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The role of aberrant glycosylation in autoimmune disease development and progression

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ABSTRACT

Protein glycosylation is a covalent attachment of complex oligosaccharides to proteins and lipids, is a ubiquitous and essential post-translational modification (PTM) that significantly expands the functional diversity of the proteome. While fundamental to processes such as protein folding, trafficking, and signal transduction, disruptions in normal glycosylation are increasingly recognized as central drivers of immune dysregulation and tissue damage. This review provides an overview of *N*- & *O*-linked glycosylation mechanisms and evaluates their profound influence on protein stability, activity, and the pathophysiology of common autoimmune disorders. This review focus on recent literature, focusing on the pathways of endoplasmic reticulum (ER) and Golgi apparatus, alongside advancements in mass spectrometry-based glycomics, to explore the relationship between altered glycan structures and clinical disease states. Specific glycans are identified as hallmarks of various conditions: Immunoglobulin G (IgG) agalactosylation in Rheumatoid Arthritis and IBD; increased sialylation and *N*-glycan bisection in Type 1 Diabetes; and elevated N-acetylglucosamine in Systemic Lupus Erythematosus; in Celiac Disease, we highlight the mechanistic role of galactose-deficient IgA1 and the mislocalization of the receptor in facilitating pathogenic antigen trafficking serving as sensitive biomarkers for disease activity and treatment adherence, glycan alterations actively modulate the inflammatory milieu. These glycosylation pathways offer a promising frontier for therapeutic intervention. Continued integration of glycomics into personalized medicine is essential for improving the diagnostic and prognostic accuracy for patients suffering from multisystemic autoimmune diseases.

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INTRODUCTION

Addition of carbohydrates to proteins, lipids is a frequent post-translational alteration known as glycosylation (Wu and Kohler, 2019). This process involves covalent bonding oligosaccharides or multi sugar polysaccharides to particular targeted proteins. Glycosylation represents a frequent biochemical alteration that dictates how proteins behave, remain stable, and reach their cellular destinations. By adding these sugar groups, the functional capacity of a protein is expanded far beyond what is initially encoded in the genome (Eichler, 2019). Glycosylation is a ubiquitous and physiologically significant modification that is increasingly acknowledged in biology. Numerous critical biological processes depend heavily on glycosylation, including the control of protein folding also trafficking, protein ligand interactions, signal transduction, cell to cell interactions, and cell matrix interactions. *O*-glycosylation, *N*-glycosylation are the two primary forms of this modification (Patwary *et al.*, 2025). Over 7,000 proteins in humans undergo *N*-glycosylation, which is a highly conserved glycan alteration essential for biological activities like protein folding, trafficking, and signal transduction (Hirata *et al.*, 2021). Particularly localized in the endoplasmic reticulum (ER), *N*-glycosylation are the attachment of sugar molecules to the asparagine (Asn) amino acid in the specific Asn-X-Ser/Thr sequence, where X-ser/thr stands for any amino acid except proline (Patwary *et al.*, 2025). This process occurs in two primary phases: the creation of a lipid-linked oligosaccharide (LLO) and its subsequent transfer to particular asparagine residues of polypeptide chains. During LLO biosynthesis at the ER membrane, specific glycosyltransferases catalyze the creation of the branching oligosaccharide in a highly specific manner. Oligosaccharide transferase forms the *N*-glycosidic link between the oligosaccharide and the asparagine side-chain amide. This ER-localized mechanism alters the proteome and provides the basis for Golgi-catalyzed modifications, yielding enormous cellular diversity (Breitling and Aebi, 2013). Beyond natural biology, *N*-linked glycosylation is also utilized in medicine to increase the half-lives of various therapeutic proteins (Águila *et al.*, 2021). In contrast, *O*-glycosylation is an Genetically conserved modification of membrane-bound and secreted proteins (Tran and Ten Hagen, 2013). It primarily focuses on the attachment to sugars with amino acids like serine (Ser), threonine (Thr) which are frequently found, extracellular and secreted glycoproteins. *O*-linked glycosyltransferases (GTs) act by moving a GlcNAc from UDP-GIcNAc to the hydroxyl oxygen of a serine or threonine remains. Specific modification of glycosylation plays critical roles in protein secretion, stability, processing, lastly function (Tran and Ten Hagen, 2013). *O*-linked glycosylation is essential for fundamental biological processes such as transcription, metabolism, subcellular localization, and immune response *(*Lu R. *et al.*, 2023). Glycosylation is a key change proteins undergo when passing between the Golgi apparatus and the ER, ultimately determining whether a protein will be secreted or remain membrane-bound. Crucially, protein glycosylation alterations in the immune system and target tissues are closely associated with autoimmune disorders. The most researched change in autoimmunity is the agalactosylation of immunoglobulin G (IgG). While this specific alteration is mostly seen in Rheumatoid arthritis (RA), it has also been documented in inflammatory bowel disease (IBD) and systemic lupus erythematosus (SLE) (Ząbczyńska *et al.*, 2021). Anomalies in *O*-glycosylation are also considered the root cause of various human diseases and are associated with specific disease risk factors (Tran and Ten Hagen, 2013). While modern mass spectrometry techniques offer the greatest tools for detecting the glycosylation state of proteins, the field of glycobiology presents significant analytical challenges. For instance, entry to mass spectrometry and glycobiology is frequently hampered by the intricate language, techniques, and knowledge needed (Patrie *et al.*, 2012). Furthermore, multimodal mass spectroscopy has proven particularly difficult in assessing *O*-linked glycosylation because conventional MS/MS methods (like CID) yield little to no signal for glycan-carrying ions. This difficulty largely stems from the fact that glycosidic linkages are

