Association of Protein Glycosylation Disorders with Human Diabetes Diseases

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Abstract
Glycosylation is a vital post-translational modification crucial for protein function, folding, and stability. Disorders of protein glycosylation have significant implications for human diseases, including diabetes mellitus. This review explores the biological mechanisms underpinning protein glycosylation, types of glycosylation disorders, and their clinical manifestations, focusing on their association with diabetes. Recent studies demonstrate shared molecular pathways between glycosylation disorders and diabetes pathophysiology, emphasizing oxidative stress, inflammation, and impaired insulin signaling. Understanding these links offers prospects for novel diagnostic strategies and therapeutic interventions. Continuous research into the molecular crosstalk between glycosylation and glucose metabolism is essential for developing precision medicine approaches to manage diabetes and related complications.

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1. Introduction

Glycosylation is the most frequent post-translational protein modification, where a specific glycan is added to a protein of interest. It has a critical part in pointing protein into appropriate compartments within our body and is an important structure that affects protein function in broader aspects. Most proteins need their sugars for proper folding (Keser *et al*., 2017) [1]. Moreover, since many cellular adhesion proteins, especially integrins, contain glycans, they play a critical role in the immune system as well. The symptoms that show glycosylation defect are quite varied. As glycosylation affecting the immune system, glycosylation disorders would make patients vulnerable to numerous infections. It changes the way in which proteins in immune cells work. The broadest group of glycosylation disorders are congenital disorders of glycosylation, with symptoms encompassing growth retardation, dysmorphic features, liver involvement, and more. Since genes being estimated to control glycosylation were way over 700, it was predicted that numerous rare genetic disorders would emerge as glycosylation was being studied in a more comprehensive approach (Naseri *et al*., 2020) [2]. It is only a decade ago that research on glycosylation and many decades on N- and O-linked protein glycosylation have now shown that protein secretion in yeast, a simple one-celled organism on the evolutionary scale, shows features close to those of typical mammalian cells, including humans. Given the biological process is similar, yeast can be used as a study model for the protein glycosylation disorder's emergence in humans. Additionally, it enables the development of drugs for more than 50% of proteins with potential glycosylation disorders on the market. Very few patients now have mammalian protein glycosylation disorders. This sign implied that many are going below the radar.

2. Overview of Protein Glycosylation

Protein glycosylation is the process of attaching carbohydrates to proteins. This co-translational or post-translational modification is the most prevalent modification. Glycans, or carbohydrate polymers, form covalent bonds with some asparagine, serine, or threonine residues on the protein forming glycoproteins. Unlike the amino acid sequence that encodes the information of its three-dimensional structure, the glycan sequence is not template-based, leading to the synthesis of a highly diverse and

heterogeneous range of glycoconjugates (Pasala *et al*., 2024) [3]. Although glycosylation remains a considerable enigma in cellular biology, it has been observed to play a particularly important role in several aspects of cell signaling, cell-cell adhesion, cellular recognition, and molecular stability, summing up to a role with significant implications on biology, health, and disease (E Sparks, 2012) [4].

Protein glycosylation is an essential biological process in which a broad range of N-glycan sequences and structures are added to specific asparagine residues in many proteins. This attachment significantly affects the efficiency of protein folding, distribution, and function throughout the body, making it vital to the biological clockwork of multicellular eucaryotic organisms. Due to its crucial clinical relevance, several studies of the past several decades were undertaken to dissect the fundamental phenomena of glycosylation, resulting in a basic understanding of the complex cellular pathways underlying this process. First, there is the synthesis of the glycosyl donor molecule in a cellular organelle, which requires the import of an activated precursor sugar. Second, the glycosylation of target proteins is catalyzed by a cellobioc-based enzyme cascade. This can occur under specific conditions as the target protein obtains the adequate conformation. Finally, the protein-glycan structure may undergo specific modifications before being considered fully mature, which might vary significantly between different organisms.

3. Types of Protein Glycosylation Disorders

Abnormality in the synthesis of glycoprotein can result in disorders known as protein hypoglycosylation diseases, numerous of which are inherited. The structure and functionality of glycans in glycoconjugates are determined by glycosyltransferases and glycosidases during or after their synthesis. The former catalyzes the sequential addition of sugar moieties from sugar donors to the hydroxyl group of acceptors (usually saccharides themselves), and the latter removes specific sugar residues. Different kinds of glycan linkages require different sets of enzymes and occur within distinct cellular compartments: N-glycan synthesis mainly takes place in the endoplasmic reticulum and golgi, while O-glycans are assembled primarily in the golgi. Because very diverse patterns of protein glycosylation are possible, a defect in a glycosylation step might have largely different consequences (E Sparks, 2012) [4]. Carbohydrate-deficient glycoprotein syndromes arising from this basic concept are heterogeneous with respect to genetic underpinning, glycoprotein targets and accompanying phenotypes. Despite this, genes whose mutation could give rise to a glycosylation-related disorder can be catalogued, and physicians who care for patients with them might find it useful to consider the safety of administering growth factors or neuropeptides that are glycosylated (Supraha Goreta *et al*., 2012) [5]. Miscues in counseling could be made as a result of misidentifying critical illness as drug abuse. Congenital Disorders of Glycosylation (CDG): At least partially as an effect of the concerted efforts of many working groups, there have been substantial advances in the understanding of the genetic and molecular bases of the congenital disorders of glycosylation (CDGs). An effort was expended on the classification of newly discovered subtypes that were indicative of a clinical phenotype as a result of comparative analysis of the phenotypes of patients with changes in the same metabolic pathway. Glycogen Storage Disorders (GSD): Glycogen metabolism is associated with a diverse set of disorders stemming from congenital or acquired conditions. In addition, the biosynthesis and catabolism of glycogen is related to the processes of glycosylation or deglycosylation of proteins. Glycosylation is absolutely critical for the functionality of numerous proteins, whose diversity in size, structure and function is huge. Despite the variety, some disorders occur commonly enough to warrant attention and are described. Other rare disorders: Some rare glycosylation-related disorders may not belong to the main classes of CDG or other known types of glycosylation defects, but their relevance for public health underlines the necessity of awareness or further research.

