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Biomarker-Guided Drug Discovery for Diabetes Mellitus and Its Cardiometabolic Comorbidities

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ABSTRACT

Diabetes mellitus nowadays is one of the most prominent issues in global health and is, together with other obesity, hypertension, dyslipidemia, and cardiovascular diseases, a part of the cardiometabolic syndromes. Bio marker guided drug discovery and development is a potential way to enhance therapeutic precision, drug response

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prediction, and target refinement. With the advances in genomics, proteomics, metabolomics, and bioinformatics, the incorporation of biomarkers in the early stages of drug development is much easier, increasing the success rates of candidate validation and lowering candidate attrition. New and developing biomarkers, such as those of insulin resistance and β-cell dysfunction, as well as oxidative stress and inflammation, are of great interest. This approach will stimulate the further development of stratified medicine, will improve the effectiveness of therapeutic interventions, and fulfills the available gaps in the treatment of the diabetes and its cardiometabolic complications.

Key Words: Diabetes Mellitus, Biomarkers, Co-morbidities, Drug, Discovery

Introduction

Diabetes represents a growing global health concern, placing a considerable burden on healthcare systems. Current projections estimate that by 2030, approximately 366 million individuals will be affected worldwide, with the majority being over 65 years of age. Sedentary lifestyles and declining levels of regular physical activity are recognized as major contributors to the rising prevalence of obesity, particularly in the United States, which in turn fuels the incidence of diabetes. Broadly, diabetes is categorized into two forms: type 1 diabetes mellitus (insulin-dependent, IDDM) and type 2 diabetes mellitus (non-insulin dependent, NIDDM). Type 1 diabetes mellitus is primarily linked to autoimmune and genetic factors, whereas type 2 diabetes mellitus is often associated with persistent insulin resistance, although both forms may share overlapping pathogenic features.

Rising diabetic incidence correlates strongly with sedentary lifestyle patterns, diminished physical engagement, and escalating obesity rates. Pakistani epidemiological research conducted in 1994 examined age-stratified diabetes distribution, revealing elevated disease susceptibility among individuals aged 25 years and above within Sindh province and rural Baluchistan regions, encompassing study populations of 967 and 570 participants respectively (Wild, Roglic et al. 2004). Comorbidity manifestations, characterized by concurrent multiple pathological conditions within individual patients, represent prevalent phenomena particularly among geriatric populations (Weiss, Boyd et al. 2007). Clinical investigations demonstrate approximately 75% of diabetic patients' exhibit dual or multiple

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concurrent disease states, substantially complicating therapeutic management protocols beyond inherent treatment complexities (Kerr, Heisler et al. 2007).

Epidemiological evidence establishes obesity as a predominant diabetic risk determinant, with duration of excessive weight burden demonstrating greater predictive significance for disease development than absolute body mass index measurements (Abdullah, Wolfe et al. 2012).

Diabetes mellitus is broadly classified into two categories: type 1 and type 2, distinguished primarily by their relationship to insulin dependence. Type 2 diabetes, which accounts for nearly 80% of all cases, is characterized by insulin resistance rather than absolute insulin deficiency. Over time, however, sustained insulin resistance can place excessive stress on pancreatic β-cells, leading to compensatory hyperplasia and eventual β-cell failure. This progression can result in insulin deficiency, effectively resembling type 1 diabetes. In contrast, type 1 diabetes is less common, affecting approximately 5–10% of patients, and is defined by autoimmune-mediated destruction of β-cells. Strong genetic associations, particularly with HLA class II alleles, have been observed in type 1 diabetes mellitus, highlighting the role of immune dysregulation. Indeed, auto antibodies are present in nearly 90% of individuals with type 1 diabetes, while the remaining cases are often linked to hereditary β-cell dysfunction. Interestingly, some patients with type 2 diabetes also exhibit increased autoantibody levels, suggesting overlapping mechanisms in the pathogenesis of both forms of the disease. (Maiese, Chong et al. 2011).

