

Original Article

Serum levels of soluble CD30 and total IgE in alcoholics

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ABSTRACT

Background: Total serum IgE may be increased in alcoholics. IgE synthesis depends on B cell activation by Th2-type cytokines. Serum sCD30 has been proposed as a marker of Th2 responses. The aim of the present study was to evaluate serum sCD30 levels in alcoholics and their relationship with serum IgE values.

Methods: Twenty-five active alcoholics and 18 healthy controls were included in the study. All subjects were non-atopic (asymptomatic from the allergologic point of view and Phadiatop® (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden) negative). Serum IgE was measured by chemiluminescent enzyme immunoassay and serum sCD30 was assayed by ELISA.

Results: Total serum IgE was higher in alcoholics than in controls (median (range) for alcoholics and controls 59 (15.8–236) vs 24 (4–103) IU/mL, respectively; $P = 0.003$). Conversely, median serum sCD30 levels were lower in alcoholics than in controls (< 1 (< 1 –144) vs 7.3 (< 1 –83) U/mL, respectively; $P = 0.02$). Among the alcoholics, a negative correlation between serum IgE and sCD30 values was observed.

Conclusions: Increased serum IgE in non-atopic alcoholics is associated with low serum sCD30 concentrations. In so far as sCD30 is a marker of Th2 activation, total serum IgE elevation in alcoholics does not seem to be related to Th2 dominance.

Key words: alcohol, IgE, Ki-1, sCD30.

INTRODUCTION

CD30 is a cytokine receptor that was originally described as the surface molecule recognized by the Ki-1 monoclonal antibody in Hodgkin's and Reed–Sternberg cells, as well as in a variety of non-Hodgkin's lymphomas.¹ The extracellular portion of CD30 can be split to produce an 88 kDa soluble form of the molecule (sCD30), which is released by CD30-expressing cells.² Membrane CD30 is preferentially expressed (and, therefore, sCD30 released) by human T cells producing Th2-type cytokines.^{3,4} Moreover, sCD30 has been proposed as a marker of Th2-type responses *in vivo*.^{3,4}

IgE synthesis needs Th2-type cytokine (particularly interleukin (IL)-4 and IL-13) action on B cells and, therefore, conditions involving increased IgE levels are suggestive of Th2 cytokine predominance.⁵ Accordingly, many Th2-driven disorders, such as atopy, Hodgkin's disease, human immunodeficiency virus (HIV) infection, infectious mononucleosis, measles, chronic hepatitis B, systemic lupus erythematosus, bullous pemphigoid and Ommenn's syndrome, are characterized by both increased total serum IgE levels⁶ and increased serum sCD30 concentrations.^{7–15}

Alcoholism is associated with increased total serum IgE levels.^{16–20} Ethanol intake in mothers is related to elevated cord blood IgE levels in their offspring.²¹ Experimental ethanol administration in mice induces an increase in IgE.²² Alcohol abuse is accompanied by profound alterations of the cytokine balance.^{19,20,23} It could be suggested that a Th2-predominance was responsible for increased serum IgE levels in alcoholics. The aim of the present study was to evaluate the possible correlation between serum IgE values and sCD30 levels in alcoholics.

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METHODS

Subjects

Twenty-five patients (21 males; 84%) with a median age of 41 years (range 30–70 years) entered the study. All were admitted to hospital with ethanol withdrawal symptoms. They were chronic alcohol abusers, with an average alcohol intake of more than 120 g/day for a minimum of 5 years up to 24–48 h before admission. Ten (40%) were current smokers. Eighteen healthy volunteers (personnel and students from our center), aged 22–60 years, 15 males (83%), with an average alcohol intake lower than 30 g/week, were used as controls. Six healthy controls (33%) were smokers.

All patients and controls included in this study were non-atopic. They denied a present or past history of allergic diseases and had a negative serum UniCAP™-Phadiatop® test (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden). Phadiatop® is a single serologic test (qualitative fluoroenzymeimmunoassay) for the differential determination of specific IgE antibodies to common inhalant allergens, which evaluates the overall degree of sensitization to these allergens. It may be a useful tool to classify individuals as atopics or non-atopics in epidemiologic studies with a particularly high negative predictive value.²⁴ Other known causes of either IgE increase or sCD30 elevation were absent in all subjects studied.

