentrations are increased in alcoholics when compared with healthy controls. Total serum IgE levels decrease after ethanol abstinence in alcoholics. Total serum IgE is increased in moderate alcohol consumers with respect to abstainers. Alcohol consumption in mothers may be associated with increased cord blood IgE levels in their offspring. IgE elevation in alcohol consumers is independent of potential confounders such as age, sex, liver disease, cigarette smoking or atopic status. Experimental studies in animals further support that ethanol administration is followed by an increase in serum IgE concentrations. In atopic patients, regular alcohol consumption is associated with increased serum specific IgE levels against some aeroallergens. Preliminary reports suggest that alcohol intake is associated to variable risk of sensitization to some aeroallergens. The possible

mechanisms of alcohol-induced alterations in IgE levels and IgE-mediated diseases are discussed.

2. INTRODUCTION

Immunoglobulin E (IgE), discovered in the mid 1960s by Ishizaka, Ishizaka and Johansson (1-3), is the main specific molecule responsible for allergic diseases. The term "allergy", meaning a "changed reactivity" after contact with some external "agents", was coined by Clemens von Pirquet in 1906 (4), and has become synonymous with immediate, type-I, or IgE-mediated hypersensitivity (5). The term "atopy" was introduced by Coca and Cooke in the early 1920s to designate a qualitatively abnormal response occurring in particular individuals (atopics), clinically characterized by hay fever and bronchial asthma, and associated with immediate-type skin reactions (6). Nowadays, atopy is defined as a personal or familial tendency to produce IgE antibodies in response to low dose of aeroallergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis, or eczema/dermatitis (7). In absence of a genetic marker, the atopic individual cannot be identified before developing IgE-mediated sensitization. Atopy is therefore clinically recognized by the presence of positive skin prick tests against aeroallergens common in the environment (8).

Serum concentrations of IgE are very much lower than those of the remaining isotypes of antibodies, but IgE plays a major role in mucosal immunity in both health and disease. Once produced after contact with an allergen in a mucosal surface, specific IgE binds to mast cells and basophils and sensitizes them for months. Subsequent contacts with the allergen drives mediator release and local inflammation, a mechanism that may be important in host defence against parasitic worms (5). In atopic subjects, a similar mechanism is developed against innocuous environmental allergens (5,9). Serum IgE concentrations are highly variable, following a non-normal distribution skewed toward low values (9). Total serum IgE levels are determined by genetic background (5,10), but can be influenced by a number of factors (9). Atopic subjects show increased levels of total serum IgE (5,9). Total serum IgE is therefore routinely requested in Allergy clinics as a diagnostic tool, although the overlap between IgE concentrations between atopic and nonatopic individuals reduces the diagnostic value of total serum IgE as a screening test for atopy (9). With these limitations, total serum IgE values below 100 IU/mL are considered "normal" in most studies (9,11).

Atopy affects as much as a quarter of some populations and is ever increasing in frequency (12,13). The atopic immune system is characterized by a Th2 deviation, determined by genetic and a number of environmental factors (14). Many of genetic alterations associated to atopy include genes responsible for synthesis of Th2 cytokines and other molecules related to IgE production (15). Environmental factors associated with atopy include allergen exposure, air pollution and lack of exposure to some infections in childhood (14,16,17). The latter can be involved in the rising incidence of atopic disorders in socioeconomically developed countries (16,17). Tobacco smoking (18-23) and alcohol drinking are probably associated to increased total serum IgE levels and variable risks of allergen sensitization. This article reviews available data on the association of alcohol consumption on both total serum IgE concentrations and specific allergies in human subjects.

