frontiers | Frontiers in Immunology

TYPE Mini Review
PUBLISHED 15 August 2025
DOI 10.3389/fimmu.2025.1655560

OPEN ACCESS

EDITED BY
Ana C. Maretti-Mira,
University of Southern California,
United States

REVIEWED BY
Tatsuki Ichikawa,
Nagasaki Harbor Medical Center, Japan

*CORRESPONDENCE
Wen-jing Cao
bessiejing@163.com
Shu-zhi Wang
shu-zhi.wang@usc.edu.cn
Wei Li
byebye770514@sina.com

RECEIVED 28 June 2025
ACCEPTED 28 July 2025
PUBLISHED 15 August 2025

CITATION
Chen K-q, Cao W-j, Wang S-z and Li W (2025) Mini-review: Serum immunoglobulins and MASLD. *Front. Immunol.* 16:1655560. doi: 10.3389/fimmu.2025.1655560

Mini-review: Serum immunoglobulins and MASLD

Ke-qian Chen[1], Wen-jing Cao[1]*, Shu-zhi Wang[2]* and Wei Li[1]*

[1]Department of Clinical Pharmacy, Xiangtan Central Hospital (The Affiliated Hospital of Hunan University), Xiangtan, China, [2]Institute of Pharmacy and Pharmacology, School of Pharmaceutical Sciences, University of South China, Hengyang, China

With the development of society and the economy, metabolic dysfunction-associated steatotic liver disease (MASLD) has become a major chronic disease in contemporary society. Finding a safe, effective, and economical diagnostic method is essential for the prevention of MASLD. Serum immunoglobulin is a protein produced by the B cells after the body is stimulated by an external antigen or pathogen. It is very interesting and valuable to explore the relationship between serum immunoglobulins and MASLD. Unfortunately, only a small number of studies have explored the relationship between serum immunoglobulins and MASLD. Therefore, we review the research progress of serum immunoglobulins in MASLD. At the same time, we also discuss the shortcomings of these studies. We hope this review will provide experience and reference for the prevention of MASLD in the future.

KEYWORDS

serum immunoglobulins, serum biomarker, MASLD, NASH, fibrosis

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a clinicopathologic syndrome characterized by excessive fat deposition in liver cells, which is caused by no-alcohol and other specific liver damaging factors (1). In recent decades, with the increase of sedentary lifestyles and Western dietary patterns, MASLD has gradually become a growing public health problem (2). Therefore, how to diagnose MASLD and judge the development of MASLD is very significant. Studies have shown that the stages of MASLD include metabolic-dysfunction associated steatotic liver (MASL), metabolic dysfunction-associated steatohepatitis (MASH), liver fibrosis, and cirrhosis (3). In 1998, British scholars proposed the "two-hit" theory for the first time in the world (4). The theory suggests that the first shock is liver lipid deposition and insulin resistance, and the second shock is oxidative stress. However, current research indicates that the pathogenesis of MASLD is quite complex. MASLD may be the result of a combination of factors, including genetic factors, nutritional factors, metabolic conditions, drug use, and surgical conditions (5). Because MASLD is a complex and progressive disease, it is necessary to establish a reliable diagnostic method. Currently, liver biopsy is considered the gold standard for the diagnosis of MASLD (6). However, it is an invasive method with serious limitations. Liver biopsy is not suitable for all MASLD patients. Other diagnostic methods also have limitations: For example, traditional ultrasonography largely depends on the experience

of the ultrasound examiner, which is highly subjective and may result in missed diagnosis of MASLD patients. CT scans can detect lipid accumulation in liver cells, but cannot determine the stage of liver fibrosis. Serum immunoglobulin is a protein produced by the B cells after the body is stimulated by an external antigen or pathogen (7). As an important part of human humoral immunity, they participate in the resistance to viral and bacterial infections by binding antigens or pathogens. Earlier studies found that serum immunoglobulin (IgA) concentrations were commonly elevated in alcoholic liver disease (ALD) patients (8). MASLD and ALD have common pathophysiological features and histological features, suggesting that they may have a common pathogenic mechanism. In addition, elevated serum immunoglobulins have been observed in autoimmune hepatitis (raised IgG) and primary biliary cirrhosis (raised IgM) (9, 10). B cells, which produce immunoglobulins, are also the most common immune cells in the liver. Emerging evidence has demonstrated that B cell activation is an important event in the progression of MASLD (11). In liver biopsies of MASLD patients, the accumulation of B cells was positively correlated with the MASLD activity score (11). Serum B-cell activating factor was also elevated in MASH patients (12). During MASH, B cells can aggravate insulin resistance, hepatic inflammation, and liver damage by producing pathogenic antibodies (lgG) (13). As mentioned above, we speculate that the development of MASLD may also be related to serum immunoglobulins. Immunoglobulins may play an important role in the diagnosis of MASLD. Unfortunately, only a small number of studies have explored the relationship between serum immunoglobulins and MASLD. Therefore, we review the research progress of serum immunoglobulins in MASLD. At the same time, we also discuss the shortcomings of these studies. We hope this review will provide experience and reference for the prevention of MASLD in the future.

