Immunoglobulins are antibodies that play important roles in preserving our immune system. They have the ability to initiate humoral responses and remove antigen from the body. Out of the five major isotypes of immunoglobulins, IgG are most abundantly found in human serum. Abnormalities – deficiency or elevation in the level of IgG are found to be associated to the occurrence of several autoimmune diseases. These may include rheumatoid arthritis, Crohn’s disease, Mikulicz’s disease, Kuttner’s tumour and Hashimoto’s thyroiditis. Apart from autoimmune diseases, IgG has been found to play a role in initiating anaphylaxis, a severe and life threatening form of allergy and lately it has been discovered in cases of dengue virus infection too. It is important to acknowledge the roles of IgG on diseases especially subclass IgG4 which the elevation has been tied to numerous diseases such as Kuttner’s tumour and Hashimoto’s thyroiditis hence termed IgG4-related diseases. In addition, the roles of IgG in anaphylaxis are of importance, too, as IgG has been used in allergy immunotherapy. Hence, this review is a mini compilation of effects of IgG abnormalities based on their subclasses. Hopefully it will provide insightful understanding on the development of diagnostic and therapeutic courses for the aforementioned IgG abnormalities in the future.

**Keywords:** Immunoglobulin G (IgG), abnormalities, autoimmune diseases, anaphylaxis, dengue virus infection

**1.0 Introduction**

What are immunoglobulins?

Immunoglobulins, also known as antibodies, are immunity-conferring proteins. Immunoglobulins are categorised into two groups namely B cell membrane-bound antibodies and secreted antibodies. They are able to initiate humoral immune responses and help remove antigens in the effector phase of such responses (Abbas and Lichtman, 2006). Immunoglobulins are further subdivided into five major isotypes based on their heavy chains - immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), immunoglobulin E (IgE) and immunoglobulin D (IgD) (Schroeder and Cavacini, 2010).

Immunoglobulins G (IgG) are most abundantly found in human serum, comprising of about 10 - 20% of plasma protein. They are made up of 82 - 96% protein and 4 - 18% carbohydrate. IgG can be divided into four subclasses - IgG1, IgG2, IgG3 and IgG4 (Vidarsson *et al.*, 2014). Their main functions involve opsonisation, complement activation, antibody-dependent cell-mediated cytotoxicity, neonatal immunity and feedback inhibition of B cells (Abbas and Lichtman, 2006). The different subclasses of IgG have been implicated in certain diseases such as autoimmune diseases, infections and allergies. IgG subclass abnormalities have been reported in patients of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Crohn’s disease, tuberculosis (Karsten and Köhl, 2012) and allergy (Meulenbroek and Zeijlemaker, 2008). On the other hand, a group of diseases termed as IgG4-related diseases have an elevated IgG4 concentration.

*Four subclasses of IgG*

Structurally, IgG molecules have similar features as seen in other immunoglobulin subclass. Generally, they are made up of two identical 50 kDa γ heavy chains and two identical 25 kDa κ or λ light chains held together by inter-chain disulfide bonds. The four subclasses of human IgG share similar structures where there is over 90% homology in their amino acid sequence as stated by Vidarsson *et al.* (2014). Differences in this subclass members are found mainly in the hinge region and N-terminal CH2 domain and this variation affects the binding to accessory molecules and receptors and thus defining their functionality (Vidarsson *et al.*, 2014). These differences are as shown in Table 1.
2.0 **Association of IgG Subclasses in Diseases**

**IgG1**

IgG1 is the most abundant IgG subclass and low level of this immunoglobulin subclass can lead to hypogammaglobulinaemia (Vidarsson et al., 2014). This condition is seen in a number of primary and secondary antibodies deficiencies which are reflected by decrease in total IgG level (Vidarsson et al., 2014). An individual with IgG1 deficiency experiences recurrent infections (Meulenbroek and Zeijlemaker, 2008). IgG1 deficiency has also been reported in patients of chronic fatigue syndrome (Meulenbroek and Zeijlemaker, 2008). Increased levels of IgG1 have also been reported in diseases such as RA, Sjögren’s syndrome and haemolytic diseases of the newborn.