Procedures

Samples of sera were taken during the first 24 h of the hospital stay and stored at -80°C until tested. Serum sCD30 values were assayed by means of a commercially available ELISA kit (Dako CD30; DAKO A/S, Glostrup, Denmark). The lowest detection limit of the assay was 1 U/mL. Total serum IgE was measured by a chemiluminescent enzyme immunoassay (Immulite™; Diagnostic Products, Los Angeles, CA, USA). The lowest detection limit for total serum IgE was 2 IU/mL. Routine serum biochemical parameters in alcoholics were assayed in a Hitachi 747 autoanalyzer (Boehringer-Mannheim, Mannheim, Germany).

Ethical issues

The study was performed in accordance with the principles of the 1975 Declaration of Helsinki and was approved by the local Research Committee.

Statistical analysis

The Chi-squared test was used to compare dichotomous variables. The two-tailed Mann–Whitney *U*-test was used to compare continuous variables, because most of them did not fulfill criteria of normality. For the same reason, Spearman's rank test was used for bivariate correlation. For statistical analysis, values below the aforementioned levels of detection were considered as zero. $P < 0.05$ was considered statistically significant.

RESULTS

Serum IgE and sCD30 concentrations in alcoholics and controls are shown in Fig. 1. Total serum IgE levels were higher in alcoholics than in controls (median (range)

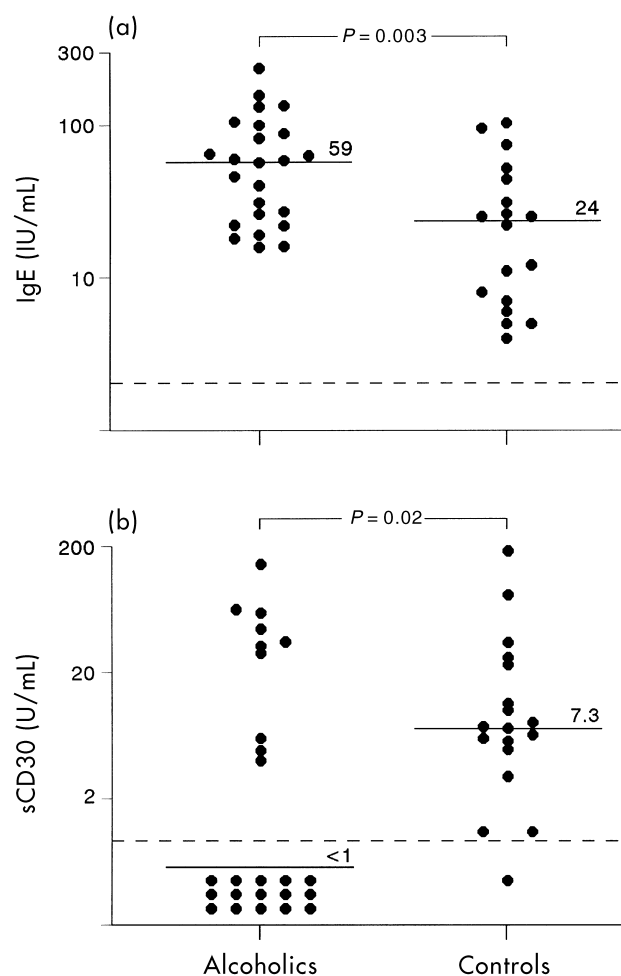


Fig. 1 Serum levels (log) of (a) total IgE and (b) sCD30 in alcoholics and healthy controls. Horizontal solid lines represent median values. Horizontal dashed lines represent the lower reference threshold levels.

values of 59 (15.8–236) vs 24 (4–103) IU/mL, respectively; $P = 0.003$). Conversely, serum sCD30 levels were lower in alcoholics than in controls (< 1 (< 1 –144) vs 7.3 (< 1 –83) U/mL, respectively; $P = 0.02$). Fifteen alcoholics (60%) had undetectable serum sCD30 levels compared with only one control (5%; $P < 0.001$). A comparison of epidemiologic and biologic data between alcoholic patients with detectable and undetectable sCD30 values is given in Table 1. Age, gender, smoking habit and liver function tests were similar in patients with detectable and undetectable sCD30 concentrations. Serum IgE values were significantly higher in cases with undetectable sCD30 concentrations (Table 1). Serum sCD30 levels showed a weak but statistically significant negative correlation with serum IgE concentrations ($r = -0.40$; $P = 0.008$). Such a correlation was observed in the group of alcoholics ($r = -0.48$; $P = 0.01$), but not in the control group ($r = 0.10$; $P = 0.6$).

