

Chapter 13

Immunoglobulin G Glycosylation in Diseases



Marija Pezer

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Abstract Changes in immunoglobulin G (IgG) glycosylation pattern have been observed in a vast array of auto- and alloimmune, infectious, cardiometabolic, malignant, and other diseases. This chapter contains an updated catalog of over 140 studies within which IgG glycosylation analysis was performed in a disease setting. Since the composition of IgG glycans is known to modulate its effector functions, it is suggested that a changed IgG glycosylation pattern in patients might be involved in disease development and progression, representing a predisposition and/or a functional effector in disease pathology. In contrast to the glycopattern of bulk serum IgG, which likely relates to the systemic inflammatory background, the glycosylation profile of antigen-specific IgG probably plays a direct role in disease pathology in several infectious and allo- and autoimmune antibody-dependent diseases. Depending on the specifics of any given disease, IgG glycosylation read-out might therefore in the future be developed into a useful clinical biomarker or a supplementary to currently used biomarkers.

Keywords IgG glycosylation · Differential glycosylation · Disease · Biomarker

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Abbreviations

ACPA	Anti-citrullinated protein antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
Asn	Asparagine
CH2	Constant heavy 2
Fab	Fragment antigen binding
Fc	Fragment crystallizable
FcγRs	Fcγ receptors
FNAIT	Fetal and neonatal alloimmune thrombocytopenia
GlcNac	<i>N</i> -acetylglucosamine
HFD	High-fat diet
HDFN	Haemolytic disease of the fetus and newborn
IgG	Immunoglobulin G
IVIg	Intravenous immunoglobulin
RA	Rheumatoid arthritis

13.1 Introduction

Since the first reports on glycans attached to immunoglobulin G (IgG) in the 1970s (Ciccimarra et al. 1976; Williams et al. 1973; Koide et al. 1977; Hymes et al. 1979) and the seminal papers by Parekh and al. on the association of a changed IgG glycome composition with a diseased status and aging, (Parekh et al. 1985, 1988) IgG glycans are today universally recognized as modulators of IgG activity (Yamaguchi and Barb 2020). The importance of IgG glycome composition is implied in various physiological and pathological states. IgG glycans are discussed as potential contributors to disease development and progression, as well as a diagnostic, prognostic, and follow-up biomarker. This chapter is a brief update and extension of our comprehensive review on IgG glycosylation in aging and diseases published 3 years ago (Gudelj et al. 2018a), with a focus on the potential functionality of the skewed IgG glycosylation pattern. The table presents the updated list of publications that examined IgG glycosylation in various diseased states.

13.2 IgG Glycans are an Integral Structural and Functional Part of the Molecule

IgG glycans represent about 15% of the molecule's weight (Arnold et al. 2007). Each IgG molecule contains an N-glycan covalently attached to the conserved asparagine (Asn) at position 297 within the Fc region on each of the two heavy chains (Shade and Anthony 2013). In addition, 15–20% IgG molecules contain an

N-glycan within the Fab region, attached to the asparagine within an N-glycosylation sequon formed by somatic hypermutation during affinity maturation (Dunn-Walters et al. 2000; van de Bovenkamp et al. 2016).

Fc N-glycans are placed in the cavity between the CH2 domains of the two opposing heavy chains (Pincetic et al. 2014; Deisenhofer et al. 1976) and are important for the molecule's structural integrity, stability, and serum-half life (Boune et al. 2020; Cymer et al. 2018). They are also involved in the modulation of IgG effector functions, by affecting the molecule's affinity toward its ligands and receptors: type I and type II Fc receptors, C1q complement component, mannan-binding lectin, etc. (Pincetic et al. 2014; Peschke et al. 2017; Malhotra et al. 1995; Dekkers et al. 2017). Although markedly less explored than Fc glycans, Fab glycans are also reported to affect IgG's biological properties and effector functions, such as half-life, stability, solubility, and antigen-binding (van de Bovenkamp et al. 2016, 2018a; Wu et al. 2010; Wright et al. 1991; Higel et al. 2016; Liu 2015, 2018).

13.3 IgG Glycans Affect IgG Functions

The composition of both Fab and Fc glycans has been confirmed to influence IgG functionality and activity. Since this has been described in detail in Chap. 12, the main findings are only briefly summarized here as a reminder for the reader.

13.3.1 *Fc Glycans*

Due to the positioning of the Fc N-glycan at the Asn-297, structural differences of the N-glycans attached to the Fc region influence the affinity to the IgG ligands and receptors that interact with IgG at the CH2 domain and the CH2-CH3 domain interface (Dekkers et al. 2017; Reusch and Tejada 2015; Li et al. 2017; Wada et al. 2019; Vidarsson et al. 2014).

Core-Fucosylation Contrary to most other plasma proteins, over 90% of all Fc glycans are core-fucosylated (fucosylated glycans, F) (van de Bovenkamp et al. 2016; Štambuk et al. 2020; Baković et al. 2013; Clerc et al. 2016). The lack of core fucose significantly increases the IgG's affinity for the Fc γ receptor III (Fc γ RIII), both A and B, enhancing the Fc γ RIII-mediated effector functions, particularly the antibody-dependent cell-mediated cytotoxicity (ADCC) (Dekkers et al. 2017; Shields et al. 2002; Shinkawa et al. 2003). This prominent effect of alternative Fc glycosylation on the IgG function found its application in the industrial production of therapeutic monoclonal antibodies (Garber 2018).

Bisection Up to 10% of all IgG Fc glycans are bisected, i.e., contain a bisecting *N*-acetylglucosamine (GlcNAc) (bisected glycans, B) (van de Bovenkamp et al. 2016). Since the presence of GlcNAc and core fucose, to a degree, preclude each

other during glycan synthesis (Benedetti et al. 2017; Schuster et al. 2005; Ferrara et al. 2006), the increase in binding affinity for Fc γ RIII sometimes associated with bisected glycans (Umaña et al. 1999; Davies et al. 2001; Lively et al. 1995) cannot be easily uncoupled from the same effect observed for core-fucosylated IgG glycans (Shinkawa et al. 2003).