3.1. Congenital Disorders of Glycosylation (CDG)

Type 1 Congenital Disorders of Glycosylation (CDG) is a group of inherited metabolic disorders caused by defects in the glycosylation of glycoproteins. In normal cells, protein glycosylation occurs through multiple cytoplasmic reactions. Enzymes in the cytoplasm and endoplasmic reticulum (ER) biosynthesis of lipid-liked carbohydrates and the branching of carbohydrates, while others convert proteins to glycosylate carrier lipids. In the Golgi apparatus, glycosylation of proteins produced from translocation and folding happens, nonglycosylated proteins are degraded, and folded proteins are released. CDG occurs when these pathways break down and compounds created for the glycosylation of glycoproteins build up in cells. This disorder can be caused by mutations in the CDG genes. It is estimated that CDG affects between 1 in 20,000 and 1 in 40,000 births. (Supraha Goreta *et al*., 2012) [5] There are 33 different protein glycosylation enzyme activities described. There are more than 100 CDG gene types.

CDG gene mutations are recessive

Symptoms of patients with CDG, although individual, are heterogeneous and due to the functioning of many systems. Different systems can be affected in the same patient. In about half of CDG patients, neural symptoms are growing. Most neural symptoms are caused by malformations due to a lack of glycosylation to form correctly and neuroinisis. Other symptoms can be at different times, sweating, fatigue, vision problems, hormonal problems, diarrhea or constipation, language problems, skin cracks, abnormal eczema, easily breakable, easily disassembled HL, frequent infections. There are many subtypes of CDG which describe different types of defects in glycosylation enzymes. The name of each subtype is made by the first letter of the protein glycosylation enzyme its defect description. It also describes the number of the enzyme that affects this enzyme defect. Most of these subtypes have multiple genes hidden in genes. GCD treatments comprise enzymes that restore CDG cells as well as the treatment of disease-related problems. Treatments for individual growth are also a possible future.

3.2. Glycogen Storage Disorders (GSD)

Glycogen Storage Disorders (GSD) are a diverse group of genetic diseases causing systemic, yet disproportional glycogen accumulation in the liver and muscle, often accompanied by variable metabolic derangements in lipid and protein metabolism. Glycogen is a main storage form of glucose and is composed of branched structures of glucose monomers. Glycogen synthesis starts with the action of UDP-glucose pyrophosphorylase (UGP) that produces glucose-1-

phosphate (G1P). Subsequently, glucose-1-phosphate uridyltransferase (GALT) converts G1P to UDP-glucose, which serves as the glucosyl donor for glycogen synthesis following branching by the enzyme glycogen branching enzyme (GBE1). On the other hand, glycogen breakdown (i.e. glycogenolysis) is initiated by glycogen phosphorylase (PYGL), which sequentially removes glucose monomers from the non-reducing ends of the polysaccharide until four glucose residues remain on the branch point, which can only be removed by debranching enzyme (AGL).

Glycogen Storage Disorders (GSD) comprise a heterogeneous group of monogenic diseases caused by at least 21 different genetic defects in distinct enzyme deficiencies. Defects in the glucose-6-phosphatase catalytic subunit 1 gene (G6PC) cause GSD1 (von-Gierke Disease), which is a complex disease with a broad range of symptoms, including hepatomegaly, fasting hypoglycemia, hyperlipidemia and growth retardation. GSD1 is divided into GSD type 1A (GSD1A; MIM#232200), which is the classic form, representing 80-90% of GSD1 cases, and GSD type 1B (GSD1B; MIM#232220). Different from GSD1, most of GSD0 patients show a mild clinical presentation with fasting hypoglycemia and growth retardation. Glycogenin deficiency (GSD0a; MIM#611556) is a rare autosomal recessive disorder of glycogen metabolism, caused by mutations in the GYG1 or GYG2 gene. Glycogenin is the primer protein that catalyzes the self-glycosylation of its own tyrosine residues. It is proposed that insoluble hyperphosphorylated glycogen particles which can act as glucose buffer pile up in cells (Gümüş & Özen, 2023) [6]. On the contrary, it has been hypothesized that the lack of a primer protein, glycogenin, in GSD0a could cause reduction in the branching of glycogen, leading to the greater availability of limit dextrin for rapid degradation (Andjelkovic *et al*., 2022) [7].

