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Integration of omics technologies for the identification of predictive biomarkers in type 2 diabetes: a comprehensive analysis of recent literature

Integração de tecnologias ômicas para a identificação de biomarcadores preditivos no diabetes tipo 2: uma análise abrangente da literatura recente
Integración de tecnologías ômicas para la identificación de biomarcadores predictivos en diabetes tipo 2: un análisis exhaustivo de la literatura reciente

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The insights about the role of omics technologies in type 2 diabetes mellitus (T2DM), represent potential for aiding developing countries in addressing the growing problem of diabetes. Accessible omics-based biomarkers could improve early detection, optimize treatment allocation, and inform resource-efficient healthcare strategies, thereby enhancing diabetes management in resource-limited settings.
Originality/value:
This review offers a comprehensive synthesis of high-quality studies showcasing the transformative potential of omics technologies in unraveling novel biomarkers and molecular pathways for type 2 diabetes mellitus.

ABSTRACT

Background: Omics technologies, such as genomics, proteomics, metabolomics, and Transcriptomics are being used for identifying biomarkers. These biomarkers are unraveling the molecular mechanisms underlying type 2 diabetes mellitus (T2DM), which can help to promote more personalized treatment strategies and advance our understanding of disease pathogenesis. Omics approaches enable the examination of genetic, protein, metabolic, and gene expression profiles more comprehensively while offering insights into T2DM risk, progression, and potential therapeutic targets. **Methods:** This review follows a systematic methodology, aimed at evaluating omics technology's role in diabetes research. Utilizing literature searches, we got an initial pool of 257 studies with a rigorous selection process and narrowed the selection to 10 high-quality studies. Our methodology approach ensured the inclusion of relevant, peer-reviewed articles that contribute significantly to understanding the application of omics technologies in predicting biomarkers for type 2 diabetes. **Results:** The systematic review identifies ten high-quality studies illuminating substantial omics technology's role in advancing our understanding of type 2 diabetes (T2D). Collectively, these studies demonstrate how genomics, proteomics, metagenomics, metabolomics, and Transcriptomics have uncovered novel biomarkers and molecular pathways for T2D. Our findings underscore all the omics potentials specifically for developing predictive biomarkers, enhancing diagnostics, and tailoring personalized treatment strategies. Genetic variations, metabolic alterations, and protein and RNA expression profiles were highlighted as key areas where omics technologies offer insights into the pathophysiology and management of T2D.

Keywords: Omics Technologies, Transcriptomics, Type 2 Diabetes Mellitus, Biomarker Discovery.

RESUMO

Contexto: Tecnologias ômicas, como genômica, proteômica, metabolômica e transcriptômica estão sendo usadas para identificar biomarcadores. Esses biomarcadores estão desvendando os mecanismos moleculares subjacentes ao diabetes mellitus tipo 2 (DM2), o que pode ajudar a promover estratégias de tratamento mais personalizadas e a avançar na nossa compreensão da patogênese da doença. As abordagens ômicas permitem o exame de perfis genéticos, proteicos, metabólicos e de expressão gênica de forma mais abrangente, ao mesmo tempo que oferecem insights sobre o risco, progressão e possíveis alvos terapêuticos do DM2. **Métodos:** Esta revisão segue metodologia sistemática, com o objetivo de avaliar o papel da tecnologia ômica na pesquisa do diabetes. Utilizando pesquisas bibliográficas, obtivemos um conjunto inicial de 257 estudos com um processo de seleção rigoroso e restringimos a seleção a 10 estudos de alta qualidade. Nossa abordagem metodológica garantiu a inclusão de artigos relevantes revisados por pares que contribuem significativamente para a compreensão da aplicação de tecnologias ômicas na previsão de biomarcadores para diabetes tipo 2. **Resultados:** A revisão sistemática identifica dez estudos de alta qualidade que iluminam o papel substancial da tecnologia ômica no avanço da nossa compreensão da diabetes tipo 2 (DT2). Coletivamente, esses estudos demonstram como a genômica, a proteômica, a metagenômica, a metabolômica e a transcriptômica descobriram novos biomarcadores e vias moleculares para o DM2. Nossas descobertas ressaltam todos os potenciais ômicos especificamente para o desenvolvimento de biomarcadores preditivos, melhorando o diagnóstico e adaptando estratégias de tratamento personalizadas. Variações genéticas, alterações metabólicas e perfis de expressão de proteínas e RNA foram destacados como áreas-chave onde as tecnologias ômicas oferecem insights sobre a fisiopatologia e o manejo do DM2.

Palavras-chave: Tecnologias ômicas, Transcriptômica, Diabetes Mellitus Tipo 2, Descoberta de Biomarcadores.

