

EDITORIAL

Alcoholic drink consumption: a role in the development of allergic disease?

Introduction

Although it is increasingly clear that alcoholic drinks are important triggers of asthma, the mechanisms involved are not fully understood. Both alcohol and the non-alcohol components of these drinks, have been implicated as playing a role in these responses, and both allergic and non-allergic mechanisms have been demonstrated [1, 2]. Interestingly, alcoholic drink consumption may also play a role in the development of allergic disease. However, previous studies addressing this issue have been conducted in individuals consuming large amounts of alcohol, or in highly selected populations, and hence the relevance for the wider community is unclear. In the current issue of *Clinical and Experimental Allergy*, two articles address this gap in the literature and report data from population-based studies that support the notion that moderate levels of alcoholic drink consumption may play a role in the development of allergic disease [3, 4]. Whilst both of these studies need to be interpreted with some caution, their findings are clearly interesting and deserve further exploration.

Alcoholic drink consumption and allergic disease

Several studies have indicated that serum IgE levels in individuals who drink excessive alcohol are elevated when compared with healthy controls [5–11]. This effect has been found to be unrelated to the extent of liver damage [6, 8] and appears to be independent of confounders such as age, gender, smoking, nutritional status or the existence of parasitic infections [6, 8–10, 12, 13]. A direct effect of alcohol on the immune system has been postulated, which is supported by the fact that IgE levels have been found to decrease after a short period of alcohol abstinence [5, 6, 8]. Further support for alcohol-mediated increases in IgE levels comes from the observation that alcohol abuse during pregnancy has been found to be associated with an increase in cord blood IgE levels in the newborn [12], and in animal models, alcohol administration has been found to be associated with raised serum IgE levels [13].

Moderate levels of alcoholic drink consumption have also been associated with increased IgE levels [14, 15]. In a cross-sectional study of patients recruited from a lipid research clinic, a strong association between alcohol consumption in males and serum IgE levels was demonstrated [14]. Importantly, this relationship remained after adjusting for age, smoking, and personal and family history of allergies. In a second more recent study of consecutive patients from an adult allergy clinic, the consumption of higher than 70 g of alcohol per week was associated with increased total IgE levels in these patients [15]. Interestingly, in those who were shown to be allergic to house dust mite (*Dermatophagoides pteronyssinus*), the concentrations of specific IgE to this allergen were found to be significantly

higher in regular alcohol consumers when compared with those who did not drink alcohol.

The two articles in this issue of the Journal suggest that the relationship between moderate levels of alcoholic drink consumption and increased IgE levels extend to more representative populations. Gonzalez-Quintela and colleagues [4], in an age-stratified cross-sectional study conducted in 2000 in the municipality of A-Estrada in Spain, report that moderate levels of alcoholic drink consumption are associated with increased serum IgE levels. Whilst alcoholic drink consumption was not associated with an increased prevalence of allergic sensitization *per se*, a significantly higher prevalence of pollen sensitization was observed amongst alcoholic drink consumers. The article by Linneberg and colleagues [3] is one of a number of reports from a population-based cross-sectional study conducted in Copenhagen in 1990 addressing the prevalence and risk factors for allergic disease (Copenhagen Allergy Study) [16–23]. In the current report, moderate levels of alcoholic drink consumption amongst non-atopics are reported to be associated with increased serum IgE levels, which complements previous data from this same cohort in which an association between alcoholic drink consumption and the prevalence of allergic sensitization (as assessed by skin prick test positivity) was observed [18]. In the present study, in which subjects were followed for up to 8 years, the risk of developing skin prick test positivity appeared to increase with increasing levels of alcoholic drink consumption, although this association was not found to be statistically significant [3].

Although the above findings are of considerable interest, it is important not to over-interpret them at this early stage. Firstly, there are a number of potential influences on IgE levels and, as has been suggested by Gonzalez-Quintela et al. [4], the relative importance of alcoholic drink consumption in modulating IgE levels is likely to be small. Certainly, the fact that the association between alcoholic drink consumption and increased IgE levels was only true for non-atopics in the study by Linneberg et al. [3], and that it was clearly far stronger for non-atopics in a previous study [15], suggests that genetics have a far greater influence on IgE levels than alcohol consumption. Nevertheless, since these drinks are consumed extensively and there is an equally high prevalence of allergic disease in our society, if a link between moderate levels of alcoholic drink consumption and raised IgE concentrations can be confirmed, the public health implications may be significant. This is of greater relevance given that the prevalence of allergic disease has been increasing over the past few decades [24], and that this increase is likely to be largely driven by environmental and lifestyle factors [25].