MASLD and immunoglobulins

It is well known that the liver is a complex and important organ in the human body. Exploring the relationship between immunoglobulins and liver is also of great significance for us to understand the relationship between immunoglobulins and MASLD. Yu Lei et al. examined the expression of immunoglobulins in the liver of humans and rats (14). They found that hepatocytes can synthesize lgG, IgA and IgM, but not IgD and IgE. In addition to normal hepatocytes, malignant hepatocytes can also produce immunoglobulins. These immunoglobulins play an important role in the liver and other organs. For example, IgA in the liver can protect other organs from pathogens through portal circulation (15). As a growth factor, IgG has significant effects on the proliferation, apoptosis and migration of hepatocytes (16). The body's immune system is mainly defended by two types of lymphocytes (T cells and B cells) (17). B cells are derived from stem cells in bone marrow. Its main function is to produce antibodies (18). T cells are derived from lymphoid stem cells in the thymus. On the one hand, it can directly kill target cells. On the other hand, it can assist or inhibit the production of antibodies (19). It is well known that antibodies are the body's immune products against pathogen infection. In essence, it is a globulin with immune function. For this reason, antibodies are also called immunoglobulins. Studies have shown that immunoglobulins are present in serum, body fluids, and some cell membranes (20). Immunoglobulin molecule is composed of two identical light chains (L chain) and two identical heavy chains (H chain). L chain and H chain are connected by disulfide bonds to form a tetrapeptide chain molecule (monomer of Immunoglobulin molecule), which is the basic structure of immunoglobulin molecule. According to the structure of H chain constant region, immunoglobulins are divided into five types: IgG, IgA, IgM, IgD, and IgE (21).

MASLD and IgG

Immunoglobulin G (IgG) is the main component of serum immunoglobulins, accounting for about 75% of the total immunoglobulins. As the most important antibody in the primary immune response, IgG is mainly synthesized and secreted by plasma cells in the spleen and lymph nodes. When the human body is infected by pathogens, IgG appears late and has the longest half-life (22). Meanwhile, IgG is the only immunoglobulin that can cross the placental barrier (23). It plays a protective role in the infection of young mammals and newborns. At present, many studies have explored the relationship between lgG and immunoglobulins. In MASH mice, oral administration of lgG can alleviate chronic inflammation and liver injury (24). Shao Mei Sun et al. performed a cross-sectional study to assess the relationship between serum immunoglobulin concentrations and MASLD (25). The study evaluated 11261 Chinese adults recruited from January 2010 to December 2015 via multiple logistic regression analysis. They found that the prevalence of MASLD was negatively associated with IgG. Karrar A found that MASLD patients had significantly lower levels of IgG when compared with controls. IgG may play a protective effect role in the pathogenesis of MASLD (26). Paradoxically, some studies have put forward opposite results. Osman HA et al. also performed a cross-sectional study to assess the role of serum immunoglobulins in MASLD. Their study involved 100 MASLD patients and 100 healthy volunteers. They found that IgG were increased in MASLD patients. IgG may be involved in the progression of MASLD (27). In a prospective multi-center cohort study, De Roza MA et al. found that IgG was elevated in MASH patients. The mechanism may be related to IgG production induced by oxidative stress in MASH (28). Besides the MASH, Albano et al. also found that IgG was significantly elevated in the advanced fibrosis stage of MASLD patients (29). We think there are some flaws in the above results. The sample sizes of some studies are small and the diagnosis of MASLD is based on an unblinded histological interpretation of the local pathological team. Therefore, the factor of interobserver bias cannot be ruled out. Nevertheless, these studies still suggest that IgG may be involved in the pathogenesis of MASLD. Therefore, a large amount of research is still needed in the future to explore the relationship between MASLD and lgG.

