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*Case Report*

# Serendipity in Medicine-Elevated Immunoglobulin E Levels Associated with Excess Alcohol Consumption

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**Abstract:** Making a diagnosis of alcoholic liver disease is not always easy. There are problems in obtaining an accurate and reliable history of alcohol consumption. Laboratory findings and hepatic imaging studies are neither sensitive or specific, and newer test are being considered. Recently, a patient was admitted with possible alcoholic hepatitis. The first-year resident who admitted the patient mistakenly ordered a blood test for serum IgE. The result was a markedly elevated −6440 IU/mL. There was no evidence of parasitic infections, atopy or autoimmune disease nor was there any eosinophilia. A literature search showed that elevated IgE levels are associated with alcohol abuse. This association has been forgotten and does not appear in standard reference sources such as UptoDate or Harrison's Principles of Internal Medicine. This judicious use of examining serum IgE levels may aid in the diagnosis of alcoholic hepatitis.

**Keywords:** alcohol consumption; biomarkers; immunoglobulin IgE; alcohol-induced liver damage



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## 1. Introduction

Increasingly, modern medical care is being protocol-driven, both in terms of diagnosis and therapy. Many electronic medical records bundle various steps of the diagnostic and therapeutic cascade in order to facilitate compliance. We have recently encountered a case where the ordering of a blood test that was off protocol gave a result that proved to be clinically useful and reminded us of a well described, but forgotten, laboratory test.

Excessive alcohol consumption is a worldwide phenomenon and a major cause of cirrhosis and its complications including hepatocellular carcinoma. The diagnosis of alcoholic liver disease can be challenging. The history of excessive alcohol consumption is often denied by both the patient and the family. The finding of a steatotic liver on imaging tests is very common and can be due to metabolic-associated steatotic liver disease (MASLD), alcoholic liver disease (ALD) and a combination of the two: metabolic- and alcohol-related/associated liver disease (Met-ALD).

## 2. Case Report

A 60-year-old man was admitted to our department due to abdominal pain and jaundice. The pain was in the inguinal area and was exacerbated by coughing. In addition, he had lost 20 kg in weight during the previous 6 months. Furthermore, he reported yellow urine with no pruritus for the last week. His past medical history included a road traffic accident in 1988 previously accompanied by post-traumatic stress disorder (PTSD), accompanied by the daily consumption of 2 L of vodka per day for the last 30 years and a 30 pack history of cigarette smoking, which had ceased 10 years previously. His regular medication consisted of mirtazapine and trazodone, which he had been receiving for many years.

On examination, he was clinically jaundiced, with a blood pressure of 157/103 mmHg and a pulse rate of 123 per minute, and apyrexial. His heart sounds were regular and normal, and there were no clinical signs of heart failure. His abdominal examination was normal except for mild inguinal tenderness with no evidence for hernias. There was no hepatosplenomegaly. The remainder of the examination was non-contributory.

Both a chest X-ray and an abdominal X-ray were normal. An ultrasound examination of the abdomen showed a fatty liver of normal size (Figure 1), no splenomegaly, no dilation of the biliary ductal system and no evidence of either cholelithiasis or cholecystitis. A doppler examination showed normal portal blood flow.