RA is an autoimmune disease caused by inflammation in the joints and sometimes in the blood vessels, lungs and other tissues (Abbas and Lichtman, 2006). IgG was reported to play a role in RA especially in the activation of complements via alternative pathway in a mouse model of K/BxN serum-transferred arthritis which mimicked human RA or in juvenile arthritis patients (Karsten and Köhl, 2012). A rather high IgG1 level was seen in this mouse model (Karsten and Köhl, 2012). This could be due to high level of agalactosyl-IgG-G0 glycoform terminating in N-acetyl-glucosamine (GlcNAc) as a result of undesired activation of complement by the lectin pathway (Karsten and Köhl, 2012). Apart from that, human rheumatoid factors (RF) have been shown to bind specifically to IgG1 followed by IgG2 and IgG4 (Meulenbroek and Zeijlemaker, 2008). Human RFs are IgG, IgA or IgM antibodies that are against the Fc fragment of immunoglobulins and in most cases of RA, RFs are found to bind to the Fc fragments of IgG (Meulenbroek and Zeijlemaker, 2008).

Increased level of IgG1 is also seen in patients of Sjögren’s syndrome. Sjögren’s syndrome, as defined by the Sjögren’s Syndrome Foundation (2016), is a systemic autoimmune disease and the symptoms include dry eyes, dry mouth, fatigue and joint pain. This syndrome arises as a consequence of restricted oligoclonal B cell response that may in turn lead to the development of benign B cell lymphoma (Meulenbroek and Zeijlemaker, 2008).

Haemolytic diseases of the newborns cause them to be presented with anaemia due to breakdown of erythrocytes in response to high levels of IgG antibodies (Meulenbroek and Zeijlemaker, 2008). This is mainly triggered by maternal IgGs that have inadvertently been passed through the placental barrier and bind to foetal erythrocytes as described by Meulenbroek and Zeijlemaker (2008). The severity of disease is more profound when both IgG1 and IgG3 are present in these newborns compared to IgG1 alone (Meulenbroek and Zeijlemaker, 2008).

**IgG2**

IgG2 is the second most abundant subclass of IgG. Its main role is to fight against bacterial capsular polysaccharide antigens (Vidarsson et al., 2014). Its deficiency is equivalent to the virtual absence of anti-carbohydrate IgG antibodies that leads to increased susceptibility to bacterial infections (Vidarsson et al., 2014). Sibler et al. (1990) found that there was a correlation between low IgG2 concentration and decreased response to infections by encapsulated bacteria (Meulenbroek and Zeijlemaker, 2008). In addition, Umetsu et al. (1985) also found that after immunisation with polysaccharide antigens, there was a low level of IgG2 and these patients were constantly presented with recurrent respiratory tract infections by pneumococci and/or *Haemophilus influenza* type B (Meulenbroek and Zeijlemaker, 2008).

When a patient is presented with low levels of IgG2, his IgG4 and IgA levels are expected to be low too (Meulenbroek and Zeijlemaker, 2008). This is seen in patients diagnosed with chronic mucocutaneous candidiasis (Meulenbroek and Zeijlemaker, 2008) in which patients suffer from recurrent or persistent infections by *Candida albicans* and sometimes *Staphylococcus aureus* on their skin, nails, oral and genital mucosae (Puel et al., 2011). This is also recorded in patients with ataxia telangiectasia (AT) (Meulenbroek and Zeijlemaker, 2008). AT is a rare autosomal recessive disorder, caused by a defective or missing ataxia telangiectasia mutated (ATM) gene and the symptoms include progressive cerebellar degeneration and greatly increased susceptibility to cancers (Weyemi et al., 2015). Low level of IgG2 was recorded in sera of 8 out of 61 children who contracted human immunodeficiency virus infection even though the levels of total IgG were increased and this was due to elevation in both IgG1 and IgG3 (Bartmann et al., 1991).