Galactosylation Galactosylation is the IgG glycosylation trait with the most pronounced inter-individual variation (Huhn et al. 2009; Gornik et al. 2012). On average, about 35% of IgG Fc glycans contain no terminal galactose residues (agalactosylated glycans, G0), about 35% contain one (monogalactosylated glycans, G1), and about 15% contain two terminal galactoses (digalactosylated glycans, G2) (Baković et al. 2013; Huffman et al. 2014). Terminal galactoses modulate IgG inflammatory potential by affecting binding affinities to complement components and Fc γ Rs. Agalactosylated Fc glycans are considered to act pro-inflammatory by activating the complement through the alternative pathway (Banda et al. 2008), and the lectin pathway after binding to the mannose-binding lectin (Malhotra et al. 1995; Ji et al. 2002; Arnold et al. 2006). Galactosylation was also held responsible for the anti-inflammatory activity of immune complexes by binding to the inhibitory Fc γ RIIB (Karsten et al. 2012). However, Fc galactosylation has also been reported to enhance complement-dependent cytotoxicity (CDC) through the classical complement pathway by increasing the IgG's affinity for the C1q complement component (Peschke et al. 2017; Boyd et al. 1995; Hodoniczky et al. 2005). Likewise, by increasing the affinity of IgG for Fc γ Rs, it enhances the downstream processes mediated by Fc γ Rs, in particular ADCC (Dekkers et al. 2017; Kumpel et al. 1994, 1995; Houde et al. 2010; Subedi and Barb 2016). We should therefore not rush to proclaim terminal IgG galactosylation simply “anti-inflammatory,” before considering the entire context and the nature and extent of IgG involvement in the process we are investigating.

Sialylation On average, 10–15% of IgG Fc glycans carry a single terminal sialic acid (monosialylated glycans, S1) or two sialic acids (disialylated glycans, S2) (Baković et al. 2013; Huffman et al. 2014). Similar to terminal galactosylation, sialylation is most often discussed as a modulator of IgG functions regarding inflammation (Böhm et al. 2014).

The importance of sialylation became evident when the presence of the sialylated Fc fraction was discovered indispensable for the anti-inflammatory activity of the intravenous immunoglobulin (IVIg) preparation in a K/BxN serum-transfer mouse model of RA (Kaneko et al. 2006). Mouse studies on several antibody-dependent autoimmune disease models helped elucidate the mechanistic pathway for its activity, starting with the binding of the sialylated Fc fraction to specific ICAM-3 grabbing non-integrin-related 1 (SIGN-R1) on the surface of splenic macrophages and ending in enhanced Fc γ RIIB expression on the effector macrophages (Kaneko et al. 2006; Schwab and Nimmerjahn 2013; Anthony et al. 2008, 2011; Schwab et al. 2012, 2014; Washburn et al. 2015; Galeotti et al. 2017; Fiebiger et al. 2015). However, this finding did not hold in several other *in vitro* and *in vivo* models, nor human studies (Galeotti et al. 2017; Guhr et al. 2011; Leontyev et al. 2012; Campbell et al. 2014; Temming et al. 2019). This confirms the well-established

notion that the IVIg mode of action is complex and tightly connected with the corresponding immune context.

Depending on the sialylation status of the Fc glycan, the Fc domain is suggested to adopt either an “open” or a “closed” conformation, for sialylated and asialylated glycans, respectively. The “open” conformation favors binding to the type I FcγRs, whereas the “closed” conformation favors the binding of type II FcγRs (Pincetic et al. 2014; Sondermann et al. 2013). Terminal sialylation is thus proposed to act as a switch between two distinct immunological effector functions.

To summarize—agalactosylated, asialylated, and bisected IgG molecules are often simply described as “pro-inflammatory,” and terminally galactosylated and sialylated IgG molecules as “anti-inflammatory,” while afucosylated IgG has an augmented capacity to trigger ADCC through enhanced FcγRIIIA binding. We should, however, always bear in mind that this generalization is a simplification, and exercise caution when considering its implications.

13.3.2 *Fab Glycans*

As expected, Fab glycans are mostly reported to affect antigen-binding (Wright et al. 1991; Coloma et al. 1999; Schneider et al. 2015; Wallick et al. 1988; Tachibana et al. 1997; Leibiger et al. 1999; Khurana et al. 1997; Man Sung Co et al. 1993; Fujimura et al. 2000; Van De Bovenkamp et al. 2018b). Besides the obvious, they are also suggested to influence IgG aggregation and precipitation (Courtois et al. 2016), immune complex formation (Gutierrez et al. 2006), and have a role in the IVIg mode of action (Käsermann et al. 2012; Wiedeman et al. 2013; Massoud et al. 2014; Séité et al. 2010, 2014).

13.4 Regulation of IgG Glycosylation

IgG glycosylation is a complex trait, influenced by both, genetics (Menni et al. 2013; Pučić et al. 2011; Klarić et al. 2020) and the environment (Štambuk et al. 2020; Yu et al. 2016; Krištić et al. 2014; De Jong et al. 2016). More precisely, the compound IgG glycosylation pattern seems to be, to different degrees, modulated by IgG aminoacid sequence (Lund et al. 1996; Zaitseva et al. 2018; Yu et al. 2013), the intra- and extracellular milieu affecting the glycosylation machinery (Ohtsubo and Marth 2006; Oefner et al. 2012; Bartsch et al. 2020; Hess et al. 2013; Canellada et al. 2002; Gutiérrez et al. 2001; Miranda et al. 2005; Wang et al. 2011; Pfeifle et al. 2017; Liu et al. 2014; Fan et al. 2015), and environmental factors (Novokmet et al. 2014; Greto et al. 2020; Ercan et al. 2017; Engdahl et al. 2018; Klasić et al. 2018; Tijardović et al. 2019; Sarin et al. 2019; Peng et al. 2019). Solving the outstanding question of IgG glycosylation regulation would likely bring us one step closer to understanding the possible functionality of changes in IgG glycan composition in different physiological and pathological states.

