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GLYCATION AND SKELETAL MUSCLE DYSFUNCTION IN DIABETES: INSIGHTS INTO MOLECULAR PATHWAYS AND THERAPEUTIC STRATEGIES

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ABSTRACT

Skeletal muscle, accounting for nearly 40% of body weight, plays a pivotal role not only in locomotion but also in metabolic and endocrine regulation. Muscle health and adaptability depend on progenitor cells, including satellite and non-satellite populations, which are compromised in disease states such as diabetes mellitus. Aging further exacerbates muscle decline, with sarcopenia contributing to frailty, disability, and mortality. A key molecular mechanism underlying skeletal muscle dysfunction is non-enzymatic glycation, leading to the formation of advanced glycation end-products (AGEs). These accumulate in structural proteins such as collagen and plasma proteins like albumin, disrupting their biological functions, impairing regeneration, and stiffening the extracellular matrix. AGEs also engage the receptor for advanced glycation end-products (RAGE), triggering oxidative stress, mitochondrial dysfunction, and inflammatory pathways, with implications for cancer, insulin resistance, and neuro-muscular degeneration. Therapeutic interventions targeting AGE formation and signaling include aminoguanidine, pyridoxamine, benfotiamine, statins, thiazolidinediones, and emerging agents like alagebrium and soluble RAGE. Natural antioxidants such as phenolic acids show potential, though their effects remain inconsistent. Clinical translation of anti-AGE strategies emphasizes patient-specific molecular profiles, precision medicine, and the integration of biomarkers to optimize treatment outcomes. This review underscores the importance of understanding glycation-mediated muscle dysfunction, highlights novel therapeutic strategies, and explores translational opportunities to bridge basic science with clinical practice, ultimately aiming to improve muscle health and reduce age- and diabetes-related complications.

KEYWORDS: Glycation, skeleton muscle dysfunction, Diabetes, Therapeutic strategies.

INTRODUCTION

Skeletal muscle has the ability to adjust to various stimuli, which is reflected in changes to its size, fiber type distribution, and metabolic processes. Muscle progenitor cells play a vital role in the maintenance and adaptability of skeletal muscle. The alterations in these progenitor cells are regulated by a complex interplay of internal and external factors, which both affect and are influenced by the health of skeletal muscle. Conditions like diabetes mellitus can adversely impact muscle health by diminishing the quantity and function of these progenitor cells. Therefore, targeting these progenitor cells—or specific subpopulations of them—may be crucial for addressing muscle health declines associated with disease progression. While satellite cells are the most well-known progenitor cells, recent research has uncovered various non-satellite progenitor populations that also contribute to the upkeep of skeletal muscle in both healthy and diseased states.[1][2]

Skeletal muscle, the largest organ in the body, comprises about 40% of total body weight. Its primary function is to contract and facilitate movement, but it also plays a significant metabolic role in the storage and supply of nutrients like glucose, lipids, and proteins.

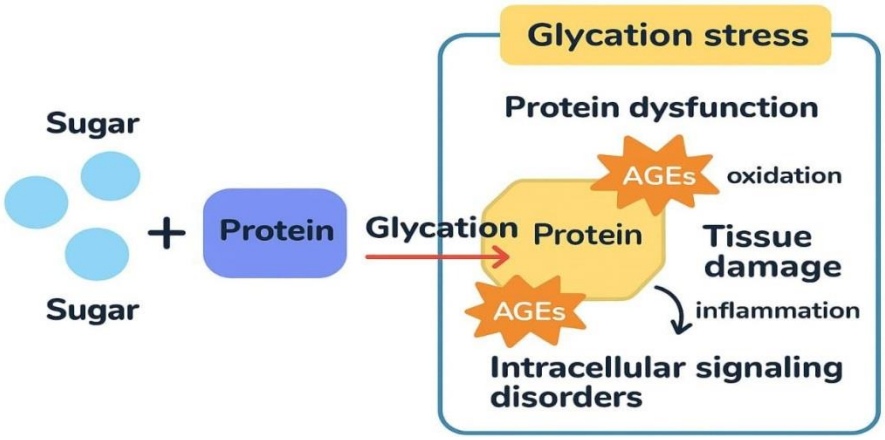
Additionally, skeletal muscle functions as a secretory organ, releasing cytokines and peptides known as myokines that act similarly to hormones. Thus, it is crucial for maintaining health not only in locomotion but also in metabolic and endocrine functions. After the age of 50, individuals experience an annual loss of approximately 1-2% in muscle mass and 1.5-5% in muscle strength.[3] This decline, termed sarcopenia, is linked to various negative outcomes, including frailty, disability, morbidity, and increased mortality.

