JCB
J Circ Biomark 2026; 15: 38-46
ISSN 1849-4544 | DOI: 10.33393/jcb.2026.3772
REVIEW

From glycosylation to inflammation: insights from NMR-Derived GlycA and GlycB

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ABSTRACT

Post-translational modifications (PTMs) play a crucial role in increasing proteomic diversity. N-linked glycosylation acts as a key regulatory layer that influences protein stability, trafficking, circulation, and immune responses. Unlike conventional inflammatory biomarkers that measure individual proteins, nuclear magnetic resonance (NMR) spectroscopy identifies the combined signals GlycA and GlycB from glycoproteins, offering an overall view of systemic glycoprotein changes. These signals represent the N-glycosylation patterns of several abundant acute-phase proteins (APPs), giving detailed molecular insights.

This review offers a detailed assessment of GlycA and GlycB as mechanistically grounded indicators of liver glycoprotein remodeling and systemic inflammation. GlycA mainly indicates the levels and structural complexity of N-acetylglucosamine (GlcNAc) and N-acetylgalactosamine (GalNAc) residues linked to acute-phase glycoproteins and glycan branching. In contrast, GlycB reflects changes in terminal sialylation, which influences glycoprotein half-life, immune recognition via lectins, and inflammatory signaling. Collectively, these biomarkers combine measurements of hepatic APP production with variations in glycan structure, offering mechanistically anchored reporters of hepatic glycoprotein remodeling.

We explore the enzymatic pathways responsible for N-glycan branching, fucosylation, and sialylation, as well as the roles of major APP scaffolds in the GlycA and GlycB resonances. We also highlight the emerging clinical significance of these signals across infectious, autoimmune, cardiovascular, metabolic, neurodegenerative, and cancer-related diseases. Rather than serving simply as markers of inflammation, GlycA and GlycB provide mechanistically interpretable readouts of cytokine-driven hepatic glycoprotein remodeling and systemic immune activation, supporting their application in disease risk stratification, longitudinal monitoring, therapeutic response assessment, and precision medicine.

Keywords: Post-translational modification, N-glycoproteins, Nuclear magnetic resonance spectroscopy, GlycA, GlycB, Inflammation

Background

Post-translational modifications (PTMs) are chemical changes that happen after protein synthesis and are key to creating the functional diversity of the proteome. By adding a complex layer to protein function, these modifications allow a relatively small number of genes to produce a wide variety of functional proteins (1). Therefore, the precise control of PTMs is crucial for maintaining cellular balance; their disruption is associated with various diseases, including cancer, neurodegenerative disorders, autoimmune diseases, and cardiovascular conditions. Among these modifications, glycosylation is one of the most common PTMs in eukaryotic cells, involving the covalent attachment of carbohydrate groups to proteins. The structural diversity of glycans makes glycosylation one of the most dynamic PTMs in cellular regulation. In mammals, this process is mainly divided into two types based on where the glycan is attached: N-linked and O-linked glycosylation. N-linked glycans are covalently bound to the nitrogen atom of asparagine (Asn) residues. This form is vital for the stability and function of secreted glycoproteins such as immunoglobulins and acute-phase proteins (APPs). O-linked glycans are attached to the oxygen atom of serine (Ser) or threonine (Thr) residues and are essential for protein trafficking and cell signaling (2).

Nuclear magnetic resonance (NMR) spectroscopy offers a reliable and straightforward method for both qualitative and quantitative analysis of various blood components, from

Received: February 27, 2026
Accepted: August 20, 2026
Published online: September 11, 2026

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small metabolites to lipoproteins. Additionally, NMR detects plasma signals associated with the N-linked glycosylation patterns of circulating APPs, including α1-antichymotrypsin, haptoglobin, α1-antitrypsin, transferrin, and α1-acid glycoprotein (3). These signals originate from glycan structures (Fig. 1) containing N-acetylglucosamine and N-acetylgalactosamine, collectively known as GlycA, and from N-acetylneuraminic acid (also called sialic acid), known as GlycB, which appear as two separate resonances in NMR spectra. Unlike targeted proteomic tests that measure individual proteins, NMR-derived GlycA and GlycB serve as composite molecular fingerprints of systemic inflammation (4). These markers reflect coordinated changes in liver protein synthesis and N-glycan remodelling. By combining information about structural aspects such as branching and sialylation with quantitative changes in inflammation, these signals offer a more stable and biologically relevant measure of chronic immune activation than traditional biomarkers (5).

