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Implications of aberrant glycosylation on age-related disease progression

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ABSTRACT

Glycosylation, the enzymatic attachment of glycans to proteins, is a ubiquitous post-translational modification in eukaryotes, responsible for many essential physiological processes such as moderating protein folding, stability, trafficking, and cell-cell communication. Through *N*-linked and *O*-linked glycosylation pathways, complex glycoforms are formed that are indispensable for maintaining cellular homeostasis. Emerging evidence suggests that glycosylation patterns undergo significant alterations with aging and across a range of diseases, including cancer, diabetes mellitus, neurodegenerative disorders, hypertension, osteoporosis and cardiovascular diseases. Age-associated reductions in galactosylation and fucosylation of serum *N*-glycans have been recognized as biomarkers of biological aging. Additionally, hyperfucosylation of glycoproteins has been reported in age-related malignancies, while altered glycosylation patterns are associated with osteoporosis. Moreover, increased glycosylation of glial fibrillary acidic protein (GFAP) contributes to reactive astrogliosis in Alzheimer's disease, while altered glycan profiles of α-synuclein are associated with protein aggregation in Parkinson's disease, highlighting the role of glycoform modulation in the progression neurodegenerative disorders. Additionally, dysregulated *O*-GlcNAcylation pattern impairs insulin signaling and β-cell viability in metabolic disorders such as diabetes. Likewise, aberrant *N*- and *O*-glycan structures derive cancer progression and metastasis by altering cell adhesion, promoting immune evasion, and modulating extracellular matrix interactions. In cardiovascular diseases, abnormal IgG glycosylation and elevated O-GlcNAcylation of vascular proteins promote pro-inflammatory and pro-fibrotic responses. Similarly, changes in the glycosylation of osteogenic proteins, including osteopontin and alkaline phosphatase, impair bone formation and remodeling in osteoporosis. Collectively, this review aims to highlight the most commonly associated age-related disease and the connection of glycosylation in both the pathophysiology and its therapeutic aspects.

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INTRODUCTION

Glycosylation, a process of attaching sugar molecules to proteins and lipids, is a highly compelling area of research, as glycans are ubiquitously expressed on cell surfaces and undergo extensive structural modification. Glycosylation is mainly of two types: *O*-Glycosylation and *N*- Glycosylation. *O*-glycosylation mostly deals with attachment of sugars to amino acids such as Serine (Ser) or Threonine (Thr), these are found to be common in extracellular and secreted glycoproteins. *N*-glycosylation particularly is an attachment of sugar molecules to Asparagine (Asn) amino acid in the Asn-X-Ser/Thr motif (X represents any amino acid except for proline) particularly in the endoplasmic reticulum (Reily *et al.*, 2019). It has been observed that patterns of glycosylation change with ageing, as reports show aberrant protein *N*-glycosylation after the age of 40, leading to the formation of unique glycoforms. Studies have found that some glycans change in quantity with age. Even though the degree of change was small, it was significant-specifically, the age-associated reductions in galactosylation and fucosylation of *N*-linked oligosaccharides in human serum may serve as potential biomarkers of aging (Paton *et al.*, 2021). The central nervous system (CNS) responsible for the neurological function of the entire body has been found to be an area of heavy glycosylation. As such glycosylation is key in regards to receptor function, cell adhesion and transmission of signals, therefore glycosylation is significant in the glycosylation changes for developments of biomarkers in neurodegenerative diseases (Zhang *et al.*, 2024). Such as in Alzheimer's disease (AD), proteins such as glial fibrillary acidic protein (GFAP) was more glycosylated. There is a direct correlation in the upregulation of GFAP with AD and reactive astrocytes (D). Whilst it is lucrative to think about utilizing glycosylation for biomarker purposes, obtaining glycan structures and information from protein from isolation to purification is quite challenging. Many have tried and new technologies are being developed such hydrophilic interaction liquid chromatography (HILIC) but these are far and few. But the high diagnostic potential of glycomic studies as biomarkers are very lucrative in physiological and age-related pathogenesis (Miura and Endo, 2016). Even though galactosylation and sialylation levels differ with diseases related to age, then fucosylation as well increased in cancer related diseases. Thereby, techniques such as capillary electrophoresis (CE) are utilized for the efficient separations, ion-mobility mass spectrometry (IMMS) a technique quite worthwhile for its ability to separate sialic acid glycoconjugate isomers, nuclear magnetic resonance (NMR) for mass analyses that keeps the sample intact and mass spectrometry (MS) is so far the best technique regarding working with these inconsistent and vast array of glycans (Paton *et al.*, 2021).

