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Review Article

Biomarkers in diabetes mellitus: Advancements, challenges, and future perspectives

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ABSTRACT

Diabetes mellitus (DM) represents a multifaceted metabolic disorder characterized by hyperglycemia and dysregulated metabolism, stemming from a myriad of factors including insulin insufficiency and impaired glucose utilization. Its complications span a broad spectrum, encompassing vascular diseases and neurological impairments. While some risk factors are beyond control, such as age and genetics, others like diet and exercise offer avenues for risk mitigation. This review delineates the distinct pathogenic processes of the two primary forms of DM, type 1 and type 2, emphasizing their differential etiologies and epidemiological trends. Biomarkers play a pivotal role in the diagnosis and management of DM, offering insights into disease progression, beta-cell function, and therapeutic responses. Traditional biomarkers, alongside predictive markers like autoantibodies, facilitate early detection and intervention strategies. Moreover, advancements in high-throughput "-omics" technologies have unraveled the molecular intricacies underlying disease progression, heralding the discovery of potential serum protein biomarkers in type 1 DM and unveiling promising candidates such as unmethylated insulin DNA and dysregulated microRNAs. In type 2 DM, traditional biomarkers like fructosamine, glycated albumin, and 1,5-anhydroglucitol offer valuable tools for glycemic control assessment, with emerging biomarkers like zinc-alpha-2-glycoprotein holding promise for diabetic nephropathy detection. Despite challenges, ongoing research endeavors hold promise for refining these biomarkers and enhancing diabetes management strategies, thus improving patient outcomes.

1. Introduction

Diabetes mellitus (DM) presents as a multifaceted metabolic disorder marked by high blood sugar levels and disrupted metabolic processes. Its origins lie in various factors including inadequate insulin production, either due to genetic predisposition or acquired deficiencies, impaired insulin function, and insufficient glucose utilization alongside excessive glucose production. The etiology of diabetes is intricate, often involving a combination of immunological and metabolic dysfunctions as primary contributors[1]. Several risk factors have been associated with the development of long-term complications related to diabetes mellitus. These include dietary habits, obesity, smoking, alcohol consumption, physical activity levels, hormonal imbalances, certain medical treatments, viral infections, vascular or cardiovascular diseases, atherosclerosis, heart conditions, stroke, kidney disease, eye disorders, nerve damage, cognitive impairment, susceptibility to infections and wounds, cancer, musculoskeletal disorders, pregnancy-related complications, emotional stressors, insulin shock, diabetic ketoacidosis, and hyperosmolar hyperglycemic nonketotic state. Uncontrollable risk factors such as age and genetic

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predisposition cannot be altered by individuals. However, adopting healthier lifestyle choices such as improved dietary habits and increased physical activity can help mitigate controllable risk factors, thus reducing the likelihood of developing diabetes.[2] Type 2 diabetes mellitus, previously associated mainly with adults, is now affecting children too, highlighting a concerning trend. This type of diabetes arises when the body's cells fail to respond adequately to insulin. While it traditionally appeared in adulthood, the growing prevalence of obesity among young people has contributed to its emergence in children and adolescents. This shift emphasizes the influence of lifestyle factors like diet and exercise on the disease's onset. Moreover, genetic and metabolic irregularities contribute to the insufficient response to insulin observed in children with type 2 diabetes mellitus.[3,4] Various types of diabetes encompass conditions that disrupt glucose tolerance, genetic disorders, and abnormalities in metabolism and mitochondria. Over the past two decades, diabetes has surged in prevalence worldwide, emerging as one of the most widespread health conditions globally. Recent reports from esteemed health organizations like the International Diabetes Federation (IDF) and the World Health Organization (WHO) highlight diabetes as the sixth leading cause of death worldwide, indicating an epidemic if left unaddressed, akin to other major illnesses such as cancer and cardiovascular diseases. Diabetes mellitus (DM) is not exclusive to humans; it also affects certain animals like dogs and cats. Among the different types of diabetes, type 2 DM is notably more common than type 1 DM.[5] Type 2 diabetes mellitus exhibits a higher prevalence in developing nations like Pakistan compared to developed countries. Assessing the exact incidence of this disease in any country, whether developed or developing, poses challenges. It is evident that the prevalence of diabetes is increasing exponentially due to a myriad of factors, including genetic predisposition, environmental influences, and metabolic abnormalities.[6] A biomarker refers to a biological molecule present in blood, bodily fluids, or tissue, indicating a normal or abnormal process, condition, or disease. Biomarkers play a crucial role in monitoring the body's response to therapy when treating a disease or condition.[7] Example Hemoglobin A1c (HbA1c) is an example of a biomarker in the context of diabetes or pre-diabetes. It serves as a valuable indicator of long-term glycemic control, reflecting hyperglycemia over several weeks preceding the test. Persistently elevated HbA1c levels are associated with an increased risk of diabetic complications such as retinopathy, nephropathy, and cardiovascular disease. By monitoring HbA1c levels, healthcare providers can assess the effectiveness of diabetes management strategies and tailor treatment plans to minimize the risk of complications.[8]