Diabetes mellitus precipitates extensive pathological sequelae that manifest as concurrent comorbid conditions. Clinical manifestations encompass cardiovascular pathology, ocular retinal complications, digestive system disturbances, and musculoskeletal alongside pulmonary dysfunction. Associated morbidities frequently incorporate neuropsychiatric disturbances including depressive episodes, affective alterations, and neurocognitive impairment (Schram, Sep et al. 2014). Additional concurrent pathological processes involve hepatic functional compromise, hematological platelet abnormalities, and nephropathic disease progression (Maiese, Chong et al. 2011).A variety of biomarkers have been identified that aid in the diagnosis of diabetes, assessment of disease progression, and

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evaluation of the risk or presence of complications and co-morbidities. Among the most widely used is hemoglobin A1c (HbA1c), along with several modified biomolecules generated through oxidative stress and non-enzymatic glycation under chronic hyperglycemia. These altered molecules contribute to vascular injury and are recognized as risk factors for the development of vascular complications (Maiese et al., 2011). Biomarkers function as indicators of physiological status: values within the normal range reflect normal biological processes, whereas abnormal values often signal the presence of pathological changes. Beyond diagnosis, biomarkers are also valuable in therapeutic monitoring, as they can provide insight into the efficacy of pharmacological interventions (Atkinson Jr et al., 2001). In this sense, biomarkers act as "molecular sentinels," offering critical information about disease presence, severity, and associated co-morbid conditions. Figure 1 illustrates some of the commonly reported biomarkers relevant to diabetes.

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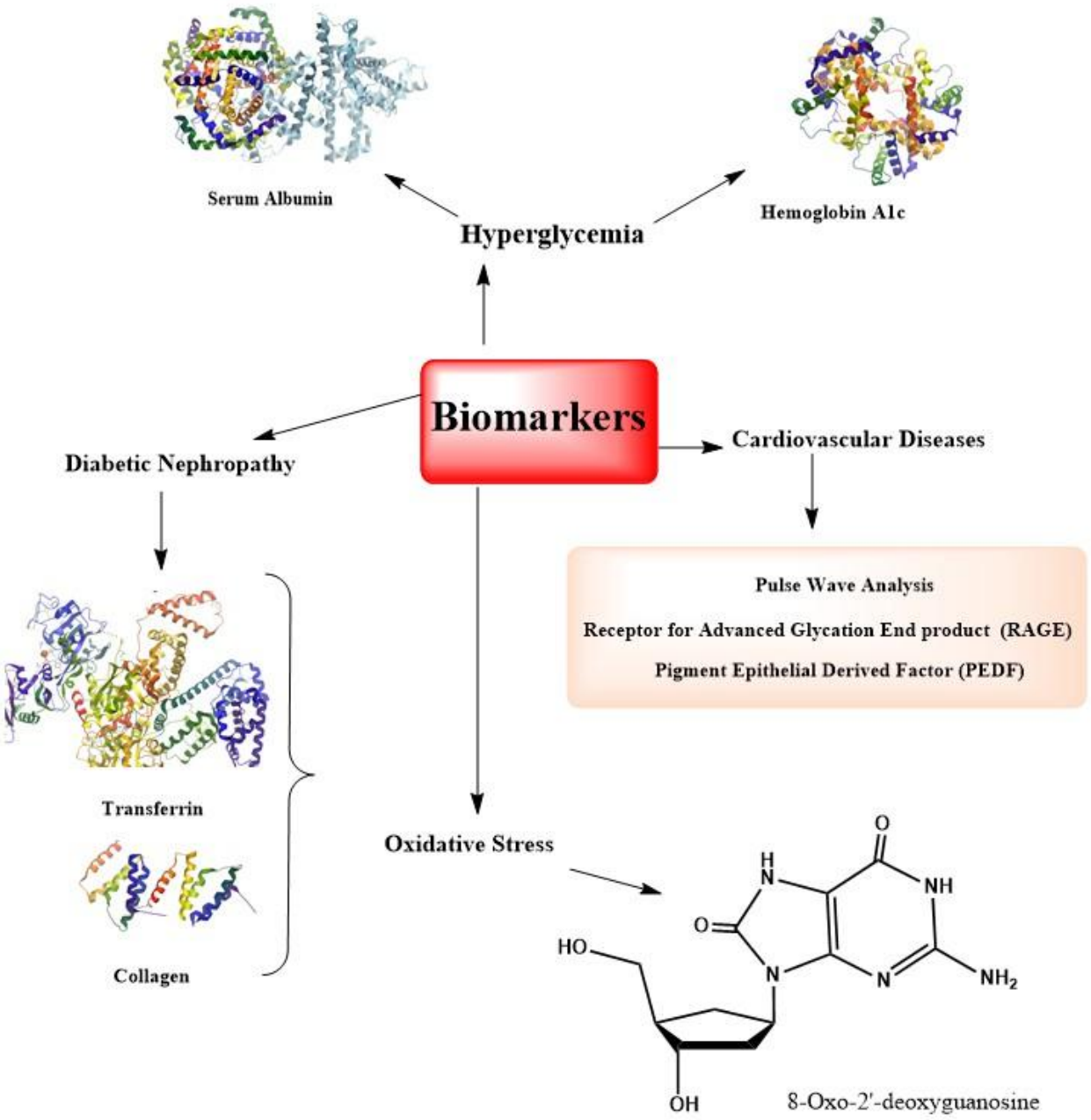