3. ALCOHOL CONSUMPTION AND TOTAL SERUM IgE

3.1. IgE studies in alcoholics

3.1.1. Total serum IgE concentrations in alcoholic patients

Several cross-sectional observational studies (summarized in table 1) consistently show an increase in serum IgE levels in alcoholics (24-38). These studies were performed in very different countries, in a variety of settings, and in substantial number of cases (table 1). Some studies were specifically focused on alcoholics, while the remainder usually studied alcoholic patients amongst a miscellaneous group of patients with liver disease (table 1). All studies demonstrated increased serum IgE levels in alcoholics, statistically significant with respect to controls in most of them (25,26,28-30,32-38). Nonatopic alcoholics show median serum IgE levels between 130 and 150 IU/mL, while nonatopic healthy controls show median serum IgE levels between 20 and 40 IU/mL in the same studies (33-35). Most alcoholics therefore show increased serum IgE concentrations. Moreover, a significant proportion (about 15%) of nonatopic alcoholics show total serum IgE levels higher than 1000 IU/mL (25,33-35). Such levels are very rarely observed in nonatopic healthy individuals (9). It should be noted, however, that not all alcoholics have increased serum IgE concentrations. Furthermore, some alcoholics have IgE concentrations lower than 10 IU/mL (33-35) with similar amounts of regular alcohol intake than patients with very increased IgE concentrations (35). This suggests that either additional factors or an increased individual susceptibility must be present for such an increase of serum IgE in alcoholics, as discussed below (see below, 3.4. *Possible mechanisms of alcohol-induced changes in total serum IgE concentrations*).

3.1.2. Assessment of potential confounding factors

As already mentioned, IgE concentrations are under genetic control but may be influenced by a number of additional factors (9). Some of these factors (such as liver disease, smoking, parasite infestation, malnutrition, atopy, age and sex) may be also associated with chronic alcohol consumption. The potential either confounding effect or interaction induced by these factors has been addressed in some studies, as follows:

3.1.2.1. Liver disease

Alcohol induces liver disease, and liver diseases are associated with hypergammaglobulinemia (39,40). In patients with alcoholic liver disease, a selective serum IgA

Table 1. Observational studies demonstrating increased total serum IgE in alcoholics

Author	Ref.	Year	Country	Number of cases	Patient's characteristics/setting
Heiner & Rose	24	1970	USA	18	Patients with conditions other than allergy
Van Epps *et al.*	25	1976	USA	46	Patients with miscellaneous liver diseases
Joske *et al.*	26	1976	Australia	25	Patients with miscellaneous liver diseases
Husby *et al.*	27	1977	Norway	29	Patients with miscellaneous liver diseases
Smith *et al.*	28	1980	USA	42	Patients with different stages of alcoholic liver disease
Cirasino *et al.*	29	1981	Italy	16	Patients with liver cirrhosis of varied etiology
Hällgren & Lundin	30	1983	Sweden	106	Atopic and nonatopic alcoholics
Minuk *et al.*	31	1989	Canada	15	Patients with miscellaneous liver diseases
Vidal *et al.*	32	1994	Spain	27	Nonatopics with liver cirrhosis
González-Quintela *et al.*	33	1995	Spain	186	Nonatopic alcoholics with different stages of liver disease
González-Quintela *et al.*	34	1999	Spain	65	Nonatopics with alcohol withdrawal syndrome
Domínguez-Santalla *et al.*	35	2001	Spain	25	Atopics and nonatopics with alcohol withdrawal syndrome
Raithel *et al.*	36	2001	Germany	41	Nonatopics with chronic pancreatitis
Medina-Santander *et al.*	37	2001	Venezuela	63	Patients with fatty liver
González-Quintela *et al.*	38	2002	Spain	25	Nonatopics with alcohol withdrawal syndrome

increase is commonly found (33,41). Therefore, alcoholic liver disease has been considered an IgA-associated disorder (42). First studies that reported an association between alcohol and IgE were performed in groups of patients with liver disease (table 1). Moreover, some initial studies concluded that liver disease is a prominent cause of serum IgE elevation (25). However, several data support both that IgE increase in alcoholics is not a mere part of hypergammaglobulinemia of chronic liver diseases and that liver disease *per se* is not a cause of serum IgE increase. First, serum IgE levels are not increased in most patients with non-alcoholic liver diseases. Increased IgE concentrations have been reported in patients with hepatitis A and B (43,44), but normal IgE levels have been found in patients with chronic hepatitis C (45) and in patients with autoimmune chronic active hepatitis (31). Furthermore, low or undetectable serum IgE levels have been frequently observed in patients with primary biliary cirrhosis (31). Among patients with liver cirrhosis, increased IgE concentrations were only found in cases of alcoholic origin (32,46). Second, IgE increase in alcoholics is not clearly related either to the severity of alcoholic liver damage or the necro-inflammatory activity within the liver. Smith *et al* suggested that IgE elevation in alcoholics is restricted to cases with liver fibrosis or cirrhosis (28), but a larger study reported that IgE increase is similar in patients with fatty liver, liver fibrosis, alcoholic hepatitis or cirrhosis (33,35). Moreover, no correlation is observed between serum IgE and parameters of liver dysfunction (30-35). Finally, IgE elevation in alcoholics is unrelated to other immunoglobulins (IgG, IgM, or IgA) (32,33,34). Unlike IgE, IgA levels are clearly correlated with parameters of liver dysfunction and are significantly higher in cases of liver cirrhosis (33). This suggests that the cause of liver disease (particularly alcohol) and not liver disease *per se* is the cause of increased serum IgE concentrations in patients with liver damage.