Since N-linked glycosylation is a key factor in maintaining the structural integrity and functional capacity of circulating proteins, the ability to monitor these modifications throughout the body is of great biomedical significance. However, the translational relevance of these biomarkers relies on a thorough understanding of their natural biological variability. This review aims to emphasize the role of N-linked glycosylation in inflammatory processes and to assess the clinical utility of NMR-derived GlycA and GlycB as system-wide biomarkers reflecting dynamic changes in the circulating glycoproteome.

N-Linked Glycosylation: Enzymatic Pathways and Biological Scaffolds

N-linked glycosylation is a highly regulated, template-independent enzymatic process governed by substrate availability, localized enzyme activity, and the cellular microenvironment. In mammals, glycans are assembled from a conserved set of monosaccharides, primarily glucose, galactose, mannose, fucose, N-acetylglucosamine (GlcNAc), N-acetylgalactosamine, and sialic acid (6).

The biosynthetic pathway (Fig. 2) begins in the endoplasmic reticulum (ER), where the oligosaccharyltransferase (OST) enzyme complex transfers a preassembled oligosaccharide precursor (Glc3Man9GlcNAc2) onto Asn residues of nascent polypeptides within the Asn-X-Ser/Thr consensus motif (7). This initial attachment is vital for protein proteostasis, which plays a critical role in proper folding, stability, and quality control (8). Subsequent trimming of glucose and mannose residues by ER glycosidases (glucosidases I and II, and mannosidases) enables the glycoprotein to engage chaperones such as calnexin and calreticulin, ensuring correct folding and quality control (9).

As proteins transit to the Golgi apparatus, they undergo extensive remodeling by a suite of glycosyltransferases. The N-acetylglucosaminyltransferase (MGAT) family catalyzes the addition of GlcNAc residues to generate complex branched architectures, which modulate receptor stability and cell-cell adhesion (10). Fucosyltransferases (FUTs) further diversify these structures by adding fucose residues, influencing immune recognition and blood group antigenicity (10). Finally, sialyltransferases (particularly ST6GAL1) cap the glycan termini with sialic acid. This terminal sialylation imparts a negative charge, enhances protein circulatory half-life, and regulates immune signaling (10).

While soluble secretion is a primary route for chemical endocrine signaling molecules and protein growth factors, a substantial fraction of these glycoproteins may also be exported via extracellular vesicles (EVs), particularly exosomes (11). These nanometer-sized vesicles originate from inward budding of late endosomal membranes, forming multivesicular bodies (MVBs), and are distinguished by a dense, functionally active surface glycocalyx (11). The