2. Traditional Biomarkers Involved in T1DM

2.1. Serum diagnostic markers

2.1.1. Glucose-related biomarkers:

Glucose-related biomarkers play a crucial role in diagnosing diabetes, especially in cases where hyperglycemia is not evident. Diagnosis typically involves two consecutive positive results from glucose-related tests. For individuals exhibiting typical hyperglycemia symptoms or hyperglycemic crises, a random plasma glucose level exceeding 200 mg/dL indicates diabetes. Common blood-based assays used for glucose assessment include the oral glucose tolerance test (OGTT), fasting plasma glucose (FPG), and hemoglobin A1c (HbA1c), which reflects non-enzymatic glycation. Each test has specific criteria, sensitivity, and specificity for diabetes diagnosis. According to the American Diabetes Association (ADA), diabetes can be diagnosed if the 2-hour plasma glucose level during OGTT exceeds 200 mg/dL, FPG is equal to or greater than 126 mg/dL, or HbA1c levels reach or exceed 6.5%. While HbA1c provides an indirect measure of average blood glucose over the past two to three months, reflecting chronic hyperglycemia, it is less sensitive than FPG and OGTT for diagnosing diabetes. Due to potential variability, repeat testing is often necessary, especially for FPG and OGTT results.[9]

2.2. Predictive biomarkers for the development of type 1 diabetes (T1D)

T1D are crucial for understanding the asymptomatic phase preceding clinical manifestation. This silent period, characterized by variable durations of β-cell destruction, offers insights into disease etiology and progression. Studying this phase is essential for identifying predictive or prognostic biomarkers that could aid in early detection and intervention strategies for T1D.[10]

2.2.1. Autoantibodies

Autoantibodies (AAbs) serve not only as diagnostic markers but also as the primary method for predicting the development of Type 1 Diabetes (T1D). Despite their significance, the exact role of islet AAbs in T1D pathogenesis remains uncertain. They are believed to indicate immune activation against specific autoantigens in insulin-producing β-cells, rather than being the direct cause of T1D. Commonly detected AAbs, including ICA, GADA, IAA, IA-2A, and ZnT8A, are highly sensitive and specific markers for T1D diagnosis and prognosis. Screening high-risk individuals, such as first-degree relatives of T1D patients or those with high-risk HLA genotypes, for these AAbs is recommended to assess T1D risk. Seroconversion to two or more AAbs substantially increases the likelihood of developing clinical T1D over time. However, the rate of progression varies based on multiple factors, including

AAb phenotype, genotype, and age. Children with multiple AAbs have a significantly higher risk of developing T1D compared to those with a single AAb. Although AAbs are valuable predictors, they have limitations, such as being recommended only for specific populations and not tracking disease progression accurately. Consequently, there is a growing need for additional biomarkers to predict disease stages, guide intervention timing, and monitor therapeutic responses effectively. In recent years, efforts have focused on leveraging new technologies to discover novel serum biomarkers for these purposes.[11–16]

