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# The role of IgG *N*-galactosylation in spondyloarthritis

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ABSTRACT

Spondyloarthritis (SpA) is a group of chronic inflammatory arthritic diseases causing inflammatory back pain and stiffness, leading to irreversible damage of joint and spine, seriously affecting the quality of life. However, the exact pathogenesis of SpA is still unknown, although the blockers of tumor necrosis factor (TNF) are a major therapeutic advance. Of interest is the association between SpA and Immunoglobulin G (IgG) *N*-glycosylation. IgG *N*-glycosylation is a process of post-translational modification (PTM) that takes part in regulating anti- and pro-inflammatory effects. A relationship between IgG *N*-glycosylation and the development of inflammatory arthritic diseases exists, in addition this relationship often occurs before the onset of disease. There are studies reporting the association between IgG *N*-glycosylation and SpA, leading to a significant amount of data being generated. Analysis of this data in a rigorous form is greatly needed, hence this review will focus on identifying the relationships that exist between IgG *N*-glycosylation in inflammatory arthritis. More specifically, the modification to the structure of IgG *N*-glycosylation via TNF blockers as a treatment, the link between disease activity and IgG *N*-glycosylation, and the predictive capacity of IgG *N*-glycosylation in SpA. Investigation of IgG *N*-glycosylation has demonstrated that IgG *N*-galactosylation plays an important role in the development and prognosis of SpA. This association provides a novel pathway to further research to improve early diagnosis and possible biomarkers for treatment of patients with SpA.


## 1. Introduction

Spondyloarthritis (SpA), also called spondyloarthropathy, is a group of chronic inflammatory arthritic diseases, such as ankylosing spondylitis (AS), undifferentiated spondyloarthritis (USpA), reactive arthritis (ReA), psoriatic arthritis (PsA), including arthritis associated with inflammatory bowel disease (SpA-IBD) and a subgroup of juvenile idiopathic arthritis (JIA). According to predominant articular features at clinical presentation SpA can divide into axial SpA (axSpA), and peripheral SpA.[1] AxSpA includes radiographic axial spondyloarthritis (AS), and non-radiographic axial spondyloarthritis (nr-axSpA).[2] The main clinical symptoms of SpA are inflammatory back pain, stiffness, and swelling of the joints and spine. In addition, peripheral arthritis, enthesitis, and dactylitis are always observed.[3]

The global prevalence of SpA is approximately 0.1%–1.7%, but this varies depending on the population and ethnicity.[4,5] For example, the prevalence of SpA increases from 0.5% in the China to 2.5% in the Alaskan Eskimo population.[4,6] SpA has both a genetic and environmental (gut dysbiosis) influence, yet the pathogenesis and etiology of SpA have not been clarified.[3] The typical features of SpA predominately include inflammation, structural damage, and new bone formation.[2] At present, the diagnosis criteria of SpA always depending on the clinical symptom and imaging test. Due to SpA lack of a high sensitivity and specificity diagnosis method, the diagnosis process is generally draw out to 6–8 years.[7] Therefore, it

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is essential to explore the novel pathways and potential biomarkers to improve diagnosis times and the treatment options for patients with SpA.

Immunoglobulin G (IgG) *N*-glycosylation is an important post-translational modification (PTM) process, which through affecting the binding affinity of different fragment crystallizable receptors (FcRs) and complement protein C1q to mediate a wide range of pro- and anti-inflammatory effect, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP).[8] Thus, IgG *N*-glycosylation involved in many biological processes, including cell adhesion, molecular trafficking and clearance, receptor activation and signal transduction.[9,10] Glycosylation alternations have been found to be associated with many chronic inflammatory based diseases, such as cardiovascular disease, neurodegenerative disease, cancer and metabolic syndrome.[11–15] In addition, antibody *N*-glycosylation can occur before the onset of disease. For example, the decrease of galactose residues of anticitrullinated protein antibodies (ACPA) occurred around three months prior to diagnosis in RA patients.[16] Furthermore, several studies have shown that IgG *N*-glycans could be as the potential biomarkers in diseases, such as in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), IBD, and AS.[17–20] Besides, antibody *N*-glycosylation can affect the disease activity by regulating the initiation and resolution of inflammation while releasing inflammatory factors.[21,22] It is known that IgG *N*-glycosylation plays a role in SpA; however, the structure of *N*-glycan has not been elucidated nor how IgG *N*-glycosylation specifically impacts the development.