MASLD and IgA

Studies have shown that IgA can be divided into secretory IgA (SIgA)and serum IgA. The content of serum IgA is second only to IgG, accounting for about 15% of serum immunoglobulins (30). However, serum IgA does not show immune function in serum. The SIgA is a dimer. As the main antibody against infection in the mucosal area of the body. SIgA mainly exists in the mucosa of respiratory tract, digestive tract, and urethra (31). When the synthesis of SIgA is insufficient, the respiratory tract and digestive tract of newborns are more susceptible to infection. Studies have shown that IgA cannot cross the placenta (32). Although IgA is not present in neonatal serum, SIgA can be obtained from breast milk (32). The cross-sectional study by Shao Mei Sun and Osman HA indicated that the prevalence of MASLD was positively correlated with IgA. Tomita K et al. want to determine whether serum IgA could diagnose fibrosis in MASLD patients (33). They studied 151 biopsy-proven Japanese MASLD patients and 22 healthy control subjects between April 2002 and December 2010 at Keio University Hospital. The results suggest that serum IgA was a valid independent predictor for assessing pre-cirrhosis progression of MASH. Stuart McPherson et al. want to evaluate serum immunoglobulin levels in biopsy-proven MASLD patients (34). They studied 285 patients who attended a tertiary fatty liver clinic between 1999 and 2009. These patients were tested for serum immunoglobulins within 6 months of liver biopsy. They found that serum IgA levels were elevated in MASLD patients. Serum IgA levels can be an independent predictor of advanced fibrosis. Maleki I et al. tested serum IgA levels in 50 biopsy-proven MASLD patients (35). They found that the higher the IgA levels, the higher the degree of fibrosis. IgA shows its value in distinguishing fibrosis in MASLD patients. In a large cohort of MASLD patients (941 patients), Elias E et al. also found that about 25% of MASLD patients had elevated serum IgA levels (36). Paradoxically, in a large pediatric cohort, Mouzaki M et al. found that serum IgA levels were elevated in only 4% of patients (37). Serum IgA is not an optimal biomarker for MASLD children. We think that the limitation of this study include its retrospective nature. In addition, their cohort was predominantly non-Hispanic and reflected the demographics of their regional pediatric MASLD population. A large number of studies have shown that intestinal dysbiosis is related to the severity of human MASLD. Interestingly, the mucosal immune system may further affect the function of serum IgA (38). When the mucosal barrier is damaged, Kupffer cells in the liver trigger the expression of FcaRI. Then IgA induces Kupffer cells to phagocytize fcari (39). Therefore, intestinal dysbiosis may partially explain the relationship between MASLD and IgA levels.

MASLD and IgM

Immunoglobulin M (IgM) is the largest immunoglobulin with molecular weight, accounting for about 10% of the total immunoglobulins (40). As a pentamer, IgM is also known as macroglobulin and is mainly secreted by plasma cells in the spleen and lymph nodes (40). Studies have shown that IgM is mainly present in the blood and mucosal surface and divided into IgMl and IgM2 two subtypes (41). When the body is infected, the first antibody that appears is IgM. Therefore, the detection of IgM levels can be used as an early diagnostic indicator of infectious diseases. Unfortunately, IgM has the disadvantages of high molecular weight and not easy to penetrate blood vessels. At present, only a small number of studies have explored the association between lgM and MASLD. Sun SM et al. found that the prevalence of MASLD was negatively associated with IgM (25). Hendrikx et al. found that IgM titers against oxidation-specific epitopes (OSE) were less in subjects who had MASLD than controls in two cohorts from USA (42). These results suggest that the lower level of IgM antibodies against oxidized lipids might be specific for MASLD.

MASLD and IgD

The molecular structure of IgD is very similar to IgG, accounting for about 1% of the total immunoglobulins. Studies have shown that IgD is unstable and easily cleaved by enzymes (43). However, the exact function of IgD in serum remains unclear. Its main physiological function may be to prevent immune tolerance and some hypersensitivity reactions (44). Regrettably, only one study explored the relationship between lgD and MASLD. Moreover, this study did not observe any significant changes in the level of secreted IgD in the plasma of MASLD mice (45). Therefore, we speculate that there is no association between lgD and MASLD. A large amount of research is still needed in the future to explore the relationship between MASLD and lgD.