Role of glycosylation

Glycosylation is the covalent attachment of complex oligosaccharides or multi-sugar polysaccharides to specific target proteins. Protein glycosylation being one of the more prevalent post-translational modifications, has a tremendous impact in directing protein function, stability, subcellular localization, and various characteristics to expand the function of protein by few folds than its original part as translated by the genome (Eichler, 2019). The widespread and physiologically relevant post-translational modification of proteins known as glycosylation is becoming more commonly recognized. The best tools for determining the glycosylation status of proteins are provided by modern mass spectrometry techniques. The complex terminology, methods, and expertise required for mass spectrometry and glycobiology present a barrier to admission for others (Patrie *et al.*, 2012). In every aspect of life, protein glycosylation has been observed. For example, studies have demonstrated that prokaryotes include *N*-linked glycosyltransferases (GTs), which are quite similar to the eukaryotic STT3 family (Tran and Ten Hagen, 2013). *N*-glycosylation is a strongly conserved glycan modification, with over 7000 proteins undergoing *N*-glycosylation in humans. Numerous biological processes, including signal transduction, trafficking, and protein folding, depend on *N*-glycosylation. Thus, numerous biological and clinical processes are

significantly impacted by the alteration of proteins by glycans (Hirata and Kizuka, 2021). *N*-linked glycosylation is one essential post-translational modification affecting protein structure, function, and clearance. In medicine, N-linked glycosylation is also employed to extend the half-lives of several proteins (Águila *et al.*, 2021).

Glycan adherence to protein asparagine residues is a common and extremely conserved necessary alteration. The two main stages of the *N*-glycosylation process are forming a lipid-linked oligosaccharide (LLO) and its transfer to specific asparagine residues of polypeptide chains. Several particular glycosyltransferases catalyze the construction of the branching oligosaccharide in a very specified manner during the biosynthesis of the LLO, which occurs at both sides of the endoplasmic reticulum (ER) membrane. Oligosaccharyltransferase (OST) creates the *N*-glycosidic bond between the oligosaccharide and the asparagine side-chain amide by choosing the Asn-X-Ser/Thr consensus sequence on polypeptide chains. The great diversity of the N-glycoproteome in cells is produced by this ER-localized process, which modifies the proteome systemically and serves as the foundation for the Golgi-catalyzed alteration of the N-linked glycans (Breitling and Aebi, 2013).

Proteins that are membrane-bound and secreted have an evolutionarily conserved alteration called *O*-glycosylation. *O*-glycosylation abnormalities are linked to risk factors for disease and are the cause of some human illnesses. Mucin-type *O*-glycosylation has been shown in recent research to have crucial roles in protein secretion, stability, processing, and function (Tran and Ten Hagen, 2013). Multimodal mass spectroscopy proved especially challenging in characterizing *O*-linked glycosylation because traditional MS/MS techniques (such as CID) produce little to no signal for glycan-carrying ions. This is mostly because glycosidic bonds are more labile than peptide ones (Bakhtiar and Guan, 2005). A GlcNAc moiety is transferred from UDP-GlcNAc to the hydroxyl oxygen of a serine or threonine residue by *O*-linked glycosyltransferases (GTs). It has been claimed that basic biological functions such as transcription, signal transduction, metabolism, subcellular localization, and immune response depend on *O*-linked glycosylation (Lu *et al.*, 2023). Proteins undergo numerous changes as they move through the Golgi apparatus and endoplasmic reticulum (ER) one of which is glycosylation as they are making way to the secretory apparatus, which determines whether the protein is to be secreted or membrane bound. Extracellular proteins can be glycosylated in two ways either by the *N*-link to asparagine or *O*-linked to threonine, serine, or hydroxylysine and the categories of *O*-linked glycans are vast (Zhang and Ten, 2023).

Role of glycosylation in age-related diseases

To elucidate the role of glycosylation on age-related diseases, an increasing number of studies have focused on the glycosylation patterns of key proteins, which are delineated in the following sections and concisely summarized in Table 1 and Fig. 1.