Molecular therapeutics encompass a broad range of treatment strategies that leverage our understanding of molecular pathways, genetics, and biomarkers to develop targeted therapies for various diseases, including personalized medicine approaches and specific treatments for infectious diseases. These therapies may include monoclonal antibodies or small molecule inhibitors that focus on essential molecules or pathways involved in disease mechanisms. In infectious disease contexts, they aim to hinder pathogen entry and replication or facilitate vaccine development against specific antigens, such as those for SARS-CoV-2. Unlike conventional therapies, which often produce non-specific systemic effects, molecular therapeutics concentrate on addressing the root causes of diseases, thereby protecting healthy tissues and reducing adverse effects. The importance of molecular therapeutics lies in their potential to revolutionize customized medicine. By tailoring treatments to individual patients based on their distinct molecular profiles, these therapies enhance treatment effectiveness and minimize the risks of resistance and side effects. This approach has shown great promise in treating various conditions, particularly cancer, by specifically targeting molecular abnormalities in cancer cells, leading to significant improvements in survival, quality of life, and remission rates in previously untreatable cases. Beyond cancer, molecular therapeutics also offer hope for managing autoimmune disorders, rare genetic diseases, and infectious diseases, paving the way for precision medicine with personalized treatments for each patient.[4]

Mechanisms of Glycation in Skeletal Muscle

Throughout their lifespan, proteins encounter various modifying factors, including both enzymatic and non-enzymatic processes. Oxidation and glycation are significant non-enzymatic mechanisms that can impact tissues and accumulate over time, influencing metabolism. While these molecular and cellular changes may start off harmless, they can become harmful and pathogenic when they reach high levels. Blood plasma is particularly vulnerable to alterations,

being constantly exposed to various metabolites that can induce oxidative stress. For example, hyperglycemia can lead to non-enzymatic glycation of several proteins in the bloodstream, with albumin being the most notable.[5]