MASLD and IgE

IgE is the lowest immunoglobulin in the serum. Current studies have shown that IgE is mainly distributed in the respiratory tract and intestinal mucosa (46). Its main function is related to inhibiting parasitic infection (47). At present, only a small number of studies have explored the association between lgE and MASLD. Sun SM et al. detected a higher level of serum IgE in MASLD participants. However, no significant relationship between MASLD and IgE was detected after adjustment for confounding factors. It is worth noting that a slightly elevated IgE concentration may be associated with the advanced fibrosis in MASLD. Therefore, it is necessary to further study the role of IgE in MASLD.

The spectrum of MASLD includes MASL, MASH, and fibrosis. Only 20% of MASL patients will progress to MASH, and among these MASH patients, 20% will develop fibrosis (48).

Discussion

The above results indicate that IgG and IgA play an important role in MASLD (Table 1, Figure 1). Immunoglobulin type

TABLE 1 A summary of reports on IgG, IgA, IgA/IgG, and MASLD.

Population (MASLD)	IgA	IgG	IgA/IgG	Ref.
4598	↑	↓	\	(25)
98	—	↓	\	(26)
100	↑	↑	\	(27)
261	\	↑	\	(28)
167	\	↑	\	(29)
285	↑	—	\	(34)
50	↑	\	\	(35)
941	↑	↑	\	(36)
478	↑	↑	↑	(50)

↑, Increase ↓, Decrease —, No change \, No report.

conversion is a biological mechanism that enables B cells to transform the antibodies they produce from one type to another. Among immunoglobulins, IgA and IgG can be converted from IgM (7). Meanwhile, IgA and IgG are also the main forces of the body's anti-infection defense. The main difference between them lies in their functions: IgA promotes the secretion of secretory peptides through mucosal surfaces, while IgG does not. Additionally, IgA and IgG differ in their transport methods, complement activation, and roles in passive immunity (49). Similarly, IgA/IgG ratio also plays an important role in MASLD. Ichikawa T et al. evaluated the clinical significance of IgA in 478 new patients who visited the Outpatient Clinic of Nagasaki Harbor Medical Center. They found that the IgA/IgG level was highest in patients with ALD, followed by those with MASLD and non-SLD (50).

With the development of economy and the change of life style, MASLD has become a major chronic disease in contemporary society. Finding a safe, effective, and economical diagnostic method is essential for the prevention of MASLD. The liver is one of the most important internal organs of the human body. On the one hand, the liver plays an important role in endocrine and exocrine activities. On the other hand, the liver also plays a key role in the immune system. Many studies have shown that immunotherapy can improve liver damage. Therefore, exploring the relationship between serum immunoglobulins and MASLD is very interesting. At present, compared with other serum biomarkers for diagnosing MASLD, serum immunoglobulins have advantages and importance. On the one hand, the relative molecular mass and content of serum immunoglobulins are higher than other serum biomarkers (CK-18, miRNA), and the detection accuracy is relatively high (51). On the other hand, serum immunoglobulins are more accurate than other serum biomarkers (adipocytokines) in diagnosing the liver fibrosis stage of MASLD (51). Immunoglobulin as a serum biomarker also has many limitations: Firstly, only a few clinical studies investigated serum immunoglobulins in MASLD patients, and a large number of studies are still needed in the future to explore its accuracy. Secondly, serum immunoglobulins levels may vary due to various diseases, which may reduce the specificity in diagnosing certain conditions such as MASLD. Thirdly, serum immunoglobulins levels may vary with different stages of MASLD, which also reduce the specificity in diagnosing certain conditions such as MASLD. Moreover, there are conflicting results in these studies. We think that the conflicting results may be due to the different stages of MASLD or different methods of serum immunoglobulin measurement. These clinical studies should be improved. First, serum immunoglobulin levels should be assessed in a larger cohort of patients with MASLD.