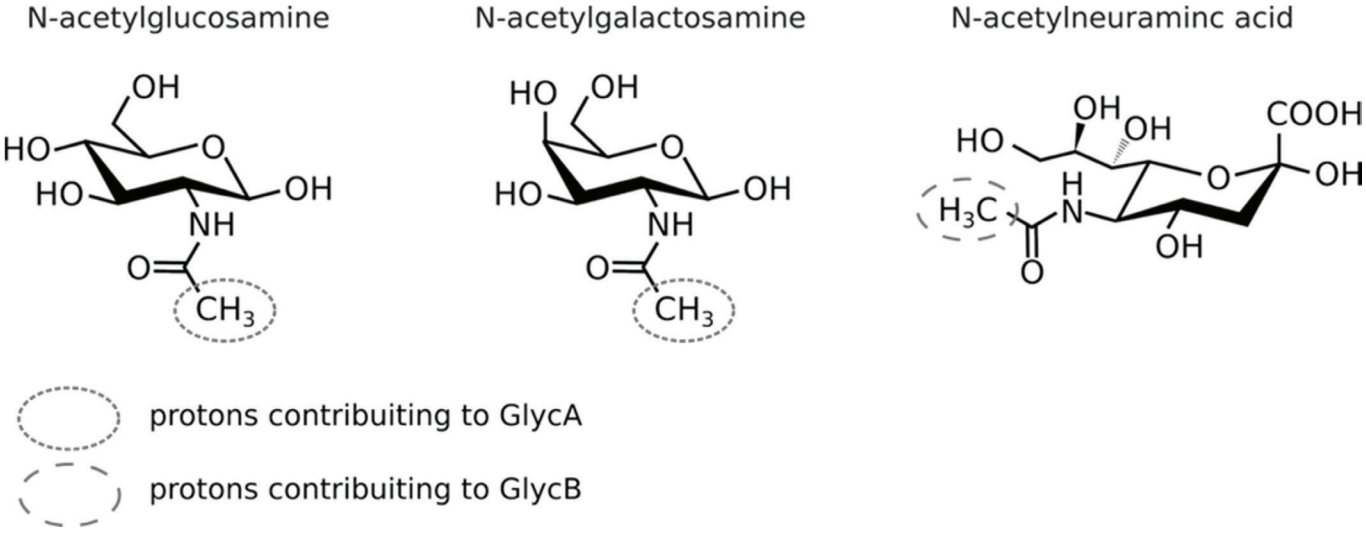

FIGURE 1 - Structural representation of N-acetylglucosamine, N-acetylgalactosamine, and N-acetylneuraminic acid and their anomeric configurations in aqueous solution with the protons contributing to GlycA and GlycB signals indicated.

glycan composition within these trafficking pathways is highly selective and strictly regulated. Exosomal surfaces are frequently enriched in complex-type N-glycans, including bisecting N-acetylglucosamine and α2,6-linked sialic acids (12). These structures confer protection against premature hepatic clearance mediated by the asialoglycoprotein receptor, thereby enhancing the circulatory stability and half-life of these glycoproteins (13). Increased β1,6-GlcNAc branching, often driven by elevated MGAT5 activity together with hypersialylation, not only stabilizes circulating APPs but also amplifies the composite NMR signals of GlycA and GlycB used to quantify systemic inflammatory burden (14). Consequently, whether present as freely circulating proteins or as membrane-associated components of EVs, N-glycans function as a collective molecular barcode of intracellular biosynthetic activity, reflecting the specific enzymatic environment of the Golgi and the physiological state of the cell of origin (15). The biological output of this enzymatic machinery is reflected in the glycan microheterogeneity of circulating APPs. These proteins serve as the primary scaffolds for the N-acetyl groups that generate the NMR-derived GlycA and GlycB signals (16). Following maturation in the Golgi apparatus, glycosylated APPs are sorted into distinct secretory pathways for systemic release (31).

Moreover, APPs are diverse plasma proteins whose concentrations fluctuate in response to inflammation, infection, trauma, or malignancy (17). The liver primarily orchestrates their synthesis in response to proinflammatory cytokines, most notably interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor-α (TNF-α) (18). APPs are functionally categorized into positive APPs, which increase during inflammation [e.g., C-reactive protein (CRP), haptoglobin, α1-acid glycoprotein, and α1-antitrypsin], and negative APPs, which decrease as the liver reprioritizes protein synthesis toward host defense (e.g., albumin and transferrin) (19). These APPs serve as the primary molecular scaffolds for GlycA and GlycB NMR signals, each playing a distinct role in systemic inflammation. α1-Acid glycoprotein (AGP) is a heavily glycosylated protein that possesses five N-linked glycosylation sites that can host bi-, tri-, and tetra-antennary complex glycans (23). During systemic inflammation, AGP undergoes a marked shift toward highly branched (tetra-antennary) glycan structures, significantly increasing the concentration of N-acetyl groups detectable by NMR (24). The main role of AGP is modulating immune responses and carrying drugs. Haptoglobin is a tetrameric glycoprotein with several N-glycosylation sites per subunit. From a glycoproteomic perspective, Hp is characterized by a high degree of fucosylation and branching (25). In states of malignancy and chronic inflammation, remodeling of haptoglobin glycans serves as a robust indicator of altered hepatic glycosylation (26). Hp shields tissues from oxidative injury by binding free hemoglobin and aids iron recycling. α1-Antitrypsin (AAT) is the major serine protease inhibitor in plasma. It carries three N-linked glycan chains. Structural variation of these chains is highly sensitive to the inflammatory milieu; shifts in AAT glycoforms reflect systemic activation of glycosyltransferases in response to cytokines like IL-6 (27). α1-Antichymotrypsin (ACT) is highly responsive to acute stimuli. Its N-linked glycans exhibit increased complexity and branching during the acute-phase response, providing additional GlcNAc resonances that contribute to the GlycA signal intensity (28). AAT and ACT protect tissues by inhibiting neutrophil proteases during inflammation. Transferrin (Tf) generally has two N-linked bi-antennary glycans. Although it is classified as a negative APP because its levels decrease during acute stress, Tf is an essential indicator of glycosylation status. It plays a key role in iron regulation, restricting microbial access. These findings suggest that GlycA and GlycB reflect coordinated responses across various physiological defenses rather than alterations in individual glycoproteins.