3.3. Other Rare Glycosylation Disorders

Beside the well-determined categories of protein glycosylation disorders N-glycosylation and O-glycosylation defects and deficiencies in the metabolism of the sugar nucleotides disorders affected many other glycosylation pathways (Supraha Goreta *et al*., 2012) [5]. An emerging group of other rare CDGs due to defects in glycosylations of 2nd sugars of sugars itself of the macromolecule or defect of transfer of sugar onto macromolecule otherwise mostly lipid have in common a defect of transfer of sugar unit. CDG-IIc/CDG-IId: LAD II – LAD bloodneutrophils - fucose transfer onto carbohydrate, X-DIS syndrome - β-linked sugar transfers. N-linked fucose and xylose are unique since they are transferred onto the sugar part of N-linked glycans. XGALT deficiency is X-linked attention defect disorder with convulsion and autophagia. In COG7 and COG8 JS CdLS-like syndrome glycosylations of cargo proteins for secretion are altered with high-mannose glycoproteins. This makes these defects also different from all other established CDGs that are due to alterations of glycosylation in ER or Golgi both for Dol-P-P-, Asn-linked and Ser-Thr-linked sugars. Unique defects with ST3GAL3 and SLC35A1 genes lead to underglycosylation of mucin O-linked glycoproteins causing for example cataracts or developmental delay with neurological, movement, vision, and hearing problem. Rare defects that only affect glycosylation of select proteoglycans have also been identified among the glycosylation disorders possibly due to the fact that sugar transfer onto proteoglycans happens in a very specialized way. Pan-glycosylation defects have been identified in DPM1-9 small and hydrophobic glycoproteins that require DLO transport from Cytosol to ER for N-linked glycosylation. Kind-3 and Kind-4 gene defect lead to a pan-hypoglycosilation disorder with reduced glycosylation of Golgi-substrates. Kindlin-3 knock-out mammals Gaucher's-like syndrome and in these cellular accumulation of glycosphingolipids, Proteoglycans and LAMP-1 is observed. Rapid advance in high-throughput genome sequencing will certainly help in discovery of at least some of numerous other putatively existing CDGs. Clinical manifestations of some CDGs seem to suggest that unusual or so far not recognized glycosylation pathways are altered in these patients supporting the possible existence of many more CDGs. Even for well established N- or O-linked glycosylation, lipid glycosylation, and GPI-anchor glycosylation pathways many still not understood or only recently discovered enzymes that work in these pathways are expected as well as recognition of once again totally missed or discarded glycan roles.

4. Diabetes Mellitus: Types and Pathophysiology

Diabetes mellitus is a prevalent group of metabolic disease characterized by chronic hyperglycemia due to defects in insulin secretion, insulin action, or both. The chronic state of hyperglycemia can damage multiple organs over time, including the retina, nerves, kidneys, heart, and blood vessels. Diabetes can causally cause severe complications with multiple etiologies, primarily identified by persistent hyperglycemia. Early detection and control of this disorder can alleviate or prevent such complications. Diabetes is generally classified into four types, which are Type 1 diabetes mellitus (T1DM), Type 2 diabetes mellitus (T2DM), gestational diabetes, and diabetes from specific causes or genetic syndromes (Mahjabeen, 2018) [8]. Others are the Category of Diabetes. The Type 1 diabetes is characterized by severe immune-mediated beta-cell destruction of the pancreas. It usually presents in childhood but can occur at any age. Pierced fasting glucose values of 100 to 125 and glucose values of 140 to 199 two hours after the oral glucose tolerance test are considered pre-diabetes. Diabetes-wise complex metabolic disorders with hyperglycemia as major abnormalities are T2DM. The global epidemic of diabetes could lead to several million deaths in the next decade. There is a strong association of T2DM with obesity, largely due to increasing sedentary habits and altered food habits coupled with increasing industrial development (Crist, 2015) [9]. Mineral composition of drinking water plays a role in the expression of various clinical conditions.

4.1. Type 1 Diabetes

Type 1 diabetes (T1D) is characterized by insulin-dependence and represents approximately 5-10% of diabetes cases. T1D primarily results from T cell-driven autoimmune destruction of pancreatic β cells, normally causing an absolute insulin deficiency. People with T1D depend on the exogenous supply of insulin for life. T1D is also accompanied by an autoimmune response that affects another group of β cells in the pancreatic islets. Cumulative incidence increases with age until early adulthood, then plateauing (Du *et al*., 2022). T1D has substantial genetic predispositions, but environmental factors such as viral infections may also play significant roles. There is a wide spectrum of concurrent autoimmune and non-immune co-morbid conditions that contribute to the burden of diabetes, including mental and

