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Evaluation of Novel Biomarkers in Early Detection of Type 2 Diabetes: Review of the literature

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ABSTRACT

Type 2 diabetes mellitus is a tremendous global health challenge, caused mainly by a sedentary lifestyle and constantly rising obesity rates. Early recognition of individuals at risk is significant to prevent complications. Advances in biochemical and molecular biomarkers now provide opportunities to detect subtle metabolic changes before diabetes becomes clinically evident. Eligible articles that we found for this review comprised original and review papers describing novel circulating, metabolic, genetic, or protein biomarkers with potential for early diagnosis of T2DM or prediabetes. Evidence from recent studies identifies various biomarkers, including metabolic, protein, and nucleic-acid biomarkers such as circulating metabolites, adipokines, microRNAs, circular RNAs, and others, as potential early indicators of T2DM. All of them show promise for early recognition of insulin resistance and β-cell dysfunction, so future research should focus on validating and translating these biomarkers into clinical practice. One of the most significant limitations is that many biomarkers still lack clinical standardization and external validation, which delays their adoption in diagnostic practice.

Keywords: type 2 diabetes mellitus, biomarkers, early detection, metabolomics, microRNA.

1. INTRODUCTION

T2DM remains one of the greatest Public Health Challenges. It has created an increasing burden on Health Care Systems due to an ageing population, urbanisation, the development of obesity-promoting environments, sedentary lifestyles, and the resultant impacts on both Health and Economics. Although treatments are developed and available to the patient, the diagnosis is usually made many years after the onset of progressive hyperglycaemia, when vascular complications, both microvascular and macrovascular, develop. The long time taken to diagnose T2DM creates an opportunity for earlier detection of risk and intervention, which are not currently possible with the existing definitions and criteria for diagnosis (Laakso, 2019).

While traditional methods of assessing glycemic status (fasting blood glucose, oral glucose tolerance test, and glycated hemoglobin) measure glycemic status, they do not accurately reflect a patient's earliest physiological transition: the development of insulin resistance and β-cell impairment. These traditional tests are influenced by lifestyle and biological factors, overlook individual differences, and offer limited insight into the mechanisms driving disease (Zhang et al., 2023). Consequently, there is intense interest in novel biomarkers that reflect early biological changes and enable earlier disease detection, before overt hyperglycaemia emerges (Laakso, 2019; Sochein, 2024; Joseph, 2021).

Biomarkers provide objective measures of normal biological processes, pathological processes, or responses to therapeutic interventions. Candidate biomarkers for T2DM studies exist at multiple levels of molecules and across many biological compartments. That includes circulating metabolites (branched-chain amino acids, acylcarnitines), proteins and peptides (adipokines, inflammatory cytokines). There was also an investigation into various substances, including nucleic acids (e.g., microRNA/circular RNA) and the contents of extracellular vesicles (EV), as well as composite panels generated from multi-omic profiling. The benefit of multi-omic profiling is that it uses data from multiple molecular levels (Genomics, Proteomics, Metabolomics, Transcriptomics) rather than relying on a single molecular level (Sochein, 2024; Ngoc Le Msc et al., 2024; Kretowski, 2024). Metabolomics-based studies can potentially be used to determine risk for dysglycaemia and insulin resistance in the future (Laakso, 2019; Ngoc Le Msc et al., 2024). Protein-based biomarkers reflect inflammation, oxidative stress, and hormonal disruption that contribute to the early development of metabolic disorders.

The presence of adiponectin, leptin, CRP, and interleukin groups consistently indicates early-stage metabolic dysfunction. MicroRNAs, including miR-126 and miR-375, which are involved in insulin secretion, and members of the let-7 family, are also potential minimally invasive biomarkers on a cellular regulatory level because they directly link β-cell stress to insulin signalling at a mechanistic level (Joseph, 2021; Belongie et al., 2017). Many metabolomic and proteomic studies have demonstrated that biochemical irregularities appear several years before hyperglycaemia develops, highlighting the value of biomarkers for detecting early changes that occur before clinical symptoms develop.