Cancer

Glycosylation affects how cells interact with the matrix by changing the anchorage and how the extracellular basement membrane proteins work. These proteins include laminin, fibronectin, integrins, and collagen in the ECM. Integrins are transmembrane proteins that directly interact with extracellular matrix (ECM) proteins to maintain cytoskeleton architecture and stimulate cell growth and proliferation. Many clinical illnesses, including muscular dystrophy, cardiovascular diseases, neurological diseases, and cancer, would arise from changes in the glycosylation of anchoring proteins (Thomas *et al.*, 2021). Due to its function in carcinogenesis, development of cancer, and metastasis, aberrant glycosylation has been defined as a cancer biomarker. This has given researchers a new angle on cancer research that includes examining the underlying mechanisms, clinical translation, and application. Glycoproteins (such as CA125 in ovarian cancer, AFP in liver cancer, for colon cancer CEA, and PSA in prostate cancer) or glycan-related indicators (such as CA19-9, for gastrointestinal and pancreatic

cancer also called sialyl-Lewis A) are the major biomarkers for tumours in clinical settings (Wang, Zhu *et al.*, 2019). Numerous roles are played by cell surface glycosylation, and its dysregulation in cancer leads to compromised signaling, metastasis, and immune response evasion. Reduced anti-tumor immune responses have recently been associated with several glycosyltransferases that result in altered glycosylation: B3GNT2, which confers cancer resistance to T cell cytotoxicity; FUT8, which fucosylates B7H3; and B3GNT3, which is implicated in PD-L1 glycosylation in triple-negative breast cancer. The development of techniques that enable an objective examination of cell surface glycosylation status is imperative, given the growing recognition of the significance of protein glycosylation (Čaval *et al.*, 2023). Cancer cells rewire their metabolism to support growth, survival, proliferation, and long-term maintenance. Even in the presence of oxygen, cancer cells frequently increase their glucose uptake and ferment it to lactate. This metabolic rewiring, known as the Warburg effect, keeps cancer cells' high energy demands stable (Warburg, 1925).

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

Diseases	Glycosylation		References
	Aberration	Therapy/Biomarkers	
Cancer	Shortened O-glycans, which are expressed in the stomach, pancreas, and ovaries	UN1 mAb can be used to detect aberrant CD43 glycoforms and aberrant CD43 glycosylation	(Guo *et al.*, 2022), (Tuccillo *et al.*, 2014)
Diabetes	In T2DM, abnormal N-glycosylation of the pancreatic beta cell glucose transporter-2 (Glut-2) impairs the release of insulin	T cells of Ulcerative Colitis patients along with extra GlcNAC and increased levels of N-glycosylation on T cell receptor hence a decrease in pro inflammatory cytokines.	(Rudman *et al.*, 2019) (Reily *et al.*, 2019)
Hypertension	O-GlcNAc is closely linked to pathways related to vascular function, the disruption of which are causes for arterial hypertension.	Use of IgG Fc N-glycosylation to diagnose hypertension and the inflammation surrounding it, In Chinese ethnic groups, IgG specific Fc glycans are directly associated with hypertension	(Vang *et al.*, 2022), (Lima *et al.*, 2009)
Atherosclerosis	Glycosylated lipoproteins are prone to lipoprotein oxidation, this changes LDL and HDL which hinders their uptake through the normal receptors; hence their uptake becomes dependent on the scavenger receptors. Utilizing the scavenger receptor to get through to cells causes the accumulation of cholesterol eventually giving way to atherosclerotic plaque	Protective aspects of OGlcNAcylation also has inhibitory effect on NF-κß which is responsible for the production of inflammatory cytokines which causes activation of macrophages hence causing inflammation on site of production, and can progress towards the condition of atherosclerosis	(Loaeza-Reyes *et al.*, 2021), (Luo *et al.*, 2019)
Alzheimer's	Involves abnormal glycosylation of key proteins. APP is misdirected inside cells, reducing its release and disrupting iron balance, while tau protein becomes prone to pathological aggregation.	Restoring O-GlcNAcylation levels can decrease tau pathology, providing a possible therapeutic approach for delaying or halting the progression of AD, according to growing evidence from both human research and experimental models.	(Xie *et al.*, 2014), (Iqbal *et al.*, 2014), (Conroy *et al.*, 2021)
Parkinson's	The binding of α-dystroglycan to extracellular matrix components is hindered by hypoglycosylation, which may jeopardize neuronal integrity and contribute to neurodegeneration	In neural models, increased O-GlcNAcylation decreases cytotoxicity and prevents α-synuclein aggregation. Thus, pharmacologically raising O-GlcNAc levels has been suggested as a neuroprotective tactic.	(Ohtsubo and Marth, 2006), (Videira and Castro-Caldas, 2018)
Osteoporosis	OGT decreases the activity of O-GlcNAcylated alkaline phosphatase (ALP), hampering osteogenic differentiation of periodontal ligament cells	O-GlcNAc modification at N3646R site of SIRT1 promotes osteoprotective effect by stimulating osteoblast proliferation	(Lin *et al.*, 2025)