13.5 Common IgG Glycosylation Pattern in Inflammatory Diseases and Aging

Advances in the development of high-throughput glycomic and glycoproteomic analyses (Huhn et al. 2009; Mariño et al. 2010; Trbojević-Akmačić et al. 2016, 2017) have enabled a significant number of large-scale epidemiological studies examining total IgG glycosylation pattern in diseased vs. healthy control subjects (Štambuk et al. 2020; Singh et al. 2020; Lemmers et al. 2017; Menni et al. 2018; Šimurina et al. 2018; Theodoratou et al. 2016; Wahl et al. 2018). In many of the diseases that were studied, a similar pattern emerged: diseased subjects often exhibited a decreased abundance of galactosylated, sialylated, and—occasionally—an increased abundance of bisected bulk IgG glycans when compared to healthy controls (Fig. 13.1). In addition, the trend was often associated with disease severity and reverted to baseline values upon successful application of therapy. Interestingly, the same pattern that was observed in diseases with an inflammatory component was also evident in aging subjects (Fig. 13.1) (Gudelj et al. 2018a; Lauc 2016). This “pro-inflammatory IgG glycome composition” is likely associated with

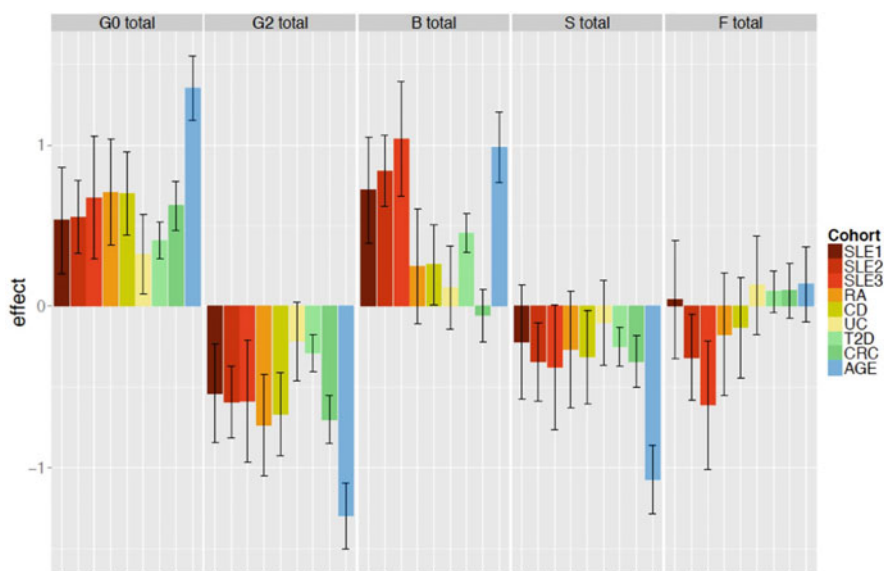


Fig. 13.1 General patterns of IgG glycosylation changes are similar in several diseases and aging. The effect (shown on the y-axis) is shown as the difference between means of case and control populations (for aging, population over vs. population under 50 years of age), expressed in standard deviations. The whiskers represent the 95% confidence interval. The reference populations for disease cohorts are age- and sex-matched healthy controls. *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis, *CD* Crohn’s disease, *UC* ulcerous colitis, *T2D* type 2 diabetes mellitus, *CRC* colorectal carcinoma. *G0* agalactosylated glycans, *G2* digalactosylated glycans, *B* bisected glycans, *S* sialylated glycans, *F* core-fucosylated glycans. Reused with permission from Lauc (2016)

the common background inflammatory component of the studied diseases. In some cases, it might reflect a predisposition toward disease development, or/and even be involved as an effector of inflammation. Additionally, it might represent a consequence of environmental exposure to antigens through a lifetime or unhealthy lifestyle choices.

Indeed, the composition of IgG glycome was reported to associate with many physiological and biochemical traits, as well as with traits correlated to inflammation and poor metabolic health (Gudelj et al. 2018a) and the expected lifespan (Štambuk et al. 2020). IgG glycome was thus suggested to be a biomarker of general immune activation (De Jong et al. 2016), while we propose total IgG glycoprofile can be positioned as a read-out of a general state of health, i.e. biological age (Vilaj et al. 2019).

13.6 Role of Skewed IgG Glycosylation in Diseases

When we take into account the complexity of the IgG's multiple roles in our immune system, it is no wonder there is no single common interpretation of the altered IgG glycopattern across the wide spectrum of diseases (Table 13.1). The multiple pleiotropic loci, i.e. shared associations of IgG glycome composition and autoimmune, inflammatory, and other diseases (Klarić et al. 2020; Lauc et al. 2013), as well as the changes in IgG glycopattern preceding disease development—such as in the case of RA (Gudelj et al. 2018b) and cardiovascular diseases (Menni et al. 2018)—suggest that a skewed bulk serum IgG glycoprofile might reflect a disease risk or predisposition. This predisposition can manifest through an inherited (Klarić et al. 2020; Lauc et al. 2013) or acquired propensity for inflammation modulation (Franceschi et al. 2018).

In most other cases, when it comes to glycosylation of the bulk serum IgG, the role of a shifted glycosylation pattern is not clear. As already mentioned, decreased galactosylation and sialylation often accompany diseases that involve an inflammatory immune response. The evidence that would enable us to unambiguously determine whether the “pro-inflammatory” IgG glycoforms represent one of many drivers of disease pathology or merely byproducts of the inflamed immune system is still lacking. The current consensus is that total IgG glycopattern is likely relevant in the general modulation of the immune activation threshold.