3. Potential Novel Biomarkers

Due to their ability to capture molecular changes across the entire system as a disease progress, high-throughput "-omics" technologies have emerged as powerful platforms for discovering new biomarker candidates. These technologies often utilize various samples, including primary cells, immortalized cells, mouse islets, and human pancreatic tissues, ranging from single islet sections to small amounts of islets obtained through laser microdissection or sorted cell sources. Although several of these investigations may not directly focus on serum, they play a crucial role in pinpointing potential candidates for serum biomarkers and shedding light on the dysregulated pathways associated with the disease. Through the application of these techniques, novel biomarker candidates may be identified, aiding in the assessment of β-cell mass, dysfunction, and extent of β-cell death in serum, as well as ongoing immune responses.[17,18]

3.1. Protein biomarkers

3.1.1. Serum protein biomarkers

The identification of serum proteins as potential biomarkers for diseases is a widely explored area in biomarker research, with proteomics investigations offering promising avenues for improving disease prognosis and prediction. However, analyzing the serum proteome poses significant challenges due to its complexity and wide dynamic range, compounded by the low abundance of potential biomarkers originating from disease-specific tissues like pancreatic β-cells. Overcoming these obstacles requires sophisticated proteomics technologies and experimental designs, along with statistical considerations. Current proteomics workflows typically involve two phases: a discovery phase utilizing bottom-up proteomics to identify biomarker candidates, followed by a verification phase using targeted proteomics analysis or immunoassays. Although strategies such as removing high-abundance proteins or employing extensive serum protein fractionation are utilized to improve the detection of low-abundance candidate biomarkers, the discovery of serum protein biomarkers unique to type 1 diabetes mellitus (T1DM) remains in its early stages. This is attributed in part to the progressive loss of β-cells and the inherent challenges in identifying specific biomarkers amidst the disease's heterogeneity and individual variations. Additionally, inconsistencies among studies and the absence of largely accepted protein biomarkers highlight the necessity for more comprehensive profiling using advanced technologies and refined experimental designs. These efforts are essential for uncovering specific biomarkers that exhibit significant changes during the continuation of the disease, thereby enhancing our understanding and management of T1DM.[19–21] In Table 1 Different types of protein biomarkers with their function are summarized.

Table 1: Different types of protein biomarkers with their function

Gene Symbol	Protein name	Function
ADIPOQ	Adiponectin	Glucose homeostasis
APOA4	Apolipoprotein A-IV	Leukocyte adhesion
APOC4	Apolipoprotein C-IV	Viral infection
AZGP1	a-2-glycoprotein 1 (zinc)	Lipid mobilization activity
BTD	Biotinidase	Biotinidase activity
C3	Complement C3b	Innate immunity, complement activation
C4A	Complement C4-A	Innate immunity, complement activation
CLU	Clusterin	Cytoprotective capability
KNG1	Kininogen 1 isoform 1	Innate immunity, DC activation
LUM	Lumican	Extracellular matrix structural constituent
SERPINA6	Corticosteroid-binding protein	Correlate to insulin deficiency or response
SERPINF2	Alpha-2-antiplasmin	Serine protease inhibitor
TTR	transthyretin	Involve in β-cell stimulus-secretion coupling

3.1.2. Nucleic acid biomarkers

The existence of small circulating DNA fragments in serum, present in low concentrations, has been well-documented, with origins traced back to apoptosis, necrosis, or active secretion pathways. These nucleic acids carry the potential to encapsulate genetic and epigenetic changes associated with the development and advancement of diseases. Recently, there has been growing interest in circulating unmethylated insulin DNA as a promising biomarker for the early detection of β-cell death in type