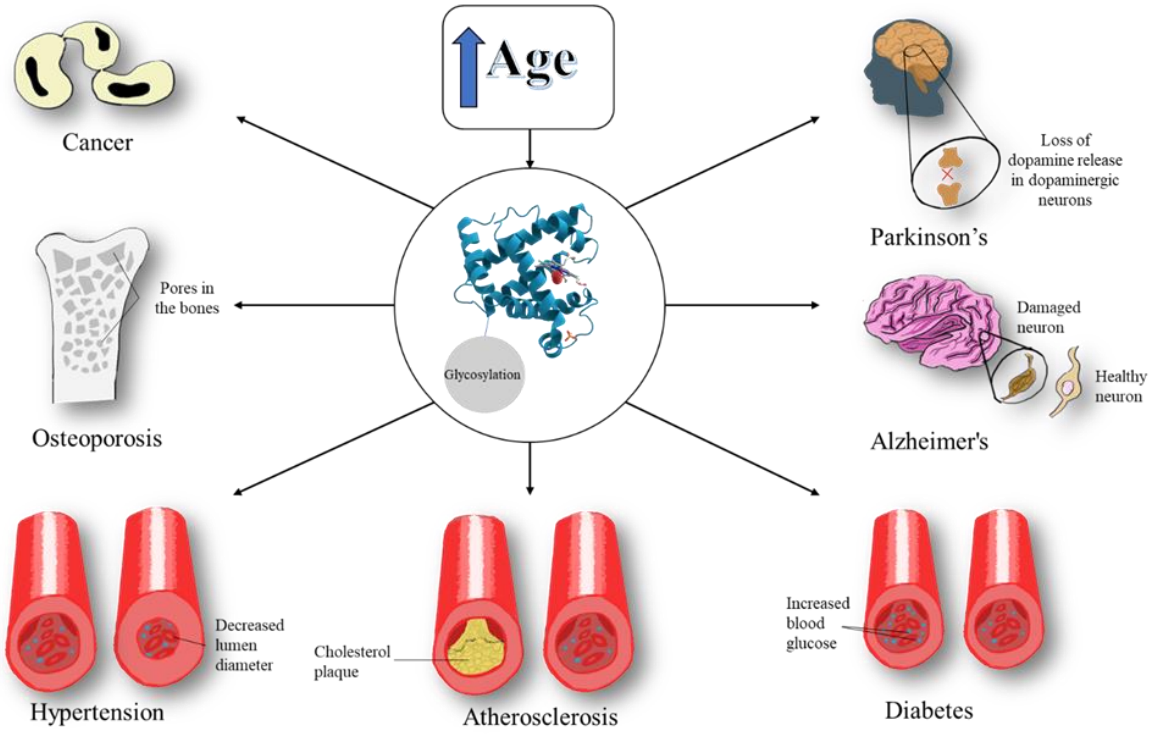

Fig. 1. Overview of aberrant glycosylation associated with various pathological conditions

One of the characteristics of cancer is abnormal glycosylation. *O*-linked glycan, sialylation, and *N*-linked glycan branching are a few tumor-associated aberrant glycosylations that are abnormally prevalent in cancer and aid in the growth and dissemination of the disease. When the glycosylation differences between breast cancer and normal cells were compared using lectins, it was discovered that tumor cells showed a higher affinity for binding lectins, suggesting that they contain more of a particular mucopolysaccharide. 90% of breast tumors have shortened *O*-glycans, and mucin is one of the first serum indicators for breast cancer. Tn (GalNAc-Ser/Thr), T (Gal-GalNAc-Ser/Thr), and Sia-Tn (STn, Sia-GalNAc-Ser/Thr) are examples of truncated *O*-glycans, which are also referred to as CA72-4 antigen. With elevated expression in the stomach, pancreas, and ovaries, truncated *O*-glycans are one of the examples of aberrant glycans in cancer (Guo *et al.*, 2022). Glycan structure aberrations can be treated to improve current serum cancer biomarkers. The capacity to differentiate between cancer and regulate patients' differences in protein glycosylation highlights glycobiology as a potentially fruitful area for biomarker discovery. The emergence of protein glycoforms as cancer biomarkers and the aberrant glycosylation of proteins related to human cancer. Potential use of the UN1 monoclonal antibody (UN1 mAb) to detect aberrant CD43 glycoforms and aberrant CD43 glycosylation as a diagnosis of cancer (Tuccillo *et al.*, 2014). Glycan-based therapeutics, including glycosyltransferase-inhibiting agents, glycomimetics, glycan/glycopeptide vaccinations, antibody treatments, and antibody-based immunotherapies, have been developed to treat cancer and other diseases because of the physiological and pathological significance of glycans found on a variety of biomolecules (Ho *et al.*, 2016). Numerous cellular modification is require to turn cancer into the threat that it is and evidence has been found that altered glycans are at the forefront for tumorigenesis. Biomarkers such as CA125 and CA19.9 are three decades old (Thomas *et al.*, 2021); but, their functions and specificity still remains a mystery. Due to the various isoforms a single glycosyltransferase can create for a single glycan epitope studying the effects of glycosylation properly remains a challenge, yet the potential for

therapy by tackling problems of glycosylation machinery keeps ongoing.