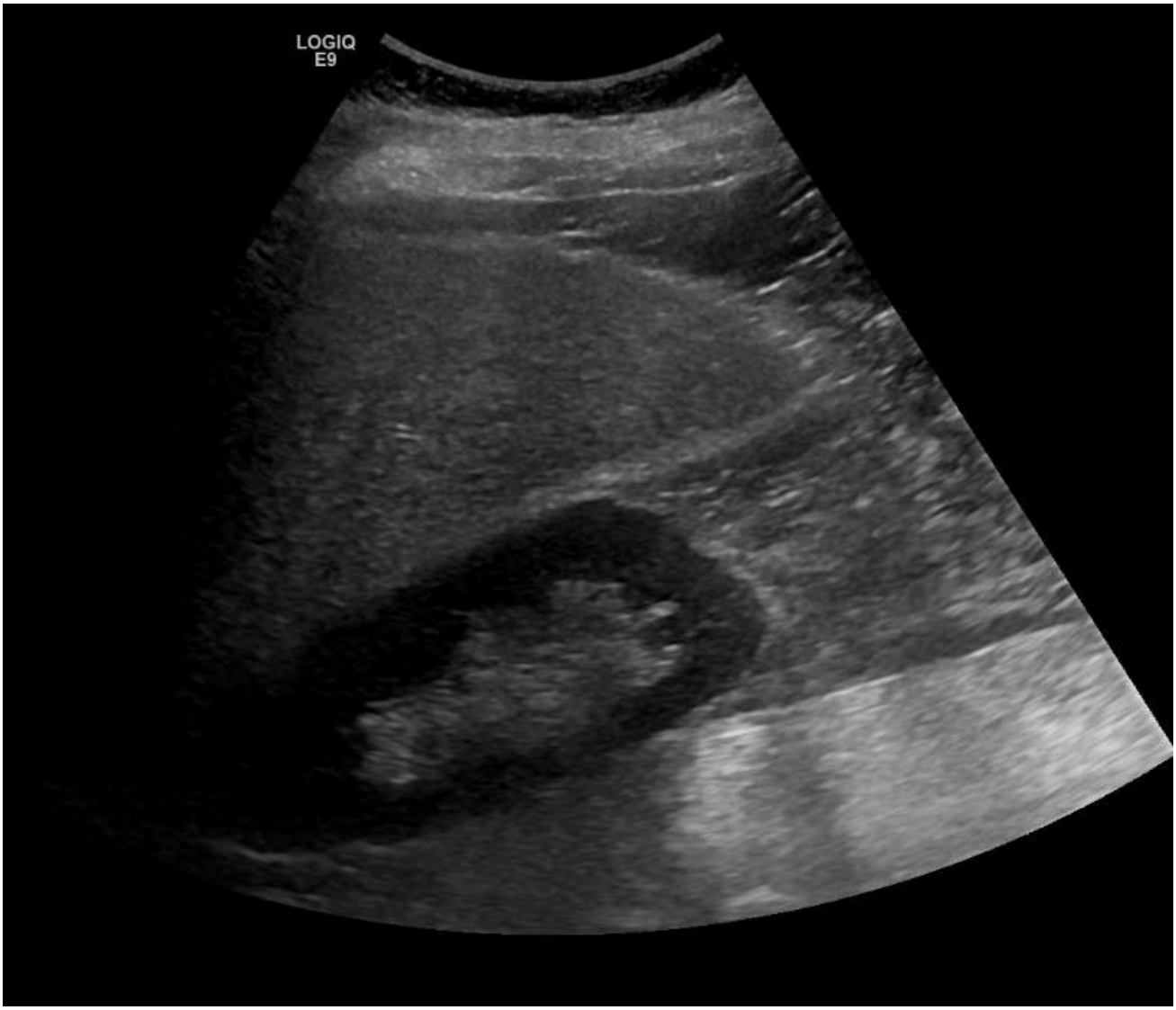


**Figure 1.** An ultrasound examination showed a hyperechogenic liver compared to the kidney consistent with steatosis.

The laboratory test results are shown in Table 1. There is an elevation of the liver enzymes, with an AST/ALT ratio higher than 2 on only two tests and a GGT level higher than 1000 IU/L. On the 28th of November, the AST/ALT ratio was 1.45 when the serum IgE was elevated. Thus, the diagnosis was supported prior to the determination of the AST/ALT ratio being above 2. These findings are suggestive of a toxic hepatitis and, in view of the history of chronic alcohol abuse, suggestive of alcoholic hepatitis. In addition, the MCV was 102.7 fL with a normal vitamin B12 level, normal folic acid level, normal

thyroid function and no evidence for hemolysis which is consistent with excess alcohol consumption.