This review aims to provide a comprehensive overview of the structure and function of antibody (mainly immunoglobulin G, IgG) *N*-glycosylation and the relationship between IgG *N*-glycosylation and the development and prognosis of SpA.

## 2. The structure and function of antibody glycans

### 2.1. Antibody glycan structure

Glycan refers to a complete structural form of the monosaccharides, such as fucose, galactose, bisecting *N*-acetylglucosamine (GlcNAc), mannose, and sialic acid connected by glycoside bonds.[23] Glycosylation is the process by which glycans are connected to proteins or lipids under the action of glycosyltransferases, which play an important role in post-translational modification.[24] There are 16 types of glycosylation pathways in humans, for example, two types of lipid glycosylation, and 14 distinct types of protein glycosylation, including *N*-glycosylation, 11 types of O-glycosylation, *C*-mannosylation, and glycosylphosphatidylinositol (GPI)-anchored proteins.[25] Among these glycosylation pathways, *N*-glycosylation is the most prevalent, which accounts for more than half of human protein glycosylation, as roughly 90% of serum proteins are *N*-glycosylated.[26]

Immunoglobulins are a group of glycoproteins (IgG, IgM, IgA, IgE, and IgD),[27] where IgG is the most abundant and represents a class of antibodies in human serum (>80% of serum Igs).[28] IgG contains two functionally distinct domains, the fragment antigen-binding (Fab) and Fc region.[29] Within the IgG Fc, there is a common conserved site of N-linked glycosylation, asparagine 297 (Asn297).[23] The constant core of *N*-glycan consists of GlcNAc and mannose residues, which often contains an additional bisecting GlcNAc residue linked to the first mannose, terminal galactose, or sialic acid residues. Furthermore, a core fucose residue is attached to the first GlcNAc residue in most IgG-associated glycan (Fig. 1).[23] Compared with IgM or IgA, IgG is a highly stable antibody with a half-life of approximately 21 days due to the glycans attached to IgG.[8] Therefore, the advantages of abundance, stability, and relative persistence make IgG important.

### 2.2. IgG N-glycans biosynthesis

IgG is synthesized and secreted by terminally differentiated B cells called plasma cells. After translation, the biosynthesis of the N-glycan core of IgG begins in the endoplasmic reticulum (ER) and continues through cis- and medial Golgi, while the majority of features characteristic for IgG glycans are created in the trans-Golgi.[29] In the ER, a lipid-bound oligosaccharide (usually with a Glc3Man9GlcNAc2-like motif) is transferred “en bloc” to the Asn297 sequence, which is the consensus sequence specifically recognized by oligosaccharide transferase.[31] After that, three terminating Glc are removed and the glycoprotein with attached Man9GlcNAc2 oligosaccharides is transferred to the cis portion of the Golgi apparatus and then to the trans Golgi.[32,33] In the area, different glycosyltransferases and glycosylhydrolases add and remove different sugar nucleotides respectively, resulting in the variety of the IgG N-glycome composition.[29] IgG N-glycosylation is more likely to be regulated by the expression level, intracellular localization or substrate availability of major enzymes than by impaired protein function.[34]

### 2.3. The function of IgG N-glycans in inflammation

There are 24 different N-glycan structures of IgG in human serum (Fig. 2).[35] N-glycans are known to stabilize the structure of the IgG Fc domain and contribute to the recognition of the target FcRs of inflammatory cells and modulate the pro- and anti-inflammatory systems and the development of inflammatory arthritis.[36,37] IgG Fc domains that lack fucose are up to one hundred times more efficient at activating ADCC.[38] Several studies have demonstrated that the lack of IgG fucosylation plays a critical role in enhancing ADCC and promotes natural killer cell activation.[29] IgG's that lacks galactose (IgG-G0) however increased pro-inflammatory effects.[29] For example, the absence of the terminal galactose results in a higher affinity of GlcNac to mannose-binding lectin (MBL) and initiating ADCC.[39]