Diabetes

Diabetes is a condition indicated by poor insulin secretion and insulin resistance, which raises blood glucose levels (hyperglycemia). The occurrence is due to either they body being unable to produce insulin which is usually type 1 diabetes mellitus (T1DM) or when the body is unable to utilise the insulin it has produced usually identified as type 2 diabetes mellitus (T2DM). The immune system of the patient with T1DM destroys the pancreatic cells that produce insulin. It's an autoimmune disease. T2DM is the alternative type of the disease. It occurs when the body's cells either do not respond to insulin appropriately or the pancreas does not make enough of it (Cloete, 2021). Consequently, the person develops hyperglycemia, or consistently elevated blood sugar. About 90–95% of all cases of diabetes globally are of this kind, making it the most prevalent type. Both type 1 and T2DM are characterized by an excess of glucose in the blood, which inevitably results in a range of glycosylation diseases. Insulin synthesis, activity, and survival of pancreatic β-cells are all impacted by *O*-GlcNAcylation. Young mice with transgenic mice that overexpress OGA in their pancreatic islet β-cells had lower insulin levels and worse glucose tolerance. Age-induced increases in *O*-GlcNAcylation of pancreatic islets led to a progressive recovery of β-cell function (He *et al.*, 2024). Diabetes is intimately related to the regulation of OGT (*O*-GlcNAc transferase). The overexpression of OGT in the muscles, adipose tissues, and liver results in insulin resistance. Cells respond to insulin196 by adding GlcNAc to Ser or Thr residues through a process called *O*-GlcNAc glycosylation, which is catalyzed by OGT (Ma and Hart, 2013; Reily *et al.*, 2019). In T2DM, abnormal N-glycosylation of the pancreatic beta cell glucose transporter-2 (Glut-2) impairs the release of insulin (Rudman *et al.*, 2019). The hexosamine biosynthesis pathway (HBP) in T2DM results in elevated UDP-*N*-acetylglucosamine (UDP-*N*-GlcNAc) levels. In such a process, OGT is an enzyme that catalyses the reversible form of *O*-glycosylated protein, it uses UDP-GlcNAc as its primary sugar donor substrate (Buse, 2006). A study conducted in 2014 revealed that T2DM patients with metabolic syndrome have altered *N*-glycan profiles. *N*-glycan level assessment may be a non-invasive surrogate sign for T2DM (Testa *et al.*, 2015). By altering important glycoproteins that are involved in metabolism and immunology, *N*-glycosylation also plays a role in diabetes. For example, in Type 1 diabetes, autoimmune responses are influenced by altered N-glycan branching in T cells, but in T2DM, alterations in serum *N*-glycans are linked to insulin resistance and inflammatory indicators (Wang WenFei *et al.*, 2018). Through *O*-GlcNAcylation, a nutrient-sensitive alteration controlled by the hexosamine biosynthesis pathway (HBP), glycosylation plays a significant role in diabetes. Excess glucose flux via the HBP causes elevated levels of UDP-GlcNAc, the substrate for OGT, in hyperglycemic circumstances. As a result, proteins become hyper *O*-GlcNAcylated, interfering with insulin signalling pathways. Abnormal glycosylation patterns have been identified as important factors in the development and evolution of diabetes mellitus, both T1DM and T2DM, with consequences for insulin resistance, β-cell dysfunction, and long-term problems. Overall, the metabolic abnormalities associated with diabetes are both caused by and reflected by dysregulated glycosylation.

Hypertension

Hypertension is one of the major and sever cardiovascular complications and cause of mortality, as described by American College of Cardiology a systolic blood pressure over 130 mm Hg and diastolic blood pressure over 80 mm Hg can be classified as symptoms of hypertension for which anti-hypertensive medication can be prescribed for treatment (Carey *et al.*, 2022).

Metabolic dysregulation is observed to change glycan structures which can cause malignancy in cells due to the glycans of the membrane changing and influencing the cellular microevent.