In some cases, however, a clear link/evidence for the functionality of IgG glycans is provided. A mouse study investigating the link between obesity and the development of hypertension resulted in a very intriguing observation. Hyposialylated IgG from mice in which obesity was induced by a high-fat diet (HFD) induced an elevated blood pressure when transferred to IgG-deficient mice. Moreover, supplementing HFD-feed mice with a sialic acid precursor, *N*-acetyl-D-mannosamine (ManNAc), resulted in the restoration of the baseline level of IgG sialylation and protected them from obesity-induced hypertension development (Peng et al. 2019). This finding thus demonstrated the functional role of IgG glycans

Table 13.1 Diseases exhibiting an altered serum IgG glycosylation profile

	↓	↑
G	<p>Inflammatory diseases and states</p> <p>Takayasu's arteritis (Hernandez-Pando et al. 1994)</p> <p>Adult periodontal disease (Novak et al. 2005)</p> <p>Nonalcoholic steatohepatitis (Vanderschaeghe et al. 2018)</p> <p>IgG4-related disease (Culver et al. 2019)</p> <p>Primary sclerosing cholangitis (Culver et al. 2019)</p> <p>Autoimmune diseases</p> <p>Rheumatoid arthritis—total (Parekh et al. 1985, 1988; Bond et al. 1996; Van de Geijn et al. 2009; Young et al. 1991; Axford et al. 1992; Engdahl et al. 2018; Gudelj et al. 2018b; Gindzienska-Sieskiewicz et al. 2007; Tomana et al. 1988; Bodman-Smith et al. 1996; Gindzienska-Sieskiewicz et al. 2016; Pekelharing et al. 1988; Pilkington et al. 1995), ACPA (Ercan et al. 2010; Rombouts et al. 2015; Bond et al. 1997, 2018), RF (Matsumoto et al. 2000)</p> <p>Osteoarthritis (Parekh et al. 1985; Bond et al. 1997)</p> <p>Juvenile onset rheumatoid arthritis (Parekh et al. 1988; Flögel et al. 1998; Sumar et al. 1991; Ercan et al. 2012; Cheng et al. 2017)</p> <p>Systemic lupus erythematosus (Tomana et al. 1988, 1992; Pilkington et al. 1995; Bond et al. 1997; Vučković et al. 2015)</p> <p>Lupus nephritis (Bhargava et al. 2021)</p> <p>Inflammatory bowel disease: Crohn's disease and ulcerative colitis (Šimurina et al. 2018; Tomana et al. 1988; Bond et al. 1997; Dubé et al. 1990; Go et al. 1994; Shinzaki et al. 2008; Nakajima et al. 2011; Trbojevic Akmacic et al. 2015; Parekh et al. 1989; Miyoshi et al. 2016)</p> <p>Sjögren's syndrome (Bond et al. 1996, 1997)</p> <p>Neonatal lupus (Pilkington et al. 1996a)</p> <p>Spondyloarthropathy (Bond et al. 1997; Leirisalo-Repo et al. 1999)</p> <p>ANCA-associated vasculitis—total (Holland et al. 2002, 2006; Espy et al. 2011; Kemna et al. 2017; Wuhrer et al. 2015), ANCA (Kemna et al. 2017; Wuhrer et al. 2015)</p> <p>Coeliac disease (Cremata et al. 2003)</p> <p>Lambert–Eaton myasthenic syndrome (Selman et al. 2011)</p> <p>Myasthenia gravis (Selman et al. 2011)</p> <p>Myositis (Perdivara et al. 2011)</p> <p>Guillain–Barré syndrome (Fokink et al. 2014a; b)</p>	<p>Alloimmune diseases</p> <p>Fetal or neonatal alloimmune thrombocytopenia—anti-HPA (Sonneveld et al. 2016; Wuhrer et al. 2009)</p> <p>Hemolytic disease of the fetus and newborn—anti-c, anti-E (Sonneveld et al. 2017a)</p> <p>Cancers</p> <p>Thyroid cancer (Chen et al. 2012)</p> <p>Multiple myeloma (Mittermayr et al. 2017)</p> <p>Mammary gland hyperplasia (Meng et al. 2020)</p> <p>Infectious diseases</p> <p>Measles—anti-measles (Larsen et al. 2020)</p> <p>Mumps—anti-mumps (Larsen et al. 2020)</p> <p>Parvovirus-B19 infection—anti-B19 (Larsen et al. 2020)</p> <p>COVID-19—anti-S (Larsen et al. 2020), anti-N (Larsen et al. 2020)</p> <p>RSV infection—anti-RSV (van Erp et al. 2020)</p> <p>Tuberculosis—antigen-specific (Lu et al. 2020)</p> <p>Other diseases</p> <p>Parkinson's disease (Russell et al. 2017)</p>

(continued)

Table 13.1 (continued)

↓	↑
<p>Poor glycemic control and impaired renal function in type I diabetes (Bermingham et al. 2018)</p> <p>Autoimmune hemolytic anemia—total and anti-RBC (Sonneveld et al. 2017b)</p> <p>Membranous nephropathy (Haddad et al. 2021)</p> <p>Alloimmune diseases</p> <p>Hemolytic disease of the fetus and newborn—anti-K (Sonneveld et al. 2018)</p> <p>Cancers</p> <p>Multiple myeloma (Nishiura et al. 1990; Aurer et al. 2007)</p> <p>Bone disease in multiple myeloma (Westhrin et al. 2020)</p> <p>Ovarian cancer—total (Gerçel-Taylor et al. 2001; Saldova et al. 2007; Alley et al. 2012; Qian et al. 2013; Ruhaak et al. 2016), tumor-reactive (Gerçel-Taylor et al. 2001)</p> <p>Prostate cancer (Kanoh et al. 2004a, 2008, 2009; Kazuno et al. 2016)</p> <p>Non-small cell cancer (Kanoh et al. 2006)</p> <p>Gastric cancer (Kanoh et al. 2004b, 2008; Bones et al. 2010, 2011; Kodar et al. 2012)</p> <p>Lung cancer (Kanoh et al. 2004b, 2008; Chen et al. 2013)</p> <p>Colorectal carcinoma (Theodoratou et al. 2016; Vučković et al. 2016)</p> <p>Breast cancer (Kawaguchi-Sakita et al. 2016)</p> <p>Malignant hematological diseases^a (de Haan et al. 2018a)</p> <p>Infectious diseases</p> <p>Leprosy—Erythema nodosum leprosum (Filley et al. 1989)</p> <p>Tuberculosis (Rook et al. 1994; Pilkington et al. 1995, 1996b; Parekh et al. 1989; Filley et al. 1989; Rademacher et al. 1988; Lu et al. 2016)</p> <p>Infective endocarditis (Bond et al. 1997)</p> <p>HIV infection—total (Ackerman et al. 2013; Moore et al. 2005; Muenchhoff et al. 2020), anti-HIV (Ackerman et al. 2013; Larsen et al. 2020)</p> <p>Hepatitis C: liver fibrosis, cirrhosis—anti-Gal (Mehta et al. 2008)</p> <p>Hepatitis B: chronic infection (Ho et al. 2015); liver cirrhosis – total (Ho et al. 2015), anti-Gal (Mehta et al. 2008)</p> <p>Visceral leishmaniasis (Gardinassi et al. 2014)</p> <p>CMV infection—anti-CMV (Larsen et al. 2020)</p>	