**Table 1.** Biochemical markers.

| | AST (GOT) U/L | ALT (GPT) U/L | LDH–U/L | ALK PHOSPHATASE—U/L | GGT—U/L | BILIRUBIN TOTAL—mg/dL | BILIRUBIN DIRECT mg/dL | IgE IU/mg |
|---|---|---|---|---|---|---|---|---|
| 19 January 2021 | 58 | 56 | - | - | - | - | - | - |
| 21 January 2021 | 149 | 115 | - | 87 | 216 | 1.14 | 0.27 | - |
| 17 January 2022 | 20 | 17 | - | 81 | 25 | 0.7 | 0.13 | - |
| 28 June 2023 | 245 | 183 | - | - | 219 | - | - | - |
| 27 November 2023 | 273 | 168 | 855 | 125 | 1109 | 5.2 | 3.3 | - |
| 28 November 2023 | 182 | 130 | 685 | 101 | 1007 | 5.5 | 3.5 | 6440 |
| 29 November 2023 | 261 | 156 | 819 | 124 | 1144 | 6.2 | 4.1 | - |
| 30 November 2023 | 329 | 145 | 696 | 115 | 984 | 4.7 | 3.4 | - |
| 01 December 2023 | 329 | 160 | 731 | 127 | 1053 | 4 | 2.8 | - |
| 03 December 2023 | - | 204 | - | 136 | 1081 | 2.9 | - | - |
| 04 December 2023 | 314 | 190 | 552 | 140 | 943 | 2.3 | 1.4 | - |
| 05 December 2023 | 338 | 191 | 573 | 134 | 866 | 2 | 1.3 | 5010 |

The patient was treated with the serotonin inhibitors mirtazapine and trazodone for PTSD. These medications could be a cause of hepatotoxicity with idiosyncratic reactions and changes in immunoglobulins [1,2]. The reports of hepatotoxicity range from a few days to 3 years [1].

However, our patient was treated with these medications for much longer. Thus, it is unlikely that the change in liver enzyme levels was a result of a drug-induced liver injury.

A markedly elevated serum immunoglobulin E (IgE) level was noted. We do not routinely check IgE levels, and this test was ordered by the on-call intern in error. The reason for the marked elevation of IgE was not clear. There was no history of atopy and no peripheral eosinophilia and no evidence for parasitic infection on stool pathogen PCR testing. The IgE level decreased at discharge to 5010 IU/L but was at a similar level 2 weeks later, consistent with his continued consumption of alcohol.

A PubMed search using the keywords "immunoglobulin E and alcoholic liver disease" yielded sixteen results, of which 7 were determined to be relevant. The publication dates ranged from 1981 to 2012. In spite of this, there was no mention of elevated IgE levels being associated with excess alcohol consumption in either UptoDate or Harrison's Principles of Internal Medicine.

In addition, we have recently seen a 70-year-old man with a history of alcoholic cirrhosis who was admitted with a bilateral leg edema. There was a decrease in serum albumin to 3.1 g/dL and no evidence for deep vein thrombosis in a Doppler ultrasound examination of both legs. The serum AST was 36 U/L, the ALT 16 U/L and the GGT elevated at 241 U/L.

Echocardiography showed no evidence of systolic dysfunction, mild diastolic dysfunction and a normal pro-BNP level of 232.6 pg/mL. This patient was of Ethiopian origin and was also HIV positive but treated with emtricitabine, bictegravir and tenofovir alafenamide. There was no HIV viremia, and the CD4 count was normal.

In view of the possibility of strongyloidiasis, antibody and stool tests were ordered and were negative. The total eosinophil count was 80/mL. In view of the history of alcohol abuse with cirrhosis and previous episodes of pancreatitis, we ordered a serum IgE level

which was markedly elevated to 9170 IU/mL. These findings suggest there is ongoing alcohol misuse with no acute complications.

## 3. Discussion

The association of elevated IgE levels with alcohol misuse is not well known. It is not routinely checked in Israel in cases of alcohol misuse. As a result of the unexpected and unordered test result, we reviewed the medical literature.

There are many medical conditions that are associated with elevated serum IgE levels. These include infectious parasitic diseases such as ascaris, schistosomiasis and strongyloides. Other infectious causes include human immunodeficiency virus (HIV) infection, mycobacterium tuberculosis, cytomegalovirus, the Epstein–Barr virus, leprosy and candidiasis. Atopic diseases including allergic bronchopulmonary aspergillosis, allergic fungal dermatitis, allergic asthma, and allergic rhinitis are also associated with elevated IgE levels. There was no evidence in our patients of any of these illnesses after carrying out the routine laboratory testing. Other rarer causes of elevated IgE include immunodeficiency syndromes such as hyperimmunoglobulin E syndrome, Wiskott–Aldrich syndrome, Netherton disease, Nezelof syndrome, Omenn syndrome, atypical complete DiGeorge syndrome, immune dysregulation polyendocrinopathy, and enteropathy X-linked syndrome (IPEX) which our patient did not have. In addition, neoplastic diseases such as Hodgkin lymphoma and IgE myeloma, inflammatory disorders including eosinophilic granulomatosis with polyangiitis, Kawasaki disease and Kimura disease were not present.