From a biological perspective, elevated GlycA indicates the liver's activation of an acute-phase synthetic program, driven by cytokines producing heavily glycosylated plasma proteins with increased N-glycan branching. GlycA serves as a system-wide marker of hepatic inflammation and immune activation, not just plasma protein levels. Elevated GlycB reflects increased sialylation of glycoproteins, regulated by sialyltransferases like ST6GAL1. Since terminal sialic acids modulate interactions with Siglec receptors, protect glycoproteins from clearance by the hepatic asialoglycoprotein receptor, and extend their half-life, increased GlycB may indicate persistent hypersialylation that influences immune regulation, inflammation, and cancer progression.

The power of GlycA and GlycB lies in their status as composite biomarkers. While classical mediators like CRP or cytokines provide a snapshot of acute signaling, they often contribute negligibly to the NMR spectrum due to their lower molar concentrations and limited glycosylation density (21). In contrast, the GlycA and GlycB signals aggregate the contributions of multiple high-abundance glycoproteins, offering a high signal-to-noise ratio and greater resistance to the short-term fluctuations that can plague single-protein assays (22). These composite signals primarily reflect the circulating pool of heavily glycosylated APPs, whose concentration and glycan branching patterns dynamically change during inflammation.

Beyond simple changes in abundance, the N-linked glycosylation patterns of these proteins, specifically variations in branching, fucosylation, and sialylation, are profoundly remodeled during disease, altering their biological activity and inflammatory potential (20)

GlycA and GlycB as Inflammatory Biomarkers

GlycA and GlycB provide a comprehensive and stable representation of systemic inflammation by capturing integrated molecular signals from the circulating glycoproteome (6). Unlike targeted assays that quantify individual proteins in isolation, these NMR-derived biomarkers reflect the collective N-acetyl methyl resonances of multiple APPs and their dynamic glycosylation modifications. Elevated GlycA levels have been consistently associated with metabolic syndrome, obesity, and neutrophil activation, highlighting its utility as a marker of persistent low-grade inflammation and immune activation (23). Variations in GlycB intensity are particularly relevant in oncological and vascular contexts, where hypersialylation frequently accompanies tumor aggressiveness, immune evasion, and endothelial dysfunction (23). Circulating GlycA and GlycB concentrations