Conversely, increased galactosylation of IgG promotes binding affinity to C1q, which initiates CDC.[40] In addition, the reduction of terminal sialylation of the Fc glycan can induce IgG antibody-driven inflammation and dampen anti-inflammatory effects.[37] Blocking sialylation of IgG can exacerbate joint inflammation which has been seen in a collagen-induced arthritis (CIA) model, on the contrary, an artificial increase in IgG sialylation can attenuate arthritogenic activity.[41] Consistently, increased IgG sialylation reduces inflammatory bone loss.[42] In brief, many structures of IgG N-glycosylation have been shown to be involved in the regulation of the function of IgG in inflammation. However, which structure of IgG N-glycosylation plays a significant role in inflammatory arthritis is remains unclear. Therefore, we have reviewed all published works that research the relationship between IgG N-glycosylation and inflammatory arthritis under the heading of SpA.

## 3. Data sources and searches

PubMed, MEDLINE and Web of Science were systematically searched from inception to 2021. Both medical subject heading (MeSH) terms and text words related to IgG, glycosylation and spondyloarthritis were used to identify potentially relevant studies, with no restrictions on the language of publication. The search strategy is reported in the Electronic Supplementary Material, Appendix 1. We identified a total of 64 references from all databases and initially excluded 9 duplicates, and then we excluded 44