3.1.2.2. Smoking

Alcohol consumption and smoking are commonly associated. Cigarette smoking has been found associated with an increase in total serum IgE concentrations in several epidemiological studies (18-23). However, most of these studies did not adjust their results for alcohol consumption. In alcoholics, serum IgE elevation is independent of cigarette smoking, meaning that IgE increase is observed in both smoker and non-smoker alcoholics (32-35).

3.1.2.3. Parasite infestation

Infestation by parasite worms is a well-known cause of serum IgE elevation (9). Parasite infestation could be suspected as being frequent in indigent alcoholics, but several pieces of evidence suggest that this is not the cause of increased IgE in these cases. First, peripheral blood eosinophilia (a surrogate marker of parasite infestation) is absent in alcoholics with elevated IgE (34,35). Second, alcoholics have increased serum IgE levels with negative stool studies for parasites (29,35) and undetectable Toxocara antibodies (35). Finally, it is unlikely that parasite infestation underlies IgE elevation in alcoholics from so different countries as represented in table 1.

3.1.2.4. Malnutrition

Malnutrition and almost every cause of significant cellular immunosuppression are associated with increased serum IgE values (9), and chronic alcoholism is associated with malnutrition. However, studies that reported elevated serum IgE concentrations in alcoholics found no relationship between increased serum IgE and nutrition, as evaluated by either biochemical or anthropometric parameters (34,35).

3.1.2.5. Atopy

Atopy is, probably, the most frequent cause of increased serum IgE in developed countries (9). IgE elevation in alcoholics seems independent of atopic status of patients, meaning that IgE elevation is present in both atopic and nonatopic alcoholics (table 1). Many of these IgE studies in alcoholics either selected nonatopic subjects (33,34) or stratified subjects (30) as atopic or nonatopic by clinical history (presence of symptoms of asthma,

rhinoconjunctivitis or dermatitis). It is well know, however, that many atopic patients may be free of symptoms. Other studies which stratified alcoholic patients as atopic or nonatopic by more objective methods such as skin prick tests to common aeroallergens (35) or selected nonatopic alcoholics by the absence of specific serum IgE against aeroallergens (38) confirmed that IgE elevation in alcoholics is independent of their atopic status. The possible relationship of chronic alcohol consumption with allergic sensitization is discussed below (see below, *4.2. Alcohol consumption and risk of allergic sensitization*).

3.1.2.6. Age and gender

Total serum IgE concentrations are higher in males than in females (23,47), and IgE levels tend to decrease with ageing (47-49). In the population, alcohol abuse is usually associated to male sex. Significant IgE increase in alcoholics, however, persists when results are adjusted for age and sex (33,34).

3.1.3. Time-course changes of serum IgE levels after alcohol abstinence

IgE decrease shortly after ethanol abstinence, which is an additional evidence for the influence of regular alcohol intake on serum IgE concentrations. The half-life of serum IgE is only three days, permitting to study its variation over short periods of time. The outcome of serum IgE concentrations after abstinence in alcohol abusers was analyzed in three studies. In a cross-sectional study, Hallgren an Lundin observed that alcoholics with the shortest withdrawal period had the highest IgE levels (30). Moreover, they longitudinally followed seven alcoholics immediately after a period of heavy drinking, and found a uniform significant pattern of declining IgE levels (mean relative decrease, 40%) during the observation period (16 days) (30). In the study of Smith *et al*, admission IgE levels were compared with levels obtained 2-4 weeks postadmission in 25 alcoholics (28). Twenty of 25 alcoholics had reductions in IgE concentration, with an average decrease of 50% (28). Similarly, we found a significant decrease in serum IgE concentrations after alcohol abstinence in 39 patients admitted to the hospital (33). Median serum IgE in the initial sample was 147 IU/mL, and 106 IU/ml in a second sample taken 7-14 days after admission. The second IgE value was lower than the first one in 29 out of 39 patients, with a mean decrease of 25% in these cases (33).