far more malleable than peptide linkages (Bakhtiar and Guan, 2005). Ultimately, the goal of this review is to give a thorough overview and discuss the effects of glycosylation on protein stability and activity, as well as to explore the deep relationship between changes in glycosylation patterns and the severity of autoimmune illnesses.

Role of glycosylation

Covalent bonding of complex oligosaccharides, multi-sugar polysaccharides to particular target proteins is known as glycosylation. The common post translational modification is protein glycosylation, which greatly influences protein function, stability, subcellular localization, and other traits to increase the function of a protein by a few times compared to its original portion as translated by the genome (Eichler, 2019). Glycosylation is a ubiquitous and physiologically significant post-translational modification of proteins that is increasingly acknowledged. Modern mass spectrometry techniques offer the greatest tools for detecting the glycosylation state of proteins. For others, entry to mass spectrometry and glycobiology is hampered by the intricate language, techniques, and knowledge needed (Patrie *et al*., 2012). Protein glycosylation has been seen in all facets of life. For instance, research has shown that *N*-linked glycosyltransferases (GTs), which resemble the eukaryotic STT3 family, are present in prokaryotes (Tran and Ten Hagen, 2013). More than 7000 proteins in humans undergo *N*-glycosylation, a highly conserved glycan alteration. *N*-glycosylation is essential for many biological activities, such as protein folding, trafficking, and signal transduction. Thus, the modification of proteins by glycans has a profound impact on many biological and clinical processes (Hirata *et al*., 2021). One crucial post-translational alteration that affects the structure, function, and clearance of proteins is *N*-linked glycosylation. *N*-linked glycosylation is also used in medicine to increase the half-lives of a number of proteins (Águila *et al*., 2021). One widespread and highly conserved essential change is glycan adhesion to asparagine residues in proteins. The creation of a lipid-linked oligosaccharide (LLO) and its transfer to particular asparagine residues of polypeptide chains are the two primary phases of the *N*-glycosylation process. During the biosynthesis of the LLO, which takes place at both sides endoplasmic reticulum (ER) membrane, a number of specific glycosyltransferases catalyze the creation of the branching oligosaccharide in a highly specific manner. By selecting the Asn-X-Ser/Thr consensus sequence on polypeptide chains, oligosaccharide transferase (OST) forms the *N*-glycosidic link between the oligosaccharide and the asparagine side-chain amide. This ER-localized mechanism, which alters the proteome systemically and provides the basis for the Golgi-catalyzed modification of the *N*-linked glycans, produces the enormous diversity of the *N*-glycoproteome in cells (Breitling and Aebi, 2013). *O*-glycosylation is an evolutionarily conserved modification of membrane-bound and secreted proteins. *O*-glycosylation anomalies are the root cause of various human diseases and are associated with risk factors for disease. Recent studies have shown us the critical roles that mucin-type *O*-glycosylation plays in protein secretion, stability, processing, and function (Tran and Ten Hagen, 2013). conventional MS/MS methods (such CID) yield little to no signal for glycan-carrying ions, multimodal mass spectroscopy proved particularly difficult in assessing *O*-linked glycosylation. The main reason for this is that glycosidic linkages are more malleable than peptide ones (Bakhtiar and Guan, 2005). *O*-linked glycosyltransferases (GTs) move a GlcNAc moiety from UDP-GlcNAc to the hydroxyl oxygen of a serine or threonine residue. It has been said that *O*-linked glycosylation is essential for fundamental biological processes such as transcription, signal transduction, metabolism, subcellular localization, and immune response (Lu R. *et al*., 2023). Glycosylation is one of the many changes that proteins go through when they pass between the Golgi apparatus and endoplasmic reticulum (ER). This process determines whether the protein will be secreted or membrane-bound. There are two ways that extracellular proteins can be glycosylated: *N*-linked to asparagine or *O*-linked to threonine, serine, or hydroxylysine. There are many different types of *O*-linked glycans (Zhang and Ten