It is also important that it is recognized that an effect of alcohol consumption on IgE levels does not necessarily imply clinical relevance in the context of allergic disease. Thus, the pathological consequences of alcohol-mediated increases in IgE levels need to be determined. Clearly, increased levels of specific

IgE are likely to have greater clinical relevance than the presence of increased IgE levels *per se*, and studies (with sufficient power) that address the development of allergic sensitization need to be performed. Whether alcohol-mediated increases in IgE concentrations correspond with an increased prevalence or severity of allergic disease, or indeed alter the clinical course of allergic disease needs to be established. One must keep in mind that even though raised IgE concentrations have been demonstrated in individuals with high alcohol intakes, to date there appears to be no data suggesting that this equates to a greater prevalence of allergic disease in this group.

Why alcoholic drink consumption should be associated with sensitization to particular allergens is intriguing. The clinical relevance of the observed increased prevalence of pollen sensitization amongst alcoholic drink consumers in the study by Gonzalez-Quintela et al. [4] is unclear. Interestingly, data suggesting a lower prevalence of house dust mite sensitization amongst alcohol consumers was also reported in this study. The mechanisms underlying a possible variation in the degree of allergic sensitization to specific allergens remain elusive. It remains to be shown whether it is due to an effect of alcohol on IgE directed towards specific allergens, or whether an effect on the actual sensitization process is involved. The association between smoking and allergic disease parameters highlights the potential complexity of this relationship. Smoking has been shown in several studies to be associated with increased IgE concentrations [26–29]. However, in contrast, smoking has also been associated with reduced allergic sensitization *per se* [19, 30–34], although this relationship appears to vary between allergens, as sensitization to house dust mite appears to be increased [29, 31]. Whilst the specific mechanisms by which smoking may increase sensitization to house dust mite are not known, it has been speculated that increased permeability of the bronchus may facilitate the increased presentation of house dust mite antigen, or that a reduced capacity to inactivate allergen proteases may play a role [31].

Whilst the particular molecular mechanisms by which alcohol consumption may lead to raised IgE levels are yet to be determined, alcohol is clearly a powerful immunomodulatory drug, with both acute and chronic intake having various effects on immune function [35–37]. Of particular interest is that alcohol consumption has been associated with decreased production of cytokines from the T cell helper subsets specifically associated with cell-mediated immunity (Th1), and increased production of cytokines from T cell helper subsets associated with antibody-mediated immune responses (Th2) [9]. Similarly, in mice, alcohol consumption has been observed to polarize the immune system away from Th1 cytokine production, and consequently towards Th2 cytokine production [13, 38–40]. Whilst it has been speculated that an effect on T cell helper subsets may be responsible for increased IgE levels amongst alcohol consumers, findings which seemingly contradict this hypothesis have also been reported [9–11, 41, 42]. Alternative explanations for increased IgE levels amongst alcoholic drink consumers have been proposed. It has been suggested that increased levels of LPS absorption due to alcohol, or a direct effect of alcohol on B cells, may result in increased IgE synthesis [43]. It has also been suggested that alcohol may increase the antigen load from the gastrointestinal tract and thus promote IgE synthesis [43].

Conclusion

The notion that those who consume moderate amounts of alcohol may be at increased risk of developing allergic disease is of considerable interest and clearly deserves further investigation. Additional population-based studies, longitudinal cohort studies and experimental studies are required to answer questions posed by Gonzalez-Quintela et al. [4] and Linneberg et al. [3]. In particular, the elucidation of the underlying mechanisms for the observed increase in IgE levels may provide insights into the regulation of the immune system and factors controlling IgE production, and may further our understanding of the development of allergic disease. In addition, an understanding of the mechanisms underlying the possible differential effect of alcoholic drink consumption on sensitization to specific allergens may facilitate a greater understanding of the biology of the sensitization process. Finally, it is clear that there are a number of factors that influence IgE levels, and which may therefore play a role in the development of allergic disease. The two articles in this issue of *Clinical and Experimental Allergy* suggest that alcoholic drink consumption, even in moderate levels, is one of these factors.