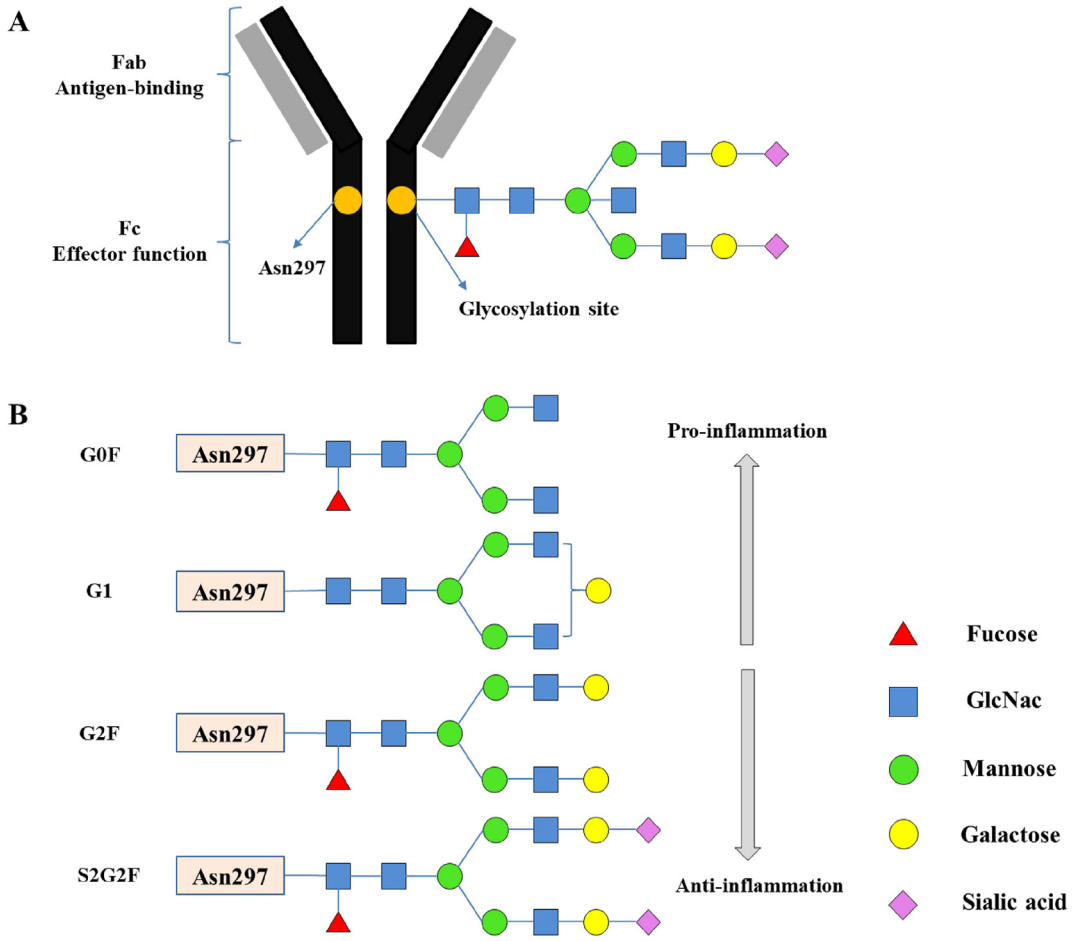


**Fig. 1. IgG N-glycans structure and function**. A, IgG structure and glycosylation site. B, IgG *N*-glycans structure and function. Fab, fragment antigen-binding; Fc, fragment crystallizable; Asn297, asparagine 297; G0F, fucosylated and agalactosylated; G1, monogalactosylated; G2F, fucosylated and digalactosylated; S2G2F, fucosylated, disialylated and galactosylated. Modified from Lauc et al.[30]

references due to there are not original study, or not associated with IgG N-glycosylation and SpA, or the references outcome were not relevant. Of these, 11 papers were selected for inclusion. The flow diagram reporting trail selection is shown in Fig. 3.

## 4. The role of IgG N-glycosylation in SpA

### *4.1. The change of IgG N-glycosylation in patents with SpA*

In 1985, the first time modification of IgG *N*-glycosylation revealed that the level of *N*-galactosylation had decreased significantly in patients with Rheumatoid arthritis (RA).[43] Many studies have reported that IgG *N*-glycosylation is involved in regulating the onset and development of inflammatory arthritis. Here, an overview of the difference in IgG *N*-glycosylation between SpA patients and healthy controls is given in Table 1.

From 1999 to 2003, three studies claimed that IgG *N*-galactosylation was associated with PsA. Interestingly, consistent studies demonstrated that IgG-G0 was increased and that either digalactosylated of IgG (IgG-G2) or IgG-G2F was decreased in patients with PsA.[44–46] Four articles demonstrated that patients with AS that either IgG-G2F or IgG-G2 was decreased.[20,44–46] In 2020, the IgG-Gal ratio (*G0*/(*G1* + *G2*2*)) was twice as high in patients with AS compared with the healthy controls.[47] More recently, Liu et al reported that with nr-axSpA, the IgG-Gal ratio was higher than that in controls, yet a further study claimed that IgG-G0/G1 ratio had decreased,[47,48] although the formula was different. More research is required to identify the relationship between IgG *N*-galactosylation and nr-axSpA. For example patients with JIA, IgG-G1 and IgG-G2 were significant decreased,[46] whereas a further study reported that IgG-G0/G1 ratio was higher in patients with JIA than that in the healthy controls.[49] Another case–control study also shown the results that the IgG-G0 in JIA patients was higher than that in controls, while the IgG-G1 and IgG-G2 were significant reduced in JIA patients.[50]

Published articles have suggested that IgG *N*-glycosylation with more terminal galactose (like G2) may reduce the development of SpA, while less terminal galactose (like G0) may raise the risk of SpA.

### *4.2. TNF blockers therapy induced IgG N-glycosylation changes in patients with SpA*

Early stage treatment of many rheumatic diseases is via non-steroidal anti-inflammatory drugs (NSAIDs) or traditional disease-modifying antirheumatic drugs (DMARDs).[51] Recently, more biological agents are used in the treatment and management of rheumatic diseases, a great many patients have shown high efficacy.[52–55] Most commonly used are tumor necrosis factor (TNF) blockers include infliximab, etanercept, and adalimumab. The