(continued)

Table 13.1 (continued)

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	<p>COVID-19 [139]</p> <p>Other diseases</p> <p>Castleman's disease (Nakao et al. 1991)</p> <p>Galactosaemia (Coss et al. 2012; Knerl et al. 2015; Maratha et al. 2016; Stockmann et al. 2016; Coman et al. 2010; Coss et al. 2014)</p> <p>Alzheimer's disease (Lundström et al. 2014)</p> <p>Asthma? (De Jong et al. 2016; Pezer et al. 2016)</p> <p>Chronic kidney disease (Barrios et al. 2016)</p> <p>Hypertension (Wang et al. 2016; Gao et al. 2017)</p> <p>Type II diabetes (Lemmers et al. 2017; Li et al. 2019)</p> <p>Nonalcoholic fatty liver disease (Zhao et al. 2018)</p> <p>Ischemic stroke (Liu et al. 2018)</p> <p>Hyperuricemia (Hou et al. 2019)</p> <p>Diabetic retinopathy (Wu et al. 2021)</p>	
S	<p>Inflammatory diseases and conditions</p> <p>Primary sclerosing cholangitis (Culver et al. 2019)</p> <p>Autoimmune diseases</p> <p>Rheumatoid arthritis—total (Parekh et al. 1985; Engdahl et al. 2018; Gudelj et al. 2018b; Gińdzińska-Sieškiewicz et al. 2016), ACPA (Scherer et al. 2010), RF (Matsumoto et al. 2000)</p> <p>Osteoarthritis (Parekh et al. 1985)</p> <p>ANCA-associated vasculitis—total (Espy et al. 2011; Kemna et al. 2017; Wuhler et al. 2015), ANCA (Kemna et al. 2017; Wuhler et al. 2015)</p> <p>Systemic lupus erythematosus—total (Vučković et al. 2015; Chen et al. 2015), ANA (Magorivska et al. 2016)</p> <p>Inflammatory bowel disease: Crohn's disease (Trbojevic Akmacic et al. 2015)</p> <p>Juvenile onset rheumatoid arthritis (Cheng et al. 2017)</p> <p>Antiphospholipid syndrome (Fickentscher et al. 2015)</p> <p>Autoimmune hemolytic anemia—? (Sonneveld et al. 2017b)</p> <p>Alloimmune diseases</p> <p>Hemolytic disease of the fetus and newborn—anti-K (Sonneveld et al. 2018)</p> <p>Infectious diseases</p> <p>Visceral leishmaniasis (Gardinassi et al. 2014)</p>	<p>Autoimmune diseases</p> <p>Autoimmune hemolytic anemia—anti-RBC (Sonneveld et al. 2017b)</p> <p>Alloimmune diseases</p> <p>Fetal or neonatal alloimmune thrombocytopenia—anti-HPA (Sonneveld et al. 2016; Wuhler et al. 2009)</p> <p>Cancers</p> <p>Multiple myeloma (Aurer et al. 2007; Fleming et al. 1998)</p> <p>Thyroid cancer (Chen et al. 2012)</p> <p>Lung cancer (Ruhaak et al. 2013)</p> <p>Infectious diseases</p> <p>Parvovirus-B19 infection—anti-B19 (Larsen et al. 2020)</p> <p>COVID-19—anti-S (Larsen et al. 2020), anti-N (Larsen et al. 2020)</p> <p>Recurrent respiratory infections (Cheng et al. 2020)</p> <p>RSV infection—anti-RSV (van Erp et al. 2020)</p> <p>HIV infection—anti-HIV (Muenchhoff et al. 2020)</p> <p>Tuberculosis—antigen-specific (Lu et al. 2020)</p>

(continued)

Table 13.1 (continued)