chronic disorders. For children aged 14 years and under, it ranks third amongst the chronic disease causes that result in the highest number of hospitalizations. Pancreatic autoimmunity is ultimately triggered by proliferation of pathogenic T lymphocytes in the peripheral lymphoid organs, moving into the pancreas. T1D is a broadly diverse illness with significant intra- and inter-individual heterogeneity attributed to genetic heterogeneity, with over 100 non-human leukocyte antigen (HLA) loci implicated in diabetes risk and modifying the course of the disease after onset. However, there have been large increases in recent onsets of children under 5 years old showing minor gender and age in disparate global areas. Symptoms of T1D usually symptomize in children or young people, frequently under the age of 40 years, and are majority-started in adolescence or childhood, although the 'double peak' in commencement is commonly observed in puberty and early adulthood. Typically detected symptoms, polyuria, polydipsia and weight loss, appear quickly over a few weeks to months and approximately a third of individuals present with diabetic ketoacidosis. Given the critical need to lower glycated haemoglobin and prevent the progression of autoimmune responses, the potential to bestow durable motivating immune-modulatory therapies remains a major research focus for the scientific community.

4.2. Type 2 Diabetes

The prevalence of both obesity and associated T2D has sharply risen over the past 30 years despite a rise in physical activity awareness and an increase in recommendations to lower fat intake and raise carbohydrates intake. Recent evidence has added a new component to the long lasting blaming of obesity. Over-feeding results in accumulation of lipids in organs such as liver and muscle leading to onset of insulin resistance, and decline in insulin's ability to stimulate glucose uptake in both muscle and adipose tissue. Fuel excess continues to cause β-cells to secrete more insulin. When compensation is no longer possible, overt T2D develops because of two major pathophysiological changes. First, because of insulin resistance, tissue cannot take up glucose at a normal rate, and this combined with the inability of insulin to suppress hepatic glucose production, further heightens fasting hyperglycemia. Secondly, β-cells lose their ability to fine-adjust insulin to the prevailing degree of insulin resistance and end up secreting sub-maximal amounts of insulin which cannot overcome the existing insulin resistance, resulting in postprandial hyperglycemia. If not controlled by lifestyle changes, the combination of both fasting and postprandial hyperglycemia will acerbate the atherogenic dyslipidaemia, particularly hypertriglyceridemia.

The aim of this text is to summarize known aspects of the pathophysiology of "common" T2D as in most patients presenting with increased adiposity and to summarize the knowledge on the much less frequently encountered lean/non-obese "type 2 diabetes". Lean/non-obese patients can be roughly divided into people with a history of major underweight/leanness and subjects who, despite looking normal/lean, are the first-degree relatives of the obesity/diabetes families. This second cluster probably represents the pre-obesity, pre-diabetes phenotype, also known as "thrifty phenotype" and their offspring is particularly susceptible to overt diabetes and obesity on the background of even moderate weight gain, in particular if this occurs early in life. An overt indication of the impairment in β-cell glucose sensitivity of non-obese "type 2 diabetes" might be short-term adjustments in insulin secretion to perturbations of plasma glucose concentration, as experimental measures of early-phase insulin secretory responses and glucose effectiveness.

5. Link Between Protein Glycosylation Disorders and Diabetes

Glycosylation is a post-translational process initiated in the endoplasmic reticulum and finished in the Golgi apparatus. It is one among other modifications for proteins to reach their full functionality (Naseri *et al*., 2020) [2]. Protein glycosylation disorders may greatly affect the phenotype. It has been well proven that glycosylation and glucose metabolism are tightly linked. However, whether defects in protein glycosylation could contribute to the pathophysiology of diabetes is currently unknown. In the present paper, shared metabolic pathways and mechanisms are discussed that could help answer this question, or at least shed light on the pathophysiology of diabetes and other metabolic disorders (Keser *et al*., 2017) [1]. Upon glycosylation, most proteins have higher metabolic stability. Under metabolic stress, like during insulin resistance onset, a consistent upregulation of degradation processes occurs, which might lead to glycoprotein underglycosylation. This causes improper folding and a quality control system-triggered degradation for precise cargo transport of glycoproteins. Consequently, glycosylation disorders exacerbate both endoplasmic reticulum stress and oxidative burden. It has recently been demonstrated that endoplasmic reticulum stress contributes to the impairment in both insulin signaling and action.

A substantial research effort has been invested in searching for novel molecular trigger points for improving glycemic control mitigation of shared mechanisms underlying insulin resistance and secretion dysfunction might lead to earlier symptoms of diabetes, like a compromised cell migration during wound repair. An in-depth investigation of a single-cell model of congenital disorders of glycosylation type Ia has found that cells lacking an essential enzyme for N-glycosylation show lower activation of some pathways essential for proper cell migration. These findings have put forward the hypothesis that glycosylation disorders could significantly exacerbate common pathways underlying impaired glycemic control and diabetes. Clinical evidence is discussed that may support this view and call for both early diagnostics in glycemic control diseases based on the glycoproteomics approach and novel dual interventions targeting both glycosylation and classic long-known ways of diabetes management. Among other chronic diabetes complications, there are peripheral neuropathy and difficult wound healing due to both excessive inflammation and reduced immune responses and other concomitant impaired physiological systems. It is suggested that a fruitful field of research is to analyze common metabolic pathways underlying the onset of seemingly very different pathologies, such as metabolic and some congenital diseases.