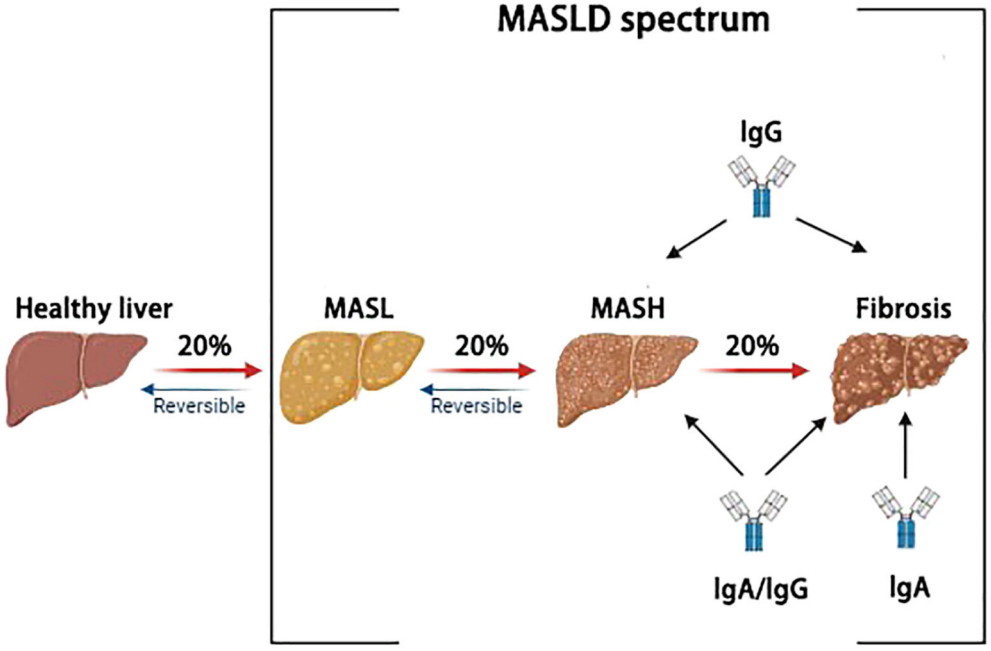

FIGURE 1
The role of immunoglobulins in MASLD.

Meanwhile, different ethnic groups are recommended in the study. Second, clinical studies should follow patients to determine whether serum immunoglobulin levels predict the subsequent course of MASLD. Third, clinical studies should increase the number of biopsy available for analysis. Meanwhile, it is also important to eliminate other unidentified factors that lead to changes of serum immunoglobulin levels.

In addition to improving clinical studies, two other questions need to be addressed. The first question is that the cause of changes of serum immunoglobulins in MASLD patients is unknown. What are the factors that affect the changes of serum immunoglobulins in MASLD patients? Do these factors also affect serum immunoglobulins in other liver diseases? The second question is whether the changes of serum immunoglobulins are involved in the pathogenesis of MASLD. Up to now, the pathological mechanism of MASLD has not been fully elucidated. Therefore, understanding the pathogenesis of MASLD has become a research hotspot in the field of liver and metabolism. Current studies have shown that the pathogenesis of MASLD includes insulin resistance, lipotoxicity, mitochondrial dysfunction, endoplasmic reticulum stress, inflammation, nutritional factors, gut microbiota, and genetic factors (52–54). Whether serum immunoglobulins can play an important role in these pathogenesis is an interesting research direction. In conclusion, serum immunoglobulin analysis is a cheap and non-invasive diagnostic method. Further studies are still needed to explore the relationship between serum immunoglobulins and MASLD.

Author contributions

KC: Writing – original draft. WC: Writing – review & editing. SW: Writing – review & editing. WL: Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

References

1. Chen KQ, Ke BY, Cheng L, Yu XQ, Wang ZB, Wang SZ. Research and progress of inflammasomes in nonalcoholic fatty liver disease. *Int Immunopharmacol.* (2023) 118:110013. doi: 10.1016/j.intimp.2023.110013

2. Yang W, Liu L, Wei Y, Fang C, Liu S, Zhou F, et al. Exercise suppresses NLRP3 inflammasome activation in mice with diet-induced NASH: a plausible role of adropin. *Lab Invest.* (2021) 101:369–80. doi: 10.1038/s41374-020-00508-y

3. Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. *Lancet.* (2021) 397:2212–24. doi: 10.1016/S0140-6736(20)32511-3

4. Pafili K, Roden M. Nonalcoholic fatty liver disease (NAFLD) from pathogenesis to treatment concepts in humans. *Mol Metab.* (2021) 50:101122. doi: 10.1016/j.molmet.2020.101122

