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RESEARCH ARTICLE

Biochemical Markers in the Diagnosis and Progression of Type 2 Diabetes Mellitus: A Comprehensive Review

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Abstract: *Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder affecting millions globally, characterized by hyperglycemia resulting from insulin resistance and progressive pancreatic β-cell dysfunction. The accurate diagnosis and monitoring of disease progression are essential for early intervention and improved patient outcomes. This review examines the current and emerging biochemical markers utilized in the diagnosis and progression assessment of T2DM, including glycemic markers, β-cell function indicators, inflammatory biomarkers, and novel molecular markers. We synthesize evidence from recent literature (2020-2025) highlighting the advantages, limitations, and clinical applications of these markers. Particular emphasis is placed on the role of HbA1c, fasting plasma glucose, C-peptide, proinsulin, and emerging biomarkers such as glycated albumin and novel inflammatory markers. This review provides clinicians and researchers with a comprehensive understanding of the current biomarker landscape in T2DM diagnosis and disease surveillance, facilitating evidence-based clinical decision-making.*

Keywords: Type 2 Diabetes Mellitus, Biochemical markers, HbA1c, C-peptide, Glycemic control, Proinsulin, Inflammatory markers.

INTRODUCTION

Type 2 Diabetes Mellitus represents one of the most significant public health challenges of the 21st century, with an estimated 537 million adults globally affected by the disease[1]. Unlike Type 1 Diabetes, which results from autoimmune destruction of pancreatic β-cells, T2DM is characterized by a combination of peripheral insulin resistance and progressive dysfunction of pancreatic β-cells[2,3]. The disease remains largely asymptomatic during its early stages, during which significant metabolic dysfunction and tissue damage may already be occurring[1].

Early diagnosis and accurate risk stratification are crucial for timely therapeutic intervention and prevention of diabetic complications. The identification and utilization of appropriate biochemical markers facilitate early detection of prediabetic states, confirmation of diabetes diagnosis, monitoring of glycemic control, and prediction of disease progression[4,5]. Over the past decades, several biochemical markers have been established and validated for clinical use; however, each possesses inherent advantages and limitations[6].

The diagnostic criteria for T2DM have evolved significantly. Traditional diagnostic methods rely primarily on glucose measurements—either fasting plasma glucose (FPG) or the 2-hour plasma glucose during an oral glucose tolerance test (OGTT)[7]. More recently, glycated hemoglobin A1c (HbA1c) has been incorporated as a diagnostic criterion, offering distinct advantages regarding convenience and reproducibility[8]. Beyond these glycemic markers, contemporary research has identified and validated numerous biomarkers reflecting β-cell function, insulin secretion capacity, and systemic inflammatory and metabolic abnormalities associated with T2DM[9,10].
This comprehensive review examines the role of established and emerging biochemical markers in T2DM diagnosis and progression assessment, providing clinicians and researchers with current evidence-based information to guide clinical practice and future research directions.

2. Glycemic Markers in Type 2 Diabetes

2.1 Fasting Plasma Glucose (FPG)
Fasting plasma glucose has historically served as the gold standard diagnostic criterion for T2DM due to its widespread availability, low cost, and compatibility with automated clinical chemistry analyzers[11,12]. The WHO and American Diabetes Association recommend an FPG ≥126 mg/dL (≥7.0 mmol/L) as diagnostic of diabetes[13].

However, FPG possesses several limitations that affect its diagnostic utility. The test requires an 8-hour fasting period, which may be inconvenient for patients and may not always be precisely followed. FPG exhibits substantial biological and diurnal variability, reflects only a single point in time, and the samples present stability issues if not processed immediately[11,12]. Additionally, FPG demonstrates relatively lower sensitivity for detecting diabetes compared to OGTT and HbA1c in certain populations[14].

2.2 Oral Glucose Tolerance Test (OGTT) and 2-Hour Plasma Glucose

The OGTT remains the most sensitive test for detecting diabetes and prediabetes, measuring plasma glucose 2 hours after administration of 75g glucose load[15]. A 2-hour plasma glucose ≥200 mg/dL (≥11.1 mmol/L) is diagnostic of diabetes[16]. The OGTT also provides information about postprandial glucose metabolism and may identify individuals with impaired glucose tolerance who are at high risk of progression to T2DM[17].