3.2. IgE studies in moderate alcohol consumers

The possible influence of moderate alcohol consumption (below the threshold of alcohol abuse) on total serum IgE levels has been addressed in three studies. All of them consistently conclude that alcohol intake is associated with an increase in total serum IgE concentrations (23,50,51). Criqui *et al* studied the epidemiology of IgE levels in a defined population (composed of 621 patients studied in a Lipid Research Clinic with an average age of 66 years) and included regular alcohol consumption in the analysis (23). They concluded that alcohol intake was significantly correlated with IgE levels, particularly in men and independently of atopy (defined by a personal or family history of allergy) and smoking (23). Miguez-Burbano *et al* studied total serum IgE levels in 83 patients with HIV infection, and also included alcohol intake in the analysis (50). The proportion of alcohol abusers among alcohol consumers was not given, but they found that alcohol intake was significantly associated with IgE elevation in multivariate analysis which included HIV status and intravenous drug use (50). In a recent study focused on the possible influence of alcohol intake on both total and specific serum IgE levels in 460 patients studied in an Allergy clinic (the setting where total serum IgE is commonly used as a diagnostic tool), we observed that regular alcohol intake higher than seven standard drinking units per week (approximately equivalent to 70g of ethanol per week) is associated with an increase in total serum IgE concentrations (51). This association was independent of age, sex, smoking habit and atopic status of subjects, defined by skin prick tests against common aeroallergens (51). All these three studies were carried out in very defined populations, but the association of total serum IgE levels with alcohol intake in these largely non-alcoholic populations suggests that alcohol, in and of itself, can increase total serum IgE levels (23,51). It should be taken into account, however, that alcohol intake explains little of the variation of total serum IgE in moderate alcohol consumers (51).

3.3. Indirect evidences of the influence of alcohol consumption on total serum IgE

3.3.1. Mother's alcohol consumption and cord blood IgE concentrations

The possible effect of alcohol intake by mothers during pregnancy on cord blood IgE levels in their offspring has been addressed in two studies, with contradictory results. Bjerke *et al* studied cord blood IgE concentrations in a birth cohort of 2631 infants in order to elucidate the association between genetic and environmental factors and fetal production of IgE (52). On multivariate analysis, regular alcohol consumption equal or higher than three standard drinking units per week by mothers was associated with elevated cord blood levels of IgE in their offspring when compared with newborns to abstainer mothers, even when adjusting for atopic heritage, sex of child, mother's weight, mother's educational background, and mother's smoking (52). In contrast, Grzybowski *et al* reported that cord IgE concentrations were lower among newborns from drinking mothers than nondrinking mothers, with a significant trend for lower cord IgE with increasing ethanol ingestion (53). However, the study included only 98 cases, and only a third of mothers were regular alcohol consumers (53).

3.3.2. Experimental studies

Experimental administration of alcohol in humans has obvious ethical limitations. We have observed that a single 60g-ethanol dose in healthy individuals may modify serum cytokine levels (54), with no significant modification of total serum IgE 36 hours later (unpublished observation). To our knowledge, the possible influence of prolonged ethanol administration on IgE levels in humans has not been reported up to date. However, the effect of

experimental ethanol administration on serum IgE levels in laboratory animals have been recently reported. In 2001, Starkenburg *et al.* reported that oral ethanol administration for 12 days in mice is followed by a rapid elevation in total serum IgE (55). IgE elevation after ethanol administration occurred in both Th1 and Th2-prone mice strains (55). Moreover, IgE levels correlate with serum alcohol levels in ethanol-fed mice (55).

3.4. Possible mechanisms of alcohol-induced changes in total serum IgE concentrations

The mechanisms of total serum IgE elevation after ingestion of alcoholic beverages are not fully understood. It is unlikely that that a substance different from ethanol and contained in the beverages was the cause of elevated IgE levels. Increased IgE levels could derive from decreased IgE catabolism but, probably, elevated IgE concentrations are the consequence of an increased IgE synthesis. In addition to antigen binding, IgE synthesis by B cells requires two signals. The first signal is delivered by Th2-derived cytokines (particularly IL-4 or IL-13), and the second one is the consequence of the interaction of the B cell surface antigen CD40 with its ligand on activated T cells (56,57). Some additional stimuli, when present along with IL-4, can induce IgE synthesis in a T-cell independent manner (56). Theoretically, if alcohol consumption induces increased IgE synthesis, it could derive from altered Th1/Th2 cytokine balance, altered CD40 ligation, T-cell independent factors or increased antigen exposure. These possible mechanisms are discussed next.