5. Wei S, Wang L, Evans PC, Xu S. NAFLD and NASH: etiology, targets and emerging therapies. *Drug Discov Today.* (2024) 29:103910. doi: 10.1016/j.drudis.2024.103910

6. Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. *Gastroenterology.* (2019) 156:1264–81.e4. doi: 10.1053/j.gastro.2018.12.036

7. Schroeder HW Jr, Cavacini L. Structure and function of immunoglobulins. *J Allergy Clin Immunol.* (2010) 125:S41–52. doi: 10.1016/j.jaci.2009.09.046

8. Ciocan D, Turpin W. New insights into an old paradigm: why IgA accumulates in alcoholic liver disease and what could be its role. *Gut.* (2023) 72:1812–4. doi: 10.1136/gutjnl-2022-329415

9. Husby G, Skrede S, Blomhoff JP, Jacobsen CD, Berg K, Gjone E. Serum immunoglobulins and organ non-specific antibodies in diseases of the liver. *Scand J Gastroenterol.* (1977) 12:297–304. doi: 10.3109/00365527709180931

10. Martin DM, Vroon DH, Nasrallah SM. Value of serum immunoglobulins in the diagnosis of liver disease. *Liver.* (1984) 4:214–8. doi: 10.1111/j.1600-0676.1984.tb00930.x

11. Bruzzì S, Sutti S, Giudici G, Burlone ME, Ramavath NN, Toscani A, et al. B2-Lymphocyte responses to oxidative stress-derived antigens contribute to the evolution of nonalcoholic fatty liver disease (NAFLD). *Free Radic Biol Med.* (2018) 124:249–59. doi: 10.1016/j.freeradbiomed.2018.06.015

12. Miyake T, Abe M, Tokumoto Y, Hirooka M, Furukawa S, Kumagi T, et al. B cell-activating factor is associated with the histological severity of nonalcoholic fatty liver disease. *Hepatol Int.* (2013) 7:539–47. doi: 10.1007/s12072-012-9345-8

13. Sutti S, Jindal A, Locatelli I, Vacchiano M, Gigliotti L, Bozzola C, et al. Adaptive immune responses triggered by oxidative stress contribute to hepatic inflammation in NASH. *Hepatology.* (2014) 59:886–97. doi: 10.1002/hep.26749

14. Lei Y, Huang T, Su M, Luo J, Korteweg C, Li J, et al. Expression and distribution of immunoglobulin G in the normal liver, hepatocarcinoma and postpartial hepatectomy liver. *Lab Invest.* (2014) 94:1283–95. doi: 10.1038/labinvest.2014.114

15. Moro-Sibilot L, Blanc P, Taillardet M, Bardel E, Couillault C, Boschetti G, et al. Mouse and human liver contain immunoglobulin A-secreting cells originating from Peyer's patches and directed against intestinal antigens. *Gastroenterology.* (2016) 151:311–23. doi: 10.1053/j.gastro.2016.04.014

16. Van Spreeuwel JP, Van Gorp LH, Nadorp JH, Janssens AR, Lindeman J, Meijer CJ. Immunoglobulin-containing cells in liver biopsies of patients with chronic hepatitis and primary biliary cirrhosis. *Histopathology.* (1984) 8:559–66. doi: 10.1111/j.1365-2559.1984.tb02368.x

17. Parkin J, Cohen B. An overview of the immune system. *Lancet.* (2001) 357:1777–89. doi: 10.1016/S0140-6736(00)04904-7

18. Mauri C, Bosma A. Immune regulatory function of B cells. *Annu Rev Immunol*. (2012) 30:221–41. doi: 10.1146/annurev-immunol-020711-074934

19. Kumar BV, Connors TJ, Farber DL. Human T cell development, localization, and function throughout life. *Immunity*. (2018) 48:202–13. doi: 10.1016/j.immuni.2018.01.007

20. Patel P, Jamal Z, Ramphul K. Immunoglobulin. In: *StatPearls*. StatPearls Publishing, Treasure Island (FL (2023).

21. Sogn JA, Kindt TJ. Immunoglobulin structure and function. *Curr Opin Immunol*. (1988) 1:73–6. doi: 10.1016/0952-7915(88)90054-4