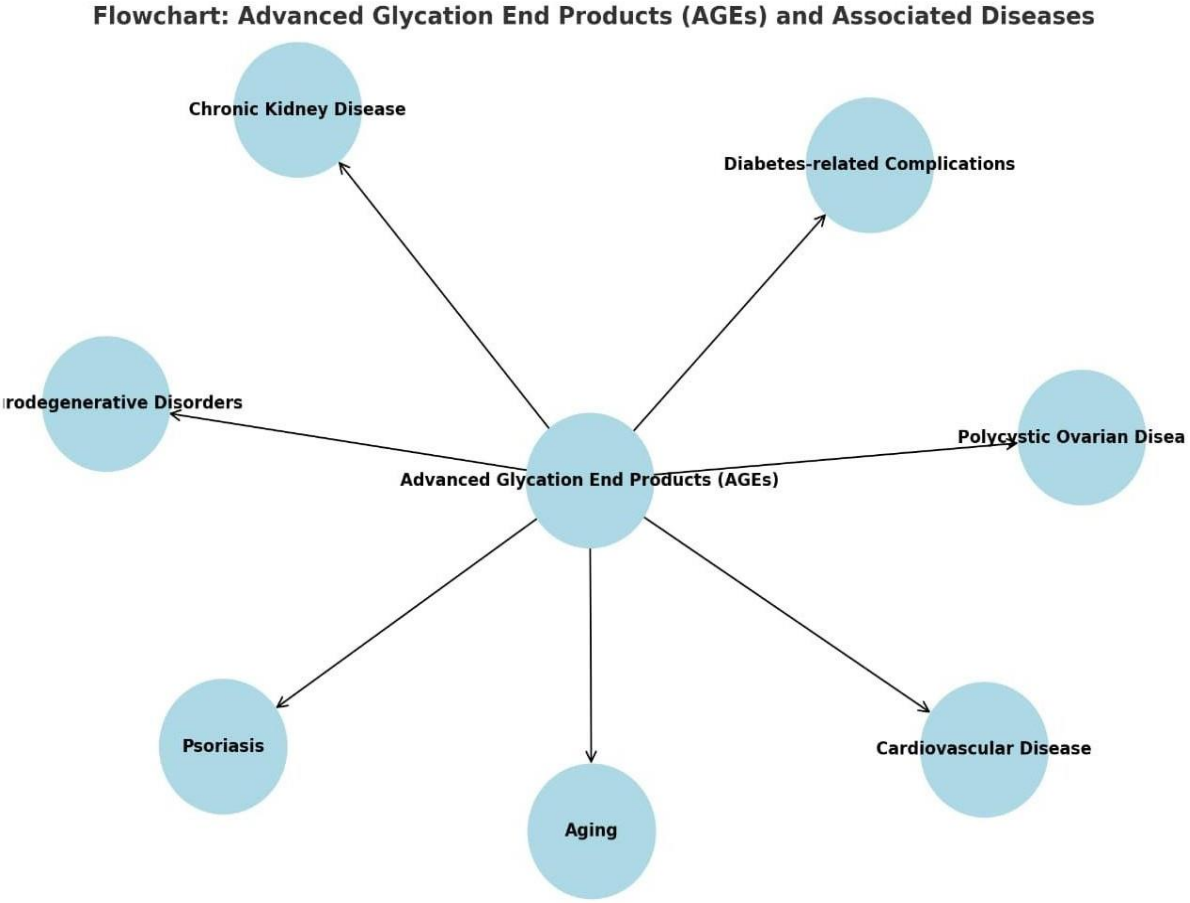


Albumin serves multiple functions, including regulating oncotic pressure, binding and transport capacities, and possessing antioxidant properties. Non-enzymatic glycation is one of the factors that can disrupt these diverse functions of albumin. This article briefly introduces albumin's properties and reviews how glycation affects its structure, biology, and physiological roles. It specifically details how glycation alters albumin's binding capabilities. Additionally, it addresses the clinical relevance of musculoskeletal injuries, which increase due to falls and other accidents in older adults. Age-related changes in skeletal muscle structure and function are significant contributors to these injuries.[6] The causes of muscle atrophy from aging, or sarcopenia, include declines in muscle strength, muscle fiber loss, increased intramuscular connective tissue, and disruptions in the muscle stem cell population, leading to weaker, stiffer, and less regenerative muscle.[7-12]

Muscular aging is multifaceted, involving both external and internal mechanisms that impact cellular components and the extracellular matrix (ECM). Advanced glycation end-products (AGEs), which result from the Maillard reaction, accumulate in musculoskeletal tissues as people age and are believed to contribute to sarcopenia.[13-16] AGEs tend to accumulate on long-lived ECM proteins like collagens, which are particularly susceptible to glycation due to their structure and the stochastic nature of their formation with glucose.[16] This non-enzymatic cross-linking by AGEs reduces collagen's degradation by matrix metalloproteinases, leading to collagen accumulation and stiffening of the normally flexible skeletal muscle ECM.[17] Few reviews focus specifically on the aging and cross-linking of sclerotic collagens in skeletal muscle, particularly regarding AGEs and sarcopenic decline,[18-23] and it has been a decade since the last thorough review on this topic.[24] Additionally, muscle-nerve interactions are crucial for muscle health, and this review discusses motor neurons to highlight the important role AGEs play at the aging motor endplate.

The review also examines glycated albumin as a biological marker for hyperglycemia and diabetes. Natural phenolic compounds, abundant antioxidants found in plants and significant in the human diet, are categorized into two types based on their phenolic ring structures: hydroxybenzoic acids (HBAs) and hydroxycinnamic acids (HCAs). HCAs, which are more prevalent than HBAs, include compounds like m-coumaric acid, ferulic acid, and caffeic acid. Caffeic acid and its esterified form, chlorogenic acid, are particularly abundant, making up a large portion of the HCA content in many fruits and coffee. These compounds are of interest due to their biological activities, including antioxidant, anti-

apoptotic, and anti-inflammatory effects. Research suggests that caffeic acid can protect against oxidative modification of low-density lipoproteins (LDL) and may help reduce coronary disease risks. However, the existing literature on the effects of phenolic acids in AGE formation is inconsistent and unclear.



Conversely, numerous studies indicate that caffeic acid can exhibit pro-oxidant activity in the presence of Cu (II), leading to LDL oxidation and lipid peroxidation, which can cause oxidative DNA damage.[25] These findings suggest that phenolic acids may have negative effects that warrant further investigation. This study aims to explore how dietary phenolic acids influence protein glycation and clarify their role in AGE-induced biological damage.[26]

Molecular Pathways Implicated in Skeletal Muscle Dysfunction

Cancer is a multifaceted disease, with only 5-10% attributed to hereditary factors, while nutrition, lifestyle, and environmental exposures account for 90-95% of cases. The rapid westernization of diets has led to increased consumption of advanced glycation end products (AGEs), which are a diverse group of compounds formed through non-enzymatic reactions between reducing sugars and the amino groups of proteins, lipids, and nucleic acids. Although AGEs are known to contribute to various chronic conditions such as diabetes, renal disease, cardiovascular issues, and aging, their role in cancer development has not been thoroughly investigated. The receptor for advanced glycation end products (RAGE) is involved in the interaction between tumor cells and their surrounding microenvironment, leading to processes such as hypoxia, mitochondrial dysfunction, endoplasmic reticulum stress, autophagy, epigenetic changes, and cancer stem cell characteristics.[27]