3.4.1. Alterations in Th1/Th2 cytokine balance

It could be hypothesized that IgE increase in alcoholics could be due to Th1/Th2 cytokine imbalance, with Th2 predominance. In rodents, and probably in humans, two polar categories of Th cells exist: Th1 cells which secrete IL-2 and interferon-gamma, and Th2 cells which secrete IL-4, IL-5, IL-10, and IL-13 (58). Th2 cytokines stimulate antibody-mediated immune responses (including IgE synthesis), while Th1 cytokines stimulate cell-mediated responses and inhibit IgE production (57,58). Conditions involving increased serum IgE levels are therefore suggestive of Th2 cytokine predominance (59). In fact, experimental ethanol administration in animals polarizes the immune response away from Th1 toward Th2 (55,60-63). Moreover, the rapid increase in serum IgE levels after ethanol administration in mice is accompanied by a decrease in Th1 function, as reflected by diminished interferon-gamma production (55).

In humans, alcohol consumption is associated to profound changes in cytokine balance (34,35,54,64-67). These include altered levels and/or production of cytokines involved in IgE synthesis (34,35,54,64-67). Serum levels of IgE, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13 and interferon gamma from a group 65 patients with alcohol withdrawal syndrome with those from a group of 40 healthy control subjects (34). In parallel with IgE increase, alcoholic patients showed increased serum levels of IL-6, IL-8, IL-10, IL-12 and IL-13 (34). Serum levels of IL-4, IL-5 and interferon-gamma were undetectable in most patients and controls (34). A weak but statistically significant correlation was observed between serum IgE and IL-13 concentrations in alcoholics (34). Serum IgE levels were also increased in alcoholics with the highest serum IL-10 values (34). These results are in accordance with the hypothesis of a Th2 predominance as the cause of IgE increase in alcoholics, but additional results are somewhat conflicting with such hypothesis. Alcoholics also have increased serum values of IL-12 (34,67), the main promoter of the development of Th1 cells from naïve CD4+ cells (68). Moreover, stimulated peripheral blood mononuclear cells (PBMC) of alcoholics may show a predominant Th1-profile of cytokine secretion (35,66). Recently, our group studied both serum IgE levels and PBMC production of IL-4, IL-10, IL-13 and interferon-gamma in a group of 25 alcoholics (five atopic and 20 nonatopic by skin prick tests) and 15 healthy controls (seven atopics and eight nonatopics) (35). Elevated levels of serum IgE in both atopic and nonatopic alcoholics occurred in spite of a paradoxically low Th2/Th1 ratio of cytokine production by phytohemagglutinin-stimulated PBMC, reflected by a low IL-4/interferon-gamma production ratio (35). Median production of IL-4 (the main Th2 cytokine responsible for IgE switch at the B-cell level) was 6-20 fold lower in alcoholics than in healthy controls (35). Interleukin-10 and IL-13 production was similar in alcoholics and in control subjects (35). Furthermore, we recently observed that increased serum IgE in nonatopic alcoholics is correlated with low serum levels of soluble CD30 (sCD30) (38), a surrogate marker of Th2 immune responses in vivo (69).

There is some discrepancy between experimental studies in animals and observational studies in alcoholics concerning Th1/Th2 imbalance induced by alcohol and IgE levels. Caution is needed in cytokine studies because of their wide range of activities, cell sources and potential inducers of each cytokine. In animal studies ethanol was administered for brief periods of time (days), while alcoholic patients included in these studies abused from alcohol for years. It should be taken into account that the paradigm of Th1/Th2 dichotomy is more evident in rodents than it is in humans. The idea of Th1 and Th2 predominance in a particular disorder should not be overemphasized, since either subset may play a role modulating the immune response over time (70). Alcoholism exemplifies this, since it may be simultaneously associated with both Th1 and Th2 phenomena.