Other causes of elevated IgE levels include tobacco smokers, cystic fibrosis, nephrotic syndrome, bone marrow transplantation, graft-versus-host disease and bullous pemphigoid. Our patient was a non-smoker for the last 10 years and did not have any of the other conditions. Rarely, the administration of the antibiotics aztreonam and penicillin G can be linked to IgE elevation, but our patient had not received these medications.

In industrialized countries, allergic disease is the most common cause, whereas parasitic infections are the commonest cause in developing countries.

In the 1980 and 1990s, there were reports of increased serum IgE levels in alcohol misusers [3–8] and also moderate drinkers [9,10]. Upon stopping alcohol consumption, there is a decrease in the IgE levels [5,11].

Nonatopic alcohol misusers have serum IgE levels between 130 and 150 IU/mL compared to nonatopic controls with levels between 20 and 40 IU/mL [5–7]. In addition, approximately 15% of nonatopic patients who misuse alcohol have IgE levels greater than 1000 IU/mL. Our patient had an IgE level of 6440 IU/mL in the absence of an infectious, allergic or systemic cause. However, some alcoholic abuse patients have serum IgE levels of less than 10 I U/mL, suggesting that other factors are involved.

Advanced liver disease often results in hypergammaglobulinemia, but it does not seem that this is the cause of the increased IgE levels. Serum IgE levels are not increased in the majority of patients with non-alcoholic liver disease. An increase in serum IgE levels has been reported in patients with hepatitis A and B [12], but normal levels were shown to be present in both chronic HCV hepatitis [13] and primary biliary cholangitis [14]. There is a report suggesting that IgE elevation is only present in cirrhosis [15], but this was not confirmed in a larger study of patients with steatotic liver disease, fibrosis, alcoholic hepatitis or cirrhosis [5,7]. IgE elevation in alcoholics is unrelated to the levels of IgA, IgM or IgG [5,6,16].

There was little laboratory evidence to explain this observation until Alonso and colleagues reported a study in mice receiving either an isocaloric semi-liquid diet or a semi-liquid diet containing alcohol [17].

Eight groups of at least six mice were studied. Two different strains of mice (Swiss and C57BL/6) were included. They were grouped by male and female gender, mouse strain, alcohol administration or control diet. This was carried out in order to examine if there was a different effect depending on mouse strain or gender. There has been reported an effect

of sex hormones on the immune response [18]. In addition, there is also an effect of gender on the immunological disturbances induced by alcohol [19–21].

Immunoglobulin levels were checked at baseline and weekly for 4 weeks. Initially, the mice aged 10–12 weeks old were fed a standard chow diet and water *ad* libitum. The mice receiving alcohol were fed ethanol at 6.5% $v/v$ and a purified rodent diet *ad* libitum. The control mice received the liquid rodent diet isocalorically matched to the mice receiving alcohol. Serum levels of IgG1, IgG2a, IgG2b, IgG3, IgA and IgM were measured in addition to serum IgE levels. Furthermore, ineterleukin-13, interleukin-4 and interferon-gamma concentrations were measured.

Within 2 weeks of initiating alcohol administration, there was an increase in levels of serum IgE but not in serum IgA or IgM. The increase in IgE was associated with an increase in the IL-13 concentration in the serum. In addition, there was a decrease in serum IgG subclass concentrations. These findings were found in both the Swiss and C57BL/6 mice strains.

Immunoglobulin levels decrease rapidly after abstinence from alcohol. The half-life of serum IgE is three days. Patients that misused alcohol with the shortest period of abstention were found to have the highest IgE levels [3]. In this study, the levels in seven patients who misused alcohol with samples taken immediately after stopping drinking were found to decline during a 16-day period of observation. Another study of 25 patients who misused alcohol that compared admission IgE levels to a repeat test 2 to 4 weeks later found reductions in 20 of these patients and an average decrease of 50% [15]. Another study of 39 hospitalized patients with alcoholic liver disease who had repeat IgE determination after 14 days found a decrease in mean serum IgE from 147 Iu/mL to 106 Iu/mL. In addition, the repeat IgE level was lower than the first one in 29 of 39 patients, with a mean decrease of 25% [22].