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	<p>Tuberculosis (Lu et al. 2016) HIV infection—total (Vadrevu et al. 2018), anti-HIV (Larsen et al. 2020) Meningococcal sepsis (de Haan et al. 2018b) CMV infection — anti-CMV (Larsen et al. 2020) COVID-19 [139] Cancers Ovarian cancer (Saldova et al. 2007) Colorectal carcinoma (Theodoratou et al. 2016; Vučković et al. 2016) Malignant hematological diseases^a (de Haan et al. 2018a) Monoclonal gammopathy of undetermined significance (Bosseboeuf et al. 2017) Multiple myeloma (Bosseboeuf et al. 2017) Bone disease in multiple myeloma (Westhrin et al. 2020) Other diseases Alzheimer’s disease (Lundström et al. 2014) Chronic kidney disease (Barrios et al. 2016) Type II diabetes (Lemmers et al. 2017) Hypertension (Peng et al. 2019; Gao et al. 2017) Parkinson’s disease (Russell et al. 2017) Ischemic stroke (Liu et al. 2018) Hyperuricemia (Hou et al. 2019) Dementia (Zhang et al. 2021)</p>	
F	<p>Inflammatory diseases and conditions Inflammation severity (Novokmet et al. 2014) Low back pain (Freidin et al. 2016) Autoimmune diseases Systemic lupus erythematosus? (Vučković et al. 2015; Sjöwall et al. 2015) ANCA-associated vasculitis—ANCA (Kemna et al. 2017) Inflammatory bowel disease: ulcerative colitis (Šimurina et al. 2018) Autoimmune thyroid diseases (Martin et al. 2020) Multiple sclerosis (Cvetko et al. 2020) Alloimmune diseases Fetal or neonatal alloimmune thrombocytopenia—anti-HPA (Kapur et al. 2014b; Sonneveld et al. 2016; Wuhler et al. 2009) Hemolytic disease of the fetus and newborn—anti-D (Kapur et al. 2014a), anti-c, anti-E, anti-K (Sonneveld et al. 2017a, 2018) Infectious diseases</p>	<p>Autoimmune diseases Juvenile onset rheumatoid arthritis (Flögel et al. 1998) Rheumatoid arthritis—total (Gińdzieńska-Sieškiewicz et al. 2016; Gornik et al. 1999), ACPA (Rombouts et al. 2015) Systemic lupus erythematosus? (Vučković et al. 2015; Sjöwall et al. 2015) ANCA-associated vasculitis (Kemna et al. 2017) Inflammatory bowel disease: Crohn’s disease (Šimurina et al. 2018) Infectious diseases Visceral leishmaniasis (Gardinassi et al. 2014) Tuberculosis (Lu et al. 2016) HIV infection—total (Vadrevu et al. 2018), anti-HIV (Muenchhoff et al. 2020) Cancers Hepatocellular carcinoma (Comunale et al. 2006) Multiple myeloma (Westhrin et al. 2020)</p>

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Table 13.1 (continued)

	↓	↑
	<p>Dengue fever progressing to dengue hemorrhagic fever or dengue shock syndrome—anti-ENV, anti-NS1, anti-HA (Wang et al. 2017)</p> <p>Meningococcal sepsis (de Haan et al. 2018b)</p> <p>HIV infection—anti-HIV (Ackerman et al. 2013; Larsen et al. 2020)</p> <p>CMV infection—anti-CMV (Larsen et al. 2020)</p> <p>Mumps—anti-mumps (Larsen et al. 2020)</p> <p>COVID-19—anti-S (Larsen et al. 2020), anti-N (Larsen et al. 2020) anti-RBD (Chakraborty et al. 2021)</p> <p>Tuberculosis—antigen-specific (Lu et al. 2020)</p> <p>Cancers</p> <p>Multiple myeloma (Mittermayr et al. 2017)</p> <p>Malignant hematological diseases^a (de Haan et al. 2018a)</p> <p>Other diseases</p> <p>Dementia (Zhang et al. 2021)</p> <p>Kidney function decline in type II diabetes (Singh et al. 2020)</p> <p>Non-malignant hematological diseases^b (de Haan et al. 2018a)</p>	<p>Other diseases</p> <p>Galactosaemia (Maratha et al. 2016)</p> <p>Hypertension (Gao et al. 2017)</p> <p>Nonalcoholic fatty liver disease (Zhao et al. 2018)</p>
B	<p>Inflammatory diseases and conditions</p> <p>IgG4-related disease (Culver et al. 2019)</p> <p>Autoimmune diseases</p> <p>Osteoarthritis (Bond et al. 1997)</p> <p>ANCA-associated vasculitis—total (Kemna et al. 2017; Wuhrer et al. 2015), ANCA (Wuhrer et al. 2015)</p> <p>Autoimmune hemolytic anemia—anti-RBC (Sonneveld et al. 2017b)</p> <p>Alloimmune diseases</p> <p>Hemolytic disease of the fetus and newborn—anti-c (Sonneveld et al. 2017a)</p> <p>Infectious diseases</p> <p>Visceral leishmaniasis (Gardinassi et al. 2014)</p> <p>HIV infection—anti-HIV (Larsen et al. 2020; Muenchhoff et al. 2020)</p> <p>COVID-19—total (Larsen et al. 2020; Petrović et al. 2020), anti-S (Larsen et al. 2020), anti-N (Larsen et al. 2020)</p> <p>Cancers</p> <p>Thyroid cancer (Chen et al. 2012)</p> <p>Other diseases</p> <p>Hypertension (Wang et al. 2016; Gao et al.</p>	<p>Inflammatory diseases and conditions</p> <p>Low back pain (Freidin et al. 2016)</p> <p>Primary sclerosing cholangitis (Culver et al. 2019)</p> <p>COPD (Pavić et al. 2018)</p> <p>Autoimmune diseases</p> <p>Rheumatoid arthritis (Pekelharing et al. 1988; Bond et al. 1996, 1997)</p> <p>Juvenile onset rheumatoid arthritis (Bond et al. 1996, 1997)</p> <p>Inflammatory bowel disease: Crohn's disease and ulcerative colitis (Bond et al. 1997)</p> <p>Lambert–Eaton myasthenic syndrome (Selman et al. 2011)</p> <p>Systemic lupus erythematosus (Vučković et al. 2015)</p> <p>Lupus nephritis (Bhargava et al. 2021)</p> <p>Alloimmune diseases</p> <p>Hemolytic disease of the fetus and newborn—anti-K (Sonneveld et al. 2018)</p> <p>Infectious diseases</p> <p>Infective endocarditis (Bond et al. 1997)</p> <p>Meningococcal sepsis (de Haan et al. 2018b)</p> <p>CMV infection—anti-CMV (Larsen et al.</p>

(continued)

Table 13.1 (continued)