While dynamic physiological indices are an informative but not very manageable method for measuring metabolic status at the population level, they pose several challenges for large-scale screening due to the need for complex sample collection protocols, numerous blood draws, and specialized analysis techniques. Existing methods cannot easily accomplish that. In addition, the observation that several proteins and small (and other-related) RNAs can correlate with an increase in the likelihood of developing an impaired glucose tolerance or with a decrease in β-cell glucose sensitivity post-OGTT indicates the viability of using additional types of biological markers as prognostic and monitoring tools within type 2 diabetes (Belongie et al., 2017). These results agree with systematic evidence showing that haematological, proteomic, cytokine, and lipid disturbances occur throughout the progression of T2DM. Collectively, they accentuate the value of integrating biological markers with clinical risk factors to enhance prediction accuracy.

Researchers currently explore several research paths. Multi-biomarker panels are likely to be more effective than single markers because they represent multiple overlapping biological pathways (insulin production, insulin resistance/inflammation, and oxidative stress), thereby compensating for much of the biological variability arising from distinct processes. By using algorithms that combine clinical characteristics and glucose level information from biomarkers, we can more effectively identify populations with prediabetes who may be more likely to respond to early intervention (Sochein, 2024). Third, the assays must be standardised and validated across different platforms and populations before we can use these biomarkers in clinical settings.

Although there is considerable enthusiasm for biomarkers to objectively identify people with diabetes, current scientific knowledge has many gaps. Researchers developed most of the proposed biomarkers in single populations, and their association with disease weakens after statistical adjustment. Studies have validated standard clinical risk assessment models using only a limited number of biomarkers. Moreover, the presence of biological diversity among individuals will have an impact on how well these markers function and will require that calibrations and cut-off points specific to an individual's context (i.e., age, fat distribution pattern, ethnicity, other health conditions, medications) be developed for their use (Laakso, 2019; Ngoc Le Msc et al., 2024). Nonetheless, converging data suggest that combining mechanistically anchored markers with standard measures could shift detection earlier in the disease course, enabling truly preventive diabetology.

Considering this background, the objective of the present review is to combine current evidence on novel biomarkers for the early detection of T2DM, with emphasis on metabolic, protein, and nucleic acid markers, as well as indices of β-cell function measurable in minimally invasive samples. Specifically, this review aims to summarise the main biomarker categories, explain their pathophysiological relevance and analytical aspects, and assess their clinical usefulness for risk prediction, screening, and monitoring.

2. REVIEW METHODS

We performed a structured literature search to identify studies evaluating novel biomarkers for the early detection of T2DM. The search focused on the time between January 2015 and July 2025- the decade with the most substantial improvements in discovering biomarkers. The databases we used were PubMed, Scopus, and Web of Science, with Google Scholar for additional coverage. We chose only peer-reviewed, open-access publications.

We used the following keywords: 'type 2 diabetes'; 'T2DM'; 'biomarker'; 'metabolomics'; 'proteomics'; 'microRNA'; 'circulating RNA'; 'early detection'. Studies were required to provide a quantitative or qualitative assessment of biomarkers measurable in blood, plasma, serum, or urine samples and to address either early diagnosis, prediabetes, or metabolic risk stratification. In this search, we excluded in vitro or animal studies without human validation, conference abstracts or editorials without peer review, and non-English or paywalled articles.

For this review, we identified 28 studies as appropriate (Figure 1). These included original research papers and systematic reviews of metabolic, protein, genetic, transcriptomic, and multi-omics/machine-learning biomarkers.