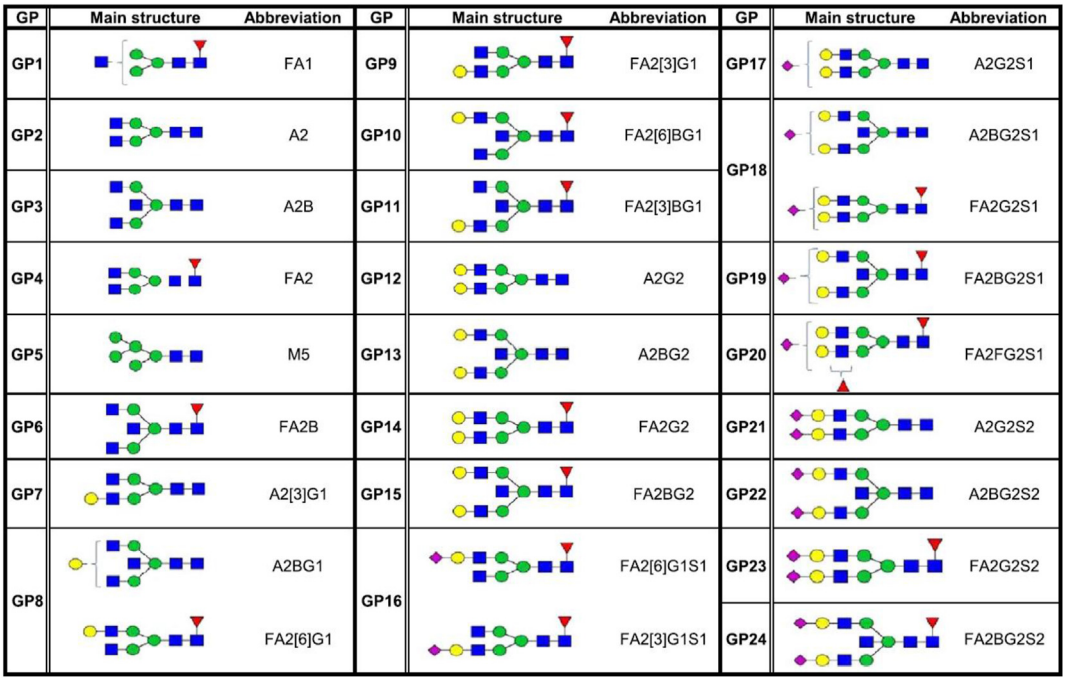


**Fig. 2. IgG N-glycan profiling:** F, α-1, 6-linked core fucose; A, number of antennae; B, bisecting GlcNac β (1–4) linked to β (1–3) mannose; M, number of mannose residues; Gx, number of β (1–4) linked galactoses; [3] G1, galactose on the antenna of the α (1–3) linked mannose; [6] G1, galactose on the antenna of the α (1–6) linked mannose; Sx, number of sialic acids linked to galactose.[35]

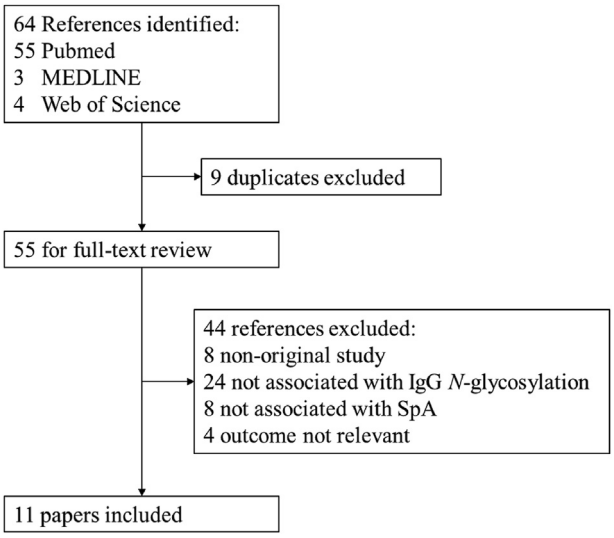


**Fig. 3.** The flow diagram of study selection.

**Table 1**
the difference between IgG *N*-glycosylation in patients with SpA and healthy controls.

| Diseases | Changes in IgG *N*-glycosylation | Ref. |
|---|---|---|
| PsA | Increased IgG-G0F, decreased IgG-G2F | 44 |
| PsA | Increased IgG-G0, decreased IgG-G2F | 45 |
| PsA | Increased IgG-G0, decreased IgG-G2 | 46 |
| AS | Decreased IgG-G2F and IgG-S2G2F, increased IgG-G0F | 44 |
| AS | Decreased IgG-G2F | 45 |
| AS | Decreased IgG-G2 | 46 |
| AS | Decreased IgG-G2F | 20 |
| AS | Increased IgG-Gal ratio | 47 |
| Nr-axSpA | Increased IgG-Gal ratio | 47 |
| Nr-axSpA | Decreased IgG-G0/G1 ratio | 48 |
| JIA | Decreased IgG-G1 and IgG-G2 | 46 |
| JIA | Increased IgG-G0/G1 ratio | 49 |
| JIA | Increase IgG-G0, Decrease IgG-G1 and IgG-G2 | 50 |