Despite its sensitivity, the OGTT has limited clinical utility in routine practice due to its time-consuming nature (2-3 hours), requirement for patient preparation and fasting state, and operator-dependent performance[15]. Variable patient compliance and the high cost restrict its widespread use in primary care settings[18].

2.3 Hemoglobin A1c (HbA1c)

HbA1c represents the glycation product of hemoglobin resulting from non-enzymatic attachment of glucose to the N-terminal amino groups of the β-globin chains[19]. Since the circulating lifetime of red blood cells is approximately 120 days, HbA1c reflects the average plasma glucose concentration over the previous 8-12 weeks, providing a long-term assessment of glycemic control[19,20].

The American Diabetes Association and WHO have endorsed an HbA1c ≥6.5% as the diagnostic threshold for diabetes[21]. This threshold was established based on the relationship between HbA1c levels and the incidence of diabetic complications, particularly retinopathy[22]. HbA1c offers several distinct advantages: it does not require fasting; can be performed at any time of day; demonstrates better standardization and reproducibility; and reflects chronic glycemic exposure[23].

A landmark meta-analysis demonstrated that HbA1c is linked to diabetic-specific complications at least as much as FPG or 2-hour PG, with a narrow threshold range in which complications begin increasing markedly[24]. HbA1c values between 5.5-6.5% identify individuals with increased cardiovascular risk and potential for progression to overt diabetes[25].

However, HbA1c measurement has recognized limitations. Common comorbidities affecting red blood cell lifespan or hemoglobin metabolism can compromise the accuracy of HbA1c. These include renal insufficiency, high-output states (iron deficiency anemia, hemolytic anemia, hemoglobinopathies), pregnancy, and certain medications[26]. Different HbA1c assay methods may yield varying results, necessitating standardization to reference values[27]. Additionally, HbA1c cannot be reliably used in neonatal diabetes or in patients with acute hemoglobinopathies[26].

2.4 Glycated Albumin (GA)

Glycated albumin, formed by non-enzymatic glycation of serum albumin, provides an intermediate-term marker of glycemic control reflecting glucose levels over 2-3 weeks, compared to HbA1c (8-12 weeks) and fasting glucose (point-in-time)[28]. Serum albumin has a half-life of approximately 20 days, making GA particularly useful in detecting short-term changes in glycemic control[29].

GA has demonstrated particular utility in clinical scenarios where HbA1c is unreliable, including pregnancy, hemolytic anemia, renal disease, and acute illness states[30]. Studies have demonstrated that elevated GA levels correlate significantly with postprandial glucose excursions and may provide superior predictive value for detecting dysglycemia in certain populations[31].

Recent studies (2024-2025) indicate that glycated albumin may serve as a complementary marker to HbA1c, particularly for monitoring glycemic control during dynamic phases of treatment initiation or disease progression[32].

3. β-Cell Function and Insulin Secretion Markers

3.1 C-Peptide

C-peptide (connecting peptide) is released in equimolar amounts with insulin from the pancreatic β-cells during the processing of proinsulin[33]. Unlike insulin, which undergoes hepatic first-pass metabolism, C-peptide circulates in biologically active form and has a longer half-life, making it a more accurate reflection of endogenous insulin secretion[34].

Fasting C-peptide levels ≥0.30 mmol/L (≥0.90 ng/mL) support the diagnosis of Type 2 Diabetes and reflect adequate pancreatic β-cell function[35]. In prediabetic individuals, elevated C-peptide levels paradoxically indicate enhanced β-cell compensatory activity in response to peripheral insulin resistance; however, higher fasting C-peptide is prospectively associated with increased risk of progression toward overt T2DM[36].

Stimulated C-peptide (measured following a standardized secretory stimulus such as glucose or glucagon challenge) provides dynamic information about β-cell reserve and secretory capacity[37]. A systematic review by Maddaloni et al. (2022) involving multiple cohort studies demonstrated that higher baseline C-peptide levels are significantly associated with more rapid progression from prediabetes to diabetes, with risk increasing progressively across quartiles of C-peptide concentration[38].