22. Papadea C, Check IJ. Human immunoglobulin G and immunoglobulin G subclasses: biochemical, genetic, and clinical aspects. *Crit Rev Clin Lab Sci*. (1989) 27:27–58. doi: 10.3109/10408368909106589

23. Ben-Hur H, Gurevich P, Elhayany A, Avinoach I, Schneider DF, Zusman I. Transport of maternal immunoglobulins through the human placental barrier in normal pregnancy and during inflammation. *Int J Mol Med*. (2005) 16:401–7. doi: 10.3892/ijmm.16.3.401

24. Adar T, Ben Ya'acov A, Lalazar G, Lichtenstein Y, Nahman D, Mizrahi M, et al. Oral administration of immunoglobulin G-enhanced colostrum alleviates insulin resistance and liver injury and is associated with alterations in natural killer T cells. *Clin Exp Immunol*. (2012) 167:252–60. doi: 10.1111/j.1365-2249.2011.04511.x

25. Sun SM, Wang YY, Zhang Q, Liu L, Meng G, Yao ZX, et al. Serum levels of immunoglobulins in an adult population and their relationship with nonalcoholic fatty liver disease. *J Dig Dis*. (2018) 19:498–507. doi: 10.1111/1751-2980.12646

26. Karrar A, Stepanova M, Alaparthi L, Lingam S, Younoszai Z, Zheng L, et al. Anti-adipocyte antibody response in patients with non-alcoholic fatty liver disease. *J Gastroenterol Hepatol*. (2015) 30:900–8. doi: 10.1111/jgh.12856

27. Osman HA, Tag-Adeen M, Abdelaal UM, Elgezawy E, Nasif KA, Nafady A. Different aspects of immunological profile in patients with Non-Alcoholic Fatty liver disease. *Acta Gastroenterol Belg*. (2024) 87:274–81. doi: 10.51821/87.2.12205

28. De Roza MA, Lamba M, Goh GB, Lum JH, Cheah MC, Ngu JHJ. Immunoglobulin G in non-alcoholic steatohepatitis predicts clinical outcome: A prospective multi-centre cohort study. *World J Gastroenterol*. (2021) 27:7563–71. doi: 10.3748/wjg.v27.i43.7563

29. Albano E, Mottaran E, Vidali M, Reale E, Saksena S, Occhino G, et al. Immune response towards lipid peroxidation products as a predictor of progression of non-alcoholic fatty liver disease to advanced fibrosis. *Gut*. (2005) 54:987–93. doi: 10.1136/gut.2004.057968

30. Woof JM, Kerr MA. The function of immunoglobulin A in immunity. *J Pathol*. (2006) 208:270–82. doi: 10.1002/path.1877

31. Kumar Bharathkar S, Parker BW, Malyutin AG, Haloi N, Huey-Tubman KE, Tajkhorshid E, et al. The structures of secretory and dimeric immunoglobulin A. *Elife*. (2020) 9:e56098. doi: 10.7554/eLife.56098

32. Maertens K, De Schutter S, Braeckman T, Baerts L, Van Damme P, De Meester I, et al. Breastfeeding after maternal immunisation during pregnancy: providing immunological protection to the newborn: a review. *Vaccine*. (2014) 32:1786–92. doi: 10.1016/j.vaccine.2014.01.083

33. Tomita K, Teratani T, Yokoyama H, Suzuki T, Irie R, Ebinuma H, et al. Serum immunoglobulin a concentration is an independent predictor of liver fibrosis in nonalcoholic steatohepatitis before the cirrhotic stage. *Dig Dis Sci*. (2011) 56:3648–54. doi: 10.1007/s10620-011-1771-2

34. McPherson S, Henderson E, Burt AD, Day CP, Anstee QM. Serum immunoglobulin levels predict fibrosis in patients with non-alcoholic fatty liver disease. *J Hepatol*. (2014) 60:1055–62. doi: 10.1016/j.jhep.2014.01.010

35. Maleki I, Aminafshari MR, Taghvaei T, Hosseini V, Rafiei A, Torabizadeh Z, et al. Serum immunoglobulin A concentration is a reliable biomarker for liver fibrosis in non-alcoholic fatty liver disease. *World J Gastroenterol*. (2014) 20:12566–73. doi: 10.3748/wjg.v20.i35.12566

36. Elias E, Uhanova J, Li Q, Zhang M, Minuk G. Serum immunoglobulin A levels and non-alcoholic fatty liver disease. *Can Liver J*. (2018) 1:248–55. doi: 10.3138/canlivj.2018-0005