IgG-Gal ratio = $G0/(G1 + G2*2)$.

therapeutic mechanism of TNF blockers is based on inhibiting the affinity of TNF-α-receptor to interrupt the cell signaling pathway of pro-inflammatory cytokines.[56]

So far, three studies have described changes of IgG *N*-glycosylation via TNF blockers treatment for patients with SpA (Table 2). In 2009, in Belgium, patients with SpA in a study using infliximab were followed for eight months. The finding showed that the IgG *N*-galactosylation could be reversible during the infliximab treatment.[57] TNF blockers (etanercept or adalimumab) were used to treat patients with PsA, as IgG *N*-galactosylation and IgG-G2F were found to be significantly increased.[58] Another study gave etanercept to patients with AS and followed them for one year, identifying that the IgG-Gal ratio was significantly decreased over that year.[59] Thus, all studies agreed that the IgG *N*-galactosylation might well be increased via the TNF blocker.

### *4.3. The relationship between disease activity and IgG N-glycosylation in patients with SpA*

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are the existing markers of SpA activity, they are the most commonly used diagnostic test for detecting inflammation and progression of SpA. These are frequently used for identifying an effective treatment response for inflammatory arthritic diseases.[60,61] IgG *N*-glycans have been reported to be associated with the extent of disease in patients with SpA (Table 3). In 2020, a large-scale study including 558 patients with SpA showed that the IgG-Gal ratio was positively associated with CRP and ESR (Pearson coefficient $r = 0.25$ and 0.26, respectively).[47] A weak correlation was

**Table 2**
therapy-induced IgG *N*-glycosylation changes in patients with SpA.

| Drugs | Changes in IgG *N*-glycosylation | Disease | Ref. |
|---|---|---|---|
| Infliximab | Increased IgG *N*-galactosylation | SpA | 57 |
| Etanercept or adalimumab | Increased IgG *N*-galactosylation and IgG-G2F | PsA | 58 |
| Etanercept | Decreased IgG-Gal ratio | AS | 59 |

**Table 3**
the association of disease activity markers with IgG *N*-glycosylation in SpA.

| Disease activity markers | Association with IgG *N*-glycosylation | Pearson coefficient (*r*) | Diseases | Ref. |
|---|---|---|---|---|
| CRP | Positive correlation with IgG-Gal ratio | 0.25 | SpA | 47 |
| | Weak increase trend with IgG-G0/G1 ratio | – | axSpA | 48 |
| | Positive correlation with IgG-G0/G1 ratio | 0.17 | JIA | 49 |
| | Positive correlation with IgG-G0F, Negative correlation with IgG-G2 | 0.38, −0.64 | PsA | 58 |
| ESR | Positive correlation with IgG-Gal ratio | 0.26 | SpA | 47 |
| | Correlation with IgG-G2F | 0.42[a] | AS | 20 |
| | Positive correlation with IgG-G0/G1 ratio | 0.17 | JIA | 49 |

[a] This Pearson coefficient is an absolute value.

identified between the IgG-G0/G1 ratio and CRP and ESR in patients with JIA.[49] Furthermore, IgG-G0F was significantly increased with CRP in PsA patients, and IgG-G2 was strongly negative with CRP. However, Schwedler et al identified a weak increasing trend between the IgG-G0/G1 ratio and CRP, without significant statistics, in patients with axSpA.[48] A correlation between the level of IgG-G2F and ESR in patients with AS ($|r| = 0.42$) was identified.[20] Therefore, IgG *N*-galactosylation may be involve in regulating the disease activity in patients with SpA. Moreover, this could be a novel direction to explore the pathogenesis of SpA and reflected the status of the disease.