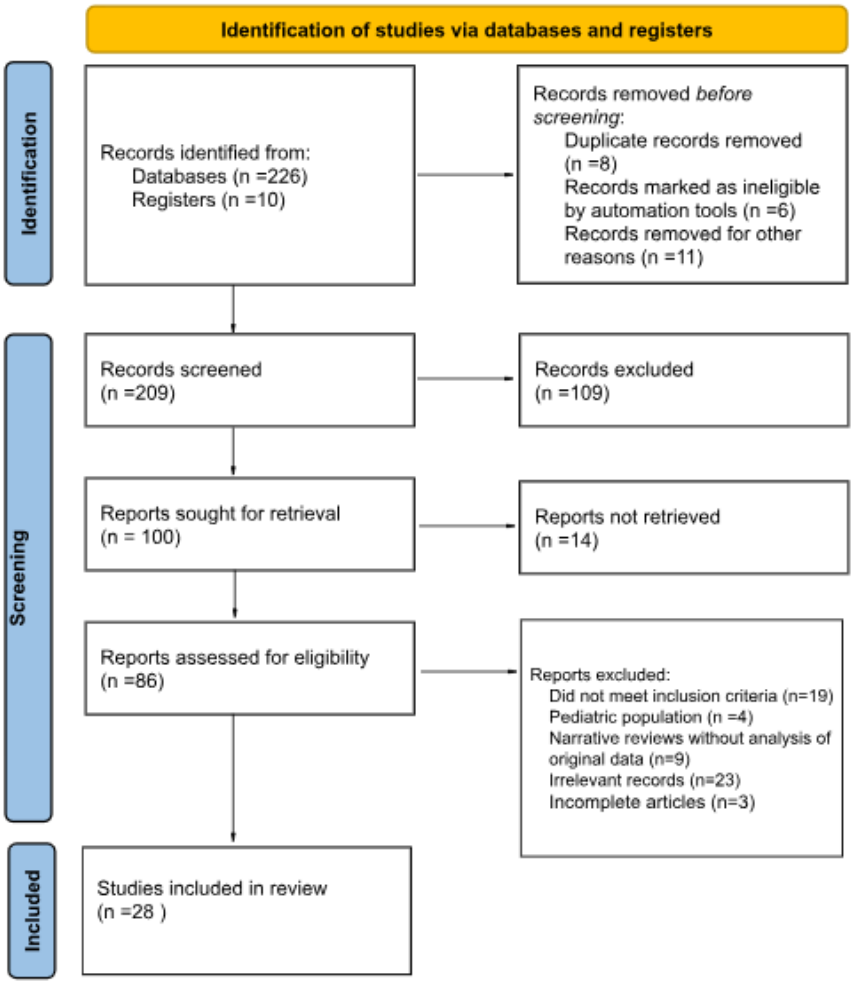

Figure 1. Flow chart

3. RESULTS & DISCUSSION

Overview of Biomarker Categories in Early T2DM Detection

Research into new biomarkers has led to a greater understanding of the metabolic and molecular processes that occur before the development of T2DM. Researchers have classified biomarkers into the following categories: metabolic, protein-based, genetic, epigenetic, and extracellular vesicle-derived. There are also panels that combine many markers across multiple biological layers across

these categories. Together, they represent interconnected pathways that contribute to insulin resistance, β-cell dysfunction, and vascular damage. Studies have examined metabolic biomarkers as early indicators of abnormal glucose metabolism. Studies found a direct association of insulin resistance with elevated levels of branched-chain amino acids in plasma (BCAAs: leucine, isoleucine, valine), aromatic amino acids like tyrosine, phenylalanine, and tryptophan, and ceramides, diacylglycerols, and acylcarnitines- lipid intermediates (Kretowski, 2024; Morze et al., 2022; Sierawska & Niedźwiedzka-Rystwej, 2022). Several compounds, such as HODE-12- & 10-(Z, E)-hydroxyoctadecadienoic acid, along with pyruvate, lactate, and α-hydroxybutyrate, reflect oxidative stress and mitochondrial impairment and may also indicate subclinically developing dysglycemia (Umeno et al., 2015).

Protein and peptide biomarkers, especially adipokines and inflammatory cytokines, provide some insight into the connection between adipose tissue dysfunction and systemic inflammation. Decreases in adiponectin and increases in leptin, resistin, and visfatin, combined with elevated levels of TNF-α, IL-6, and C-reactive protein (CRP), indicate chronic inflammation. Proteins such as fibroblast growth factor 21 (FGF21) and irisin are markers of mitochondrial stress and dysregulated thermogenesis (Hliel et al., 2024; Sierawska & Niedźwiedzka-Rystwej, 2022).