The assessment of C-peptide trajectory over time provides prognostic information regarding disease progression and may help identify individuals most likely to benefit from intensive early therapeutic intervention[39].

3.2 Proinsulin and Proinsulin:C-Peptide Ratio

Proinsulin, the insulin precursor molecule, is normally processed efficiently to insulin and C-peptide during secretion from β-cells[40]. Elevated circulating proinsulin levels or an elevated proinsulin:C-peptide ratio (PI:C ratio) suggests β-cell dysfunction characterized by inefficient proinsulin cleavage or increased demand for insulin secretion[40,41].

Recent landmark investigations (2023-2025) have established the PI:C ratio as a novel biomarker of β-cell stress and dysfunction[42,43]. Studies utilizing advanced proteomic approaches have identified that elevated baseline PI:C ratios strongly predict more rapid disease progression in diabetic populations[43]. The PI:C ratio has demonstrated utility in identifying individuals at highest risk of progression from impaired glucose tolerance to overt diabetes and in predicting differential responses to therapeutic interventions[42,44].

A 2025 study demonstrated that the PI:C ratio independently predicts diabetes progression even after adjustment for baseline C-peptide levels, suggesting that the ratio captures aspects of β-cell dysfunction beyond total insulin secretory capacity[45].

4. Inflammatory and Metabolic Biomarkers

4.1 Inflammatory Markers

Chronic low-grade systemic inflammation represents a key pathophysiologic feature of T2DM and predicts progression from normal glucose tolerance to diabetes[46]. Multiple inflammatory biomarkers have been investigated as potential diagnostic and prognostic markers.

Tumor Necrosis Factor-alpha (TNF-α): Elevated serum TNF-α levels have been documented in T2DM patients and correlate with both insulin resistance and progressive β-cell dysfunction[47]. TNF-α promotes insulin resistance through multiple mechanisms including interference with insulin receptor signaling[48].

Interleukin-6 (IL-6): Prospective epidemiologic studies have consistently demonstrated that elevated baseline IL-6 levels predict incident diabetes independent of conventional risk factors[49]. IL-6 may promote β-cell dysfunction and enhance hepatic glucose production[49].

High-Sensitivity C-Reactive Protein (hsCRP): Elevated hsCRP serves as a marker of systemic inflammation and has demonstrated modest predictive value for diabetes incidence in population studies[50]. hsCRP correlates with insulin resistance measures and cardiovascular risk in T2DM[51].

Adiponectin: This adipokine exhibits anti-inflammatory and insulin-sensitizing properties. Multiple studies have documented that hypoadiponectinemia precedes the development of T2DM and independently predicts disease incidence[52].

4.2 Lipid Profile and Free Fatty Acids

Dyslipidemia represents both a consequence and contributing factor to T2DM pathogenesis. Elevated fasting serum free fatty acids (FA) concentrations increase in T2DM due to elevated blood glucose and impaired lipid metabolism[53,54]. Serum FA levels may serve as a glycemic marker useful for discrimination between normoglycemic and diabetic individuals[53].

Studies examining the relationship between HbA1c and lipid profile have demonstrated that HbA1c shows direct and significant positive correlations with total cholesterol, triglycerides, and LDL-cholesterol, with inverse correlation with HDL-cholesterol[55]. These findings suggest HbA1c provides supplementary information about circulating lipid patterns beyond its primary role in glycemic monitoring[55].

5. Novel and Emerging Biomarkers

5.1 Proteomic and Genetic Biomarkers

Contemporary proteomic and genomic approaches have identified novel circulating proteins and genetic markers associated with T2DM susceptibility and progression. Recent systematic reviews (2024-2025) have identified distinct biomarker profiles in T2DM including hematological, proteomic, lipid, and cytokine profiles[56].