DISCUSSION

Previous studies have demonstrated that serum IgE is elevated in alcoholics, independent of age, gender, smoking, nutritional status, liver function or parasite infestation.^{18–22} However, most of these studies classified patients as atopic or non-atopic only by clinical history.^{16–19} Atopy affects as much as 30% of the population and is associated with Th2 dominance and increased serum concentrations of both sCD30 and IgE.⁷ In the present study, increased serum IgE was confirmed in a group of non-atopic (clinically asymptomatic and Phadiatop[®] negative) alcoholics. Similar results were

obtained when alcoholics were stratified as atopics or non-atopics by means of skin prick tests.²⁰

A Th2-cytokine predominance could be a hypothesis for IgE increase in alcoholics. Total serum IgE increase in alcoholics was found to be associated with elevated circulating levels of IL-10 and IL-13.¹⁹ However, Laso *et al.* demonstrated that peripheral blood T cells from active alcoholics produce increased quantities of interferon- γ , the main Th1 cytokine.²⁵ Similarly, we observed that increased IgE in alcoholics is associated with a paradoxically low production of IL-4, the main Th2 cytokine.²⁰ Furthermore, alcoholics show increased levels of IL-12,¹⁹ the main promoter of Th1 development. Here, increased IgE in non-atopic alcoholics was associated with low serum sCD30 levels. Low serum sCD30 values in alcoholics could be due to either downregulated CD30 expression or decreased sCD30 release. The number of peripheral blood CD30⁺ cells was not evaluated. With this limitation, low sCD30 levels would confirm a decreased Th2 activation and, therefore, a Th1 predominance in this group of patients. However, although it is generally assumed that CD30 expression/sCD30 release represents Th2 activation, some reports conclude that CD30 may not be an exclusive marker for Th2-type responses.²⁶ Increased serum sCD30 values have been found in Th1-driven conditions, such as rheumatoid arthritis and Wegener's granulomatosis.²⁶ In Th2-mediated conditions, sCD30 could be a marker of disease activity, while in Th1-mediated diseases CD30-positive cells would exert an anti-inflammatory counter-regulatory activity.²⁶ The Th1/Th2 dichotomy is more evident in the mouse than it is in the human and, as Gerli *et al.* pointed

Table 1 Epidemiologic and biologic data in alcoholic patients with detectable (≥ 1 U/mL) and undetectable (< 1 U/mL) sCD30 values

	Detectable sCD30 (n = 10)	Undetectable sCD30 (n = 15)	P
Age (years)	48 (30–60)	41 (31–70)	0.9
No. males (%)	7 (70)	14 (93)	0.3
No. smokers (%)	4 (40)	6 (40)	1
Serum albumin (g/dL)	3.7 (2.2–4.7)	3.8 (3.0–4.8)	0.7
Serum bilirubin (mg/dL)	1.2 (0.3–7.4)	1.4 (0.5–15.9)	0.6
Serum AST (U/L)	68 (14–107)	50 (14–226)	0.9
Serum ALT (U/L)	46 (19–80)	31 (11–182)	0.3
Serum GGT (U/L)	237 (52–3850)	95 (19–997)	0.1
Prothrombin index (%)	96 (50–100)	100 (59–100)	0.4
Total serum IgE (IU/mL)	28.3 (16–100)	64.8 (15.8–236)	0.01

Data are represented as the median and range in parentheses or as absolute values and percentages in parentheses.

The upper normal reference values for aspartate aminotransferase (AST), alanine aminotransferase (ALT) and glutamyl transpeptidase (GGT) are 28, 29 and 32 U/L, respectively.

out, the concept of Th1 or Th2 predominance in a particular disease should not be overemphasized, because either subset may play a dynamic role modulating the immune response over time.²⁶ Alcoholism is such an example, because it is associated with both Th1- and Th2-driven phenomena, as mentioned previously. The mechanisms for these simultaneous Th1 and Th2 phenomena in alcoholics are unknown. Endotoxemia, which is common after ethanol intake,²⁷ could drive both Th1 and Th2 development,²⁸ including IgE synthesis,²⁹ but this hypothesis needs further investigation.

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