3.4.2. T-cell independent mechanisms

Endotoxin (lipopolysaccharide, LPS) is responsible for many of the alcohol-induced immunological aberrations in humans (64). Intestinal absorption of LPS is increased by alcohol intake, and alcohol abuse leads to endotoxemia even in patients with no signs of chronic liver disease (71). LPS has apparently opposite effects. On the one hand, LPS binding to CD14 on antigen-presenting cells leads to IL-12 production (72) and subsequent Th1 development. On the other hand, LPS enhances IL-4-dependent IgE synthesis by cultured PBMC (73). This effect is strictly monocyte-dependent, because it is completely abrogated by depletion of monocytes, but not

by removal of T cells (73). Alcohol-induced LPS absorption could therefore underlie both Th1 phenomena and increased IgE synthesis in alcoholics. Furthermore, genetic variations in CD14 (the LPS receptor) could underlie the wide variation of IgE levels in alcoholics. It must be remembered that IgE is not increased in all alcoholics. Moreover, IgE levels in alcoholics may be significantly different in subjects with similar amounts of ethanol intake. This suggests that some kind of individual susceptibility must exist. IgE levels are determined by genetic factors and, perhaps, environmental factors modify IgE concentrations to some extent from a genetically given level. The genetic locus of CD14 is close to the genomic region controlling IgE levels, and recently described genetic polymorphisms in the CD14 promoter region are associated with IgE levels (73-75). Genetic variation in CD14 may modulate the effects that exposure to bacterial ligands has on the development of IgE responses (75). LPS absorption could be responsible for increased IgE synthesis after alcohol intake, and genetic variations in CD14 could explain individual variations in this response, but this is just an hypothesis which is currently under investigation.

Additional T-cell independent mechanisms for IgE elevation after regular alcohol intake include direct effects of ethanol on B cells favoring IgE switching. It is known that other alcohols, such as salbutamol or propranolol, can stimulate IgE synthesis via interaction with either the beta-2-adrenergic receptor or other cell receptors (76,77). Effects of ethanol on B cells could also include post-receptor intracellular alterations in molecules involved in IgE switching (56). These hypotheses would also need further studies.

3.4.3. Antigen shedding/exposure

It has been suggested that alcohol intake could break oral tolerance and promote IgE synthesis through increased antigen load from the gastrointestinal tract with subsequent increased exposure to the immune system. Such excess of antigen load could derive from either decreased liver clearance or increased intestinal absorption. The liver may play a critical role in the induction of tolerance to antigens absorbed through the portal system, the so-called portal venous tolerance (78-80). Kupffer cells, the resident liver macrophages, are probably responsible for this phenomenon since Kupffer cell blockade abrogates portal venous tolerance (79,80). In rats, no serum specific antibodies can be detected after experimental intragastric or intraportal ovalbumin administration, but an increased IgE or IgG1 specific response is observed when Kupffer cells are blocked with gadolinium chloride prior to antigen administration (81,82). Both advanced liver disease and alcohol impair Kupffer cell function (83). In a study of Kupffer cell phagocytic activity (liver radiocolloid uptake), serum IgE levels and skin prick test reactivity to a battery of food allergens in a group of 52 cirrhotics (27 of them of alcoholic origin), we observed that IgE elevation was restricted to alcoholic cirrhotics, and unrelated to either liver phagocytic function or skin test reactivity to food allergens (32). In summary, these results do not support that increased IgE levels in alcoholics are the result of liver Kupffer cell dysfunction.

Raithel *et al* studied the relationship between total serum IgE, pancreatic insufficiency (in patients with chronic pancreatitis) and alcohol consumption (36). They found that increased total serum IgE levels were independently associated with pancreatic insufficiency and alcohol consumption, and concluded that a reduced rate of antigen digestion in exocrine pancreatic insufficiency may lead to increased intestinal antigen load, and that alcohol consumption may further contribute to this by damaging the mucosal barrier (36). However, these mechanisms do not explain serum IgE increase in alcoholics with normal pancreatic function or in subjects with moderate alcohol consumption. Furthermore, as previously mentioned, there is no evidence for increased food allergen sensitization in previous studies in alcoholics (32).