Similarly, in a variable glucose intake can cause pulmonary arterial hypertension (PAH), rather a strong correlation has been found in elevated glycan levels and idiopathic PAH, furthermore glucose intolerance and insulin intolerance are present as well (Vang *et al.*, 2022). *O*-GlcNAc is closely linked to pathways related to vascular function, the disruption of which are causes for arterial hypertension. Increase levels of *O*-GlcNAc seems to enhance chemotaxis of leukocytes as well as stimulating the hexosamine biosynthetic pathway which leads to the expression of prosclerotic genes as well as plasminogen activator inhibitor-1 which leads to eventual hypertensive nephropathy. Even though *O*-GlcNAcylation is known to have atheroprotective effects it is being hypothesized that under increased blood pressure the atherprotective pathways in turn assist in the vascular damage that leads to hypertension (Lima *et al.*, 2009). A notable biomarker is the use of IgG Fc *N*-glycosylation to diagnose hypertension and the inflammation surrounding it, as in Chinese ethnic groups it has been found that IgG specific Fc glycans are directly associated with hypertension. Mainly in individuals with hypertension a noticeable decrease in galactosylation has been noticed which are present in diseases such as Parkinson's and in some allergies as well (Liu *et al.*, 2018). Similarly in another study by Kifer *et al.* (2021) they also managed to find a direct correlation of IgG *N*-glycome to hypertension, their study was carried out with data from the UK. They have found that the simple glycan structures consisting of a fucose core, those being B, GP4 and GP9 were increased in incidents of hypertension; often all four of them in a linear manner, furthermore their suspicion is that it has to something to do with B cell activation (Kifer *et al.*, 2021).

Atherosclerosis

Atherosclerosis is an inflammatory cardiovascular disease where leukocytes are bound to the endothelial cells of the arterial intima which is facilitated by the sugar structures of the adhesion molecules present there, alongside vascular smooth muscle cells (VSMC) and lipids accumulate forming a plaque which reduces the volume through which blood can pass through the artery causing hypertension and in severe cases could block the circulation through that artery completely (Pu and Yu, 2014). *O*-GlcNAcylation is linked to various CVDs including atherosclerosis. It has been seen that *O*-GlcNAcylation plays a both pro atherogenic and protective effects as well, in the pro atherogenic aspect it hampers the production and secretion of eNOS (endothelium nitric oxide synthase) a key component of vasodilation and vascular smooth muscle cell relaxation, hence leading to vessel stiffness and hypertension leading to more damage of the cell lining of blood vessels which is the initiator of atherosclerosis. However, in protective aspects it also has inhibitory effect on NF-κß which is responsible for the production of inflammatory cytokines which causes activation of macrophages hence causing inflammation on site of production, and can progress towards the condition of atherosclerosis (Loaeza-Reyes *et al.*, 2021). It has been seen that in atherosclerotic plaque development, desialylation of LDL (Low density lipoprotein) by some cell types including macrophage take place which is a key step in the accumulation of cholesteryl ester and the formation of foam cells (Pirillo *et al.*, 2021). Glycosylated lipoproteins are prone to lipoprotein oxidation, this changes LDL and HDL which hinders their uptake through the normal receptors, hence their uptake becomes dependent on the scavenger receptors. Utilising the scavenger receptor to get through to cells causes the accumulation of cholesterol eventually giving way to atherosclerotic plaque (Luo *et al.*, 2019). In other studies, small dense LDL (sdLDL) is a highlight when it comes to the pathophysiology of atherosclerosis. SdLDL has been seen to be more prone to glycation, hence it has a tendency to become advanced glycation end product (AGE) and it is prone to oxidation as well. The small size and its proatherogenicity allows it to invade cell lining much more easily and its low affinity to LDL receptor makes it so that it remains in the plasma longer therefore induce the deposition of cholesterol and other lipoproteins it is even a good marker for cardiovascular occurrences (Poznyak *et al.*, 2023). As mentioned earlier sialylation is a key component in development of atherosclerosis, as found in an article by Pu and Yu

(2014) α2,3-sialyltransferase IV (ST3Gal-IV) is essential in formation of atherosclerosis. It was observed in mice that deficiency of ST3Gal-IV led to atheroprotective effects in mice as deficiency of this enzyme leads to impairment of binding of leukocytes to the endothelial cell lining one of the key factor in atherosclerosis, furthermore, selectin ligands which help leukocyte in binding to receptors are also hampered. ST3Gal-IV is sought to be a key component in the formation of atherosclerotic plaques because of the wide range of effects that were observed, thereby, it is also seen as a potential therapeutic target for the treatment or reduction of inflammation and the development of atherosclerotic plaques in risky individuals (Pu and Yu, 2014).