Renal biomarkers-including nephrin, neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, transforming growth factor-β1 (TGF-β1), and vascular endothelial growth factor A (VEGF-A)-are increasingly recognized as early marks of microvascular and renal injury in T2DM.

MicroRNAs, such as miR-126, miR-375, miR-122, miR-29a/b, miR-146a, and others (biological and transcriptomic), have been identified as among the many genetic and biological factors that influence insulin secretion, insulin resistance, and pancreatic β-cell function. There is evidence suggesting that these microRNAs may help identify prediabetes. Typical markers of insulin resistance are lncRNAs H19, MALAT1, and MEG3. They have been shown to play important roles in regulating inflammation and stabilising glucose levels; however, their clinical significance remains uncertain (Ahmed et al., 2025; Lu et al., 2021).

Epigenetic biomarkers, including aberrant DNA methylation of IRS1, PDX1, FTO, ADIPOQ, and PPARGC1A, as well as histone modifications (H3K9me3, H3K27ac), explain the correlations between exposures to many environmental factors, metabolic stress, and gene expression regulation. These marks may appear before biochemical abnormalities, and researchers increasingly view them as the fourth generation of molecular predictors of T2DM.

Studies show that extracellular vesicle (EV)-shuttled molecules carry both disease signals and miRNAs (23a, 223, and 320a). Lately, researchers have begun using panels that include multiple biomarkers. Metabolic, proteomic, and transcriptomic markers have all been proposed in these combined approaches. They supposedly have greater predictive accuracy than approaches that consider only a single biomarker (Kretowski, 2024; Ortiz-Martinez et al., 2022; Umeno et al., 2015).

Metabolite-based biomarkers have also demonstrated diagnostic potential in patients with prediabetes, indicating that metabolic changes develop well before diabetes can be clinically detected. Elevated concentrations of branched-chain amino acids, ceramides, and lysophosphatidylcholines in people with impaired fasting glucose or impaired glucose tolerance suggest an early metabolic profile associated with increased disease risk (Long et al., 2020). Integrating these metabolomic patterns with known indicators of β-cell function would allow us to detect Type 2 Diabetes much earlier and intervene earlier to prevent its development.

In summary, current evidence indicates that type 2 diabetes involves a complex network of biomarkers reflecting metabolic, molecular, and epigenetic changes. Combining information from these different biological levels can improve risk assessment and allow earlier detection of diabetes or prediabetes, as each biomarker type reflects a distinct aspect of disease development.

Metabolic Biomarkers: Amino Acids, Lipids, and Acylcarnitines

A variety of research studies have provided evidence that metabolic disturbances occur long before the development of T2DM. Some of the repeatedly noted changes in this regard have been observed in studies of amino acid, lipid, and acylcarnitine levels, which showed abnormal patterns predictive of insulin resistance and mitochondrial dysfunction. These metabolites suggest dysregulation even before glucose levels rise.

Elevations of branched-chain amino acids (leucine, isoleucine, and valine) and aromatic amino acids (tyrosine, phenylalanine, and tryptophan) are frequently observed in individuals with prediabetes. In addition, this abnormality indicates incomplete amino acid oxidation and an altered state of the mTOR signaling pathway. Reductions in glycine and serine further suggest oxidative imbalance and decreased insulin sensitivity. Together, these shifts form an early biochemical signature of metabolic inflexibility- the impaired ability to switch between energy substrates such as glucose and lipids (Morze et al., 2022).

Lipid-related metabolites also play a central role in early disease detection. Increases in ceramides, diacylglycerols, and long-chain acylcarnitines interfere with mitochondrial β-oxidation and insulin signaling. According to many sources, oxidized lipid products serve as markers of oxidative stress; elevated plasma levels of HODE (10- and 12-(Z, E)-hydroxyoctadecadienoic acid) can differentiate patients with impaired glucose tolerance from those with normoglycemia (Umeno et al., 2015).