5.1. Shared Pathways and Mechanisms

Recently, the shared pathways and mechanisms that connect protein glycosylation disorders with diabetes have attracted increasing interest. First, protein glycosylation aberrations can cause dysregulation of the signaling pathways that are critical to the metabolism of insulin and glucose homeostasis (Olapeju Bolanle & M. Palmer, 2022). Second, inflammation

has been recognized as an emerging common mechanism that contributes to both diseases. Metabolic dysregulation could trigger an inflammatory response, whereas chronic inflammatory states elicited by multiple stimuli has the potential to impair pancreatic β cell function and promote the development of autoimmune diabetes. Third, oxidative stress may be a critical factor that affects both protein glycosylation and diabetes. The increased level of oxidative stress in diabetes patients could exacerbate insulin resistance through promoting serine/threonine phosphorylation of IRS-1 and reducing tyrosine phosphorylation of IRS-1, thereby impairing insulin signal transduction (Naseri *et al*., 2020) [2]. The increasing evidence of the existence of the shared pathways and mechanisms between disorders of protein glycosylation and diabetes offers a broad horizon for exploring effective therapeutic targets. On the one hand, the emphasis on the common mechanisms may increase the potential for the identification of novel biomarkers for the prognosis and diagnosis of diseases and thus suggest combinatorial intervention strategies for novel therapeutic options. On the other hand, the necessity for a strategy to improve treatment outcomes through exploring integrated health systems and the development of novel research methods and tools with potential applications for both diseases. With the deep dive in research, researchers could decipher more on the overlaps in pathophysiology between the disorders, which may enable more favorable outcomes in therapeutic research and the personalized management of these complex and intractable diseases.

5.2. Clinical Manifestations

This subsection (5.2) of the manuscript focuses on clinical aspects of human diabetes diseases and protein glycosylation disorders. Protein glycosylation disorders may pose a secondary issue in diabetes due to overlapping clinical manifestations. The role of protein glycosylation disorders in clinical severity of metabolic symptoms of diabetes is overlooked. This subsection is designed to highlight the forgotten context as a platform for future studies or awareness. Glycosylation disorders elicit a wide array of symptoms, where some mimic diabetes disease (Naseri *et al*., 2020) [2]. Glycemic abnormalities, which characterize diabetes, may exacerbate properties of glycosylation disorders and vice versa. The overlapping clinical aspect can be a challenge in terms of diagnosis and therapeutic management. Thus, possible mechanisms of mutual interaction between human diabetes diseases and protein glycosylation disorders are summarized as a framework for clinical concerns. In the complex interplay between genetic background and environmental factor, multiple comorbidities are accumulated in a single body. Thus, it is rare to observe a patient having only one medical concern. Protein glycosylation disorders have been turning into highlighted issues in diverse disease backgrounds, including familiar diabetes. However, the role of protein glycosylation disorders in the clinical presentation and severity of diabetes diseases may be overlooked. Previously described metabolic consequences of glycosylation disorders are difficult enough to manage metaphorically compounded by diabetes. In addition, the deficiency of hormones associated with glycemic control is common in glycosylation disorders, which may potentiate specific diabetic conditions like insulin resistance. On the other hand, some metabolic manifestations of diabetes may exacerbate properties of glycosylation disorders with a high glycol-phenotype. Given the characteristics of each disorder, underdiagnosis of diabetes disease due to the misleading presentation may become a potential concern. Beyond metabolic disturbances, both disorders can cause multi-organ dysfunction. Some glycosylation disorders can mimic the growth failure seen in childhood-onset diabetes disease. Likewise, well-known late complications of diabetes disease overlap the organ dysfunction in glycoprotein disorders. As both diseases have common clinical signs, a comprehensive understanding of these shared symptoms is important for patient management, tailored intervention, and constructive suggestions. Hence, clinicians should be aware of these links in diverse patient populations to timely detect the overlapping sign and efficiently implement healthcare strategies, such as coordinate evaluation and comprehensive risk score to maximize diagnostic and therapeutic effects and improve clinical outcomes.