Alzheimer's disease

Alzheimer's disease is a neurological condition that increases over time and impairs behavior, thought, and memory. The leading cause of dementia, a term used to describe blurred memory and cognitive decline that interferes with day-to-day functioning, is this. Neuritic plaques, also known as senile plaques, and neurofibrillary tangles (NFTs) are two major neurological abnormalities that are symptomatic of Alzheimer's disease (AD). In the brain, aberrant protein fragment clusters called neurotic plaques form between nerve cells, or neurons. The main constituent of neuritic plaques is beta-amyloid, a sticky protein fragment derived from amyloid precursor protein (APP), a larger protein. The other biomarker for Alzheimer's disease (AD) is NFTs, composed of twisted fibers known as paired helical filaments (PHFs). The cytoplasm contains a protein called tau, which is the primary component of these filaments. Tau protein is mildly phosphorylated and typically contains two to three phosphate groups per molecule in a healthy brain, which is essential for its proper operation. However, tau is excessively phosphorylated in Alzheimer's disease, three to four times more than usual. Tau proteins clump together to create aberrant filaments (PHFs), which then clump into NFTs as a result of this.

Hence, the abnormal hyperphosphorylation of tau is critical to the molecular pathogenesis of Alzheimer's disease (AD) (Liu *et al.*, 2004). Changes in complex carbohydrate metabolism and N-linked glycosylation were found in recent proteomic and glycoproteomic investigations of CSF from AD patients, suggesting that abnormal N-glycosylation may be a biomarker for the advancement of Alzheimer's disease. Important neuropathological proteins in Alzheimer's disease (AD) have been shown to have dysregulation of N-linked glycosylation. remarkably, Alzheimer's disease patients' brains show different glycosylation patterns in the amyloid precursor protein (APP), which undergoes proteolytic processing to produce amyloid-β (Aβ) peptides. These alterations in glycosylation cause APP to be more localized inside microsomal compartments and secrete less extracellularly, which affects the iron homeostasis of neurons. In the same way, aberrant glycosylation of tau protein, a microtubule-associated protein linked to Parkinson's disease (PD) and Alzheimer's disease (AD), contributes to its pathological aggregation. These results indicate that the molecular pathophysiology of neurodegenerative diseases is significantly influenced by abnormal N-linked glycosylation of neuronal proteins (Conroy *et al.*, 2014). The development and progression of Alzheimer's disease (AD) is linked to the dysregulation of *O*-glycosylation, which is essential for controlling tau protein function, especially in the form of *O*-GlcNAcylation (Iqbal *et al.*, 2014). In AD, tau protein, which keeps microtubules in neurons stable, is abnormally hyperphosphorylated, which causes neurofibrillary tangles to form. Tau phosphorylation is negatively regulated by *O*-GlcNAcylation; higher tau phosphorylation is linked to lower *O*-GlcNAcylation levels. Research has indicated that the brains of Alzheimer's disease patients have much lower amounts of *O*-GlcNAcylation than those of healthy controls. Increased tau phosphorylation and aggregation are correlated with this decrease (Liu *et al.*, 2004). Since the GlcNAc donor (UDP-GlcNAc) is a byproduct of the glucose-dependent hexosamine biosynthesis pathway, *O*-GlcNAcylation is susceptible to glucose metabolism. One characteristic of AD brains is impaired glucose metabolism, which decreases *O*-GlcNAcylation and promotes tau hyperphosphorylation (Iqbal *et al.*, 2014; Liu *et al.*, 2004). The regulation of glycosylation, especially *O*-GlcNAcylation, is essential for

preserving the homeostasis of neuronal proteins. The development and progression of Alzheimer's disease is directly influenced by abnormal glycosylation, particularly decreased *O*-GlcNAcylation of tau protein. This decrease is mostly caused by the AD brain's poor glucose metabolism, which reduces the amount of UDP-GlcNAc available for appropriate glycosylation.

Thus, tau is excessively phosphorylated, aggregates into neurofibrillary tangles, and eventually causes neuronal malfunction and death due to a disruption in the balance between phosphorylation and glycosylation. Restoring O-GlcNAcylation levels can decrease tau pathology, providing a possible therapeutic approach for delaying or halting the progression of AD, according to growing evidence from both human research and experimental models. In summary, glycosylation is a crucial modulator of tau function and brain health, and its dysregulation is a major molecular process in Alzheimer's disease. It is not merely a passive protein modification.