A 2025 study utilizing machine learning algorithms identified SERPINB2 (serpin B member 2) and TNFRSF1A (TNF receptor superfamily member 1A) as co-expressed biomarkers significantly associated with T2DM diagnosis and metabolic dysfunction[57]. These genes regulate immune function and inflammatory pathways implicated in T2DM pathogenesis[57]. The diagnostic models incorporating these novel markers demonstrated significantly improved sensitivity and accuracy for identifying T2DM, particularly in patients with associated metabolic comorbidities[57].

Differential expression analysis coupled with weighted gene correlation network analysis (WGCNA) has identified 354 candidate genes in T2DM-related datasets, with pathway analysis revealing central roles for inflammation, immune dysregulation, and cell interaction processes[57].

5.2 Advanced Glycation End Products (AGEs)

Advanced glycation end products represent irreversible modifications of proteins and lipids occurring through non-enzymatic glycation in hyperglycemic environments[58]. Tissue and serum AGE accumulation accelerates diabetic complication development[58]. Elevated serum AGE levels correlate with glycemic control, duration of diabetes, and presence of microvascular complications[59].

The measurement of skin autofluorescence as a non-invasive proxy for tissue AGE accumulation has emerged as a potential biomarker for diabetes risk stratification; however, clinical utility in routine practice remains limited[60].

6. Diagnostic Applications and Clinical Algorithms

The World Health Organization and various national diabetes societies recommend hierarchical diagnostic algorithms incorporating multiple biochemical markers[61]. For individuals with symptoms of hyperglycemia, a single elevated glucose measurement (FPG ≥126 mg/dL, random PG ≥200 mg/dL, or OGTT 2-h PG ≥200 mg/dL) is diagnostic[62].

For asymptomatic individuals or population-based screening, diagnosis requires confirmation with a repeat elevated measurement, ideally using a different test modality[62]. Current 2025 International Diabetes Federation recommendations suggest utilizing HbA1c as a first-line screening and diagnostic test due to standardization improvements and greater convenience[63].

In individuals with intermediate HbA1c values (5.5-6.4%), supplementary assessment using FPG or OGTT may be warranted to clarify glucose status and identify those with impaired glucose tolerance versus impaired fasting glucose, as these phenotypes differ in their progression rates and complications patterns[64].

7. Biomarkers for Assessing Disease Progression and Risk Stratification

7.1 Progression from Prediabetes to Overt Diabetes

Progression rates from prediabetes to diabetes vary significantly among individuals, ranging from 3-10% annually depending on baseline glucose status, age, and additional risk factors[65]. Biochemical markers beyond glucose have demonstrated utility in identifying individuals at highest progression risk.

Elevated baseline C-peptide levels, particularly when accompanied by elevated PI:C ratio, identify prediabetic individuals at substantially increased risk of rapid progression[36,45]. A 2024 systematic review examining biomarkers in T2DM identified that multi-marker approaches incorporating C-peptide, inflammatory markers (TNF-α, IL-6), and lipid metrics provide superior predictive value for progression compared to glucose-based measures alone[56].

7.2 β-Cell Dysfunction and Insulin Resistance

The homeostasis model assessment of insulin resistance (HOMA-IR) and HOMA-β (β-cell function) indices, derived from fasting glucose and insulin measurements, quantify insulin resistance and relative β-cell function[66]. While primarily research tools rather than routine clinical markers, HOMA-β decline over time predicts progression from normal glucose tolerance to diabetes[67].

C-peptide and proinsulin measurements provide more direct assessment of β-cell secretory capacity than calculated indices. Declining C-peptide trajectory over time indicates progressive β-cell deterioration and may prompt therapeutic intensification[39].

8. Limitations of Current Biomarkers and Considerations for Clinical Practice

8.1 Assay Standardization

Significant between-laboratory variation exists for many biochemical markers, particularly for C-peptide, proinsulin, and inflammatory markers measured using different assay methodologies[68]. The lack of international standardization for these markers limits their comparability across settings and complicates interpretation of results[68].

HbA1c standardization has improved dramatically following implementation of International Federation of Clinical Chemistry (IFCC) reference standards; however, variations still occur particularly in low-resource settings[69].