New research has shown that changes in circulating free fatty acid levels are one of the earliest indicators of abnormal lipid metabolism in diabetics. Elevated concentrations of palmitic, oleic, and linoleic acids are positively correlated with loss of tissue sensitivity and defects in beta-cells, resulting from dysregulation of lipid metabolism via oxidative processes and lipid accumulation. Increased levels of certain acylcarnitines (C3, C5, & C16:0) were also present, indicating inhibited mitochondrial beta-oxidation (inability of mitochondria to catalyze the breakdown of fatty acids) (Ma et al., 2021).

Acylcarnitines mirror disruptions in mitochondrial fuel use. Short-chain fatty acids (C3-C5) accumulate when it is impossible to properly break down branched-chain amino acids, while long-chain fatty acids (C14:1-C16:0) are associated with defective fatty-acid catabolism. These patterns correlate with hepatic lipid accumulation and fasting insulin elevations.

The integration of amino-acid, lipidomic, and acylcarnitine profiles into predictive models yields greater accuracy for early diabetes risk prediction than using each biochemical assay in isolation. Together, these metabolites indicate early metabolic changes associated with insulin resistance and could help identify individuals at higher risk of developing diabetes (Kretowski, 2024; Merino et al., 2018; Liu et al., 2025).

Protein and Peptide Biomarkers: Adipokines and Inflammatory Cytokines

When T2DM starts, many molecular changes occur, including those that affect circulating proteins that help communicate between adipose tissue, the liver, and skeletal muscle. Adipokines and inflammatory cytokines serve as key regulators linking obesity-induced metabolic stress to insulin resistance and β-cell dysfunction. Adiponectin is one of the most consistently reduced markers in individuals with insulin resistance. Activation of the AMP-activated protein kinase and PPARα signaling pathways mediates the anti-inflammatory and insulin-sensitizing effects of lethyrosine. At the same time, the increased leptin levels seen with obesity and prediabetes indicate chronic oxidative stress and show evidence of leptin resistance. Visceral fat primarily secretes two chemicals, resistin and visfatin, which cause inflammation in the blood vessels that surround the organs and contribute to cardiometabolic diseases. Decreased adiponectin levels, in addition to elevated leptin or resistin levels, may also indicate that someone is developing early T2DM (Ngoc Le Msc et al., 2024; Sierawska & Niedźwiedzka-Rystwej, 2022).

Cytokines and inflammatory markers

There are many metabolites that promote chronic metabolic inflammation, for example, cytokines such as tumor necrosis factor α (TNFα), interleukin 6 (IL-6), and C-reactive protein (CRP). TNFα inhibits serine phosphorylation of IRS-1, preventing proper signalling through insulin receptors. CRP levels are associated with changes in glycaemia and the risk of vascular complications (Kretowski, 2024). On the other hand, IL-6 stimulates increased hepatic glucose production. Elevated concentrations of these substances happen before hyperglycaemia, marking the transition from metabolic stress to clinical diabetes.

The results suggest that adipokines and cytokines form a cohesive network of proteins that are biomarkers for early inflammatory and vascular disturbances associated with T2DM. Their simultaneous evaluation may enhance the identification of individuals at high risk of developing diabetes and, therefore, help build individualized preventive strategies (Ngoc Le Msc et al., 2024; Sierawska & Niedźwiedzka-Rystwej, 2022).

Genetic and Epigenetic Biomarkers (microRNAs, circRNAs, DNA methylation)

Lately, there has been significant interest in identifying molecular markers reflecting gene regulation and methylation that may serve as early indicators of T2DM. These include circulating microRNAs (miRNAs), circular RNAs (circRNAs), and epigenetic modifications.