37. Mouzaki M, Bramlage K, Arce-Clachar AC, Xanthakos SA. Serum immunoglobulin A levels do not correlate with liver disease severity in pediatric nonalcoholic fatty liver disease. *J Pediatr Gastroenterol Nutr*. (2018) 67:631–4. doi: 10.1097/MPG.0000000000002104

38. Leong KW, Ding JL. The unexplored roles of human serum IgA. *DNA Cell Biol*. (2014) 33:823–9. doi: 10.1089/dna.2014.2639

39. van Egmond M, van Garderen E, van Spriel AB, Damen CA, van Amersfoort ES, van Zandbergen G, et al. FcalphaRI-positive liver Kupffer cells: reappraisal of the function of immunoglobulin A in immunity. *Nat Med*. (2000) 6:680–5. doi: 10.1038/76261

40. Li Y, Wang G, Li N, Wang Y, Zhu Q, Chu H, et al. Structural insights into immunoglobulin M. *Science*. (2020) 367:1014–7. doi: 10.1126/science.aaz5425

41. Klimovich VB. IgM and its receptors: structural and functional aspects. *Biochem (Mosc)*. (2011) 76:534–49. doi: 10.1134/S0006297911050038

42. Hendrikx T, Watzenböck ML, Walenbergh SM, Amir S, Gruber S, Kozma MO, et al. Low levels of IgM antibodies recognizing oxidation-specific epitopes are associated with human non-alcoholic fatty liver disease. *BMC Med*. (2016) 14:107. doi: 10.1186/s12916-016-0652-0

43. Gutzeit C, Chen K, Cerutti A. The enigmatic function of IgD: some answers at last. *Eur J Immunol*. (2018) 48:1101–13. doi: 10.1002/eji.201646547

44. Nguyen TG. The therapeutic implications of activated immune responses via the enigmatic immunoglobulin D. *Int Rev Immunol*. (2022) 41:107–22. doi: 10.1080/08830185.2020.1861265

45. Petriv N, Suo H, Hochnadel I, Timrott K, Bondarenko N, Neubert L, et al. Essential roles of B cell subsets in the progression of MASLD and HCC. *JHEP Rep*. (2024) 6:101189. doi: 10.1016/j.jhepr.2024.101189

46. Rahman RS, Wesemann DR. Whence and wherefore IgE? *Immunol Rev*. (2024) 326:48–65. doi: 10.1111/imr.13373

47. McDonnell JM, Dhaliwal B, Sutton BJ, Gould HJ. IgE, IgE receptors and anti-IgE biologics: protein structures and mechanisms of action. *Annu Rev Immunol*. (2023) 41:255–75. doi: 10.1146/annurev-immunol-061020-053712

48. Samy AM, Kandeil MA, Sabry D, Abdel-Ghany AA, Mahmoud MO. From NAFLD to NASH: Understanding the spectrum of non-alcoholic liver diseases and their consequences. *Heliyon*. (2024) 10:e30387. doi: 10.1016/j.heliyon.2024.e30387

49. Macpherson AJ, McCoy KD, Johansen FE, Brandtzaeg P. The immune geography of IgA induction and function. *Mucosal Immunol*. (2008) 1:11–22. doi: 10.1038/mi.2007.6

50. Ichikawa T, Yamashima M, Yamamichi S, Koike M, Nakano Y, Yajima H, et al. Serum immunoglobulin A levels: Diagnostic utility in alcoholic liver disease and association with liver fibrosis in steatotic liver disease. *BioMed Rep*. (2024) 21:142. doi: 10.3892/br.2024.1830

51. He XM, Huang J. [Recent advances in serum biomarkers for liver fibrosis]. Zhonghua Gan Zang Bing Za Zhi. *Chinese* (2015) 23:874–7. doi: 10.3760/cma.j.issn.1007-3418.2015.11.016

52. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). *Metabolism*. (2016) 65:1038–48. doi: 10.1016/j.metabol.2015.12.012

53. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. *Nat Med*. (2018) 24:908–22. doi: 10.1038/s41591-018-0104-9

54. Byrne CD, Targher G. NAFLD: a multisystem disease. *J Hepatol*. (2015) 62:S47–64. doi: 10.1016/j.jhep.2014.12.012