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Review Article

Immunoglobulin: Specific Marker for Hepatic Diseases

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Abstract

Heavy chain C domains are divided into five categories. IgM, IgG, IgA, IgD, and IgE isotypes are defined by each class. IgM was found to be a sensitive and specific marker for primary biliary cirrhosis, with mean IgM levels in primary biliary cirrhosis being greater than in other diagnostic categories. The most common cause of increased IgA levels was alcoholic liver disease. IgA was able to detect 95% of alcoholic illness, but it was not very specific. There was a correlation between increased IgA levels and the degree of alcoholic damage. IgG levels were highest in chronic active hepatitis and alcoholic hepatitis with cirrhosis, but they were not substantially different from those in other diagnostic categories. This review gives a brief idea of immunoglobulin as a diagnostic use in liver diseases.

Keywords: *Immunoglobulin; Techniques; Safety; Classes*

Introduction

The presence of an agent in the blood that neutralizes diphtheria toxin has been documented [1]. Also proved that serum from rabbits inoculated with tetanus toxin had activity against the "tetanus poison," and that this serum might protect healthy rabbits from tetanus [2]. Many studies have shown that serum from both animals and people can be used to prevent or treat a variety of ailments [3]. Antibodies are defined as an agent's ability to distinguish between two immunological compounds. Furthermore, the 'Antisomatogen' or the substance that produces the antibody is a chemical that encourages the creation of an antibody. The term antigen is a shortening of the phrase. A classic tautology is defined as a relationship between an antibody and its antigen [1].

The vaccinated serum was separated into albumin, alpha-globulin, beta-globulin, and gamma-globulin fractions using electrophoresis. The gamma-globulin fraction was eaten by the serum against the antigen, giving rise to the terms gamma globulin, immunoglobulin (Ig), and immunoglobulin (IgG). Immunoglobulins were divided into heavy (IgM), regular (IgA, IgE, IgD, IgG), and light (IgA, IgE, IgD, IgG) categories using column sorting (light chain dimers). Immunoglobulins also serve two purposes: antigen-binding receptors on cell surfaces that allow for cell signalling and activation, and soluble effector molecules that can bind and destroy antigens at a distance [1].

Techniques of production and safety

Ig is a sterile preparation of concentrated antibodies (immunoglobulins) derived from large pools of healthy donor plasma. As a result of the use of large plasma pools for the generation of Ig, different types of antibodies are produced, which increases the risk of infection. This reality has prompted an unwavering effort to improve the safety of Ig while maintaining its tolerability.

The selection of donors for plasma collection is the first step in the synthesis of immunoglobulins. This fact implies that Ig formulations are not equal, since they are dependent on the antibody composition of the donor population, which varies based on the presence of live illnesses in that community. Antibody levels against hepatitis A were also reported to varied significantly between different Ig formulations [4].

Plasma for Ig production should come from healthy blood donors who have a clear medical history and no known risk factors for blood-borne disorders [5]. Plasma fractionation and purification are phases in the Ig manufacturing process. Plasma fractionation can be divided into two categories. The first is plasma precipitation (using ethanol as a harmless precipitant), and the second is chromatographic method (which uses cylindrical columns holding synthetic resins that permit protein separation) [6] (Figure 1).

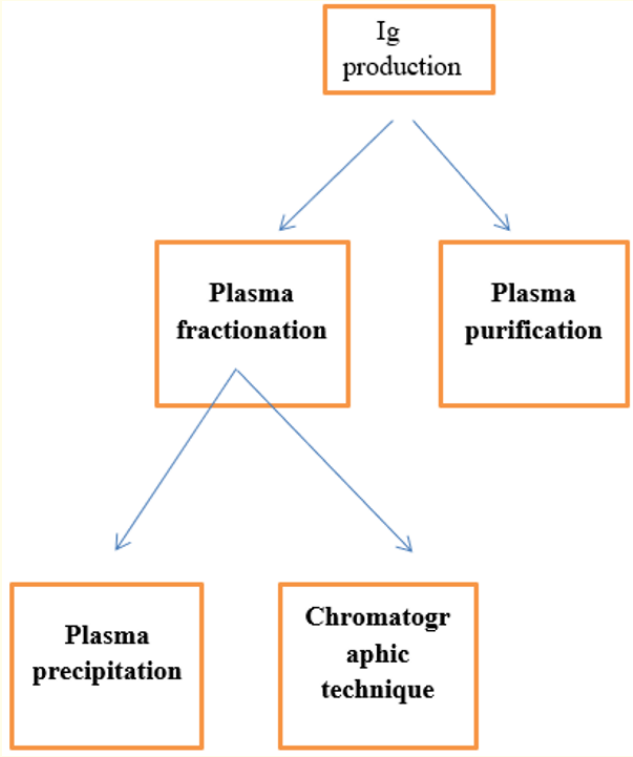

Figure 1: *Techniques of production.*

At least three ways are now being used to produce Ig in order to improve tolerability and reduce disease transmission risks. Every stage in the plasma processing process might change the protein structure and biological activity. As a result, the tolerability of commer-