Hagen, 2023). Aberrant glycosylation associated with various pathological conditions is overviewed below (Fig. 1, Table 1).

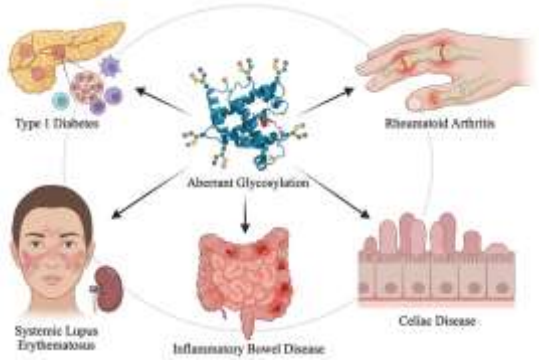

Fig. 1. Overview of aberrant glycosylation associated with various pathological conditions

Type 1 diabetes

Type 1 diabetes seems to be a condition marked by the immune-mediated death of insulin-secreting pancreatic beta cells, leading to insulin insufficiency. It is important to distinguish type 2 diabetes, which is mostly common in older populations, from type 1 diabetes, which is less common in adults than younger people. Who have type 1 diabetes, they need exogenous insulin replacement for the rest of their lives. Patients may have life-threatening diabetic ketoacidosis and severe hyperglycemia in the absence of insulin. Insulin producing pancreatic beta-cells are destroyed by the immune system in type 1 diabetes (T1D), which results a complete lack of insulin. Age-related variations in T1D's metabolic, genetic, and immunogenetic features call for a modified strategy for each patient. Many people who have the illness have underlying genetic risk. The American Diabetes Association advises that first- and second-degree relatives who have relatives with T1D undergo examination through T1D auto-antibody analysis (Lucier *et al.*, 2024). Other side, complex oligosaccharide forms, or glycans, are covalently bonded to proteins through glycosylation, a tightly controlled enzyme reaction under intricate genetic regulation that frequently affects the function of proteins. It was discovered that alterations in protein glycosylation are typical of many human clinical illnesses, and in many instances, a change in glycosylation was determined to be the primary cause of the sickness, underscoring the significance of this modification (Rudman *et al.*, 2019). Type 1 diabetes represents an autoimmune illness characterized by the development of a number of autoantibodies and the death of insulin-producing pancreatic beta cells by T lymphocytes (including CD4+ helper and CD8+ killer cells). However, pancreatic autoantibodies are absent in a small percentage of patients who have type 1 diabetes, and islet autoimmunity is present in certain patients with a clinical diagnosis of diabetes. An estimated 3% more children and adolescents are being diagnosed with type 1 diabetes each year (Rudman *et al.*, 2022). Children and teenagers (0.6–19.1 years) who have a type 1 diabetes diagnosis, in a subsequent investigation, the outcomes for 188 of these individuals were contrasted with those of their 244 siblings who were not impacted. General linear modeling was used to determine the correlation between *N*-glycan abundance and the number and levels of several autoantibodies (against IA-2, GAD, ZnT8R, and ZnT8W), with sex and age at diagnosis. Linear mixed model elastic net regression was used for create a disease prediction model, which was then assessed using a 10-fold cross-validation (Rudman *et al.*, 2022). Moreover, several glycosylation characteristics, such as fucosylation, galactosylation, and sialylation, were linked to common and incident problems of diabetes in a recent study on two sizable Dutch cohorts that used mass spectrometry to measure total plasma *N*-glycome. Increased 2,6-sialylation on tri-antennary glycans was seen in cases of prevalent nephropathy, whereas high levels of *N*-glycan bisection were closely linked to prevalent cardiovascular disease (Demus, 2024; Nemčić *et al.*, 2023). Pancreatic autoantibodies are absent in a small percentage of patients who clinically have T1D, and conversely, islet autoimmunity can be present in patients who do not meet clinical diagnostic criteria. Need for Personalization, Because T1D's metabolic, genetic, and immunogenetic features vary by age.