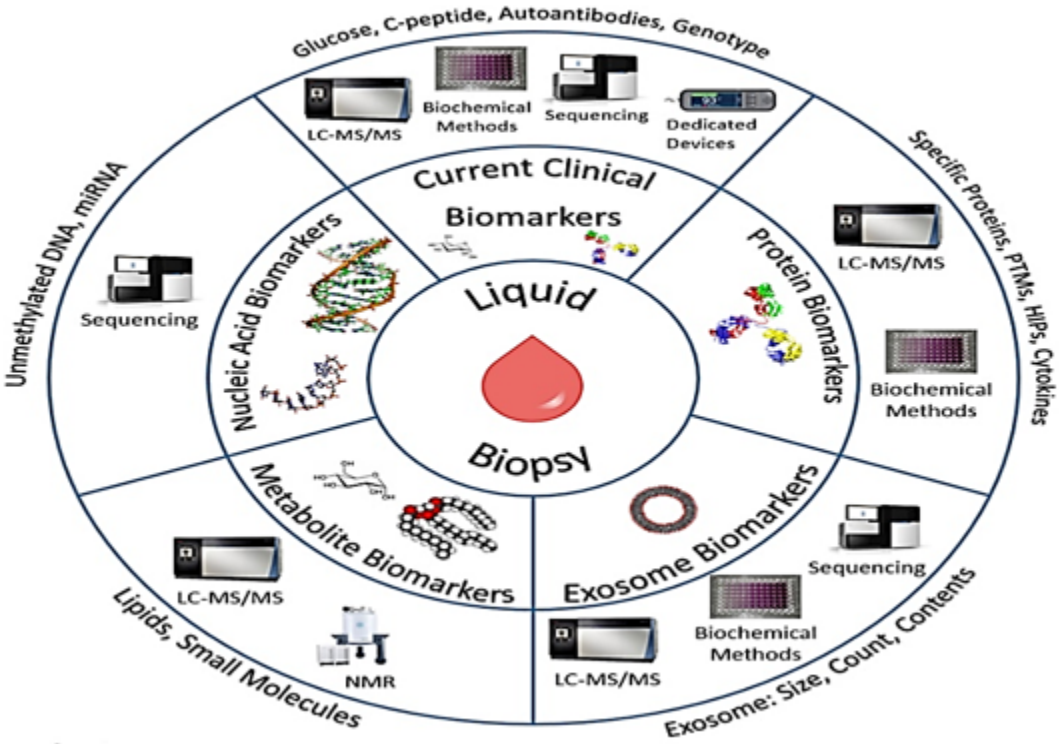

Figure 1: Different types of biomarkers with diagnostic tool

1 diabetes mellitus (T1DM). Specific cytosine-guanine (CpG) sites within the insulin gene remain unmethylated in pancreatic β-cells but undergo methylation in most other tissues. Consequently, as T1DM progresses, fragments of unmethylated insulin DNA, resulting from the death of β-cells, are released into the bloodstream, where they become detectable, serving as indicators of β-cell death extent. Advanced techniques such as methylation-specific real-time PCR and sequencing have proven sensitive and specific for quantifying unmethylated insulin DNA in blood. Additionally, transcriptomic profiles in T1DM have been investigated in various blood-derived samples, revealing type 1 interferon (IFN)-related signatures detectable before the onset of T1DM-associated autoantibodies. Furthermore, dysregulated microRNAs (miRNAs), which play novel roles in T1DM pathogenesis and β-cell activity regulation, have been identified in serum samples from T1DM-affected individuals. While elevations in serum miR-375 have been linked to β-cell damage, its limited contribution from β-cells raises concerns about its utility in reflecting β-cell loss. Nevertheless, miR-21, miR-24, miR-148a, miR-181a-5p, and miR-210–5p have shown consistent elevation in blood from T1DM subjects across multiple studies. Moreover, exosome-derived blood samples have been explored for miRNA assessment, given their ability to transfer miRNAs during cell-to-cell contact.[22–25]

4. Traditional Biomarkers Involved in T2DM

A. Fructosamine: Fructosamine (FA) encompasses stable ketoamines formed when circulating serum proteins undergo glycation without enzymatic involvement. These glycation products, termed advanced glycation end products (AGEs), are irreversible conjugates formed through complex processes. Elevated serum FA levels in patients with type 2 diabetes mellitus (T2DM) correlate with higher blood glucose levels, making it a potential marker for glycemic distinction between individuals with and without diabetes. Unlike HbA1c, which reflects long-term glucose changes due to the extended lifespan of hemoglobin, FA mirrors glucose levels over a period of 2 to 3 weeks. Additionally, FA tests are simpler and more cost-effective than HbA1c assays. Colorimetric-based techniques are widely utilized for fructosamine (FA) evaluation due to their rapidity, technical simplicity, affordability, and potential for automation. Robust correlations between FA and HbA1c in type 2 diabetes mellitus (T2DM) underscore its sensitivity and specificity for diabetes differentiation. Moreover, FA testing does not require fasting, enhancing its practicality in clinical settings. Elevated FA levels are linked to heightened vascular complications and trajectory in T2DM, emphasizing its prognostic value. Although FA assays can assist in T2DM detection and monitoring, they are typically employed alongside conventional markers.