Possible mechanisms for the increase in serum IgE in patients who misuse alcohol have been discussed by Gonzalez-Quintela et al. [5]. The authors suggest that it is unlikely that the increased levels of IgE are a result of decreased catabolism and more probable to result from an increase in IgE synthesis. IgE synthesis requires a twostep mechanism—the first is from Th2-derived cytokines (IL4 or Il-13) and the second results from the response of surface antigen CD-40 with a ligand on activated T cells [23,24].

It seems that the IgE increase associated with alcohol misuse is not related to the severity of the liver injury. There is a report of IgE elevation only being present in patients with fibrosis or cirrhosis [15]. However, larger studies have found that the IgE increase is similar in patients with fatty liver, liver fibrosis, alcoholic hepatitis or cirrhosis [7,22].

The diagnosis of alcohol abuse disorder can be challenging. The medical history is unreliable, often from both the patients and their families and friends. Attempts to improve the diagnostic accuracy include the use of the CAGE questionnaire [25] and the AUDIT-C test in primary care [26]. The combination of these questions and laboratory tests can improve the diagnostic accuracy [27]. Patients with alcoholic hepatitis often have an increased MCV, an elevated GGT and an AST/ALT ratio greater than 2 [28,29]. This ratio may help distinguish alcoholic hepatitis from NAFLD [30]. In our patient, the ratio of AST/ALT was only greater than 2 on one test. In this case, the extreme elevation in the serum level of IgE and its subsequent decline upon the cessation of alcohol consumption supported the diagnosis. Recently, it has been proposed to test for elevated ethyl glucuronide levels in hair, which may be present for up to 3–6 months after the cessation of alcohol consumption [31]. Due to the elevated BMI and hypertension, it is likely that this patient had the metabolic syndrome as well. Another test used to determine the alcohol misuse is carbohydrate-deficient transferrin (CDT) [32,33]. CDT has received attention as a potential biological marker for heavy drinking or as an objective marker of relapse in patients who are treated for alcohol detoxification and is used to monitor patients misusing alcohol and presenting other co-morbidities [34–37].

Medicine is an inexact science, and the diagnosis of alcoholic hepatitis and alcoholic liver disease is not always obvious. The forgotten test of elevated serum IgE levels deserves

rehabilitation and may aid clinicians in search of a diagnosis. In the era of MASLD and the new diagnosis of Met-ALD, there may be a role for the selective determination of serum IgE for assessing for alcohol misuse disease. The lack of mention of an elevated IgE level associated with recent alcohol misuse in major textbooks is important. These sources are in widespread use on a daily basis worldwide in order to provide the best information available at the bedside. The fact that a simple and easily available test may aid in the diagnosis of patients with alcohol misuse and be an aid in checking for abstinence is important. SDHM is an experienced internist and gastroenterologist and was not aware of this finding. Most of his colleagues are not aware of this finding, and thus, it is not part of their teaching to the next generation of physicians. The data are available via a PubMed search, but this will not be routinely conducted by practicing physicians. As a result of this case, we are planning a prospective study, in our institution, to further investigate the clinical use of IgE determinations and its sensitivity in diagnosing current alcohol misuse in patients and specifically in patients with MASLD, and we will also be checking IgA levels, since IgA may be elevated in up to 70% of patients with ALD [38].

There is a need to further explore the role of IgE determination and its sensitivity and specificity for diagnosing alcohol misuse, the timeline of the decrease in levels after abstaining from alcohol and any correlation with markers of fibrosis. Since the 1980s and 1990s, there have been many changes in our understanding of the diagnosis and natural history of what is now termed steatotic liver disease. The central connection to the metabolic syndrome was not initially recognized, and there was not the range of either biochemical tests for predicting severe fibrosis or the absence of fibrosis and non-invasive imaging techniques such as elastography. The use of IgE as a marker for recent alcohol misuse may help improve the diagnostic accuracy for diagnosing MASLD and for detecting those patients who do not volunteer their history of increased alcohol consumption. Large population studies will be necessary in order to determine if there is any elevation of IgE in patients with the metabolic syndrome. In addition, by employing modern non-invasive methods of determining liver fibrosis, it will be possible to examine if IgE elevation is related to the severity of hepatic injury.