Table 1. Comprehensive overview of diseases linked to aberrant glycosylation patterns and their corresponding therapeutic strategies

Diseases	Glycosylation aberration	Therapy/Biomarkers	References
Type 1 Diabetes	N-glycosylation of plasma proteins and IgG. Increased 2,6-sialylation on tri-antennary glycans is linked to nephropathy, while high N-glycan bisection is linked to cardiovascular disease.	N-glycan abundance correlates with autoantibodies (IA-2, GAD, ZnT8R, ZnT8W). These patterns can be used to create disease prediction models.	Rudman *et al.*, 2019; Demus, 2024
Rheumatoid Arthritis (RA)	Marked by agalactosylation of immunoglobulin G (IgG). Also presents changes in immunoglobulin A (IgA) and total serum N-glycome (TSNG).	Glycosylation changes can distinguish RA patients from healthy controls and act as a proxy for evaluating disease activity.	Deng *et al.*, 2023; Ząbczyńska *et al.*, 2021
Systemic Lupus Erythematosus (SLE)	Agalactosylation of IgG. Patients with Lupus Nephritis (LN) show elevated bisected N-acetylglucosamine (GlcNAc) and decreased sialylation, galactosylation, and core fucosylation.	Specific IgG N-glycans (like GP8, GP10, GP18) can be used as biomarkers to effectively distinguish female SLE patients with LN from those without it.	Lu X. *et al.*, 2023
Inflammatory Bowel Disease (IBD)	Agalactosylation of IgG. Associated with altered expression of terminal glycan structures and increased expression of truncated O-glycans in the intestinal epit helium.	Intestinal epithelial glycosylation is being investigated as a key mechanism that interacts with host genetics, gut microbiota, and immune dysregulation.	Ząbczyńska *et al.*, 2021
Celiac Disease	Agalactosylated profile in serum IgG Fc N-glycosylation (increased G0F). Elevated galactose-deficient O-glycans in IgA1 (specifically anti-TG2 IgA1). Alterations in mucin/glycocalyx motifs.	Galactose-deficient TG2-specific IgA1 decreases on a gluten-free diet (GFD), making it a valuable biomarker for monitoring activity and diet adherence. Serum IgG Fc indices and CD71 tissue transport phenotypes serve as adjunct biomarkers.	Lindfors *et al.*, 2011