6. Diagnostic Approaches

For healthcare professionals, the recognition of protein glycosylation disorders and a better understanding of their association with human diseases such as diabetes are of paramount importance. Most glycosylation disorders are difficult to diagnose due to limits in advanced diagnostics. Accurate and timely diagnosis is critical to guide management and treatment of the patient and to provide genetic counselling to family members. Several tactics are employed in the recognition of glycosylation disorders, focusing on diagnostics underlining the correlation between protein glycosylation disorders and types of diabetes. Phenotypic abnormalities in glycosylation affect the clinical spectrum and can be disclosed by biochemical testing of body fluids or other cell components. Furthermore, standard biochemistry can screen for N-glycosylation and O-glycosylation in the bloodstream. The development of biomarkers and new glycosylation candidate genes playing a role in human diseases is creating the basis for scientific advancement in this area. Abnormal file intensity structures in the brain, liver, and kidneys may be revealed by imaging techniques. Besides the anatomical location, functional developmental abnormalities outside the nervous system may also be disclosed. Genetic tests are vital in providing proper diagnosis. Genetic tests can confirm diagnoses and uncover abnormal glycosylation - aspects that are not readily accomplished by any other means. Identifying the genetic mutation enables genetic counselling and possible pre-natal diagnosis for subsequent pregnancies. Many protein glycosylation will share presenting symptoms with diabetes, complicating diagnostics for the clinician. This means that prompt demands for the discovery of methods for the accurate and timely diagnosis of these disorders are to be made. It is recommended that healthcare professionals follow a specific action protocol when they suspect a glycosylation disorder. This will support the early differentiation between CDG and other disorders possibly seen in everyday medical practice. The listing recommends appropriate clinical, laboratory, and imaging tests that should be performed in a comprehensive search for molecular defects in glycosylation. Many aspects of protein glycosylation, and particularly the clinical consequences, reflection in diseases such as diabetes, remain undiscovered, so a concerted approach involving all medical disciplines and basic research is required to further advance diagnostics in this rapidly evolving field.

6.1. Laboratory Tests

Laboratory tests are a critical component of the diagnostic evaluation of protein glycosylation disorders affecting diabetes diseases. Various tests can detect abnormalities in glycosylation patterns and elucidate underlying metabolic derangements. This evaluation is essential to ascertain the efficacy and safety of these new monitoring methods. A substantial body of literature is dedicated to place these tests' validation into proper contexts and to foster meaningful linkages among researcher, clinicians, patients, payors, policy makers, and industry.

Serum protein electrophoresis, both agarose and capillary, to optimally detect protein glycosylation disorder. Testing of the glycation of specific amino acids in serum proteins, using results with HPLC-ESI-tandem mass spectrometry. Glycated albumin testing in serum, using new results with LC-MS methods; Further expansion of the use of mass spectrometry to all aspects of glycosilated proteins. The routine availability of automated high throughput new methods for glycosylation similarly allows for a facile extension of traditional measurements to broad glycosylation evaluation. Given added stimulus to improve the technology, the patient's needs and clinicians, bioscientists, and the biotechnology industry. And, it would been granted expectations that analytical technologies provide some bounds on rapid improvements (Wada, 2020). The following critiques of both papers, solely meant to assess the basic tenets and methods described in them, are intended to foster such a critical dialog. In addition, without a broad interdisciplinary communication, these new assays and any developed screening tests, will never achieve implementable relevance to better understanding, diagnosing, and patient management of glycosylation disorders. Such broader communication is therefore strongly encouraged between the many parties potentially interested and effected; including, of course, researchers, clinicians, and patients, but also, payors, policy makers, industry, and to encourage and facilitate broader interaction, any and all comments received will be made freely available.

6.2. Genetic Testing

Protein glycosylation disorders can occur through congenital conditions, lead to diseases like diabetes. Genetic testing forms the diagnosis of congenital disorders and a basis of assessing the risk for developing diabetes diseases. Personalized medicine is an opportunity based on genetic findings for treatment and therapy of glycosylation disorders. Genetic testing is more and more recognized as an essential aid in the detection of protein glycosylation disorders. While genetic testing in general does become more frequent due to its growing prominence as a tool in research, it also comes into focus of more medical attention. Using a whole-exome sequencing approach for diagnostics, a mutation was detected in the regulatory region of the ATP6V0A2 gene indicating that the idiopathic condition of the patient can be diagnosed as an occurrence of a complex hernia with visible features of AROA2 (Ding *et al*., 2021). Current developments on this topic are highlighted and illustrated using examples concerning the occurrence of defects of N- and O-glycosylation as single conditions, as well as in relation to more complex disorders like congenital disorders of glycosylation (CDG) or Costello syndrome. Understanding a patient's genetic disease is not just a crucial way of diagnosis, but more importantly it is an invaluable instrument for the development of personalized medicine, suggesting a therapy based on sound genetic findings. Personalized medicine, currently seen as a possible future treatment only for a limited number of maladies, can offer a wide range of options, from simple support measures based on a better understanding of the condition, to a genetic treatment of the very gene defect. To this end, ongoing research in genetic epidemiology has the potential to enhance the understanding of population-wide implications and risk factors. An important area within this path is the genetic testing of the whole genome, which offers a broad standardization of the patient's genetic background. Genetic counseling, as part of both contemporary medical approaches and age-old ethical heritage, subjects it to the interpretation of the ambiguous results of genetic tests (G. Carmichael *et al*., 2017) [14]. A more difficult goal is to see the establishment of a genetic language that allows for a clear and nuanced explanation of the causal mechanisms leading to the condition's physiological deviations in both protein and non-protein coding genes. At the moment, genetic testing platforms still face the most extensive applications in continuous diagnoses; however, they can be expected to become a key element increasing the understanding of the relationship between congenital disorders and late-onset conditions, such as diabetes.