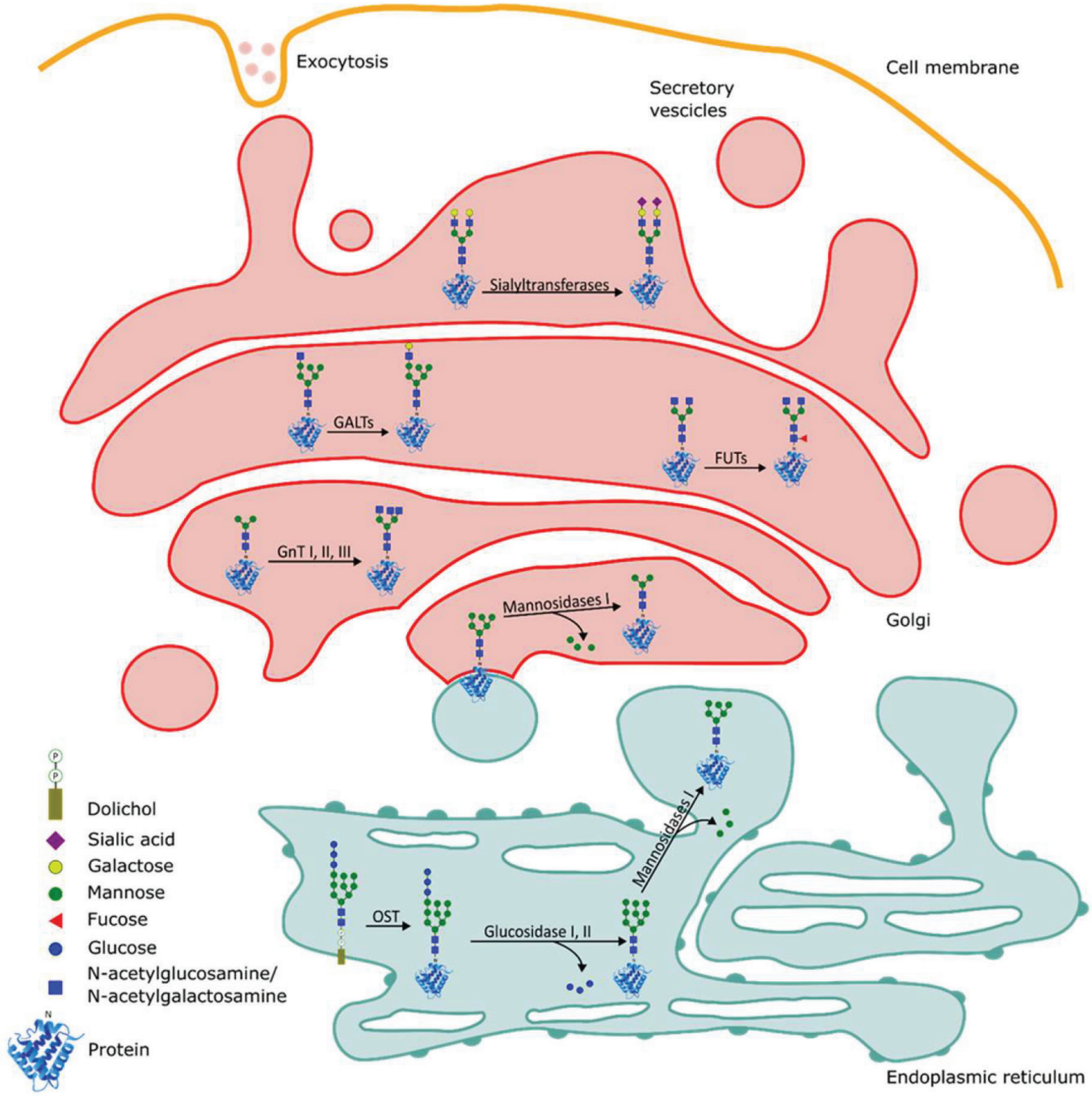

FIGURE 2 - Enzymatic pathway of protein glycosylation. This schematic illustrates the compartmentalized maturation of glycoproteins from the ER to the Golgi apparatus. The oligosaccharyltransferase (OST) complex initiates glycosylation by transferring a glycan precursor to a nascent polypeptide. Glucosidases (I and II) and Mannosidases I then sequentially trim glucose and mannose residues. The MGAT (GnT) family adds GlcNAc residues, creating the branched structures that generate the GlycA NMR signal. GALTs and FUTs add galactose and fucose, influencing immune recognition and protein stability. Sialyltransferases cap branches with sialic acid, which contributes to the GlycB NMR resonance. Mature glycoproteins are exported via secretory vesicles or exosomes.

are shaped by a dynamic interplay between genetic architecture, demographic determinants, and environmental exposures, including age, sex, and ethnicity, all of which collectively influence the baseline configuration of the plasma glycoproteome (8,32).

The clinical significance of GlycA and GlycB extends beyond their role as inflammatory markers. Instead of focusing on individual cytokines or APPs, these NMR signals provide a comprehensive, system-level view of changes in hepatic glycoprotein levels in response to inflammatory and

metabolic stress (4). Therefore, they should be considered combined indicators; elevated GlycB levels mainly reflect increased terminal sialylation of circulating glycoproteins (23). Since terminal sialic acids influence protein half-life, hepatic clearance, and immune recognition via lectin pathways, higher GlycB levels may indicate ongoing glycoprotein remodeling associated with chronic inflammation, metabolic disorders, autoimmune diseases, or cancer (23).

However, these biomarkers should not be seen as direct indicators of specific immune pathways or individual diseases. Rather, they reflect downstream effects of cytokine-induced changes in hepatic glycoproteins. GlycA and GlycB are not disease-specific markers but reflect the combined effects of cytokine signaling, liver glycoprotein production, and glycan changes (20). Their primary clinical value is in acting as mechanistically linked markers of systemic glycosylation remodeling, complementing traditional biomarkers for disease classification, ongoing monitoring, and personalized treatment in chronic inflammatory, metabolic, and cancer-related conditions (10).