Parkinson's disease

Parkinson's disease (PD) is an advancing movement disorder due to the deterioration, damage and even death of nerve cells (neurons) particularly the dopaminergic neurons in specific brain regions. This results stiffness, tremor, difficulty in moving and poor balance. Prominently the neuron death in Parkinson's is observed mostly in substantia nigra of the brain, the dopamine deficit due to loss of neurons causes the symptoms as it is required for the smooth, purposeful movement (Jankovic, 2008). According to a study, 60-80% of dopamine producing cells are lost in the substantia nigra before even the symptoms emerge, patients struggle with basic functions such as walking and talking as the symptoms worsen (Beitz, 2014). Another study which was performed in 2018, showed that the aggregation of misfolded proteins such as α-synuclein and the progressive death of dopaminergic neurons are hallmarks of Parkinson's disease. Through *O*-glycosylation and *N*-glycosylation in particular, glycosylation has become a crucial regulator in these pathogenic pathways. Reversible and dynamically controlled, *O*-GlcNAcylation frequently serves as a sensor of stress and cellular nutritional status. It has been demonstrated that *O*-GlcNAcylation alters the behavior of α-synuclein in the setting of Parkinson's disease. In neural models, increased *O*-GlcNAcylation decreases cytotoxicity and prevents α-synuclein aggregation, a crucial step in the creation of Lewy bodies (Videira and Castro-Caldas, 2018). Blood serum has been found to exhibit changed *N*-glycosylation patterns in Parkinson's disease (PD), including decreased sialylation of complex glycans and increased core fucosylation (Váradi *et al.*, 2019). These alterations might be indicative of PD patients' systemic metabolic imbalance and inflammatory state. Furthermore, for proper function, proteins like α-dystroglycan that are involved in neuronal maintenance need to be precisely glycosylated.

The binding of α-dystroglycan to extracellular matrix components is hindered by hypoglycosylation, which may jeopardize neuronal integrity and contribute to neurodegeneration (Ohtsubo and Marth, 2006). In addition to affecting misfolded protein transport and degradation, aberrant N-glycosylation may exacerbate Parkinson's disease pathogenesis. In addition to reflecting systemic metabolic and inflammatory alterations, variations in *N*-glycosylation patterns seen in PD patients' serum may potentially act as non-invasive biomarkers for early disease identification and monitoring (Váradi *et al.*, 2019).

Osteoporosis

Osteoporosis can be described as the systemic degradation of bone structure leading to poor bone quality and rigidity. This is due to a reduction in bone mineral density making them more susceptible to fractures and it is a worldwide disease affecting millions from every country (Wang *et al.*, 2020). Osteopontin an extracellular matrix protein upon undergoing *N*-glycosylation has been found to activate the NF-κß in osteoblast and osteocyte leading to decrease in bone mass, hence, targeting the *N*-glycosylation pathway of osteopontin is a potential osteoporosis treatment. OGT decreases the activity of O-GlcNAcylated alkaline phosphatase (ALP),

hampering osteogenic differentiation of periodontal ligament cells whereas *O*-GlcNAc modification at N3646R site of SIRT1 promotes osteoprotective effect by stimulating osteoblast proliferation (Lin *et al.*, 2025). Advanced glycation end products (AGE) are also thought to be able to combat osteoporosis or its progression as AGE was seen to have induced osteoclast bone resorption in rats in a study by Miyata *et al.* Additionally, it was also observed that in development stage collagen modified with AGE directed proliferation and differentiation of osteoblastic cells (Hein, 2006). In a test conducted by Wang *et al.* (2020) they tested the protease Teriparatide (PTHG-1) and its glycosylation derivatives; in their test PTHG showed statistically significant improved ALP activity which promotes osteoblast differentiation. Thereby, making this protease a therapeutic target of interest in treating osteoporosis (Wang *et al.*, 2020). It has been also been seen that glycosylation is directly related to bone health as evidence has been found linking glycosylation in determining the diameter, orientation, organization, and resistance to mechanical stress of collagen fibril; over glycosylation of collagen results in lower diameter of collagen as well as lower cross link causing brittleness of the joint. Hyperglycemia is a state often prevalent in diabetic individuals and as suspected it was seen that higher AGEs had a direct correlation in decreased femur integrity, furthermore, hyperglycemia is often associated with increased risk of fractures of other bones such as hip, and foot backed by evidences of animal models with induced diabetes (Dominguez *et al.*, 2005).

CONCLUSION

In this review we have explored the various nuances of glycosylation in common age-related diseases, which become more prone with aging. Accumulating evidence demonstrates that aberrations in glycosylation patterns occur with aging and are significantly implicated in the pathogenesis of numerous age-related diseases, including cancer, diabetes, neurodegenerative disorders, cardiovascular diseases, and osteoporosis. It has been explored the dynamics in the pathophysiology of diseases and the dynamisms of glycosylation to indicate or cause the disease.

Within this review we have managed to find many glycosylation and glycan related biomarker indicative of the particular disease and also highlighted the aberrancy that leads to the disease.

With glycosylation being such an integral post translational modification of the body we hope to highlight the potential and new approaches that lie in identifying and even therapeutic application to such common age-related diseases.

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