Figure 1. Scheme Of Different Biomarkers Associated With Their Specific Diseases

Biomarkers and their Therapeutic Roles in Diabetes and Co-Morbidities

A. Biomarkers of Hyperglycemia

Hemoglobin A1c (Hb A1c)

Glycated haemoglobin A1c emerged as a glycaemic control indicator in 1976 through initial clinical investigations. A preliminary study examined five patients

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presenting with inadequately managed diabetes prior to hospital admission, subsequently demonstrating clinical improvement. Initial assessment revealed mean fasting plasma glucose concentrations of 343 mg/dl among study participants. Following achievement of optimal diabetic management, plasma glucose values decreased substantially to 84 mg/dl. Concurrent improvements occurred in postprandial carbohydrate tolerance and urinary glucose excretion under optimal therapeutic conditions. Baseline HbA1c measurements averaged 9.8 percent across participants, declining to 5.8 percent following optimal glycaemic control, establishing a robust positive correlation between circulating glucose concentrations and HbA1c levels (Koenig, Peterson et al. 1976).

The underlying biochemical processes involve multiple haemoglobin variants circulating within human blood. Three principal haemoglobin forms exist: HbA, HbA2, and HbF, with HbA representing standard adult haemoglobin, further subdivided into HbA0 and HbA1 variants comprising approximately 94% and 5% of total haemoglobin respectively. Throughout the 120-day erythrocyte lifespan, glucose molecules preferentially conjugate with HbA1, particularly the HbA1c fraction representing the predominant subtype. Consequently, plasma glucose concentrations demonstrate direct proportionality with HbA1c levels, establishing its clinical utility as a diagnostic marker for monitoring elevated blood glucose associated with diabetic pathophysiology (Sen, Chakraborty et al. 2016).

Glycated Albumin Level

Individuals with diabetes mellitus demonstrate elevated oxidative stress burden, facilitating molecular damage to essential biomolecules including proteins, lipids, and nucleic acids through reactive metabolite formation during lipid and carbohydrate oxidative processes. These pathological changes result from dyslipidaemic conditions and persistent hyperglycaemic states characteristic of diabetic patients. Concurrent non-enzymatic albumin glycation processes generate advanced glycation end products (AGEs) through spontaneous protein modification reactions. Glycated albumin serves as a valuable diabetic biomarker, frequently demonstrating superior clinical utility compared to HbA1c measurements (Sen, Chakraborty et al. 2016).