Salivary FA levels have promising non-invasive biomarker for preoperative hyperglycemia; however, further research is warranted for clinical validation. Future investigations should delve into the association between FA and diabetic complications to gauge its efficacy as a risk indicator in diagnosed individuals.[26,27]

B. Glycated Albumin: Elevated blood glucose levels can lead to increased glycation of human serum albumin, the primary protein circulating in the blood. Glycation occurs when reducing sugars, such as glucose, bind to amine groups in proteins without the involvement of enzymes. This process forms an intermediate product, which undergoes rearrangement to produce a more stable derivative known as an Amadori product or ketoamine. Glycated albumin (GA) is formed as a result of this process and serves as an intermediate-term biomarker of glycemic management, reflecting hyperglycemic conditions. The GA ratio, in combination with albumin half-life, can be utilized to assess glycemic control. Furthermore, the formation of advanced glycation end products (AGEs) resulting from the glycation of albumin and other serum proteins is closely linked to the development and advancement of diabetic complications. Consequently, the assessment of both fructosamine (FA) and glycated albumin (GA) levels can offer significant insights not just into glycemic status for the screening and diagnosis of type 2 diabetes mellitus (T2DM) but also for evaluating its progression.[28]

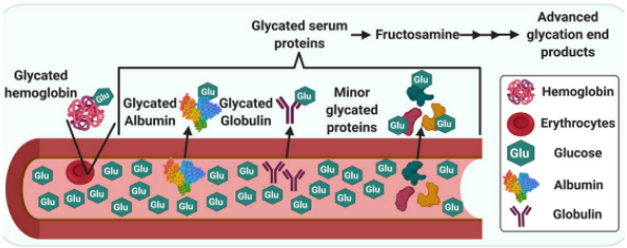

Figure 2: Conversation of glycated hemoglobin to advance glycation end products

C. 1,5;Anhydroglucitol: 1,5-Anhydroglucitol (1,5-AHG), also known as 1-deoxyglucose, is a six-carbon monosaccharide and a major polyol present in the human body. It was first isolated from the Polygala amara plant in 1888, and its structure was elucidated in 1943. Due to its metabolic stability and predominantly dietary origin, 1,5-AHG maintains steady-state tissue concentrations, facilitated by its renal reabsorption and lack of degradation pathway. Consequently, its levels in various bodily fluids exhibit stability and are closely associated with blood glucose levels.

Recognized as a promising biomarker for diabetes, the correlation between 1,5-AHG and blood glucose prompted the development of the GlycoMark® enzymatic kit, which has received approval from the US FDA for assessing short-