## 5. IgG *N*-glycosylation could serve as potential biomarkers in SpA

Except for the IgG *N*-glycan can occur before the onset of disease and be involved in regulating the development of disease, many researchers suggested that IgG *N*-glycosylation could act as novel

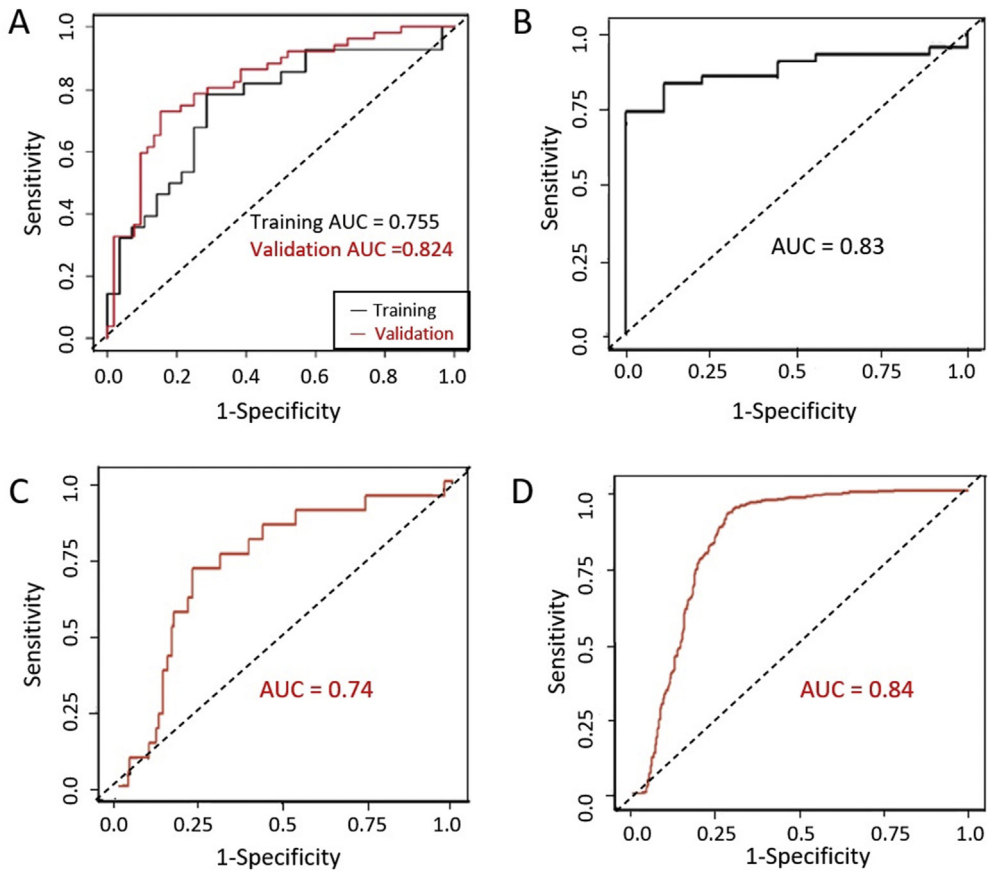


**Fig. 4. Receiver operating characteristics curves of IgG *N*-glycans for the case studies.** A, Performance of IgG-G2F in predicting AS. B, Performance of IgG-Gal ratio in predicting the response of AS patients to etanercept treatment. C, Performance of IgG-Gal ratio to distinguish AS and nr-SpA. D, Performance of IgG-Gal ratio to distinguish AS and controls.

biomarker in the inflammatory arthritis disease, such as SLE, IBD, and RA.[17,18,62,63]

In 2018, a case–control study with eighty AS patients and eighty healthy volunteers was carried out to investigate the association between AS and IgG *N*-glycosylation, where IgG-G2F demonstrated a relatively high prediction capacity for AS.[20] The area under curve (AUC) of IgG-G2F are 0.755 and 0.824 in the training set (n = 56) and validation set (n = 104) respectively, and the sensitivity and specificity were greater than 70% (Fig. 4A). In addition, a cohort study performed that 79 patients with AS during the active progression were treated with etanercept for three months. The researchers found that IgG-Gal ratio was best in prediction of patient response, compared to ESR, CRP and so on. The AUC of IgG-Gal ratio is reaching to 0.83 (Fig. 4B).[59] Furthermore, a case–control study includes 527 AS patients, 21 nr-axSpA and 725 healthy controls in China verified the association between IgG-Gal ratio and SpA.[47] The ROC curve demonstrated that the IgG-Gal ratio is powerful in distinguishing AS from nr-SpA and healthy controls (AUC = 0.74 and 0.84, respectively) (Fig. 4C and D). Therefore, these results indicated that IgG *N*-glycans might be able to be used as novel biomarker for predicting SpA.