7. Therapeutic Interventions

Glycosylation is a post-translational process in which the glycan moiety gets attached to the protein moiety of a glycoprotein. It plays a crucial role in the processing of the protein and maturity of the hybrid protein. Approximately 0.65% of proteins contain glycan. The complex procedure of glycosylation involving a sequence of events is considered as the most intricate post-translational adjustment to control protein folding and stability (Naseri *et al*., 2020) [2]. The protein-coding reading frame on mRNA instruct ribosomes through transcription of a polypeptide sequence. The hydrophobic stretches or signal peptides on polypeptide chains with peptide moieties perform the subunits of a protein molecule of the glycoprotein to be translocated into the endoplasmic memorization and transformed extracellular membrane or vesicle proteins with glycosylation. Although small components of blood provide various essential nutrients, the brain would be unlucky without glucose. Energy derived from glucose is decisive for brain function and is obtained directly through neuronal and astrocytic metabolism. This enables interactions, neurotransmission, and signal transduction between neurons that are vital to cognitive performance. Most of the functional imaging studies have suggested that glucose metabolism, as indicated by Cerebral metabolic rate of glucose (CMRglu), is affected by age. Although this increase in glucose metabolism is usually interpreted as an epiphenomenon implying an unknown physiological increase in neuronal activity, a change in the regulation of glucose metabolism may similarly impact glucose availability and uptake as glucose supply. Recently, at molecular pathways levels, few method experiments and pilot trials were conducted that specifically investigated the efficacy of diet and physical exercise on the progression of glucose metabolism. It has been suggested that this life-long change in metabolism would be severely mostly in ADP and completely at the very end of the MCI phase. However, data for glucose metabolism is counterintuitive to complex findings showing that brain hypometabolism usually is associated with cognitive decline and progression to AD.

7.1. Current Treatments

The majority of disorders of protein glycosylation are genetic diseases, and so much therapeutic effort has concentrated on supportive care, ameliorating particular symptoms, and optimizing the care of individuals with these conditions. Over the years, various therapies have been described, including dietary supplementation and enzyme replacement (Brasil *et al*., 2018) [15]. Many reviewers have suggested the need to balance new symptom-specific therapies with more general care plans. Some reports show that specific treatments may be helpful in the care of people with CDG or other problems of glycosylation. New or less well-known therapies merit wider attention, especially in view of the heterogeneity and possible rarity of the glycosylation disorders. Some CDGs can also be treated with therapy that uncovers the mechanisms of their pathophysiology. Others have symptoms that are potentially amenable to therapy that acts downstream of the glycosylation defect. There is a need for more pre-clinical investigation and controlled clinical studies of these and other novel therapies.

Gene Panels have identified new gene defects in apparently unusual patients, sometimes in unexpected disorder categories, for example, a patient with symptoms of a defect in GDP-mannose pyrophosphorylase has severe β-propeller protein-associated glycosylation disorder. Information exchanged can lead to better-informed treatment decisions, focused diagnoses, new biomarkers, and more precise elucidation of pathophysiology. A more detailed understanding of disease mechanisms ultimately leads to an increase in therapeutic opportunities and opens doors to personalized medicine. There are many possibilities for therapy in a CDG patient. Efforts must focus on finding effective solutions, starting therapy as early as possible and closely monitoring it. Patient cases highlight the critical importance of open and continued communication among all. There is a significant need for advanced clinician and patient education. Better training will lead to faster diagnosis and achieve better patient care plans. Treatments vary by individual patient, diagnosis, and symptom profile. Variations may be based on the availability of funds, ability, approach, geographic location, insurance coverage, treatment side effects, etc. The reviews reflect the widely different therapeutic approaches and paradigms currently used or underdeveloped. Any therapy depends on a solid team framework and continuous adjustment based on patient reactions.

7.2. Emerging Therapies

Tip of an Iceberg

The understanding about the importance of protein glycosylation disorders and their association with diabetes diseases is just a tip of an iceberg. Burgeoning research on screening and combating various types of glycosylation disorders arising in the processing and metabolism of proteins has now been ongoing and deepening for the past two decades. Moreover, with biotechnological advance and knowledge on both fundamental molecular processing of glycans, glycoproteins and glycolipids, there are exciting perspectives for the development of novel therapeutic approaches on glycosylation disorders and NIDDM (or type 2 DM as one of serious conditions). Along with the completion of the Human Genome Project, many hereditary glycosylation disorders whose causes are genetic mutations have been now clarified at DNA level. Therefore, there is already hope that gene therapies, at least so far for some of congenital disorders of glycosylation including I-cell disease and CDG syndromes, will become realistic (M. Sena *et al*., 2013) [16].

Ongoing clinical trials are evaluating the safety and efficacy of novel pharmacological drugs, mainly GKAs, as well as those considered chemical chaperones or proteasome inhibitors to improve the degradation of mutant proteins. As clearly illustrated by Figure 1, it may now be more visible emerging therapies are expected to tackle a huge diversity of glycosylation disorders. Nevertheless, regrettably the challenges for translations and developing promising remedies is enormous and regulatory approvals of gene and molecular therapies are extremely time-consuming (Sharma *et al*., 2024). Besides, extended multiphase human trials of innovative agents total a great fortune, far higher than established manufacturing and administrative costs for widespread distribution. When personalized medications are most promising for ethnic and individual hereditary variability, then to make and prescribe them could be too expensive. For these reasons, current text includes below only a tip of new insights on emerging molecular therapies to glycosylation disorders and their association with diabetes.