The pathogenesis of MASLD is complex, and there is an important role for the intestinal microbiome. There are similarities in many of the alterations in the microbiome between ALD and MASLD [39]. An understanding of why there is a difference in the IgE levels between these two entities and the newly defined Met-ALD is important and will require further study.

In summary, we have rediscovered the elevation of serum IgE levels in patients with ALD. Physicians need to be aware of this association, and it may aid them in detecting the undisclosed use of alcohol in patients.

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## Abbreviations

| | |
|---|---|
| ALD | Alcoholic liver disease |
| ALT | Alanine aminotransferase |
| ASH | Alcoholic steatohepatitis |
| AST | Aspartate amino transferase |
| AUD | Alcohol use disorders |
| CDT | Carbohydrate transferrin deficiency |
| MAFLD | Metabolic-associated liver disease |
| MASLD | Metabolic dysfunction-associated steatotic liver disease |
| MASH | Metabolic dysfunction-associated steatohepatitis = NASH |
| MetALD | MASLD (patients consume more than 140 g alcohol/week for women/210 g/week for men) |
| MetS | Metabolic syndrome |
| NAFLD | Nonalcoholic fatty liver disease |
| PTSD | Post-traumatic stress disorder |

## References


1. Park, S.H.; Ishino, R. Liver injury associated with antidepressants. *Curr. Drug Saf.* **2013**, *8*, 207–223. [CrossRef]
2. Billioti de Gage, S.; Collin, C.; Le-Tri, T.; Pariente, A.; Bégaud, B.; Verdoux, H.; Dray-Spira, R.; Zureik, M. Antidepressants and Hepatotoxicity: A Cohort Study among 5 Million Individuals Registered in the French National Health Insurance Database. *CNS Drugs* **2018**, *32*, 673–684. [CrossRef]
3. Hällgren, R.; Lundin, L. Increased total serum IgE in alcoholics. *Acta Med. Scand.* **1983**, *213*, 99–103. [CrossRef]
4. Gonzalez-Quintela, A.; Vidal, C.; Gude, F. Alcohol, IgE and allergy. *Addict. Biol.* **2004**, *9*, 195–204. [CrossRef] [PubMed]
5. Gonzalez-Quintela, A.; Vidal, C.; Gude, F.; Tome, S.; Lojo, S.; Lorenzo, M.J.; Becerra, E.P.; Martinez-Vazquez, J.M.; Barrio, E. Increased serum IgE in alcohol abusers. *Clin. Exp. Allergy* **1995**, *25*, 756–764. [CrossRef]
6. González-Quintela, A.; Otero-Antón, E.; Barrio, E.; Vidal, C.; Lojo, S.; Pérez, L.F.; Gude, F. Serum cytokines and increased total serum IgE in alcoholics. *Ann. Allergy Asthma Immunol. Off. Publ. Am. Coll. Allergy Asthma Immunol.* **1999**, *83*, 61–67. [CrossRef] [PubMed]
7. Domínguez-Santalla, M.J.; Vidal, C.; Viñuela, J.; Pérez, L.F.; González-Quintela, A. Increased serum IgE in alcoholics: Relationship with Th1/Th2 cytokine production by stimulated blood mononuclear cells. *Alcohol. Clin. Exp. Res.* **2001**, *25*, 1198–1205. [CrossRef]