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B. Biomarkers for Cardiovascular Diseases:

Receptor for Advanced Glycation End product (RAGE)

The receptor for advanced glycation end products (RAGE) represents a crucial biomarker associated with vascular pathology development across diabetic and non-diabetic populations following comprehensive research investigations. Endothelial tissue demonstrates RAGE expression, serving as the primary cellular interface through which AGEs mediate their pathophysiological effects. Experimental studies utilizing diabetic rodent models revealed that AGE-RAGE binding interactions precipitate increased vascular wall permeability alongside enhanced thrombotic potential within diabetic specimens. Administration of genetically modified soluble AGE receptors at predetermined therapeutic concentrations successfully attenuated this pathological hyperpermeability response (Wautier, Zoukourian et al. 1996).Critically, investigating advanced glycation end product influences on immunological dysfunction and intercellular communication networks among adipose-localized immune populations, including tissue-resident macrophages (ATMs), CD3-positive lymphocytes, regulatory T cells, and fat-storing adipocytes, represents a fundamental research priority (Kavitha et al., 2025).

2. Pulse Wave Analysis

Pulse wave analysis (PWA) is a valuable tool for assessing arterial stiffness, a parameter strongly associated with diabetes-related cardiovascular complications. The pulse wave analysis with wave analysis can assess advancement of heart injuries and diagnose early critically ill patients (Carrara et al., 2024). Pulse wave velocity, a key measure derived from PWA, often becomes abnormal during the early stages of vascular dysfunction, manifesting in conditions such as hypertension, renal disease, and connective tissue disorders. Evidence from clinical studies has shown that individuals with type 1 diabetes exhibit significantly greater arterial stiffness, or reduced vascular elasticity, compared with healthy non-diabetic controls. Given its ability to detect subclinical changes in vascular function, PWA serves as a promising biomarker for identifying vascular complications that commonly accompany diabetes (Lyons and Basu 2012).

Pigment Epithelial Derived Factor (PEDF)

Pigment epithelium-derived factor (PEDF) functions as a significant anti-angiogenic

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and antioxidant mediator. Clinical observations demonstrate elevated PEDF concentrations among diabetic patients presenting with disease-related complications. Investigational research examined potential associations between PEDF expression and diabetic pathological manifestations through comparative analysis across three distinct patient cohorts: diabetic individuals with microvascular complications (n=52), diabetic patients without comorbid conditions (n=71), and healthy control subjects (n=31). Enzyme-linked immunosorbent assay (ELISA) quantified PEDF concentrations across all study populations. Results demonstrated substantially elevated PEDF levels within the diabetic microvascular complication cohort, measuring 8.2 µg/ ml—approximately double the concentrations observed in both uncomplicated diabetic patients and non-diabetic control populations. Notably, PEDF values remained comparable between diabetic patients without complications and healthy control subjects. These findings indicate PEDF elevation occur specifically following microvascular complication development in diabetic populations, establishing its potential utility as a diagnostic biomarker for vascular complication assessment in diabetes mellitus.

(Jenkins, Zhang et al. 2007).

C. Biomarkers of Diabetic Nephropathy

Albumin

Diabetes mellitus exerts pathological effects on renal structures through direct impact on glomerular endothelium, tubular epithelial cells, podocytes, and mesangial cellular components. Albumin represents a crucial hepatically-synthesized plasma protein that undergoes minimal glomerular filtration under physiological conditions, with filtered quantities subsequently reabsorbed within tubular segments. Albuminuria, classified as microalbuminuria (30-300 mg/day) or macroalbuminuria (exceeding 300 mg/day) based on urinary albumin concentrations, constitutes a significant indicator of diabetes-related renal impairment. Urinary albumin excretion occurs when glomerular filtration mechanisms fail or tubular reabsorption processes become compromised, explaining the pathophysiological basis of albuminuria in diabetic contexts where nephropathy affects both glomerular and tubular epithelial structures. Baseline albuminuria measurements function as critical biomarkers for end-stage renal disease progression (Cohen-Bucay and Viswanathan 2012).