8. Future Directions in Research

Diabetes mellitus is one of the most common chronic endocrine illnesses in the current century, affecting more than 415 million people worldwide and that number is projected to escalate to 642 million individuals above the age of 19 by 2040. Additionally, around 193 million people remain undiagnosed. The glycemic load causes more than one million deaths yearly. The current paradigm touts that type 2 diabetes mellitus (T2DM) is an issue that emerges from a combination of environmental elements and a propagative genetic background. A sedentary lifestyle, general dietary habits, physical inactivity, and obesity are among the biggest causes of T2DM. A plethora of elements participate in the progression of this disease. Genetic factors are believed to be critical in unraveling the secrets of diabetes. Any genomic changes that hint at a predisposition to T2DM could act alone or in combination with other genomic or environmental perturbations. Nutrition is another feature that has a direct bearing on gene functionality. Recently, it was discovered that diet can influence gene expression.

The label of ‘‘genetic’’ could provide rising pressure on people and would lead to negative psychosocial implications. Diabetes is not simply an issue related to one genomic defect. Uprooting a holistic orientation in this respect could transcend understanding of the biochemical view of the disease. Efforts have been made to determine the sequence of the entire human genome to gain a comprehensive portrayal of protocinetics. Although bioinformatics created a facile platform for better understanding of the genome and the maintenance of great lakes of information pertaining to mutations, it is still astigmatic to shove aside the parameters of the biological system, operating at the karyological, mediological, proteomic, and glycoproteomic scales. There is some hope that advanced genomics and proteomics and merging these ventures could provide an effective means of surveying the variegated complexities of diabetes, akin to the variety of the biosphere. Meanwhile, innovative and individualistic soundings and broad interdisciplinary expertise could contribute to explicating the gene-environmental fury of diabetes and could provide optional

therapeutic. The role of interdisciplinary research teams could grossly extend patient-centric solutions in the management of these diseases
(Naseri *et al*., 2020) [2]. As urgent requirements in this regard, scholars have made suggestions for expanded epidemiological examination to establish the prevalence of glycosylation disorders and assess their impact upon diabetic populations, to foster a taxonomy of these disorders to discern their peculiarities and legitimize the application of efficient pharmaco-dietetic strategies, and to develop a petty confrontation solution to ascertain the beneficial applications of curative compounds to be instrumented by different bioavailability methods. Furthermore, adults with Type 2 diabetes mellitus (T2DM) could be submitted to diverse forms of advance genomic examination to detect mutations in the N-glycosylation genotype, and for those possessing inherited genetic predispositions biological vaccinations could be advised, or a specific form of personalize biscuit, drink, or some other food be prescribed. It is of paramount importance to widen the understanding of these diseases and to determine the most efficacious forms of intervention. Collaborative research endeavors are urged extensively. Public awareness concerning the manifestation of these diseases should be promoted to foster early diagnosis and the immediate application of suitable remedies. It is clear that glycosylation may be manipulated to prevent diseases or to modulate the immune phenotype during the course of diseases; for example, the glycoprotein produced by a pathogen might be manipulated post-translationally by the host. By innovative glycoengineering, it could be possible for patients to control their glycosylation patterns, which would lead to an altered immunophenotype and less debilitating disease. This creates a new dimension to the use of personalized medicine. Expertise in the medicinal field would be able to provide diabetic patients with dietetic guidelines to ameliorate their condition where indicated. Future research into these fields will be indispensable if cost-effective and rapid tests for glycoprotein glycosylation disorders are to be developed, as three are commercially available or FDA approved at present, none of which possess protection against interference in diabetic epidemiologic operations. An awareness of the growing health burden of glycosylation disorders should act as a incentive for all researchers to engage in multidisciplinary research endeavors and stimulation for innovative strategies to widen the comprehension of and to supply treatments for these diseases.

8. Conclusion

Protein glycosylation disorders constitute a critical yet underrecognized factor influencing the development and progression of diabetes mellitus. The convergence of molecular pathways involving oxidative stress, inflammation, and disrupted insulin signaling provides a mechanistic basis for the overlap between glycosylation defects and diabetes pathology. Advances in diagnostic techniques, such as mass spectrometry and genetic testing, facilitate early detection of glycosylation abnormalities, offering opportunities for personalized medicine interventions. Furthermore, emerging therapies targeting glycosylation pathways hold promise for improving diabetes management and mitigating associated complications. Future research should prioritize interdisciplinary approaches, integrating glycoproteomics, genomics, and clinical epidemiology to unravel the complex interplay between protein glycosylation and metabolic diseases. Public health initiatives must also focus on raising awareness about glycosylation disorders to promote early diagnosis and comprehensive care strategies. Overall, the intricate relationship between protein glycosylation and diabetes underscores the necessity for continued investigation to enhance therapeutic outcomes and patient quality of life.

9. References

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