Effector	Mediator	Major pathway (S)
Myostatin/Activin	+Produced by skeleton muscles	Activin receptors (ACTRIA/B)-smade2/3-IMTOR
Insulin like - growth factor (IGF)	+Stimulated by meal - induced insulin + stimulation by exercise	IGFIR-P13-AKT-MTOR
Mammalian target rapamycin (MTOR)	induced by BCAA, HMB	Interacts with protein translation machinery to facilitate inhibition and elongation
Vitamin D	+Levelase increased by diet and sunlight	Vitamin D receptors - gene expression or repression in myogenic cells
Inflammatory cytosines (TNF -alpha IL-1)	-inhibited by follistutin +unregulated by illness injury	ACTRIIA/B -FOX O-USP cytosines receptors -NFKB, P38, JAK, E3 ligases

This highlights the significance of AGEs as a crucial factor in multiple facets of cancer development, although the precise molecular mechanisms remain to be elucidated. Therefore, this review aims to explore the pathological role of AGEs at the biomolecular level concerning tumorigenesis and cancer progression, focusing on the tumor microenvironment, invasion, and metastasis. Additionally, it discusses clinical data related to the AGE-RAGE pathway across various cancers and potential inhibitors.

Insulin resistance, characterized by impaired insulin sensitivity, is defined as reduced glucose clearance in skeletal muscle, insufficient suppression of glucose production by the liver, and decreased lipolysis in adipose tissue, or a combination of these factors affecting overall glucose disposal. It can occur independently of inadequate insulin secretion and is often a precursor to type 2 diabetes. The liver is crucial for transitioning from a fasting state to a fed state, as it rapidly shifts from producing glucose to storing it. In healthy individuals, adipose tissue responds well to insulin's effects on lipolysis, but this responsiveness is diminished in conditions of insulin resistance and type 2 diabetes, which are also marked by elevated levels of triglycerides and fatty acids in the bloodstream.[28]

Impact on Muscle Function and Performance

It is widely acknowledged that inadequate muscle function and physical performance are significant predictors of clinically relevant negative outcomes in older adults. With numerous options available for assessing muscle function and performance, clinicians often find it challenging to select an appropriate and validated tool for the older populations they serve. This paper presents an overview of various methods that can be applied in clinical settings, drawing on literature reviews conducted by members of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) working group focused on frailty and sarcopenia. Following these reviews, face-to-face meetings were held to discuss and refine the recommendations.

When choosing an assessment tool, several factors should be taken into account:[29] the purpose of the assessment (such as intervention, screening, or diagnosis);[30] characteristics of the patient population (including setting and functional ability);[31] the psychometric properties of the tool (including test-retest reliability, inter-rater reliability, responsiveness, and floor and ceiling effects);[32] the tool's applicability in clinical settings (considering overall cost, time required for the assessment, necessary training, equipment, and patient acceptance); and[33] its prognostic reliability for relevant clinical outcomes.

Based on these criteria and the evidence available, the expert group recommends using grip strength to assess muscle strength and employing the 4-meter gait speed test or the Short Physical Performance Battery to evaluate physical performance in clinical practice.

Elevated glucose levels lead to the formation of covalent adducts with plasma proteins through a non-enzymatic process known as glycation. Glycation reactions that produce advanced glycation end products (AGEs) are considered major contributors to various diabetic complications.[34] High glucose concentrations can cause glycation of numerous structural and functional proteins, including plasma proteins and collagen.[35] The non-enzymatic modification of plasma proteins like albumin, fibrinogen, and globulins can result in several harmful effects, such as altered drug binding in plasma, platelet activation, generation of free oxygen radicals, impaired fibrinolysis, and disruption of immune system regulation.

Therapeutic Strategies Targeting Glycation-Mediated Muscle Dysfunction

Pharmacological treatments for humans include aminoguanidine, pyridoxamine, benfotiamine, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, ALT-711 (alagebrium), and thiazolidinediones. Among the newest and most promising anti-AGE agents are statins, alagebrium, and thiazolidinediones. The involvement of advanced glycation end products (AGEs) in various diseases, along with new compounds that modify their effects, is currently being explored in preclinical studies, with plans for clinical evaluations of these newer anti-AGE drugs in the coming years. Other compounds with anti-AGE activity that are not yet available for clinical use include ALT-946, OPB-9195, tenilsetam, LR-90, TM2002, sRAGE, and PEDF.