## 6. Expert recommendation

With the development of glycoengineering, it opens up many new possibilities for studying the structure–function relationship of antibody glycosylation.[64] Glycoengineering changes protein-associated carbohydrate to alter pharmacokinetic properties of proteins.[24] This technology has been applied to therapeutic monoclonal antibodies and intravenous immunoglobulin (IVIG). However, there is no research in drugs of the therapy according to the change of IgG *N*-glycosylation using glycoengineering in SpA. As we discussed above, the change of IgG *N*-glycans in SpA can be used as potential biomarkers in reflecting the status of the disease. It is to be expected that the potential of glycoengineering strategies will be further used in the future for the optimized production of glycoconjugates for therapeutic purposes in SpA patients.

Furthermore, although these studies agreed that IgG *N*-galactosylation is associated with the development and prognosis of SpA. Several of the studies investigated only the relationship between IgG *N*-glycosylation and inflammatory arthritis diseases, but very few focused on SpA specifically. Additionally, small populations or cohorts were often studied leading to work that is unable to be replicated in larger populations.

## 7. Conclusion

This review demonstrated that IgG *N*-glycosylation provides a significant way to regulate IgG function in inflammatory pathways. It is worth noting that IgG *N*-galactosylation may play an important role in the development and prognosis of SpA. This finding also suggests that IgG N-glycosylation, with more terminal galactose, may reduce the development of SpA, while less terminal galactose may increase the risk of SpA. In addition, IgG *N*-glycans might be used as potential biomarkers for SpA. Therefore, future research may conclude on IgG *N*-galactosylation in SpA and developing IgG *N*-galactosylation biomarkers to identify progression of the disease and possibly even for treatment.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Availability of data and materials

Not applicable.

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## Authors’ contributions

Xiaojia Xu, Zhixian Chen, Gehendra Mahara wrote the manuscript, Lois Balmer and Ling Lin revised the manuscript.

## Declaration of competing interest

All authors have none to declare.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmsr.2022.01.001.

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## Abbreviation

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| SpA: | *Spondyloarthritis* |
| TNF: | *Tumor necrosis factor* |
| ACPA: | *Anticitrullinated protein antibodies* |
| ADCC: | *Antibody-dependent cell-mediated cytotoxicity* |
| AS: | *Ankylosing spondylitis* |
| Asn297: | *Asparagine 297* |
| axSpA: | *axial SpA* |
| CDC: | *Complement-dependent cytotoxicity* |
| CIA: | *Collagen-induced arthritis* |
| CRP: | *C-reactive protein* |
| DMARDs: | *Disease-modifying antirheumatic drugs* |
| ESR: | *Erythrocyte sedimentation rate* |
| Fab: | *Fragment antigen-binding* |
| Fc: | *Fragment crystallizable* |
| FcRs: | *Fc receptors* |
| GlcNAc: | *N-acetylglucosamine* |
| GPI: | *Glycosylphosphatidylinositol* |
| IBD: | *Inflammatory bowel disease* |
| IgG: | *Immunoglobulin G* |
| IgG-G2F: | *fucosylated, digalactosylated IgG* |
| IVIG: | *Intravenous immunoglobulin G* |
| JIA: | *Juvenile idiopathic arthritis* |
| nr-axSpA: | *non-radiographic axial spondyloarthritis* |
| NSAIDs: | *Non-steroidal anti-inflammatory drugs* |
| MeSH: | *Medical subject heading* |
| PsA: | *Psoriatic arthritis* |
| RA: | *Rheumatoid arthritis* |
| ReA: | *Reactive arthritis* |
| SLE: | *Systemic lupus erythematosus* |
| USpA: | *Undifferentiated spondyloarthritis* |