8. Campos, J.; Gude, F.; Quinteiro, C.; Vidal, C.; Gonzalez-Quintela, A. Gene by environment interaction: The -159C/T polymorphism in the promoter region of the CD14 gene modifies the effect of alcohol consumption on serum IgE levels. *Alcohol. Clin. Exp. Res.* **2006**, *30*, 7–14. [CrossRef] [PubMed]
9. Linneberg, A.; Petersen, J.; Nielsen, N.H.; Madsen, F.; Frølund, L.; Dirksen, A.; Jørgensen, T. The relationship of alcohol consumption to total immunoglobulin E and the development of immunoglobulin E sensitization: The Copenhagen Allergy Study. *Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol.* **2003**, *33*, 192–198. [CrossRef] [PubMed]
10. González-Quintela, A.; Gude, F.; Boquete, O.; Rey, J.; Meijide, L.M.; Suarez, F.; Fernandez-Merino, M.C.; Perez, L.F.; Vidal, C. Association of alcohol consumption with total serum immunoglobulin E levels and allergic sensitization in an adult population-based survey. *Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol.* **2003**, *33*, 199–205. [CrossRef]
11. Coutinho, V.; Vidal, C.; Vizcaino, L.; Gonzalez-Quintela, A. Effect of alcohol consumption and cessation on serum total immunoglobulin E concentrations. *J. Investig. Allergol. Clin. Immunol.* **2011**, *21*, 327–329.
12. Levo, Y.; Shalit, M. Serum IgE levels in patients with liver disease. *Ann. Allergy* **1981**, *47*, 456–459.
13. González-Quintela, A.; Alende, M.R.; Lojo, S.; Perez, L.F.; Padin, E.; Tome, S.; Vidal, C. Total serum IgE levels in chronic hepatitis C: Influence of interferon alpha therapy. *Int. Arch. Allergy Immunol.* **2001**, *125*, 176–181. [CrossRef] [PubMed]
14. Minuk, G.Y.; Boyd, N.D.; Matheson, D.S.; Fritzler, M.J.; Green, B.J. Serum immunoglobulin E levels in patients with primary biliary cirrhosis. *J. Allergy Clin. Immunol.* **1989**, *83*, 462–466. [CrossRef]
15. Smith, W.I.J.; Thiel, D.H.V.; Whiteside, T.; Janoson, B.; Magovern, J.; Puet, T.; Rabin, B.S. Altered immunity in male patients with alcoholic liver disease: Evidence for defective immune regulation. *Alcohol. Clin. Exp. Res.* **1980**, *4*, 199–206. [CrossRef]
16. Vidal, C.; Quintela, A.G.; Millán, I.; Gude, F.; Cuervas-Mons, V. Serum IgE levels in liver cirrhosis. Contrasting results in alcoholic and non-alcoholic patients. *Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol.* **1994**, *24*, 540–548. [CrossRef]
17. Alonso, M.; Gomez-Rial, J.; Gude, F.; Vidal, C.; Gonzalez-Quintela, A. Influence of experimental alcohol administration on serum immunoglobulin levels: Contrasting effects on IGE and other immunoglobulin classes. *Int. J. Immunopathol. Pharmacol.* **2012**, *25*, 345–355. [CrossRef] [PubMed]
18. Giltay, E.J.; Fonk, J.C.M.; Von Blomberg, B.M.E.; Drexhage, H.A.; Schalkwijk, C.; Gooren, L.J.G. In vivo effects of sex steroids on lymphocyte responsiveness and immunoglobulin levels in humans. *J. Clin. Endocrinol. Metab.* **2000**, *85*, 1648–1657. [CrossRef] [PubMed]