Rheumatoid arthritis

Key indicators of the systemic autoimmune disease rheumatoid arthritis (RA) include inflammatory arthritis along with various non-joint involvements. It is a long-term inflammatory condition that is frequently brought on by a number of environmental and genetic causes (Chauhan *et al.*, 2023). It has been known since the 1980s that RA patients' antibody glycosylation differs from that of control subjects. Although reports on serum or plasma immunoglobulin G (IgG) predominate in the literature on glycosylation changes in RA, recent research has shown that glycosylation changes for immunoglobulin A (IgA) and total serum *N*-glycome (TSNG) may be equally significant and helpful in distinguishing RA patients from controls or as a proxy of disease activity (Mayboroda *et al.*, 2023). In individuals with rheumatic arthritis, autoantigen-specific IgG shows a unique *N*-glycosylation signature in the fragment crystallizable (Fc) domain, which is defined by fucosylation without sialylation or galactosylation. The fragment antigen binding domain of autoantigen-specific IgG and autoreactive B cell receptors is heavily *N*-glycosylated in rheumatoid arthritis (RA) and anti-neutrophil cytoplasmic antibody associated vasculitis *(Kissel et al.*, 2023). Serum IgG from RA patients revealed a greater affinity for the SBA lectin (recognizing glycan GalNAc), according to a thorough examination of lectin microarray and lectin blot. In terms of RA subgroups, the RA-seropositive group exhibited greater affinities to the lectins MNA-M (which recognizes glycan mannose) and AAL (which recognizes glycan fucose), while the RA-ILD group exhibited higher affinities to the lectins ConA (which recognizes glycan mannose) and MNA-M, but a lower affinity to the PHA-E (which recognizes glycan Gal\beta4GlcNAc). The corresponding viability of such biomarkers was suggested by the anticipated models. The pathophysiology of the illness may be linked to altered glycosylation levels, which could lead to the discovery of novel biomarkers (Deng *et al.*,

2023). The association is weaker than that of galactosylation; the degree of sialylation likewise shows a declining trend with an individual's age. The non-ACPA fraction consistently displayed a higher level of sialylation than the ACPA samples in all isoforms, but there was no discernible difference between the ACPA and the healthy group in the age-matched groups. The variability of the healthy group may account for the greater sialylation of non-ACPA IgG, some people may have had unexplained inflammation (Szabó *et al.*, 2025). Acute phase proteins' carbohydrate side chains are a major source of the GlycA signal. *N*-linked glycoproteins make up the majority of circulating acute phase proteins. Increased production and secretion of these glycoproteins are brought on by both acute and chronic inflammation. Additionally, increased glycosylation of proteins and branching of glycan structures are caused by inflammation. GlycA signals rise as a result of each of these glycan changes (Bartlett *et al.*, 2016). Sialylation levels has been complicated by variability in "healthy" groups, where some individuals may have had unexplained inflammation that skewed results. Despite its commonality, the full pathophysiological implications of agalactosylated IgG in RA patients are still being understood.

Systemic lupus erythematosus

Significant morbidity and mortality are linked to systemic lupus erythematosus (SLE), a multisystemic autoimmune disease. Loss of immunological tolerance against self-antigens is influenced by genetic, immunological, endocrine, and environmental variables. This results in the development of pathogenic autoantibodies which destroy tissue through a variety of methods (Vaillant *et al.*, 2023). Because of polymorphic biological changes, systemic lupus erythematosus (SLE), which is classified as an auto-immune disorder, can be thought of as a chronic inflammatory illness with clinical manifestations affecting multiple organs, including the blood vessels, brain, lungs, skin, kidneys, and joints. The affects over 3.4 million people globally, and 400,000 new cases are diagnosed annually (Dai *et al.*, 2025). A study shows differences between women with SLE with and without Lupus nephritis (LN) in nine first glycans (GP2, GP4, GP6, GP8, GP10, GP14, GP16, GP18, and GP23). While bisected *N*-acetylglucosamine (GlcNAc) glycans were elevated in LN patients, sialylated, galactosylated, and fucosylated glycan levels were considerably lower in LN patients compared to the control group. This profile, which comprised GP8, GP10, GP18, and anemia, did a good job of separating female SLE patients with LN from those without. These results show increased bisecting GlcNAc and decreased sialylation, galactosylation, and core fucosylation may contribute to the development of Lupus nephritis (LN) by increasing IgG's proinflammatory response. IgG *N*-glycans may be used as biomarkers to distinguish SLE patients with LN (Lu X. *et al.*, 2023). Changes in glycosylation have been linked to immune system modulation and the emergence of clinical symptoms. For instance, lupus-like illnesses have been seen to emerge in mouse models with changes in glycan production. Similar findings about changes in glycosylation have been noted in SLE patients and murine models (Ramos-Martínez *et al.*, 2023). Systemic lupus erythematosus (SLE) is supported by the fact that SLE patients have greater skin advanced glycation end-products levels than healthy controls. The association between skin advanced glycation end-products (AGE) levels and SLE activity and damage markers suggests that advanced glycation end-products may play a role as a new biomarker in this disease related to prognosis and management, which would have significant ramifications in a field currently unexplored in SLE (Carrión-Barberà *et al.*, 2024). The study of advanced glycation end-products (AGE) in the skin is described as a field currently unexplored in SLE, despite its potential for disease management and prognosis.