4. ALCOHOL CONSUMPTION AND SPECIFIC ALLERGIES

4.1. Alcohol consumption and serum specific IgE levels in atopic patients

In a survey of adult atopic patients studied in an Allergy clinic, we reported that serum specific IgE levels against some aeroallergens were increased in regular alcohol consumers when compared with abstainers (51). Among 220 patients allergic to house dust mites (the most common aeroallergen in the area studied), median specific IgE against *Dermatophagoides pteronyssinus* was 54 IU/mL in alcohol consumers and 25.7 IU/mL in abstainers. The proportion of patients with increased (class 5 or higher) serum specific IgE against *Dermatophagoides pteronyssinus* was 53% in regular alcohol consumers versus 28% in alcohol abstainers (51). The association of regular alcohol intake with increased serum specific IgE against house dust mites persisted after adjusting for age, sex, and smoking (51). A similar pattern was observed in 82 patients allergic to grass pollen (*Lolium perenne*), but the association between alcohol intake and specific IgE values did not reach statistical significance (51). Further studies are needed to determine whether alcohol intake is associated to increased serum specific IgE concentrations in atopic patients.

4.2. Alcohol consumption and risk of allergic sensitization

In a cross-sectional population-based study of factors related to allergic sensitization to aeroallergens in 15-69-year-old Copenhagen, Denmark, Linneberg *et al* reported an association between alcohol consumption and allergic sensitisation (84). The studied sample included 1112 subjects, 477 of them from a random group and 635 from a symptomatic group which reported nasal or bronchial symptoms on exposure to pollen or furry animals. Regular alcohol intake (coded as a trend variable) was associated with allergic sensitisation estimated by skin prick test positivity, but not when estimated by specific serum IgE positivity. The authors suggested that this finding should be interpreted with caution, since there were no previous reports addressing this relationship in the literature (84). The association between alcohol consumption and skin prick test positivity was mainly due to the consumption of wine, which could suggest that the

association was due to confounding by social status or diet. However, the association between alcohol consumption and allergic sensitization persisted after adjusting for age, sex, smoking status and educational level (84). The possible relationship between alcohol consumption and allergic sensitization is currently under research in an adult population-based survey in our area.

4.3. Alcohol consumption and development of allergic and pseudoallergic symptoms

In rare instances, alcohol ingestion is associated with type-I hypersensitivity-like reactions, such as urticaria (85-89), exacerbation of bronchial asthma (90,91) or even anaphylactoid reactions (85-88, 92-94) with very rare fatal cases (95). These reactions are most probably caused by intolerance to ethanol or its metabolites (acetaldehyde and acetic acid), and not to true ethanol allergy (85,86). Ethanol-specific IgE has never been demonstrated but oral challenge with ethanol can reproduce the symptoms (85-88, 92). Positive skin prick tests against acetic acid have been demonstrated in some case of anaphylactoid reactions to ethanol (85,87,94). Anti-acetaldehyde adducts circulating IgE antibodies have been detected in sera of subjects with alcohol hypersensitivity reactions (96). In addition, food-induced anaphylaxis (97) and exercise-induced anaphylaxis (98) may be favored by concomitant alcohol intake. Studies on the effect of alcohol intake in bronchial asthma gave conflicting results (90), but alcoholic drinks appear to be important triggers for asthmatic responses in most studies (91). Alcohol-induced asthma in Asians is associated with increased blood acetaldehyde concentration resulting from genetic abnormalities of alcohol dehydrogenase (99-101) or to increased increased airway responsiveness to acetaldehyde (102). Finally, some immediate hypersensitivity reactions after the ingestion of alcoholic beverages are due to added allergens such as preservatives (particularly sulfites) (103,104), or cereals in the case of beer (105).

5. PERSPECTIVE

IgE responses are genetically conditioned, but they are very sensitive to environmental immunomodulatory factors. It is not surprising that alcohol, a powerful immunomodulatory drug, can modulate the IgE system. An increase in total serum IgE is consistently shown in all studies performed in alcohol abusers and moderate alcohol consumers. This phenomenon should be taken into account when total serum IgE is employed as a diagnostic tool. However, it should be noted that alcohol intake explains little of the variation in serum IgE, particularly in moderate alcohol consumers. Moreover, diagnostic value of total serum IgE assay is limited. Elevation of total serum IgE associated with alcohol intake therefore carry greater pathophysiological than clinical importance. Further studies concerning the mechanisms of increased IgE synthesis in alcohol consumers could offer some insight into the mechanisms of IgE-mediated disorders.

Preliminary reports suggests that alcohol intake not only can modify total serum IgE concentrations, but also can influence both specific IgE concentrations in atopic subjects and the risk of allergic sensitization. These results need more confirmatory cross-sectional studies and, if possible, longitudinal cohort studies. If confirmed, these results would be of great importance, given the high prevalence of both alcohol consumption and allergic disorders in many populations.

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