cial Ig preparations varies, as does their efficacy [7]. Few purification processes, for example, that include the addition of chemicals or enzymes to destroy viruses or minimise the development of Ig aggregates, may also alter the structure and function of the Fc component of the IgG molecule, reducing its biological activity.

Pasteurization, solvent/detergent treatment, methylene blue therapy, caprylic acid treatment, and nanofiltration are all common procedures for reducing virus load. Caprylic acid and the solvent/detergent method are efficient against enveloped viruses, while nanofiltration is effective against both enveloped and non-enveloped viruses (parvovirus B19 and hepatitis A) [8].

Mode of action

In primary or secondary immunodeficiency, administration Ig plays a critical role in antibody replacement, and its mechanism of action is well defined: to restore IgG levels. Although, because of Ig's anti-inflammatory and immunomodulatory capabilities, several agencies have been recommended to explain the drug's effects in immune system management, some of which are shown in table 1 [9,10].

1.	Relationship with Fc fragment specific receptor (FcR)
2.	Changes of few cytokines and production of their antagonist
3.	Obstruction of differentiation and maturation of dendritic cells
4.	Apoptosis of B and T cells through the activation of Fas receptor
5.	Inhibition of self-reactivity and tolerance induction.

Table 1: *Mode of action human immunoglobulin [10].*

Ig's work on CD4+, CD25+, and FoxP3+ regulatory T cells (Tregs) has also been defined. Tregs play a critical function in maintaining the non-immune response to self-antigens as well as inhibiting immunological aggressiveness and autoimmune disorders [11]. The ability of Ig to augment and improve Treg suppressive function has been demonstrated, however the mechanism is unknown [12]. There is a theory that there is a link between Ig and dendritic cells, in addition to the linkage between IV Ig and Tregs. Antigen-presenting cells have a role in the generation of an immunogenic or tolerogenic immune response. Dendritic cells are thought to be able to conciliate the effects of Ig on T cell activation [13].

In addition, Ig formulations have been demonstrated to prevent the development and amplification of TH17 cells. These cells also communicate with a subset of T cells that, in addition to protecting against extracellular infections (such as *Klebsiella* and *Candida*), play a key role in the pathophysiology of autoimmune, allergy and inflammatory illnesses. The production of inflammatory cytokines and other pro-inflammatory mediators is reduced when TH17 cells are inhibited, interfering with the prevention of chronic inflammation [14].

Heavy chain isotypes

During early B cell growth, productively repositioned variable domains (VH and VL) are delivered in conjunction with the heavy chain to create IgM, and then IgD by alternative splicing. Following that, these variable domains may join with the other isotypes (IgG, IgA, and IgE) in a controlled manner during development and in response to antigenic stimulation and cytokine regulation [1].

IgM: During B cell development; IgM is the first immunoglobulin to appear. Multimeric (typically pentameric, occasionally hexameric) IgM is produced after maturation and antigenic stimulation, with single IgM units connected by disulfide bonds in the CH4 region. While

monomeric IgM molecules have low affinity due to their immaturity, multimeric interaction between the pentameric released antibody and the antigen can attain considerable avidity. Especially if the antigen itself has several repeated epitopes. IgM works by opsonizing (coating) antigen and fixing complement for destruction. The pentameric structure of the antibody makes it ideal for this procedure.

IgM antibodies are immunoglobulins that are associated to an initial immunological response and are frequently used to diagnose acute immunogen or pathogen exposure. Given that IgM is detected early in the formation of B cells. The heavy chain connects to VH and VL, which have not undergone substantial somatic mutation as a result of antigen exposure. As a result, IgM antibodies are more polyreactive than other isotypes, allowing B cells carrying IgM to respond swiftly to a range of antigens. As a result, these low-affinity IgM antibodies are referred to as natural antibodies. Few of these natural antibodies serve not only as a first line of defence, but also as regulators of the immune system [15]. Natural antibodies may interact with autoantigens, but they are rarely the cause of autoimmune illness. Pathogenic auto-antibodies are typically taken from the pool of somatically modified, high affinity IgG.