Studies constantly report dysregulation of several miRNAs in prediabetes and early T2DM. Decreased levels of miR-126 and miR-375 impair insulin secretion, whereas increased levels of miR-29a/b, miR-122, and miR-146a are associated with chronic inflammation and insulin resistance. The characteristics of the microRNAs to stay consistent when found in a blood sample, along with the ability to remain highly expressed, are ideal attributes for creating a less invasive type of diagnostic test. Specifically, miR-126 and miR-375 yield distinct expression profiles that can differentiate between healthy and impaired glucose tolerance individuals (Ahmed et al., 2025).

Additional studies have further characterized the clinical significance of miR-126 and miR-122. Decreased circulating miR-126 levels indicate an increased early risk of vascular disease related to endothelial dysfunction in patients with T2DM. Studies have linked miR-122, which is mainly expressed in the liver, to hepatic insulin resistance and alterations in lipid metabolism, reflecting early metabolic dysregulation even before the onset of hyperglycemia (He et al., 2022).

Circular RNAs (circRNAs): These non-coding RNAs form closed loops that protect them from RNase degradation, resulting in exceptional stability in the bloodstream. Researchers identified molecule hsa_circ_0063425 as a novel biomarker elevated in patients with T2DM and associated with β-cell dysfunction and altered glucose metabolism. Its circulating levels correlate with fasting glucose and HOMA-IR (a measure of insulin resistance), indicating potential value for early disease detection (Lu et al., 2021).

Epigenetic biomarkers: Altered DNA methylation and histone modifications constitute another level of molecular dysregulation. Methylation changes in several gene types (such as IRS1, PDX1, ADIPOQ, and FTO) reduce β-cell insulin sensitivity and alter β-cell gene expression. Environmental factors (diet, oxidative stress, and obesity) will also continue to modify these epigenetic markers due to enduring exposure, thereby developing a "metabolic memory" that maintains the disease even after near-normal glycaemic control is attained in individuals with diabetes (Munns et al., 2025).

Extracellular vesicle-associated miRNAs. Recent studies show that miRNAs encapsulated within extracellular vesicles (EVs) - such as miR-23a, miR-223, and miR-320a - have the ability to send signals between cells (Prattichizzo et al., 2021). Closing miRNAs in a capsule protects them from degradation, enabling accurate quantification in plasma or urine. These EV-derived miRNAs may serve as noninvasive indicators of early metabolic stress.

Integration of genetic and epigenetic biomarkers into clinical algorithms could substantially enhance risk prediction and enable personalized approaches to diabetes prevention and management.

Biomarkers of Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress and mitochondrial dysfunction each contribute significantly to the pathogenesis of Type 2 diabetes at its inception by inducing insulin resistance, destroying beta cells, damaging blood vessels, and causing these changes before the appearance of high blood sugar levels (Wang et al., 2023). The imbalance between antioxidant defenses and reactive oxygen species (ROS) production leads to oxidative injury of lipids, proteins, and DNA, manifesting as measurable circulating biomarkers.

Oxidative-stress biomarkers

Elevated levels of malondialdehyde (MDA), 8-hydroxy-2′-deoxyguanosine (8-OHdG), and advanced oxidation protein products (AOPPs) have been observed in prediabetic individuals and reflect early oxidative injury. Reductions of antioxidants- superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities, indicate compromised antioxidant defense mechanisms. Assessment of these antioxidant enzymes may enable the identification of individuals at high risk of developing glucose fasting abnormalities, which are associated with increased metabolic risk. Recent studies using metabolomic techniques have shown that oxidative stress markers are often observed alongside changes in mitochondrial lipid metabolism. Some of the earliest biometrical indicators of metabolic stress before the onset of type 2 diabetes include increased levels of oxidized fatty acids and a shift in the ratio of reduced to oxidized glutathione (Merino et al., 2018; Wang et al., 2023).

Adipokines and oxidative signaling

Several adipose-derived proteins, mentioned in 3.3, are indirect biomarkers of oxidative imbalance. Adiponectin exerts anti-inflammatory and antioxidant effects by activating AMPK and inhibiting ROS formation. On the other hand, Leptin and Resistin promote oxidative stress and Mitochondrial dysfunction in the tissues involved in metabolism. An imbalance characterized by decreased adiponectin and elevated leptin or resistin correlates with excess lipid peroxidation. It can also impair the development of new mitochondria, linking adipokine dysregulation with oxidative stress in the pathogenesis of T2DM. Recent findings also suggest that visfatin and omentin may reflect changes in lipid and glucose metabolism (Sierawska & Niedźwiedzka-Rystwej, 2022).