	↓	↑
	2017) Galactosaemia (Maratha et al. 2016)	2020) Mumps—anti-mumps (Larsen et al. 2020) Parvovirus-B19 infection—anti-B19 (Larsen et al. 2020) Recurrent respiratory infections (Cheng et al. 2020) Tuberculosis—antigen-specific (Lu et al. 2020) Cancers Colorectal carcinoma (Theodoratou et al. 2016) Malignant hematological diseases ^a (de Haan et al. 2018a) Other diseases Chronic kidney disease (Barrios et al. 2016) Type II diabetes (Lemmers et al. 2017) Nonalcoholic fatty liver disease (Zhao et al. 2018) Ischemic stroke (Liu et al. 2018) Kidney function decline in type II diabetes (Singh et al. 2020) Dementia (Zhang et al. 2021)
H	Inflammatory diseases and conditions IgG4-related disease (Culver et al. 2019) Infectious diseases Meningococcal sepsis (de Haan et al. 2018b) Cancers Malignant hematological diseases ^a (de Haan et al. 2018a)	
M		Autoimmune diseases Multiple sclerosis (Cvetko et al. 2020)

“Down” arrow (↓) refers to a decreased and “up” arrow (↑) to an increased proportion of the corresponding IgG glycosylation trait (as calculated in the corresponding publication) in patients suffering from the disease compared to healthy controls and/or in association with disease activity and severity. In the case of antigen-specific IgG, the arrows refer to the comparison between antigen-specific and total IgG and/or to the association with disease activity and severity. Due to the complexity of IgG glycosylation in a disease setting, the associations shown here are simplified and do not reflect the particulars, such as IgG subclass and clonality, IgG region (total vs. Fab vs. Fc), analytical methodology, calculation of derived glycosylation traits, subject demographics, clinical parameters, etc. For details, readers are advised to consult the original publications. *G* galactosylated, *S* sialylated, *F* core-fucosylated, *B* bisected, *H* hybrid, *M* high-mannose glycans. *ACPA* anti-citrullinated protein antibody, *ANA* anti-nuclear antibody, *ANCA* anti-neutrophil cytoplasmic antibody, *CMV* cytomegalovirus, *COPD* chronic obstructive pulmonary disease, *COVID-19* corona virus disease 2019, *ENV* envelope protein, *HA* hemagglutinin, *HPA* human platelet antigen, *N* nucleocapsid protein, *NS1* non-structural protein 1, *RBC* red blood cell, *RBD* receptor binding domain, *RSV* respiratory syncytial virus, *S* spike protein. Modified (updated) from our previous review (Gudelj et al. 2018a)—an open-access article, available under the terms of the Creative Commons Attribution License (CC BY): <https://creativecommons.org/licenses/by/4.0/>

^aMalignant hematological diseases: acute lymphoblastic leukemia, myelodysplastic syndrome/acute myeloblastic leukemia, acute myeloblastic leukemia

^bNon-malignant hematological diseases: thalassemia, Fanconi anemia, sickle cell disease, severe aplastic anemia, progressive bone marrow failure, neutropenia congenita, Glanzmann thrombasthenia, hemophagocytic lymphohistiocytosis, X-linked lymphoproliferative disease

in the development of hypertension. Interestingly, the same treatment restored IgG sialylation and reduced tumor load and bone loss in a mouse model of myeloma (Westhrin et al. 2020).

On the level of total serum IgG, increased level of glycosylation of the Fab region observed in some malignant diseases (Zhu et al. 2002, 2003; Radcliffe et al. 2007; Coelho et al. 2010; McCann et al. 2008) is proposed to contribute to disease development and progression by enhancing tumor cell persistence and expansion (Coelho et al. 2010; Amin et al. 2015).

Glycosylation changes on antigen-specific IgG are more likely to be directly involved in disease pathology in case of antibody-mediated auto- or alloimmune diseases or defense from pathogens in case of infectious diseases. The role of differential IgG glycosylation in these cases corresponds to the specifics of a particular disease and the molecular mechanisms underlying its pathology.

In addition to the change in total IgG, multiple infectious diseases are characterized by a distinct glycosylation pattern of relevant antigen-specific IgG in comparison to total IgG (Table 13.1). This implies a distinct regulation of IgG glycosylation, depending on both the disease and the antigen (Ackerman et al. 2013), even within a single individual (Mahan et al. 2016). This supports the notion that IgG glycome relevance should be interpreted in the disease-specific functional context.

One of the rare instances where the role of IgG glycosylation is mechanistically explained is once more linked to the enhanced affinity of afucosylated IgG molecules for Fc γ R11A. In the case of dengue fever, occasionally a secondary, heterologous dengue infection results in severe dengue hemorrhagic fever and dengue shock syndrome. This is attributed to antibody-dependent enhancement (ADE) of the disease by cross-reactivity of afucosylated anti-dengue IgG with platelet antigens, resulting in platelet depletion (Wang et al. 2017). Additionally, the enhanced binding of afucosylated IgG to Fc γ R11A and Fc γ R11A promotes the Fc γ R-mediated viral entry and signaling in cells bearing these receptors on their surface, primarily monocytes and macrophages, resulting in infection progression (Thulin et al. 2020).

A similar relevance for afucosylated antigen-specific IgG is observed in COVID-19 patients. Anti-SARS-CoV-2 IgG with a higher core-fucosylation level is associated with unaided clearance of the infection (Larsen et al. 2020). By contrast, critically ill patients display lower levels of fucosylated anti-SARS-CoV-2 IgG (Larsen et al. 2020; Chakraborty et al. 2021). Furthermore, in *in vitro* studies afucosylated anti-S/-RBD antibodies were shown to induce enhanced natural killer (NK) cell degranulation (Chakraborty et al. 2021) and elevated production of pro-inflammatory cytokines by primary monocytes and alveolar macrophages, which is likely the background of the severe disease phenotype associated with this glycoprofile *in vivo* (Larsen et al. 2020; Chakraborty et al. 2021; Hoepel et al. 2020).

Similarly, afucosylated antigen-specific IgG in fetal and neonatal alloimmune thrombocytopenia (FNAIT) and hemolytic disease of the fetus and newborn (HDFN) are thought to contribute, again through enhanced Fc γ R11A-mediated mechanisms, namely phagocytosis and ADCC, to the more severe disease phenotype (Kapur et al. 2014a, b; Sonneveld et al. 2016, 2017a).