Cystic fibrosis (CF) patients presented with chronic *Pseudomonas aeruginosa* infection were often found to have elevated levels of IgG2 and IgG3 as stated by Meulenbroek and Zeijlemaker (2008). This was highly due to the response to chronic antibiotic stimulation of *P. aeruginosa* lipopolysaccharide (Fick et al., 1986). This observation was supported by the following evidences: (1) no increase of serum IgG2 levels in CF patients not infected with *P. aeruginosa* (2) positive correlation (*r* = 0.73) between IgG2 levels and the number of colony-forming units of *P. aeruginosa* found in sputum specimens of CF patients and lastly (3) IgG antibodies eluted from *P. aeruginosa* lipopolysaccharide ligands on affinity gels were mostly of IgG2 (Fick et al., 1986).

**IgG3**

IgG3 is most commonly found together with IgG1 in antibody responses to protein antigen (Meulenbroek and Zeijlemaker, 2008). Deficiency of this IgG subclass is associated with a history of recurrent infections which lead to chronic lung diseases according to Meulenbroek and Zeijlemaker (2008). Low level of IgG3 is recorded in patients of Wiskott-Aldrich syndrome (WAS) (Meulenbroek and Zeijlemaker, 2008). WAS condition was described by Wiskott in 1937 while Aldrich, in 1954, discovered the X-linked nature of this syndrome (Zeijlemaker et al., 2008). It is a rare X-linked immunodeficiency disorder in which patients are presented with thrombocytopenia with small platelets, eczema and recurring episodes of infections (Suri et al., 2012). Deficiency of IgG3 level is also recorded in patients who have persistent respiratory infections with bronchiectasis.

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**Table 1** General property of human IgG subclasses (modified from Vidarsson et al., 2014)

<table>
<thead>
<tr>
<th></th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular mass (kD)</td>
<td>146</td>
<td>146</td>
<td>170</td>
<td>146</td>
</tr>
<tr>
<td>Number of amino acids in hinge region</td>
<td>15</td>
<td>12</td>
<td>62</td>
<td>12</td>
</tr>
<tr>
<td>Number of inter-heavy chain disulfide bonds</td>
<td>2</td>
<td>4</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Relative abundance (%)</td>
<td>60</td>
<td>32</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
IgG4

IgG4 is the least abundant immunoglobulin found in a healthy person compared to other subclasses, accounting to only 5% of the total IgG (Stone et al., 2012). Generation of immunoglobulin can be induced by allergens and they are usually formed as a result of repeated exposure to antigens in a non-infectious setting (Vidarsson et al., 2014). IgG4 deficiencies were reported in patients with recurrent respiratory tract infection, common variable immunodeficiency, Wiskott–Aldrich syndrome, chronic mucocutaneous candidiasis, and HIV-infection (stages 3 and 4). However, its significance is unclear due to its low concentration even in healthy individuals (Meulenbroek and Zeijlemaker, 2008).

On the other hand, atopic eczema and dermatitis patients were often presented with high levels of IgG4 in their sera and this could possibly due to prolonged antigenic stimulation as noted by Meulenbroek and Zeijlemaker (2008). Vidarsson et al. (2014) also stated that allergens are good inducers of IgG4.

3.0 IgG4 Related Diseases (IgG4RD)

Besides being a dominant subclass in allergy disease, elevated concentration of IgG4 has been implicated in a number of diseases and these are termed IgG4-related diseases (Vidarsson et al., 2014). IgG4-related diseases include autoimmune hypophysitis, orbital pseudotumour, Mikulicz’s disease, Kuttner’s tumour, Hashimoto’s thyroiditis, Reidel’s thyroiditis, interstitial pneumonia, autoimmune pancreatic and many more.

The fibroinflammatory process of IgG4RD arises as a result of multiple immune-mediated mechanisms (Stone et al., 2012). Although still in its early discovery, several genetic susceptibility factors for IgG4RD have been found. In a study that involved Japanese population, it was found that the HLA serotypes DRB1*0405 and DQB1*0401 increased the possibility to IgG4RD (Kawa et al., 2002). Park et al. (2008) found a relation between DQB1-57 without aspartic acid and relapse cases of autoimmune pancreatitis in Korean population. In another study by Akita and et al. (2010) on IgG4RD sclerosing disease, they found that the production of IgG4 and interleukin (IL)-10 from peripheral-blood mononuclear cells (PBMCs) were stimulated by toll-like receptor ligands, suggesting that IgG4 can be produced by different species of bacteria through innate immunity. However, this study was only done on one patient and therefore requires further investigation.