Inflammatory bowel disease (IBD)

Main feature of inflammatory bowel disease (IBD) is frequent episodes of gastro-intestinal tract inflammation caused an aberrant immune reaction to gut microbiota (McDowell *et al.*, 2023). “Ulcerative colitis and Crohn's disease” are two distinct types

chronic inflammatory bowel illnesses, albeit a tiny percentage of people have an intermediate form (Xia *et al.*, 1998). Globally, over 6.8 million people suffer from inflammatory bowel disease (IBD). Numerous factors, such as host genetics, immunological dysregulation, and changes in the gut microbiota, have been linked to the pathophysiology of IBD. Intestinal epithelial glycosylation is an underestimated mechanism that interacts with these three variables, according to emerging research. Both altered expression of terminal glycan structures and increased expression of truncated *O*-glycans are linked to IBD (Kudelka *et al.*, 2020). Investigating the role of glycosylation in IBD is motivated by several genetic and immunological research (Theodoratou *et al.*, 2014). Hyper *O*-glycosylated mucous proteins released by goblet cells (GCs) enhance the physical barrier offered by absorptive enterocytes, offering an extra line of defense from intestinal pathogens. Subpopulation of intestinal GCs that stimulate stress response genes in the mucosa of people with UC was identified by a recent single cell RNA-seq analysis, indicating dynamic segmentation of GCs during intestinal inflammation (Brazil and Parkos, 2022). Most extensively used biomarkers in current clinical practice are blood and stool tests with C-reactive protein (CRP) and faecal calprotectin (FCP), while the hunt for the ideal biomarker in IBD is still ongoing. Other fecal indicators, such fecal lactoferrin, are less commonly used (Clough *et al.*, 2024). High serum levels of IgG lacking galactose residue at the nonreducing terminal have been documented in rheumatoid arthritis patients. An *N*-linked oligosaccharide of the biantennary complex type, regardless of bisecting *N*-acetylglucosamine (GlcNAc), core fucose, a galactose, and sialic acid residues, is added to the Fc segment of IgG at asparagine 297. Although the pathophysiological implications of agalactosylated IgG in rheumatoid arthritis patients are still understood, this phenomenon is frequently seen in autoimmune illnesses and other types of chronic inflammation. The glucan structure of IgGs is often analyzed using MS in conjunction with HPLC. We discovered that IBD patients have a higher percentage of IgG with a biantennary (the ratio of fucosyl–agalactosyl to fucosyl–galactosyl) glucan structure using MS and HPLC (Miyoshi *et al.*, 2016). However, in the current study, we showed that the glycosylation profile of fecal mucins exhibited particular characteristics in both active and quiescent CD that were not present in IBS patients or HC subjects. This suggests that assessing mucin glycosylation in feces could develop into a novel noninvasive method for intestinal disease screening without the need for endoscopy. This novel method may also be useful for the diagnosis, prognosis, or treatment of colorectal cancer, given prior findings in this area and the fact that the tumor *O*-glycans found were primarily sialylated core 1 or Thomsen-nouveau antigens. A bigger prospective investigation is required to corroborate the results (Robbe Masselot *et al.*, 2023). Compared to genetics and microbiota, intestinal epithelial glycosylation is currently considered an underestimated mechanism in IBD pathophysiology. The "hunt for the ideal biomarker" is ongoing, as current clinical tests (like CRP and fecal calprotectin) have practical limitations. Recent findings regarding fecal mucin glycosylation are limited by small patient cohorts, necessitating larger prospective investigations to confirm the results.