Mitochondrial dysfunction

Impaired β-oxidation, together with decreased NADH/NAD+ ratios, indicates mitochondrial metabolic stress. Long-chain acylcarnitines accumulate during mitochondrial dysfunction and oxidative phosphorylation, leading to reduced ATP production and increased free radical (ROS) production. A decrease in mitochondrial biogenesis regulators, such as PGC-1α, intensifies these changes

and contributes to tissue resistance to insulin (Peters et al., 2017). Studies involving metabolomics have shown that individuals with high metabolic risk exhibit mitochondrial dysfunction early in the disease process, characterised by elevated plasma acylcarnitine levels and reduced levels of citrate and succinate (TCA cycle intermediates) (Merino et al., 2018).

Another marker of mitochondrial stress is oxidized lipid products, mostly 10- and 12-(Z, E)-hydroxyoctadecadienoic acids (HODEs), which serve as sensitive markers of oxidative lipid injury (Ortiz-Martinez et al., 2022). Together, these findings demonstrate that oxidative-stress markers, mitochondrial metabolites, and adipokines indicate early cellular stress associated with the onset of T2DM.

Renal and Microvascular Biomarkers

Diabetes manifests through microvascular complications, usually very early in disease progression. As a result of hyperglycemia and oxidative stress, the integrity of the glomeruli and the endothelial barrier is damaged. Inflammatory pathways are triggered by injury. Cumulation of these events could progress renal destruction (Tatli et al., 2024). Recent studies show that it's possible to detect subtle biochemical alterations long before the appearance of standard clinical markers, such as microalbuminuria.

Scientists identified several substances as predictors of renal dysfunction. Nephrin, neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, transforming growth factor-β1 (TGF-β1), and vascular endothelial growth factor A (VEGF-A) show measurable changes during early stages of nephropathy (Hliel et al., 2024).

Nephrin levels above normal indicate damage to the glomeruli or filtration system of the kidney; NGAL and cystatin C levels indicate that tubular function has failed to recover its normal ability to reabsorb products back into circulation from urine. Both nephrin and NGAL are correlated with insulin resistance, fasting glucose, and HbA1c, thereby linking subclinical renal dysfunction with metabolic dysregulation or stunted insulin action. Elevated concentrations of TGF-beta1 (signifying activation of endothelial cells) and VEGF-A (indicating early involvement in microvascular changes) indicate that early microvascular changes are occurring. In patients with elevated levels of TGF-beta1/VEGF, even if their urinary albumin excretion is within the normal range, they are offered a greater opportunity for diagnosis/early intervention before progression to nephropathy after urine specimen collection. In prospective studies, combining cystatin C and NGAL has been shown to provide greater sensitivity for detecting early nephropathy than focusing only on microalbuminuria (Karimi et al., 2023).

Microvascular injury and cardiovascular complications share an inflammatory ground. That is why renal biomarkers such as TGF-β1, cystatin C, and VEGF-A may also predict cardiac outcomes in patients with early diabetes, for example, left ventricular hypertrophy and atherosclerosis (Zhang et al., 2023; Hliel et al., 2024; Karimi et al., 2023; Peters et al., 2017).

The incorporation of renal biomarkers into evaluation offers the possibility not only of earlier detection of diabetic nephropathy but also of prognostic assessment of long-term outcomes. Studies have linked increased levels of cystatin C and NGAL to increased risk of progression to chronic kidney disease. VEGF-A and TGF-β1 reflect ongoing endothelial remodeling and fibrosis. They both predict the transition from reversible to irreversible microvascular injury.