References

- 1 Vally H, de Klerk N, Thompson PJ. Alcoholic drinks: important triggers for asthma. *J Allergy Clin Immunol* 2000; 105:462–7.
- 2 Vally H, Thompson PJ. Alcoholic drinks and asthma. *Clin Exp Allergy* 2002; 32:186–91.
- 3 Linneberg A, Peterson J, Nielsen NH et al. The relationship of alcohol consumption to total immunoglobulin E and the development of immunoglobulin E sensitization: the Copenhagen Allergy Study. *Clin Exp Allergy* 2003; 33:192–8.
- 4 Gonzalez-Quintela A, Gude F, Boquete O et al. Association of alcohol consumption with total serum immunoglobulin E levels and allergic sensitization in an adult population-based survey. *Clin Exp Allergy* 2003; 33:199–206.
- 5 Smith WI Jr, Van Thiel DH, Whiteside T et al. Altered immunity in male patients with alcoholic liver disease: evidence for defective immune regulation. *Alcohol Clin Exp Res* 1980; 4:199–206.
- 6 Hallgren R, Lundin L. Increased total serum IgE in alcoholics. *Acta Med Scand* 1983; 213:99–103.
- 7 Vidal C, Quintela AG, Millan I, Gude F, Cuervas-Mons V. Serum IgE levels in liver cirrhosis. Contrasting results in alcoholic and non-alcoholic patients. *Clin Exp Allergy* 1994; 24:540–8.
- 8 Gonzalez-Quintela A, Vidal C, Gude F et al. Increased serum IgE in alcohol abusers. *Clin Exp Allergy* 1995; 25:756–64.
- 9 Gonzalez-Quintela A, Vidal C, Lojo S et al. Serum cytokines and increased total serum IgE in alcoholics. *Ann Allergy Asthma Immunol* 1999; 83:61–7.
- 10 Dominguez-Santalla MJ, Vidal C, Vinuela J, Perez LF, Gonzalez-Quintela A. Increased serum IgE in alcoholics: relationship with Th1/Th2 cytokine production by stimulated blood mononuclear cells. *Alcohol Clin Exp Res* 2001; 25:1198–205.
- 11 Gonzalez-Quintela A, Dominguez-Santalla MJ, Perez LF, Lojo S, Vidal C. Serum levels of soluble CD30 and total IgE in alcoholics. *Allergol Intern* 2002; 51:33–7.
- 12 Bjerke T, Hedegaard M, Henriksen TB, Nielsen BW, Schiøtz PO. Several genetic and environmental factors influence cord blood IgE concentration. *Pediatr Allergy Immunol* 1994; 5:88–94.
- 13 Starkenburg S, Munroe ME, Waltenbaugh C. Early alteration in leukocyte populations and Th1/Th2 function in ethanol-consuming mice. *Alcohol Clin Exp Res* 2001; 25:1221–30.