Infectious Diseases

During the acute phase of infection, GlycA and GlycB act as integrative biomarkers of innate immune activation. In sepsis and severe bacterial infections, GlycA correlates with organ dysfunction and demonstrates strong predictive value for adverse clinical outcomes, reflecting cumulative alterations in hepatic APP synthesis and glycosylation (33). In parasitic infections such as malaria, *Plasmodium*-induced inflammation drives extensive remodeling of host glycosylation pathways (33). Elevated GlycA and GlycB levels reflect host-pathogen interactions, with altered terminal sialylation, particularly contributing to the GlycB signal, influencing immune recognition, clearance of infected erythrocytes, and regulation of effector functions (34). More broadly, sustained elevations in GlycA and GlycB across infectious diseases are associated with prolonged immune activation, cytokine-driven hepatic responses, and large-scale reprogramming of glycan biosynthesis, correlating with disease severity and long-term morbidity (23).

In SARS-CoV-2 infection, GlycA and GlycB have emerged as robust biomarkers of systemic inflammation and disease trajectory (35). COVID-19 is characterized by profound immune dysregulation, endothelial dysfunction, and cytokine-driven hyperinflammation, all of which are accompanied by marked elevations in circulating N-glycoproteins (36). Increased GlycA levels correlate with viral burden, respiratory impairment, and progression to severe disease, reflecting both the intensity and persistence of the acute-phase response. Importantly, sustained elevation of GlycA following acute infection has been associated with post-acute sequelae of COVID-19, implicating persistent glycosylation abnormalities in chronic inflammation and tissue remodeling (36).

In chronic viral infections such as HIV, GlycA and GlycB remain persistently elevated and reflect systemic immune activation rather than viral replication alone (37). These signals correlate with markers of monocyte activation and immunosenescence and are associated with increased risk of non-AIDS-related comorbidities, including cardiovascular and neurocognitive disorders, suggesting a functional role for aberrant N-glycosylation in chronic immune dysregulation (37). In tuberculosis, although direct GlycA/GlycB studies are limited, glycoprotein profiling indicates that Mycobacterium tuberculosis alters serum N-glycan composition, including changes in sialylation and fucosylation associated with inflammation and disease severity. Given the chronic granulomatous nature of TB, elevated N-glycoprotein signals are expected to correlate with inflammatory burden and treatment response, supporting their potential utility as systemic biomarkers across infectious diseases (38).

Autoimmune Diseases

In autoimmune diseases, characterized by chronic immune dysregulation, GlycA and GlycB serve as molecular barometers that integrate complex glycosylation changes across multiple APPs. Unlike conventional markers, they provide a stable reflection of the underlying autoimmune-driven milieu, offering insights into disease activity and subclinical risk (39). The integration of these markers allows for a more nuanced understanding of inflammaging and chronic disease burden across various pathologies (39). In rheumatoid arthritis, GlycA levels correlate closely with clinical measures of joint inflammation; beyond diagnosis, they also predict therapeutic success. Studies have shown that GlycA levels decrease significantly in patients who respond well to TNF-inhibitor therapy (40). This reduction makes GlycA a valuable tool for monitoring the efficacy of biologic therapies and long-term joint health. For patients with systemic lupus erythematosus (SLE), GlycA levels are often elevated even during periods of clinical quiescence. This suggests that GlycA can detect subclinical systemic inflammation that traditional markers might miss (41). Furthermore, elevated GlycA in SLE is strongly associated with an increased risk of premature atherosclerosis, linking autoimmune activity directly to cardiovascular complications (41).

GlycA levels mirror the severity of inflammatory bowel disease, proving particularly useful for distinguishing active inflammatory bowel disease from functional disorders such as irritable bowel syndrome. The signal reflects the specific hepatic and systemic glycan remodeling triggered by intestinal inflammation (42). In ankylosing spondylitis, GlycA reflects the intensity of spinal inflammation and the degree of radiographic progression (43). Its relative stability over time makes it a reliable longitudinal measure of the total inflammatory burden in axial spondyloarthritis (43). In psoriasis and psoriatic arthritis, elevated GlycA and GlycB levels reflect the psoriatic march, representing the progression from localized skin inflammation to systemic metabolic dysfunction (44). These signals correlate with the Psoriasis Area and Severity Index (PASI) and are associated with a higher risk of developing cardiovascular disease and metabolic syndrome (45). Ultimately, whether as a tool for assessing mucosal healing in inflammatory bowel disease or predicting cardiovascular risk in systemic lupus erythematosus, GlycA and GlycB represent a shift toward more personalized, glycan-based monitoring of autoimmune disease activity.