Celiac disease

Celiac disease (CD) is an immune mediated disorder. Which precipitated by exposure to gluten (wheat/barley/rye), associated with small-intestinal injury and highly specific serology to tissue transglutaminase (TG2). Population-level synthesis estimates a pooled global seroprevalence of 1.4% and a pooled biopsy-confirmed prevalence of 0.7%, with heterogeneity by age, sex, and region (Singh *et al.*, 2018). Genetic susceptibility dominated by HLA class II: DQ2.5 is reported as the strongest determinant and present in >90% of affected individuals; DQ8 is present in ~5–10%, and these alleles are necessary but not sufficient because DQ2.5 is also common in the general population (~20–30%) (Taylor, 2025). Mechanistically, TG2 is central both as an enzyme also as an autoantigen: TG2 was identified as the endomysial autoantigen, and gliadin is described as a

preferred substrate, linking the trigger to autoimmunity (Dieterich *et al.*, 1997). TG2 can shape immunogenicity through ordered deamidation of gliadin peptides, generating epitopes that bind efficiently to HLA-DQ2 and are recognized by gut-derived T cells, supporting an enzymatic "epitope generation" mechanism relevant to loss of tolerance (Molberg *et al.*, 1998).

Histopathology commonly conceptualized along a lesion spectrum that includes infiltrative, hyperplastic, and destructive stages, with standardized reporting frameworks built on Marsh-based classification proposed to improve consistency of pathology reporting (Marsh, 1992; Oberhuber *et al.*, 1999). CeD is not initiated by a primary glycosylation defect, but multiple glyco-immune and glyco-epithelial mechanisms are supported by primary studies. Serum IgG Fc *N*-glycosylation shifts toward a more agalactosylated profile in pediatric CeD: IgG *N*-glycans released and profiled by NH2-HPLC show increased relative abundance of G0F and increased Ln(G0F/G1F) compared with healthy pediatric and adult controls, indicating systemic alteration in Fc glycoforms associated with inflammation and autoimmunity (Cremata *et al.*, 2003). IgA glycosylation changes appear more disease-proximal in a mucosal autoimmune condition: IgA1 with galactose-deficient *O*-glycans is noted to have elevated affinity for the transferrin receptor, and TG2-specific IgA1 autoantibodies exhibit elevated galactose deficiency; importantly, galactose-deficient anti-TG2 IgA1 decreases on a gluten-free diet (GFD) whereas total serum galactose-deficient IgA1 does not, implying enrichment of glyco-alteration within the antigen-specific autoimmune response (Lindfors *et al.*, 2011). The epithelial interface, transferrin receptor CD71 biology connects glycosylated IgA with antigen trafficking: CD71 is upregulated and mislocalized in active CeD and mediates apical-to-basal retrotranscytosis of SIgA–gliadin complexes, with functional transport assays demonstrating substantially higher intact/active peptide passage in active disease versus treated disease or controls (Matysiak-Budnik *et al.*, 2008). Complementary study using duodenal biopsies and epithelial models reported physical interactions among SIgA, CD71, and TG2 at the apical surface and showed increased transport of intact labeled gliadin peptide in the presence of celiac IgA/SIgA, inhibited by soluble CD71 or TG2 inhibitors, supporting a transport pathway that avoids lysosomal degradation and may amplify mucosal immune activation (Lebreton *et al.*, 2012). Evidence for altered mucin or glycocalyx carbohydrate motifs is mixed: jejunal lectin-binding patterns distinguished active CeD (total villous atrophy) from remission and controls in one pediatric biopsy study (Pittschieler *et al.*, 1994), whereas duodenal lectin histochemistry targeting Gal\beta(1,3)-GalNAc and Fuc\alpha1-2Gal-R motifs found no differences across pediatric groups and no changes pre/post remission in paired samples (Toft-Hansen *et al.*, 2013). Barrier ecology microbiota context further support relevance of glycosylation-rich mucosal surfaces: fewer MUC2-stained cells and reduced goblet-cell features were reported in pediatric CeD cohorts (active and GFD) versus controls (Capuano *et al.*, 2011) and duodenal microbiota profiling with parallel mucosal gene-expression assessment has been performed in pediatric CeD versus controls, supporting investigation of coupled microbiota–mucosa mechanisms relevant to mucus/glycan biology (Cheng *et al.*, 2013). Glycosylation linked biomarkers in CeD are best framed as adjuncts to established diagnostics (anti-TG2/EMA serology and Marsh-type histology), adding value by capturing immune effector tone, antigen-specific autoimmune programming, epithelial transport activity, and diet response. Serum IgG Fc glycoform indices (example: elevated G0F and G0F/G1F) are analytically tractable and discriminate pediatric CeD from controls in chromatographic profiling, but are likely not disease-specific because Fc hypogalactosylation is a broader inflammatory phenotype (Cremata *et al.*, 2003). Glycoform-resolved anti-TG2 IgA1 (galactose-deficient TG2-specific IgA1) is mechanistically close to core autoimmunity and shows diet responsiveness, supporting potential use for activity/adherence monitoring in longitudinal settings (Lindfors *et al.*,