IgD: The serum half-life of circulating IgD was shown to be very short, which could be attributed to the molecule's reactivity, namely the hinge region, to proteolysis. The relevance of circulating IgD in key antibody effector pathways is debatable, and it is unknown whether it plays a role. Independent of the variable sections of the antibody, circulating IgD can interact with certain bacterial proteins, such as the IgD binding protein of *Moraxella catarrhalis* [16]. B cells are stimulated and activated when these bacterial proteins bind to the constant region of IgD.

So far, the membrane-bound version of IgD has gotten the most attention, but its function remains a mystery. When B cells leave the bone marrow and populate secondary lymphoid organs, IgD is expressed on their membranes. It's been proposed that membrane-bound IgD regulates B cell destiny at specific embryonic stages via varying activation status [17].

IgG: IgG is the most common isotype found in the human body. It has the longest serum half-life of all immunoglobulin isotypes and is the most well-studied immunoglobulin class. IgG subclades (IgG1, IgG2, IgG3, and IgG4) were identified. These IgG subclasses also have shown a variety of functional activities.

Within the subclasses, there are additional similarities, such as transplacental transit and participation to the secondary immunological response. The major subclass that is elicited changes within the secondary antibody response. IgG1 and IgG3 antibodies, for example, are mostly generated in response to protein antigens, whereas IgG2 and IgG4 antibodies are linked to polysaccharide antigens. The response to a specific antigen can also result in a change in IgG subclass response, which is commonly used as a source of investigation for preventive or vaccine creation [1].

IgG antibodies also have a direct role in the immune response, including toxin and viral neutralisation. The IgG subclass has an impact on the outcome of this response once again. IgG3 antibodies have been proven to be more effective at neutralising HIV than IgG1 antibodies, either due to an increase in antibody flexibility that improves antibody entry or by inducing variation in the virus's oligomer structure [18,19].

IgA: IgA levels in the blood tend to be higher than IgM but much lower than IgG. At mucosal surfaces and in secretions, IgA levels are substantially higher than IgG (like saliva and breast milk) [20]. IgA, in particular, can supply up to 50% of the protein in colostrum, the mother's "first milk" for the newborn. IgA is divided into two subclasses (IgA1 and IgA2), which differ mostly in their hinge regions. IgA1 has a longer hinge region with a duplicated length of amino acids, whereas IgA2 does not. Despite partial protection by glycans, this larger hinge region increases IgA1 sensitivity to bacterial proteases.

IgA is essential for protecting mucosal surfaces from toxins, viruses, and bacteria, either through direct neutralisation or by preventing toxins, viruses, and bacteria from attaching to the mucosal surface. Intracellular IgA may also play a role in the prevention of bacterial

and viral infection, as well as pathogenesis. The polymeric nature of secretory IgA could be critical. Polymeric IgA, for example, is more effective than monomeric IgA at protecting epithelial cells from *Clostridium difficile* toxin A damage [21]. As previously stated, glycans on IgA can dump certain microorganisms. Finally, by uptake of antigen by dendritic cells, it has been postulated that sIgA may operate as a potentiator of the immune response in intestinal tissue [22].

IgE: IgE is a very powerful immunoglobulin that is accessible at the lowest serum concentration with the shortest half-life. Hypersensitivity and allergic reactions, as well as the response to parasitic worm infections, are all linked to it. IgE binds to the FcRI, which is found on mast cells, basophils, Langerhans cells, and eosinophils, with an extraordinarily high affinity. FcR expression on these cells is upregulated by circulating IgE. The immunoglobulin's extraordinary efficacy is due to the combination of high binding and upregulation of FcR expression.

Anti-IgE antibodies are now being developed as a treatment for allergies and asthma. Antibodies are being developed to target both free IgE and B cells with membrane attached IgE, but not IgE linked to FcR, which would trigger degranulation and the release of inflammatory mediators. FcRII or CD23, which are expressed on the same cells as FcRI as well as B cells, NK cells, and platelets, have a lower affinity for IgE [1].

Immunoglobulin in the diagnosis of hepatic disease

Serum immunoglobulin (Ig) levels fluctuate regularly in hepatic disease and are widely employed as a marker for various types of hepatic damage. According to preliminary research, IgA, IgM, and IgG serum concentrations rise in alcoholic cirrhosis, primary biliary cirrhosis, and chronic active hepatitis. Extrahepatic blockage and drug-induced hepatic illness both had normal immunoglobulin outline [24]. IgA has been used to determine the degree of fibrosis in cirrhosis, while IgG has been used to determine the degree of activity [25]. Immunoglobulin outline has been used to assess the severity of alcoholic damage in alcoholic hepatic illness [26-28]. Although it suggests that any immunoglobulin composition in hepatic illness lacks diagnostic specificity [29]. Regardless, immunoglobulin levels are still recommended as a useful indicator in the diagnosis and prevention of liver disorders [30-34].