In cases of Mikulicz’s disease, sclerosing pancreatitis and cholangitis, 2h2 cells are mostly activated and high tissue mRNA expression levels of IgG2a cytokines such as IL-4, IL-5, IL-10 and IL-13 were expressed at affected sites (Stone et al., 2012). Stone et al. (2012) suggested that autoimmunity and infectious agents could be potential immunologic triggers in IgG4RD and the production of IgG4 is regulated by TH2 cells that are further enhanced by TH2 cytokines, namely IL-4 and IL-13. Zen et al. (2007) found that many lymphocytes in affected organs of sclerosing pancreatitis and cholangitis patients expressed IL-4 or IL-10. An analysis of stimulated PBMCs from these patients also indicated the presence of TH2 cytokines (Stone et al., 2012).

Activation of regulatory T (Treg) cells is often associated with IgG4RD which results in high level of IgG4 (Stone et al., 2012). As compared to classic autoimmune diseases in which the function of Treg cells is downregulated, higher expression level of forkhead box P3 (FoxP3) mRNA is found in IgG4RD patients’ tissues (Zen et al., 2007). For instance, Miyoshi et al. (2008) found a large amount of CD4+CD25+ Treg cells infiltrated affected sites while a substantial amount of CD4+CD25 high Treg cells in the blood of autoimmune pancreatitis patients.

Stone et al. (2012) indicated two possible reasons for the elevated concentration of IgG4 in IgG4RD: a) IgG4 is acting as tissue-destructive immunoglobulins or b) IgG4 is overproduced in response to an unknown primary inflammatory stimulus. Nevertheless, the pathophysiological mechanisms of IgG4RD still require more thorough scientific investigations.

Apart from the above diseases that are associated with abnormalities in the levels of different subclasses of IgG, IgGs are also involved in anaphylaxis and, most recently, reported in dengue virus (DENV) infection. However in IgG4-mediated anaphylaxis and dengue virus infection, it usually involves a combination of IgG subclasses.

4.0 IgG and Anaphylaxis

Therapeutically, IgG, in the form of polyclonal serum IgG preparations, have been used to treat autoantibody-mediated autoimmune diseases like Guillain-Barré syndrome, immunoglobulin deficiency and more recently skin blistering diseases due to its anti-inflammatory activity (Nimmerjahn, 2014). However, recent cases of anaphylaxis caused by monoclonal antibodies have demonstrated the involvement of IgG as the triggering factor (Jiao et al., 2013).

Anaphylaxis is a serious allergic reaction that happens very fast and might lead to death. It was estimated that lifetime prevalence of anaphylaxis is between 0.05% and 2%. Commonly anaphylaxis is triggered by food and this involves immunoglobulin E (IgE) and high-affinity receptors for IgE (FcεRI receptors) found on the surfaces of mast cells and basophils. Though uncommon in human anaphylaxis, IgG-mediated anaphylaxis has been reported with dextran or infusion of chimeric, humanised FcγRIIa activating factor (PAF) are the main players (Peavy and Metcalfe, 2009). Similarly, IgG-mediated anaphylaxis happens when IgG cross links with FcγRII on immune cells. Upon stimulation by allergens, cytokines such as PAF, tumour necrosis factor (TNF), interleukin (IL)-1, IL-6, IL-12 and IL-23 are released (Simons, 2010).