AGEs are signaling proteins linked to various vascular and neurological complications in both diabetic and non-diabetic patients. They have been shown to be indicators of poor outcomes in diabetes management and surgical procedures. This has led to the development of pharmacological inhibitors aimed at mitigating the effects of AGEs, resulting in numerous preclinical and clinical studies. Clinical trials involving anti-AGE drugs have gradually emerged, and this review seeks to summarize the most significant findings.[36]

Table 2: Therapeutic strategies targeting glycation - Medicated muscle dysfunction.

Therapeutic strategies	Mechanisms of Action
Aminoguanidine	Blocked of AGE production
Alagebrium (ALT7- 11)	Cross - linked beaker of AGE
Azeliragon	Small molecule inhibitor of RAGE ligand binding to the RAGE extra - Cellular V- Domain
Anti-RAGE antibodies	Blocked of ligand binding to RAGE
Endogenous RAGE	RAGE ligand binding species that seq RAGE ligand and block their biology effects
Aldose reductase inhibitor (ARI)	Blocked of aldose reductase on glucose metabolism that contributes to AGE

New therapies, as well as modifications of existing treatments, may offer greater efficacy and tolerability compared to current options. However, as the range of treatments expands, selecting first-line therapies may become more challenging, with increased attention to risk-to-benefit ratios based on early safety data. Profiles of patients that include clinical, paraclinical, and biomarker information could assist in identifying disease subtypes and predicting responses to therapy, which would help tailor treatment choices. A comprehensive discussion of all ongoing studies is beyond the scope of this review, which will focus on recent therapeutic strategies being investigated in the context of multiple sclerosis.[37]

Clinical Implications and Translational Opportunities

Translationalties	Type of Research	Product of Research
T1	Clinical efficacy research	Proof that locally delivered antibiotic and beneficial
T2	Comparative - Effectiveness and oral health services research	Beneficial to treat periodontal patient
T3	Implementation on research	Diagnoses oral cancer at earlier stage

Clinical and translational medicine facilitates the connection between basic research and clinical treatment, fostering a cycle of mutual transformation. It translates the results of fundamental research into new technologies and methods for clinical application, thereby accelerating the advancement of clinical medicine. This field emphasizes a bench-to-bedside approach, prioritizing studies and clinical observations that generate relevant hypotheses and questions related to patients and diseases, which in turn guide investigations in cellular and molecular medicine.[38]

Persistently high plasma glucose levels are a significant cause of morbidity and mortality, with adverse effects varying across different cell types. Cells that express elevated levels of glucose transporter 1 (GLUT1), such as vascular endothelial cells, struggle to regulate intracellular glucose concentrations and are more vulnerable to damage caused by hyperglycemia. Renal mesangial cells that overexpress GLUT1 exhibit characteristics typical of diabetes, including activation of the polyol pathway and increased synthesis of extracellular matrix (ECM).[39] The intricate sequence of events leading to cellular dysfunction in response to high glucose levels is not yet fully understood, one of which is the formation of advanced glycation end products (AGEs).[40] Elevated glucose levels lead to the formation of covalent adducts with plasma proteins through a non-enzymatic process called glycation.

Key issues frequently discussed in this context include cultural differences between basic scientists and clinicians, resource limitations related to workforce and infrastructure, and the complexities of the regulatory environment.[41] Clinical research involves studying human subjects through methods such as surveys, health services research, or clinical trials. Meanwhile, translational research serves as a bridge between various research domains, linking their findings to one another and ultimately to the broader community.

CONCLUSION

Skeletal muscle is the largest organ in the human body and plays a crucial role in maintaining our health, functioning not only as part of the locomotor system but also in metabolic and endocrine processes. In recent decades, various studies have highlighted the impact of glycation stress on skeletal muscle dysfunctions, such as muscle atrophy, decreased contractile ability, and insulin resistance.[42]

Diabetes mellitus (DM) is the most prevalent endocrine disorder, currently affecting over 170 million people globally, with projections suggesting that this number could rise to over 365 million by 2030.[43] Type 2 DM is rapidly becoming one of the most significant health challenges of the 21st century, with expectations of an increase in related complications, including ischemic heart disease, stroke, neuropathy, retinopathy, and nephropathy.[44] In addition to β cell failure, insulin resistance in target tissues is a key factor in the development of type 2 DM, often linked to abnormal insulin secretion. Clinically, "insulin resistance" means that higher-than-normal levels of insulin are needed to keep blood sugar levels stable. On a cellular level, it refers to the insufficient strength of insulin signaling from the insulin receptor to the pathways involved in various metabolic and growth-related.[45][46]

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