In lupus nephritis, a serious complication of SLE, the presence of core fucose was shown to induce upregulated calcium/calmodulin kinase IV expression in podocytes, leading to podocyte injury and limited nephrin synthesis. In the same experimental setting, the presence of terminal galactoses acted protectively (Bhargava et al. 2021).

An interesting recent finding on the importance of Fab glycans emerged in the most explored disease in the context of IgG glycosylation. In RA, a high percentage of anti-citrullinated protein antibody (ACPA) is additionally glycosylated at the Fab region (Rombouts et al. 2016; Hafkenscheid et al. 2017), a feature distinguishing RA patients from ACPA⁺ but healthy subjects (Kissel et al. 2019; Hafkenscheid et al. 2019). This suggests Fab glycosylation of ACPA might be mechanistically involved in RA development (Rombouts et al. 2016).

13.7 Perspectives for IgG Glycosylation in Precision Medicine

A skewed IgG glycoprofile in comparison to the personal baseline value (requiring longitudinal monitoring) or in comparison to ethnicity-, age-, and sex-matched subjects (requiring a population baseline cohort) in a cross-sectional experimental design, might indicate an increased risk for disease development (Gudelj et al. 2018b), or disease progression (Gudelj et al. 2018a). However, since the alterations in bulk serum IgG glycome composition are not disease-specific, they cannot be used as a stand-alone diagnostic marker. A total IgG glycoprofile of the composition significantly removed from the baseline can instead be used as an indication of a necessity for an examination by an expert clinician.

In case of an established diagnosis, bulk IgG glycome might serve as a predictor of disease progression—e.g., decreased IgG2/3 galactosylation in patients progressing from undifferentiated to rheumatoid arthritis (Sénard et al. 2021). Similarly, IgG glycome is proposed to bear potential for a useful add-on tool for monitoring functional disease progression and response to therapy (Parekh et al. 1988; Kanoh et al. 2004a, 2008; Váradi et al. 2015; Collins et al. 2013; Van Zeben et al. 1994; Rook et al. 1994; Pasek et al. 2006; Gindzienska-Sieskiewicz et al. 2007; Croce et al. 2007; Ercan et al. 2010).

The relevance and biomarker potential of IgG glycome analysis is more evident in some cases of antigen-specific IgG. For instance, due to the increased level of ACPA Fab glycosylation in individuals at risk for RA development, IgG glycome analysis might in the future provide the currently missing understanding (and biomarker) for the first determining pathogenic event leading to disease development (Rombouts et al. 2015; Scherer et al. 2010). Furthermore, as already mentioned, in several diseases a particular antigen-specific IgG glycopattern is associated with a risk for the severe phenotype (Kapur et al. 2014a, b; Sonneveld et al. 2016; Sonneveld et al. 2017a). Similarly, following the mechanistical explanation for the role of afucosylated anti-dengue IgG described in the previous section, afucosylated

maternal anti-dengue IgG is proposed to denote a susceptibility to symptomatic dengue infection in infants (Thulin et al. 2020). The knowledge that a particular glycan profile of antigen-specific IgG, including post-vaccination status for some infectious diseases, is related to the risk of developing (the severe form of) a disease might in the future enable or aid the stratification of patients at risk and timely preventive action.

Another sought-after biomarker type is the one enabling patient stratification aiming at improved differential (sub-)diagnosis and subsequent selection of appropriate therapeutic measures. Differential IgG glycosylation was also suggested as a possibility for such applications. Indeed, the IgG sialylation level predicted response to therapy in Kawasaki disease (Ogata et al. 2013), and the galactosylation level response to anti-tumor necrosis factor (TNF) therapy in RA and Crohn's disease (Váradi et al. 2015), and response to methotrexate therapy in RA (Lundström et al. 2017). Having the means to distinguish non-responders before the very initiation of long and expensive therapeutic treatments is truly an exciting prospect.

In summary, there are multiple possibilities for IgG glycosylation to enter the arena of clinical disease management. Currently, all of the possible applications mentioned here are still at the level of basic research and further studies are necessary to validate the initial findings and propel the IgG glycome analysis to the status of a full-fledged clinical biomarker.

13.8 Conclusions

IgG glycans can modulate virtually all of its numerous effector roles, the specifics depending on the disease and immune context. The associations of multiple IgG glycosylation traits with an immense array of heterogeneous diseases and their different stages imply that there is no single pathway connecting IgG glycome composition and disease development and progression.

Many inflammatory, autoimmune, infectious, cardiometabolic, and neoplastic diseases share a common IgG glycosylation profile of bulk (total) serum IgG, also characteristic for aging and often described as “pro-inflammatory”: a decreased level of galactosylated and sialylated glycans, and (sometimes) an increased level of bisected IgG glycans. This pattern is presumably associated with an inflammatory disease component as a part or consequence of disease pathology, or environmental events, such as antigen exposure. It might be mechanistically involved in disease advancement through modulation of inflammation, and, in some cases, manifest before the occurrence of symptoms, thus representing disease predisposition or mark the risk for disease development or progression.

When it comes to a distinct glycosylation profile of antigen-specific versus total serum IgG, IgG glycans are more likely to be directly involved in disease pathogenesis and progression through disease-specific effector mechanisms. This is often the case with afucosylated IgG glycans enhancing the affinity of IgG toward FcγRIIIA.

The read-out of IgG glycosylation has a potential for an (add-on) biomarker helping improve current algorithms for disease prediction and diagnosis, patient stratification, monitoring of disease progression, and response to therapy.

Compliance with Ethical Standards

Funding This work was supported by the European Structural and Investment Funds CEKOM (Grant# KK.01.2.2.03.0006).

Conflict of Interest MP is an employee of Genos Ltd.—a private company that specializes in high-throughput glycomic analysis and has several patents in the field, and of Genos Glycoscience Ltd.—a spin-off of Genos Ltd. that commercializes its scientific discoveries.

Ethical Approval This article does not contain any studies with human participants.

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