Prior to the discovery of IgE, IgG had been found to induce mast cells. In guinea pig, rats and mouse models of passive cutaneous anaphylaxis (PCA), IgG of selected subclasses was isolated from immune sera and found to cause PCA. The responsible IgG subclasses were IgG1 in guinea pigs and mice while IgG2a in rats (Malbec and Daeron, 2007). The role of IgG in inducing anaphylaxis was revisited in numerous studies. Researchers found that symptoms of anaphylaxis were observed in antigen-challenged mouse model depleted of mast cells, FcγRII and IgE (Finkelman et al., 2005). It was postulated that IgG, macrophages, FcγRII and PAF were involved in anaphylaxis in mice after...
ruling out the complement-dependent pathway (Finkelman et al., 2005). Mouse IgG1 have been reported to be able to mediate cutaneous anaphylaxis most likely due to the weak association with mast cell FcεRI cross-linking (Faquin-Mauro et al., 1999) and consistent with this, murine FcyRIII-dependent anaphylaxis has been found to be mediated by IgG2a and IgG2b (Daeron et al., 1982).

FcyRIII is a stimulatory receptor and the weak binding of IgE to these receptors on macrophages could bring about macrophage- dependent, FcyRIII-mediated anaphylaxis but its contribution is rather small in relation to the interaction between FcyRII and the more abundantly available IgG antibodies and this was also supported by FcyRIII-dependent anaphylaxis usually occur in IgE-deficient mice (Strait et al., 2002; Finkelman et al., 2005). Upon cross-linking of IgG and FcγRII, cytokines that lead to the onset of anaphylaxis will be released. Apart from that, IgG2b-induced passive systemic anaphylaxis (IgG2b-induced PSA) which relied solely on FcyRII and neutrophils was discovered in a study by Jönsson et al. (2011) and showed elevated serum PAF. Jönsson et al. (2011) also found that by passively administering immune complexes made of antigen-specific polyclonal IgG antibodies of the IgG1 and IgG2a/b subclasses and its corresponding antigen was able to induce anaphylaxis (Bruhns, 2012).

Yuasa et al. (2001) found that Lyn plays an important role in IgG-mediated anaphylaxis whereby in their Lyn-deficient mouse model, they found significantly reduced responses in terms of drop in rectal temperature when compared to control mice. Lyn belongs to the Src family tyrosine kinase and it is able to initiate intracellular signal transduction through the association of immune receptors bearing cytoplasmic amino acid motif termed immune receptor tyrosine-based activation motif (ITAM). FcγRIII is the main initiator of IgG-mediated immune responses in mice as pointed by Ravetch and Clynes in 1998 and it is able to bind to the same FcRβ and FcγRI ATAM-bearing subunits of FcγRI (Yuasa et al., 2001). Hence, similarly upon the binding of FcγRIII and IgG, the Lyn-Btk-PLCγ cascade will be activated (Nirmal et al., 2013) which causes degranulation of cells and the release of mediators responsible for anaphylaxis.

5.0 IgG and Dengue Infection

Dengue virus (DENV) infection affects about 400 million humans each year according to Syenina et al. (2015). DENV, a mosquito-borne virus of the Flaviviridae family, is transmitted to humans through dengue-infected mosquito bites especially Aedes aegypti and Aedes albopictus species. This infection is mostly found in tropical and subtropical regions (Koraka et al., 2001). An infected person is usually presented with symptoms of fever, chills, frontal headache, myalgia, arthralgia and rashes as stated by Koraka et al. (2001). There are a few forms of DENV disease ranging from self-resolving dengue fever (DF) to more severe forms of dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) (Syenina et al., 2015).

Multiple studies have revealed that there is an association between IgG and DENV. As early as 1996, mast cells (Fc-receptor bearing cells) activated directly by DENV (St. John et al., 2011) were reported to bind to multiple classes of antibodies, including IgE and IgG (Sylvestre and Ravetch, 1996). This phenomenon eventually leads to the pathological development of dengue virus infection by enhancing vascular leakage (Syenina et al., 2015).

IgG subclass antibodies display varying capacities in the pathogenesis and severity of DENV infection. Research has indicated the predominance of DENV-specific IgM, IgG1 and IgG3 antibodies particularly in DF, DHF and DSS whereas IgA, IgG1 and IgG4 antibodies are associated with DHF and DSS; hence significantly higher level of IgG4 in DSS patients than in control or DF patients (Koraka et al., 2001).