- 14 Criqui MH, Seibles JA, Hamburger RN, Coughlin SS, Gabriel S. Epidemiology of immunoglobulin E levels in a defined population. *Ann Allergy* 1990; 64:308–13.
- 15 Vidal C, Armisen M, Dominguez-Santalla MJ, Gude F, Lojo S, Gonzalez-Quintela A. Influence of alcohol consumption on serum immunoglobulin E levels in atopic and nonatopic adults. *Alcohol Clin Exp Res* 2002; 26:59–64.
- 16 Linneberg A, Jorgensen T, Nielsen NH, Madsen F, Frolund L, Dirksen A. The prevalence of skin-test-positive allergic rhinitis in Danish adults: two cross-sectional surveys 8 years apart. The Copenhagen Allergy Study. *Allergy* 2000; 55:767–72.
- 17 Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T. Increasing prevalence of specific IgE to aeroallergens in an adult population: two cross-sectional surveys 8 years apart: the Copenhagen Allergy Study. *J Allergy Clin Immunol* 2000; 106:247–52.
- 18 Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T. Factors related to allergic sensitization to aeroallergens in a cross-sectional study in adults: The Copenhagen Allergy Study. *Clin Exp Allergy* 2001; 31:1409–17.
- 19 Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T. Smoking and the development of allergic sensitization to aeroallergens in adults: a prospective population-based study. The Copenhagen Allergy Study. *Allergy* 2001; 56:328–32.
- 20 Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T. Secular trends of allergic asthma in Danish adults. The Copenhagen Allergy Study. *Respir Med* 2001; 95:258–64.
- 21 Linneberg A, Henrik Nielsen N, Frolund L, Madsen F, Dirksen A, Jorgensen T. The link between allergic rhinitis and allergic asthma: a prospective population-based study. The Copenhagen Allergy Study. *Allergy* 2002; 57:1048–52.
- 22 Nielsen NH, Linneberg A, Menne T et al. Allergic contact sensitization in an adult Danish population: two cross-sectional surveys eight years apart (the Copenhagen Allergy Study). *Acta Derm Venereol* 2001; 81:31–4.
- 23 Nielsen NH, Linneberg A, Menne T et al. Incidence of allergic contact sensitization in Danish adults between 1990 and 1998; the Copenhagen Allergy Study. *Denmark Br J Dermatol* 2002; 147:487–92.
- 24 Sly RM. Changing prevalence of allergic rhinitis and asthma. *Ann Allergy Asthma Immunol* 1999; 82:233–48; (quiz: 248–52).
- 25 Nolte H, Backer V, Porsbjerg C. Environmental factors as a cause for the increase in allergic disease. *Ann Allergy Asthma Immunol* 2001; 87:7–11.
- 26 Burrows B, Halonen M, Barbee RA, Lebowitz MD. The relationship of serum immunoglobulin E to cigarette smoking. *Am Rev Respir Dis* 1981; 124:523–5.
- 27 Warren CP, Holford-Strevens V, Wong C, Manfreda J. The relationship between smoking and total immunoglobulin E levels. *J Allergy Clin Immunol* 1982; 69:370–5.
- 28 Oryszczyn MP, Annesi I, Neukirch F, Dore MF, Kauffmann F. Relationships of total IgE level, skin prick test response, and smoking habits. *Ann Allergy* 1991; 67:355–8.
- 29 Jarvis D, Luczynska C, Chinn S, Burney P. The association of age, gender and smoking with total IgE and specific IgE. *Clin Exp Allergy* 1995; 25:1083–91.
- 30 Barbee RA, Kaltenborn W, Lebowitz MD, Burrows B. Longitudinal changes in allergen skin test reactivity in a community population sample. *J Allergy Clin Immunol* 1987; 79:16–24.
- 31 Jarvis D, Chinn S, Luczynska C, Burney P. The association of smoking with sensitization to common environmental allergens: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999; 104:934–40.
- 32 Wuthrich B, Schindler C, Medici TC, Zellweger JP, Leuenberger P. IgE levels, atopy markers and hay fever in relation to age, sex and smoking status in a normal adult Swiss population. SAPALDIA (Swiss Study on Air Pollution and Lung Diseases in Adults) Team. *Int Arch Allergy Immunol* 1996; 111:396–402.
- 33 Mensinga TT, Schouten JP, Rijcken B, Weiss ST, Speizer FE, van der Lende R. The relationship of eosinophilia and positive skin test reactivity to respiratory symptom prevalence in a community-based population study. *J Allergy Clin Immunol* 1990; 86:99–107.
- 34 Baldacci S, Modena P, Carrozzi L et al. Skin prick test reactivity to common aeroallergens in relation to total IgE, respiratory symptoms, and smoking in a general population sample of northern Italy. *Allergy* 1996; 51:149–56.
- 35 Cook RT. Alcohol abuse, alcoholism, and damage to the immune system – a review. *Alcohol Clin Exp Res* 1998; 22:1927–42.
- 36 Szabo G. Consequences of alcohol consumption on host defence. *Alcohol* 1999; 34:830–41.
- 37 Nelson S, Kolls JK. Alcohol, host defence and society. *Nat Rev Immunol* 2002; 2:205–9.
- 38 Peterson JD, Herzenberg LA, Vasquez K, Waltenbaugh C. Glutathione levels in antigen-presenting cells modulate Th1 versus Th2 response patterns. *Proc Natl Acad Sci USA* 1998; 95:3071–6.
- 39 Waltenbaugh C, Vasquez K, Peterson JD. Alcohol consumption alters antigen-specific Th1 responses: mechanisms of deficit and repair. *Alcohol Clin Exp Res* 1998; 22:220S–3S.
- 40 Latif O, Peterson JD, Waltenbaugh C. Alcohol-mediated polarization of type 1 and type 2 immune responses. *Front Biosci* 2002; 7:a135–47.
- 41 Laso FJ, Iglesias MC, Lopez A, Ciudad J, San Miguel JF, Orfao A. Increased interleukin-12 serum levels in chronic alcoholism. *J Hepatol* 1998; 28:771–7.
- 42 Laso FJ, Iglesias-Osma C, Ciudad J, Lopez A, Pastor I, Orfao A. Chronic alcoholism is associated with an imbalanced production of Th-1/Th-2 cytokines by peripheral blood T cells. *Alcohol Clin Exp Res* 1999; 23:1306–11.
- 43 Gonzalez-Quintela A, Vidal C, Gude F. Alcohol-induced alterations in serum immunoglobulin e (IgE) levels in human subjects. *Front Biosci* 2002; 7:e234–44.

H. VALLY*† and P. J. THOMPSON†

*National Centre for Epidemiology and Population Health,
The Australian National University, Canberra, and

†Asthma and Allergy Research Institute Inc. and
the Cooperative Research Centre for Asthma
The University of Western Australia, Perth
Western Australia

‡E-mail: hvally@cyllene.uwa.edu.au