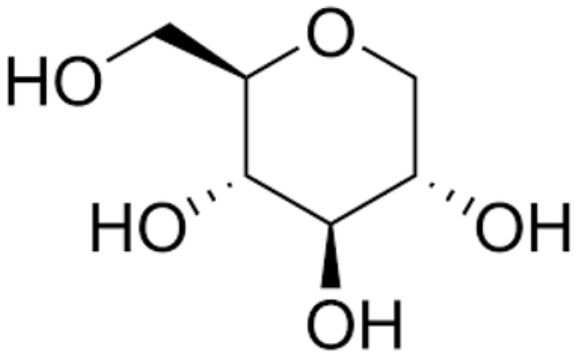

Figure 3: Structure of 1,5; Anhydroglucitol

term glycemic control. Under normoglycemic conditions, almost all of the 1,5-anhydroglucitol (1,5-AHG) is reabsorbed in the kidneys, competing with glucose for sodium-glucose linked transporters (SGLT), thereby maintaining detectable concentrations in blood and saliva. However, during hyperglycemia, the excess glucose saturates these transporters, leading to reduced serum and saliva levels of 1,5-AHG. Studies employing techniques such as GC-MS, HPLC-MS, or the GlycoMark® assay have indicated that less concentrations of 1,5-AHG reflect inadequate glycemic control over the preceding 1-2 weeks. Its utilization as a marker for glycemic control offers more benefits than conventional test, exhibiting a stronger correlation with elevated levels of glycated hemoglobin (HbA1c) than fasting plasma glucose (FPG). The integration of fasting plasma glucose (FPG) with 1,5-anhydroglucitol (1,5-AHG) enhances the early identification of type 2 diabetes mellitus (T2DM) and diminishes the requirement for oral glucose tolerance tests (OGTT), consequently reducing expenses. Moreover, 1,5-AHG differentiates between individuals with similar levels of glycated hemoglobin (HbA1c) but differing levels of glycemic control, underscoring its effectiveness in evaluating postprandial variability in comparison to glycated albumin (GA).[29,30]

D. Zinc-alpha-2-glycoprotein (ZAG): Adipokines have important role in the pathophysiology of diabetes mellitus, particularly in the context of obesity. Among these adipokines, zinc-alpha-2-glycoprotein (ZAGP) has emerged as a newly discovered adipokine that exhibits positive correlation with adiponectin expression in adipose tissue. ZAGP is implicated in lipolysis, functioning as a lipid-mobilizing factor, thus influencing metabolic processes. ZAG, the protein encoded by ZAGP, possesses multifaceted roles in various physiological processes, likes fertilization and lipid mobilization. Its structural similarity to the major histocompatibility complex (MHC) class I antigen-presenting molecule suggests potential involvement in

immune responses. Despite its diverse functions, ZAG is increasingly recognized as a biomarker for several carcinomas, although its precise physiological and pathological roles remain elusive. In diabetic conditions, ZAG exhibits altered expression patterns, particularly in diabetic nephropathy (DN). Elevated urine ZAG levels have been specifically observed in diabetic patients, suggesting its potential utility as a biomarker for diabetic nephropathy. Immunohistochemical analyses have revealed predominant ZAG expression in the tubules of the human kidney. Furthermore, studies have indicated that decreased ZAGP levels are associated with the onset of lipotoxicity, supported by its positive association with adiponectin and negative association with tumor necrosis factor-alpha (TNF-α), implying a potential anti-inflammatory role of ZAGP. Moreover, ZAGP levels exhibit significant correlations with markers of renal function and glycemic control, such as creatinine (Cr), HbA1c, urinary albumin-to-creatinine ratio (UACR), and estimated glomerular filtration rate (eGFR). Decreased ZAGP levels have been observed to coincide with disease progression in diabetic nephropathy, highlighting its potential as a negative biomarker for disease severity. Additionally, diabetic patients with high HbA1c levels have been found to exhibit significantly lower ZAGP levels, suggesting a possible link between reduced ZAGP levels, impaired lipolysis, and lipid accumulation, leading to lipotoxicity and exacerbation of diabetes-related complication0.[31–36]

5. Conclusion

In conclusion, diabetes mellitus presents a formidable challenge in healthcare due to its intricate pathogenesis and diverse complications. With type 1 and type 2 diabetes characterized by distinct etiologies, personalized approaches to diagnosis and management are imperative. Biomarkers play a pivotal role in deciphering the complexities of diabetes, offering valuable insights into disease progression and treatment efficacy. While traditional biomarkers remain fundamental in diagnosis and monitoring, the emergence of high-throughput "-omics" technologies opens new horizons for biomarker discovery. In type 1 diabetes, advancements in proteomics, transcriptomics, and circulating DNA analysis shed light on the molecular mechanisms underlying β-cell dysfunction, enabling early intervention strategies. Similarly, in type 2 diabetes, biomarkers such as fructosamine, glycated albumin, and 1,5-anhydroglucitol, along with emerging candidates like zinc-alpha-2-glycoprotein, provide crucial information on glycemic control and diabetic complications. Through continued research and validation efforts, these biomarkers hold promise for enhancing diagnostic accuracy and improving therapeutic outcomes, ultimately contributing to more effective management of diabetes mellitus and alleviating its burden on global healthcare systems.

6. Source of Funding

None.

7. Conflict of Interest

None.

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