Routine implementation of these tests could improve early risk stratification and enable the application of renoprotective therapies such as SGLT2 inhibitors or ACE inhibitors at a preclinical stage (Hliel et al., 2024). Renal biomarkers complement metabolic and inflammatory indicators by demonstrating early vascular effects of diabetes.

Integrated Multi-Omic Panels and Artificial Intelligence

One of the major limitations of traditional approaches based on individual markers is their lack of sensitivity. Models that integrate the metabolome, proteome, and transcriptome aim to capture the diverse metabolic changes that occur before symptoms appear and during disease progression. Recent research has examined how the bystander effect can affect how we use omic data and computerised analyses to identify individuals at risk of developing T2DM. As a result, multiple diagnostic models have been created with deep learning and AI to evaluate the risk of developing diabetes. Multi-omic panels analyzed through AI represent a promising future diagnostic strategy. Their integration into clinical practice may improve the early detection of T2DM (Tatli et al., 2024).

Clinical Translation, Limitations, and Future Perspectives

Various factors limit the clinical use of molecular biomarkers in diabetes. Most diagnostic strategies still rely on fasting glucose and HbA1c. It is insufficient because they detect pathological changes only after substantial β-cell loss. Novel biomarkers can identify

metabolic dysregulation years before diabetes develops. The predictive accuracy of a panel of biomarkers comprising different marker types is superior to that of a single biochemical marker (Joseph, 2021).

However, the absence of standardised assays, high analytical costs, and inconsistent results between laboratories make it harder to use biomarkers in everyday clinical practice. To implement these tools in the future, it will be necessary to harmonise the analytical platforms and validate them across different populations (Ortiz-Martinez et al., 2022).

Implementing multi-omic panels of biomarkers in healthcare could result in better prevention and management. Categorising patients by molecular profile could enable us to create individualised treatment plans. Biomarkers of insulin resistance, oxidative stress, or microvascular damage may enable implementing early use of protective therapies, including SGLT2 inhibitors or GLP-1 receptor agonists (Hliel et al., 2024).

Recent metabolomic research has extended the clinical use of biomarker profiling, showing that it can support not only early diagnosis but also the monitoring of treatment response. People who receive both drug and dietary therapy tend to show significant changes in lipid levels and amino acid profiles. Therefore, combining metabolite pattern data with treatment outcomes can help to anticipate how well different treatment types will work for them and how much they might benefit from individualized therapy modifications (Shahisavandi et al., 2023).

Future directions

Most current research centers on point-of-care assays, biosensor integration, and the artificial intelligence-based interpretation of biomarker data. Such methods could help translate laboratory discoveries into tools for clinical practice.

Limitations

Despite significant advances in biomarker discovery, many challenges still limit their use in clinical practice. Population differences, along with the lack of assay standardization and limited validation, hold back the use of biomarkers for early disease diagnosis. In the future, we should use combined datasets including markers from various categories: metabolomic, proteomic, and transcriptomic. This will give us the possibility to track early changes in molecules before diabetes starts. On the other hand, implementing this in clinical practice remains problematic because many issues remain with assay standardization, population-specific validation, and the integration of heterogeneous data (Zhang et al., 2023; Thorand et al., 2021).

4. CONCLUSION

Evidence from multiple-marker research shows that combining metabolic, protein-based, lipid-based, inflammatory, and genetic markers greatly improves the ability to detect early stages of T2DM compared to using only glucose-based markers. The use of multiple markers will improve sensitivity and specificity to identify people with T2DM at its earliest stages.

At present, diagnostic models are inadequate to determine an individual patient's risk of progressing through different stages of Type 2 Diabetes. New data show that biomarkers can help fill these gaps by detecting insulin resistance earlier. However, implementation in clinical use still requires validation and calibration specific to different populations. In summary, new diagnostic methods for T2DM should include both biochemical tests and proven, validated multi-omic biomarker panels. These future diagnostic procedures will enable us not only to detect diabetes at advanced stages but also to develop personalised prevention strategies.

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Conflict of interest
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Data and materials availability
All data associated with this study will be available based on reasonable request to the Corresponding Author.

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