IgA has been utilised as a marker for alcoholic hepatic damage in the past. It was also discovered that increases occur even before the onset of histological change [35], with values increasing as a proportion of the severity of the necro-inflammatory change [26,28]. This IgA elevation's mode is unclear. Hepatocyte-mediated IgA transport with bile secretion has been established in rats [36,37] and has been suggested to occur in humans [38,39]. Although lower IgA clearance into bile may explain for the rise in serum levels, biliary clearance of IgA in alcoholic cirrhotics may not be reduced when compared to healthy controls [40]. It has been suggested that in alcoholics, IgA synthesis is increased even before the onset of liver failure [41]. In patients with alcoholic liver disease, IgA levels rose at a random rate. Also, elevated IgA levels were found in the early stages of alcoholic liver disease (steatosis) and showed a propensity to rise with degree of injury, but the differences were not significant.

The rise in IgM value was more common in primary biliary cirrhosis than in other types, and mean IgM values were considerably higher in primary biliary cirrhosis than in other categories. A elevated IgM level should consequently prompt a diagnosis of primary biliary cirrhosis, whereas a normal IgM level renders this diagnosis less likely. As a result, the patient with the highest IgM levels did not have primary biliary cirrhosis. IgA and IgM are useful diagnostic markers for alcoholic liver disease and primary biliary cirrhosis. Most, if not all, kinds of liver illness cause an increase in IgG, IgA, and IgM levels [42].

A common complication of both acute and chronic liver illness is hypergammaglobulinemia. More studies of serum IgE levels in hepatic disease patients used less sensitive methods than those available for measuring this immunoglobulin [43,44] with mixed results.

Another study found that serum IgE levels are significantly higher in many patients with acute and chronic hepatic diseases. The radioimmunoassay utilised in this work also incorporates IgE binding to Sepharose beads. The possibility that a blocking factor could be inhibited in the serum of individuals with hepatic illness, causing falsely elevated IgE levels, was considered. Such inhibitors have been found in immunocompromised people [45] and cancer patients [46].

In the sera of patients with hepatic illness investigated, no agglutinating anti-IgE campaign was seen, and only one of five patient sera tested with a significant rise in IgE resulted in histamine release from IgE-sensitized leucocytes. Anti-IgE factors appear to be an improbable explanation for a rise in IgE in the solid immunoadsorbent assay based on these findings [47].

In a patient with alcoholism and fatty liver, it has identified extreme polyclonal hyperimmunoglobulinemia E and eosinophilia. As a result, patients with high serum IgE levels did not have eosinophilia. Increased blood IgE levels, on the other hand, did not appear to be correlated with the presence of documented allergies in the patients investigated [48].

IgD levels were shown to be higher in patients with Laennec's cirrhosis in a previous study. IgD concentrations did not differ significantly between patients with liver disease and controls in another investigation [43]. The mechanism of increased serum immunoglobulins in hepatic illness has been well researched, but the cause remains unknown. Raised immunoglobulins could result from greater immunoglobulin synthesis or decreased immunoglobulin catabolism, according to theory. The decrease of the suppressor T-cell population in patients with hepatic illness may be the cause of elevated serum immunoglobulin. With the exception of IgD, hepatic disease hyperglobulinaemia appears to involve increases in all immunoglobulin types. In terms of application, our findings show that any study involving the measurement of serum IgE level should take into account the existence of hepatic illness [47].

Conclusion

It is concluded that liver injury happens as a result of a variety of medicines, all of which have an impact on the immune system. Immunoglobulin is also one of the most common indicators of liver damage. As a result, these various types of immunoglobin levels exacerbate liver damage. This review study discusses how immunoglobulins are used as diagnostic indicators for hepatotoxicity and how they vary.

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Contribution of the Authors

Mohd Rafi Reshi and Kavita Gulati were involved in the drafting of the full manuscript. Afshana Bashir Reshi also helping and adding some study material in making this reviews paper. Arunabha Ray was involved in planning critical reviewing of manuscript. All authors approved the final version of the manuscript.

Conflict of Interest

There is no conflict of interest.

Ethical Considerations

No use of patient in this review article or animal use. So, no requirement to consult or take permission from ethical committee.

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