Neurodegenerative Diseases

Neuroinflammation is increasingly recognized as a key factor in neurodegenerative disease progression, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis (46). Peripheral immune activation is closely associated with brain atrophy, synaptic dysfunction, and cognitive decline, positioning inflammation-related biomarkers as key indicators of neurodegenerative pathology. In this context, NMR-derived glycoprotein signals, particularly GlycA, have emerged as sensitive markers of chronic systemic inflammation (47). Observational studies demonstrate that GlycA levels are significantly elevated in patients with Alzheimer's disease compared to cognitively normal controls, and higher baseline GlycA is associated with accelerated cognitive decline and reduced brain volumes in regions vulnerable to neurodegeneration (47). Moreover, in Alzheimer's disease, cerebrospinal fluid N-glycoprotein profiling reveals disease-specific signatures characterized by reduced sialylation and increased bisected N-glycans (48). These alterations are linked to overexpression of the glycosyltransferase N-acetylglucosaminyltransferase III (GnT-III), which modifies β-site amyloid precursor protein-cleaving enzyme 1 (BACE1), thereby promoting amyloidogenic processing and the accumulation of neurotoxic amyloid-β (49). Similar glycosylation-driven mechanisms have been implicated in other neurodegenerative disorders, strengthening the functional relevance of glycan remodeling in disease biology (49). GlycA may serve not only as a marker of disease presence but also as a potential predictor of disease progression, particularly during early stages such as mild cognitive impairment. In Multiple Sclerosis, GlycA constitutes a major component of the Inflammatory Vulnerability Index and is strongly associated with higher disability scores and reduced gray matter volume on magnetic resonance imaging (MRI), indicating ongoing neurodegeneration (50). Although large-scale studies specifically assessing N-glycoprotein levels in neurodegenerative disorders remain limited, the shared biochemical basis of GlycA and GlycB supports their role as integrated indicators of neuroinflammatory activity (51). Dysregulated N-glycosylation has been implicated in multiple pathogenic processes, including microglial activation, altered cytokine signaling, impaired protein clearance, and enhanced protein aggregation, all of which contribute to neurodegenerative cascades (51).

Cardiovascular Disease and Metabolic Disorders

In cardiovascular disease, low-grade chronic inflammation is a key driver of atherosclerosis, the buildup of fatty deposits in arterial walls that can lead to heart attacks and strokes (52). Elevated levels of GlycA and GlycB have been shown to correlate with increased risk of coronary artery disease and other forms of vascular inflammation (22). The biomarkers reflect the glycosylation changes occurring in haptoglobin, α1-acid glycoprotein, and fibrinogen, all of which are involved in platelet aggregation, endothelial dysfunction, and oxidative stress, processes that collectively contribute to the pathology of cardiovascular disease (52). Clinical studies have demonstrated that GlycA levels can predict adverse cardiovascular events, making GlycA a potentially valuable tool for early risk assessment and for stratifying patients for preventive therapies, including statin use (53). Inflammation is central to the initiation and progression of atherosclerosis, influencing endothelial dysfunction, lipid oxidation, and plaque instability (52).

GlycA has emerged as a strong independent predictor of cardiovascular outcomes, as its molecular signal reflects increased glycosylation and circulating concentrations of APPs during vascular inflammation. Elevated GlycA levels capture chronic systemic inflammation not fully explained by conventional inflammatory markers, providing added prognostic value (54). Molecularly, aberrant glycosylation of APPs affects their interactions with endothelial receptors, modulates leukocyte adhesion, and contributes to oxidative stress within the vascular wall (3). GlycB, thought to derive largely from terminal sialylation of glycan chains, provides complementary information by reflecting shifts in the balance between pro- and anti-inflammatory glycan structures (53). Enhanced sialylation has been associated with vascular remodeling, impaired nitric oxide signaling, and altered lipoprotein metabolism, all of which contribute to atherogenesis (54). Taken together, GlycA and GlycB provide a composite measure of systemic glycoprotein remodeling that influences both structural and functional aspects of the vascular system, positioning them as integrative markers of cardiometabolic and vascular risk (54).