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Additionally, albuminuria represents an important predictive marker for cardiovascular disease development among patients presenting with nephropathy and type 2 diabetes mellitus (De Zeeuw, Remuzzi et al. 2004). High physical activity among prediabetic patients inhibit process of occurring diabetes with albuminaria according to (Xiong et al., 2024)

Transferrin

Transferrin constitutes a plasma protein analogous to albumin, yet possesses greater molecular dimensions and undergoes more extensive glomerular filtration compared to albumin under normal physiological conditions. Certain diabetic individuals demonstrate urinary transferrin presence despite absence of concurrent albuminuria. Clinical observations indicate that urinary transferrin excretion results from diffuse glomerular lesions associated with diabetic nephropathy pathology (Cohen-Bucay and Viswanathan 2012).While additional research evidence remains necessary to establish transferrin's definitive role as a diabetic nephropathy biomarker, experimental investigations demonstrate that hyperglycaemic management in diabetic patients can effectively reduce urinary transferrin elimination, supporting its potential utility as a nephropathy indicator (Uwaezuoke 2017).

Biomarkers of Oxidative Stress

8-Oxo-7, 8-dihydro-2'-deoxyguanosine represents a significant oxidative stress biomarker that serves as an indicator of DNA oxidative damage (Dang et al., 2025). This nucleotide derivative appears initially in urinary excretion following genomic injury, maintaining its structural integrity without metabolic degradation. Clinical applications utilize this molecular marker for diabetic neuropathy identification within diabetic patient populations.

Therapeutic Roles of Biomarkers

Biomarkers should be linked to the disease mechanism in some manner, and it is only after a thorough and accurate understanding of the underlying pathology that biomarkers can be effectively utilized for developing treatment strategies. Subsequently, these treatments target the underlying pathology, either reducing or completely halting it, leading to a return to normal levels of biomarkers. The meticulous monitoring of these markers can provide valuable insights into the efficacy of a specific treatment regimen. Consequently, biomarkers can offer valuable

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information for the development of new medications to treat diseases, as biomarkers can only be established when a comprehensive understanding of the disease process is achieved. However, biomarkers do not always accurately reflect the pathogenic pathways in question. They may be loosely connected or may be the result of biochemical and molecular alterations that occur as a consequence of a disease process that has been identified (Colburn 2003).

Given that biomarkers have been shown to be useful for detecting the progression of a progressive disease like diabetes and its associated complications, it is reasonable to assume that they could also be employed to assess the therapeutic effects of medications in the context of diabetes and its consequences. By defining biomarkers as indicators of either a normal physiological phenomenon occurring within a normal range or the presence of morbidities occurring within abnormal ranges, as well as the effects of pharmaceutical drugs, the Biomarkers Definitions Working Group further specifies that biomarkers can serve as indicators of whether a treatment is successful or not (Group, Atkinson Jr et al. 2001).

Insulin-induced hypoglycemia can contribute to reduced HbA1c levels, which otherwise rise as a result of excessive hemoglobin glycation under hyperglycemic conditions. If left uncontrolled, persistent hyperglycemia triggers phosphorylation of G protein–coupled receptor kinase 3 (GRK3), ultimately leading to cardiac injury (Gao et al., 2025). Since HbA1c levels directly reflect average blood glucose concentrations, any reduction in circulating glucose achieved through insulin therapy results in lower HbA1c values (Sen et al., 2016). Similarly, nonenzymatic glycation of albumin, which promotes the formation of advanced glycation end products (AGEs) in the setting of dyslipidemia and hyperglycemia, is also mitigated when glycemic levels are normalized (Sen et al., 2016;Lee et al., 2015; Maiese et al., 2011).

Conclusion

Biomarker guided drug discovery offers a completely novel method towards the management of diabetes mellitus and its associated cardiometabolic disorders. Predictive and mechanistic biomarker discovery allows researchers to improve target validation and therapeutic optimization while minimizing development failures. Merging the omics and clinical data enables precision medicine and

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customizing treatment to the patient's data. This increases treatment effectiveness and safety while addressing the lack of clinical therapies for patients with diabetes and its disorders. In the long run, this approach improves the life of patients suffering from diabetes and its related disorders.

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