The pathogenesis of DENV infection in the presence of DENV-antibody complexes are much more serious than that caused by DENV alone (King et al., 2000). The severity of the disease is therefore influenced by pre-existing immunity through antibody-dependent enhancement (ADE) (Abraham and St. John, 2010). ADE-promoting immune complexes are produced as a result of the cross reaction between pre-existing, non-neutralising antibodies and antigenically distinct heterologous DENV serotype and this weak interactions allow the virus to bind to antibodies without killing the virus. This is then followed by attachment of immune complexes to cells which promote the uptake of virus and with the increased viral infection; ADE causes the increased secretion of vasoactive cytokines which subsequently lead to vascular leakage as seen in cases of DHF (Kilks et al., 1988; Syenina et al., 2015). However, ADE alone is not the single cause that promotes downstream pathogenesis of DHF. Other pathway such as mast cell degranulation could play a role in the vascular pathogenesis of DHF (Syenina et al., 2015).

Mast cells and basophils express Fcε receptors abundantly and Fcγ receptors to some extent; making them highly suitable targets for antibody-enhanced virus infection (King et al., 2000). The activation of antibody-sensitised mast cells during secondary infection can be achieved through the binding of pre-formed immune complexes or when there is cross-linking between the sensitized-antigen bound Ig and Fc receptors (Oshiba et al., 1996; Malbec and Daëron, 2007; Syenina et al., 2015). Takizawa et al. (1992) pointed that the affinity for the IgG receptors increases as a result of binding between antibody and immune complexes and this enhances the subsequent activation of mast cells. Recently Syenina et al. (2015) found that mast cell degranulation and mast cell-dependent vascular leakage during DENV infection were augmented by pre-existing IgG which proposes a new mechanism of antibody-enhanced immune pathology during DENV infection. This was based on the ability of pre-existing antibody to bind to DENV and this was not seen with non-binding antibody of 3HF (do not bind to DENV serotype 1). In addition, they also found that mast cell-expressed FcγRII is responsible in the IgG-enhanced mast cell responses as shown in their serum-adaptive transfer studies. It was also discovered that FcγRII-deficiency only affects the antibody-enhanced degranulation response and not on direct mast cell degranulation which supports the role of FcγRII in immune detection of IgG-DENV immune complexes by mast cells in vivo and its downstream vascular pathology upon mast cell activation (Syenina et al., 2015).

IgG subclasses - IgG1, IgG2 and IgG3 are able to fix and activate the complement system and bind to Fcγ receptors which may contribute to the development of ADE and the pathogenesis of DHF and DSS. The activation of the complement system was associated with shock syndromes, induction of clotting which may lead to intravascular coagulation - both complications seen in DHF and DSS patients (Koraka et al., 2001). DENV-specific IgG1 is predominantly found in patients throughout the course of DENV illness and remained highly expressed in DHF and DSS patients suggesting its important role in the severity of DENV infection development (similar observation was noted with DENV-specific IgG3). IL-4, a Th2 cytokine, is able to stimulate the production of IgG4 serum antibodies and Th2 responses have been found to contribute to severe pathology and exacerbation of viral infections. A shift towards Th2 responses is also noted in DSS highlighting that the elevated level of DENV-specific IgG4 level in acute DENV infection may be a good indicator for the development of DSS (Koraka et al., 2001). DENV-specific IgG4 was found in patients during acute and convalescent infection phases and significantly elevated in DSS patients compared to control and DF patients as observed by Koraka et al. (2001). Through these findings the hypothesis that immunological factor such as ADE and complement activation may contribute to the pathogenesis of the severity of DENV infection was true.
6.0 Conclusion

IgG and its subclasses definitely play important roles in the manifestations of different forms of diseases from autoimmune to allergy to virus infection. However many more studies are needed to fully understand the relationship between IgG and the diseases. It is hopeful that by doing so, better diagnostic and therapeutic courses could be implemented in the future thereby mitigate patients’ suffers.

7.0 Declaration

The authors declare no conflicts of interest in this work.

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9.0 References