19. Grossman, C.J.; Nienaber, M.; Mendenhall, C.L.; Hurtubise, P.; Roselle, G.A.; Rouster, S.; Weber, N.; Schmitt, G.; Gartside, P.S. Sex differences and the effects of alcohol on immune response in male and female rats. *Alcohol. Clin. Exp. Res.* **1993**, *17*, 832–840. [CrossRef]
20. Kono, H.; Wheeler, M.D.; Rusyn, I.; Lin, M.; Seabra, V.; Rivera, C.A.; Bradford, B.U.; Forman, D.T.; Thurman, R.G. Gender differences in early alcohol-induced liver injury: Role of CD14, NF-kappaB, and TNF-alpha. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2000**, *278*, G652–G661. [CrossRef]
21. Nanji, A.A.; Jokelainen, K.; Fotouhinia, M.; Rahemtulla, A.; Thomas, P.; Tipoe, G.L.; Su, G.L.; Dannenberg, A.J. Increased severity of alcoholic liver injury in female rats: Role of oxidative stress, endotoxin, and chemokines. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2001**, *281*, G1348–G1356. [CrossRef]
22. González-Quintela, A.; Vidal, C.; Gude, F. Alcohol-induced alterations in serum immunoglobulin E (IgE) levels in human subjects. *Front. Biosci.* **2002**, *7*, e234–e244.
23. Bacharier, L.B.; Geha, R.S. Molecular mechanisms of IgE regulation. *J. Allergy Clin. Immunol.* **2020**, *105*, S547–S558. [CrossRef] [PubMed]
24. Ryan, J.J. Interleukin-4 and its receptor: Essential mediators of the allergic response. *J. Allergy Clin. Immunol.* **1997**, *99*, 1–5. [CrossRef] [PubMed]
25. Bush, B.; Shaw, S.; Cleary, P.; Delbanco, T.L.; Aronson, M.D. Screening for alcohol abuse using the CAGE questionnaire. *Am. J. Med.* **1987**, *82*, 231–235. [CrossRef]
26. Higgins-Biddle, J.C.; Babor, T.F. A review of the Alcohol Use Disorders Identification Test (AUDIT), AUDIT-C, and USAUDIT for screening in the United States: Past issues and future directions. *Am. J. Drug Alcohol Abus* **2018**, *44*, 578–586. [CrossRef]
27. Skinner, H.A.; Holt, S.; Schuller, R.; Roy, J.; Israel, Y. Identification of alcohol abuse using laboratory tests and a history of trauma. *Ann. Intern. Med.* **1984**, *101*, 847–851. [CrossRef] [PubMed]
28. Lucey, M.R.; Mathurin, P.; Morgan, T.R. Alcoholic hepatitis. *N. Engl. J. Med.* **2009**, *360*, 2758–2769. [CrossRef]
29. Cohen, J.A.; Kaplan, M.M. The SGOT/SGPT ratio—An indicator of alcoholic liver disease. *Dig. Dis. Sci.* **1979**, *24*, 835–838. [CrossRef]
30. Sorbi, D.; Boynton, J.; Lindor, K.D. The ratio of aspartate aminotransferase to alanine aminotransferase: Potential value in differentiating nonalcoholic steatohepatitis from alcoholic liver disease. *Am. J. Gastroenterol.* **1999**, *94*, 1018–1022. [CrossRef]
31. Staufer, K.; Huber-Schönauer, U.; Strebinger, G.; Pimingstorfer, P.; Suesse, S.; Scherzer, T.M.; Paulweber, B.; Ferenci, P.; Stimpfl, T.; Yegles, M.; et al. Ethyl glucuronide in hair detects a high rate of harmful alcohol consumption in presumed non-alcoholic fatty liver disease. *J. Hepatol.* **2022**, *77*, 918–930. [CrossRef]
32. Stibler, H. Carbohydrate-deficient transferrin in serum: A new marker of potentially harmful alcohol consumption reviewed. *Clin. Chem.* **1991**, *37*, 2029–2037. [CrossRef] [PubMed]
33. Golka, K.; Wiese, A. Carbohydrate-deficient transferrin (CDT)—A biomarker for long-term alcohol consumption. *J. Toxicol. Environ. Health B Crit. Rev.* **2004**, *7*, 319–337. [CrossRef]
34. Hermansson, U.; Helander, A.; Brandt, L.; Huss, A.; Rönnberg, S. The Alcohol Use Disorders Identification Test and carbohydrate-deficient transferrin in alcohol-related sickness absence. *Alcohol. Clin. Exp. Res.* **2002**, *26*, 28–35. [CrossRef]
35. Nanau, R.M.; Neuman, M.G. Biomolecules and Biomarkers Used in Diagnosis of Alcohol Drinking and in Monitoring Therapeutic Interventions. *Biomolecules* **2015**, *5*, 1339–1385. [CrossRef]
36. Neuman, M.G.; Schmilovitz-Weiss, H.; Hilzenrat, N.; Bourliere, M.; Marcellin, P.; Trepo, C.; Mazulli, T.; Moussa, G.; Patel, A.; Baig, A.A.; et al. Markers of inflammation and fibrosis in alcoholic hepatitis and viral hepatitis C. *Int. J. Hepatol.* **2012**, *2012*, 231210. [CrossRef] [PubMed]
37. Neuman, M.G.; Schneider, M.; Nanau, R.M.; Parry, C. Alcohol Consumption, Progression of Disease and Other Comorbidities, and Responses to Antiretroviral Medication in People Living with HIV. *AIDS Res. Treat.* **2012**, *2012*, 751827. [CrossRef] [PubMed]
38. Elias, E.D.; Uhanova, J.; Minuk, G.Y. Serum immunoglobulin a levels and alcohol-induced liver disease. *Can. Liver J.* **2020**, *3*, 177–187. [CrossRef]
39. Malnick, S.D.H.; Alin, P.; Somin, M.; Neuman, M.G. Fatty Liver Disease-Alcoholic and Non-Alcoholic: Similar but Different. *Int. J. Mol. Sci.* **2022**, *23*, 16226. [CrossRef]