8.2 Population and Ethnicity-Specific Considerations

Reference ranges and diagnostic thresholds for biochemical markers were primarily established in European and North American populations[70]. Application of these thresholds to diverse ethnic populations may introduce diagnostic inaccuracy. For example, HbA1c thresholds for diabetes diagnosis vary slightly among different ethnic groups due to differences in hemoglobin glycation rates[71].

C-peptide reference ranges similarly demonstrate ethnic variation, and population-specific cut-points may improve diagnostic accuracy in non-European populations[72].

8.3 Confounding Conditions

As previously noted, multiple comorbid conditions affect the accuracy of biochemical markers. Chronic kidney disease alters glucose metabolism and interferes with HbA1c measurement[73]. Hemolytic anemias, hemoglobinopathies, pregnancy, and hepatic cirrhosis all compromise HbA1c reliability[26].

Inflammatory markers may be elevated in acute and chronic inflammatory conditions unrelated to diabetes, reducing their specificity for diabetes-related metabolic dysfunction[74].

9. Integration of Biomarkers in Clinical Practice

Contemporary management of T2DM requires integration of multiple biochemical markers to accurately diagnose disease, assess disease severity and progression, and guide therapeutic decision-making[75]. The American Diabetes Association 2025 Standards of Care recommend regular HbA1c assessment in all patients with diabetes, typically at 3-6 month intervals depending on stability and metabolic targets[75].

Utilization of glycated albumin or continuous glucose monitoring data should be considered in patients in whom HbA1c is unreliable or when shorter-term assessment is needed for recent dietary or medication changes[75].

Beyond glucose monitoring, lipid profiling, inflammatory marker assessment, and urinary albumin measurement provide complementary information regarding overall cardiometabolic risk and need for intensified interventions[76].

Emerging proteomic signatures incorporating multiple biomarkers simultaneously may enable phenotyping of T2DM heterogeneity and prediction of individual therapeutic responses in future precision medicine approaches[77].

10. Future Directions and Emerging Technologies

10.1 Artificial Intelligence and Machine Learning

Machine learning algorithms integrating multiple biochemical markers, clinical parameters, and genetic information have demonstrated superior predictive accuracy for diabetes diagnosis and progression compared to traditional single-marker approaches[78]. Future clinical practice may incorporate AI-assisted interpretation of multi-marker biomarker panels to enhance diagnostic precision[79].

10.2 Non-Invasive and Novel Assessment Methods

Development of non-invasive technologies for measuring glycemic control and β-cell function continues. Spectroscopic assessment of skin autofluorescence and advanced imaging techniques may enable bedside assessment of metabolic dysfunction without blood sampling[80].

Exosomal proteins and circulating microRNAs (miRNAs) represent emerging biomarkers that may provide superior information regarding β-cell function, pancreatic stress, and inflammatory activation[81,82].

10.3 Personalized and Precision Medicine

Recognition of T2DM heterogeneity has led to classification schemas identifying distinct metabolic phenotypes associated with differing progression patterns and treatment responses[83]. Future biomarker development will emphasize endotyping approaches enabling prediction of individual therapeutic responses and risks[84].

CONCLUSION

Biochemical markers play an indispensable role in the diagnosis, monitoring, and prognostication of Type 2 Diabetes Mellitus. HbA1c, fasting plasma glucose, and oral glucose tolerance test results remain the foundational diagnostic modalities endorsed by international guidelines. Beyond these glycemic markers, assessment of β-cell function through C-peptide and proinsulin measurement provides dynamic information regarding disease pathophysiology and progression risk.

Emerging inflammatory, proteomic, and genetic biomarkers are expanding our understanding of T2DM heterogeneity and identifying novel therapeutic targets. The integration of multiple complementary biomarkers within modern clinical decision-support systems enhances diagnostic accuracy and risk stratification compared to single-marker approaches.

Future advancement in T2DM biomarker science will emphasize standardization, development of population-specific reference ranges, and integration with artificial intelligence platforms for enhanced precision in diagnosis, phenotyping, and therapeutic decision-making. Clinicians and researchers must remain cognizant of both the clinical utility and inherent limitations of biochemical markers when applying them to individual patient evaluation and management.

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