Considering metabolic diseases such as type 2 diabetes and obesity, chronic systemic inflammation plays a central role in insulin resistance and the development of metabolic syndrome (55). Both GlycA and GlycB are elevated in individuals with obesity and diabetes, correlating with higher levels of insulin resistance, dyslipidemia, and impaired glucose metabolism (55). Elevated GlycA levels may serve as an early indicator of metabolic dysfunction, especially in individuals with central obesity, where low-grade inflammation in adipose tissue promotes insulin resistance (55). Furthermore, GlycA levels may predict the risk of cardiovascular and renal complications in diabetic patients (56).

Cancer-Associated Inflammation

Protein glycosylation serves as a central regulator of tumor progression, immune evasion, angiogenesis, and metastatic dissemination (2). Malignant transformation induces coordinated and predictable alterations in the cellular glycosylation machinery, resulting in enhanced β1,6-GlcNAc branching, increased fucosylation, and global hypersialylation (57).

These modifications extend beyond malignant cells and actively reshape the tumor microenvironment, influencing interactions among cancer cells, immune infiltrates, stromal fibroblasts, and endothelial compartments (57). Collectively, these glycan alterations promote tumor-stroma adhesion, facilitate immune escape by forming a protective glycan shield, and modulate cytokine signaling and vascular remodeling (58).

In parallel, systemic NMR-derived biomarkers reflect these local reprogramming events in glycosylation. Elevated GlycA correlates with tumor aggressiveness and total inflammatory burden, while GlycB has been associated with the

hypersialylation patterns characteristic of metastatic potential and epithelial-mesenchymal transition (59). The diagnostic and prognostic performance of these markers therefore arises not merely from increased protein abundance, but from their ability to capture cancer-specific remodeling of the circulating glycoproteome driven by tumor-associated inflammation and microenvironmental crosstalk.

In breast cancer, glycosylation changes are particularly central to cell-to-cell adhesion and the stability of growth factor receptors. Aberrant N-glycan structures on surface receptors such as HER2 and EGFR enhance downstream signaling pathways that drive proliferation, survival, and therapeutic resistance (60). Within this context, GlycA and GlycB function as dynamic, non-invasive indicators of tumor biology, with persistent elevation of both signals being associated with increased tumor aggressiveness and the development of metastatic disease (61).

Elevated GlycA in pancreatic ductal adenocarcinoma reflects the intense systemic inflammation and altered hepatic output triggered by the tumor microenvironment (62,63). Because pancreatic adenocarcinoma is often asymptomatic in its early stages, the sensitivity of GlycA to these systemic shifts may offer a potential non-invasive means to monitor disease progression and early recurrence (64).

Glycosylation plays a critical role in the epithelial-mesenchymal transition of colorectal cancer. Specifically, increased GlycB levels may reflect a hypersialylation state that promotes tumor cell detachment and immune evasion (65). High GlycA levels are independent predictors of incidence and mortality, as glycan signal intensity correlates with overall survival (66). Similarly, in prostate cancer, GlycA and GlycB correlate with Gleason scores and tumor stage (67, 32). These markers have been reported to help distinguish indolent from aggressive disease, potentially providing complementary information to prostate-specific antigen (PSA), enhancing the molecular characterization of tumor aggressiveness, and offering additional insight into the underlying biological activity (68).

Conclusion

N-linked glycosylation plays an active role in regulating protein function and immune homeostasis by coordinating cytokine signaling, hepatic acute-phase responses, and glycan remodeling. Instead of merely indicating inflammation, the NMR biomarkers GlycA and GlycB serve as mechanistically anchored reporters of hepatic glycoprotein remodeling. By capturing both quantitative and qualitative shifts in the circulating glycoproteome, these biomarkers provide meaningful biological insights into the chronic systemic inflammation that underlies metabolic, cardiovascular, autoimmune, neurodegenerative, and cancer-related diseases.

Although GlycA and GlycB are not disease-specific biomarkers, their ability to capture sustained systemic remodeling of glycoproteins makes them valuable tools for disease stratification, longitudinal monitoring, and assessment of therapeutic response. Future integration with glycoproteomics and multi-omics approaches will further refine their biological interpretation and accelerate their application in precision medicine.

Disclosures

Conflict of interest: The authors declare no conflict of interest.

Financial support: Support by The International Centre for Genetic Engineering and Biotechnology, ICGEB (SC, LFZ); ICGEB Arturo Falaschi fellowship (KCSS).

Data availability statement: No new data were generated in this study.

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