2011). Tissue-level epithelial transport phenotypes—CD71 overexpression/apical redistribution, SIgA–gliadin retrotranscytosis, and SIgA–CD71–TG2 interaction signatures are strongly mechanistic and distinguish active from treated disease in biopsy-based studies, making them attractive translational endpoints though less feasible for routine monitoring (Lebreton *et al.*, 2012; Matysiak-Budnik *et al.*, 2008). Lectin-based mucosal signatures remain inconsistent across cohorts and sites (jejunum versus duodenum; differing lectin panels), implying that robust glycosylation biomarkers may require broader motif panels or higher-resolution glycomics/glycoproteomics combined with careful anatomical sampling and clinical stratification (Pittschieler *et al.*, 1994; Toft-Hansen *et al.*, 2013).

CONCLUSION

The intricate role of glycosylation in the development and progression of common autoimmune diseases. Glycosylation, a fundamental post translational modification of proteins and lipids, plays a crucial role in immune regulation, cell to cell communication, and maintenance of immune tolerance. Disruptions in normal glycosylation processes have been shown to significantly influence immune responses, contributing to the onset and severity of autoimmune conditions. The evidence discussed in this article highlights the strong association between aberrant glycosylation patterns and the pathophysiology of autoimmune diseases like Type1diabetes, Rheumatoid Arthritis, Systemic Lupus Erythematosus, Inflammatory Bowel Disease, and Celiac Disease. This review, has identified numerous glycosylation related biomarkers that hold promise for improving disease diagnosis, prognosis, and monitoring.

Altered glycan signatures, particularly those associated with immunoglobulin G and other immune-related proteins, may serve as sensitive indicators of disease activity and treatment response. genomics and proteomics, may enhance the identification of robust biomarkers and deepen understanding of autoimmune disease mechanisms. The role of glycosylation in immune function, targeting glycosylation pathways presents an emerging and therapeutic strategy.

Modification the structure of glycosylation enzymes could potentially restore immune balance and reduce pathological inflammation. The therapeutic applications targeting glycosylation are still in early stages, ongoing advancements in analytical technologies and molecular biology are expected to accelerate their clinical translation. glycosylation represents a critical and underexplored dimension of autoimmune disease biology. Continued research into disease-specific glycosylation patterns and their functional consequences will be essential for unlocking new diagnostic and therapeutic opportunities. Deeper understanding of glycosylation may ultimately support the development of personalized medicine approaches, enabling more precise diagnosis, improved disease monitoring, and targeted treatment strategies for patients with autoimmune diseases.

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