RESUMEN

Antecedentes: Se están utilizando tecnologías ômicas, como la genómica, la proteómica, la metabolómica y la transcriptómica, para identificar biomarcadores. Estos biomarcadores están desentrañando los mecanismos moleculares subyacentes a la diabetes mellitus tipo 2 (DM2), lo que puede ayudar a promover estrategias de tratamiento más personalizadas y mejorar nuestra comprensión de la patogénesis de la enfermedad. Los enfoques ômicos permiten un examen más completo de los perfiles genéticos, proteicos, metabólicos y de expresión génica, al tiempo que ofrecen información sobre el riesgo, la progresión y los posibles objetivos terapéuticos de la DM2. **Métodos:** Esta revisión sigue una metodología sistemática, cuyo objetivo es evaluar el papel de la tecnología ômica en la investigación de la diabetes. Utilizando búsquedas bibliográficas, obtuvimos un grupo inicial de 257 estudios con un riguroso proceso de selección y redujimos la selección a 10 estudios de alta calidad. Nuestro enfoque metodológico aseguró la inclusión de artículos relevantes revisados por pares que contribuyen significativamente a comprender la aplicación de tecnologías ômicas en la predicción de biomarcadores para la diabetes tipo 2. **Resultados:** La revisión sistemática identifica diez estudios de alta calidad que iluminan el papel sustancial de la tecnología ômica en el avance de nuestra comprensión de la diabetes tipo 2 (DT2). En conjunto, estos estudios demuestran cómo la genómica, la proteómica, la metagenómica, la metabolómica y la transcriptómica habían descubierto nuevos biomarcadores y vías moleculares para la diabetes tipo 2. Nuestros hallazgos subrayan todos los potenciales ômicos especificamente para desarrollar biomarcadores predictivos, mejorar el diagnóstico y adaptar estrategias de tratamiento personalizadas. Las variaciones genéticas, las alteraciones metabólicas y los perfiles de expresión de proteínas y ARN se destacaron como áreas clave donde las tecnologías ômicas ofrecen información sobre la fisiopatología y el tratamiento de la diabetes tipo 2.

Palabras clave: Tecnologías ômicas, transcriptómica, diabetes mellitus tipo 2, descubrimiento biomarcadores.

INTRODUCTION

Diabetes Mellitus (DM) is formidable chronic metabolic disorder that affects millions of people around the world (Villa Solis et al., 2023), with elevation in blood glucose levels, and of it retains over prolonged periods it will precipitates severe damage to vital organs, including the heart, blood vessels, eyes, kidneys, and nerves, evidence by Dilworth et al., (2021) confirmed. In diabetes spectrum, Type 2 Diabetes Mellitus (T2DM) is predominant form because is more common compared to type 1 diabetes and gastric diabetes. T2DM is commonly manifesting in adults. It is characterized by the body's escalating resistance to insulin or an insufficiency in insulin production. Goyal, 2023 stated global landscape has witnessed a striking surge in T2DM prevalence across nations of varying income levels over the last three decades, recognizing it a pressing public health challenge. But research by Kupai et al., 2022 suggested the advent of omics technologies herald's transformative era in the prediction and management of Type 2 Diabetes Mellitus (T2DM), offering unprecedented insights into its pathophysiology. Major instrumental technologies genomics, proteomics, metabolomics, and Transcriptomics are identifying predictive biomarkers for T2DM. The critical data derived from these omics studies not only facilitate early diagnosis but also enable personalized therapeutic interventions, significantly enhancing patient outcomes (Kupai et al., 2022). Omics technologies in T2DM are important because they intricate molecular and biochemical networks underlying the disease, thereby identifying novel targets for prevention and treatment and they provide holistic approach towards precision medicine to control T2DM symptoms at global level (Kupai et al., 2022).

Diabetes affects an estimated 422 million adults globally, primarily in low- and middle-income countries, resulting in approximately 1.5 million deaths each year. The prevalence and incidence of diabetes has increased in the past several decades. Importantly, the number of individuals with diabetes has increased from 108 million in 1980 to 422 million in 2014. The prevalence has been notably sharper in low- and middle-income countries compared to their high-income counterparts. Diabetes acts as a principal causative factor for blindness, kidney failure, heart attacks, stroke, and lower limb amputation. Between 2000 and 2019, diabetes-induced mortality rates by age witnessed a 3% augmentation (World Health Organization: WHO & World Health Organization: WHO, 2023). Moreover, in 2019, diabetes alongside kidney disease attributed to diabetes was responsible for an estimated 2 million deaths. A healthy lifestyle encompassing a balanced diet, regular physical activity, maintaining normal body weight, and abstaining from tobacco usage stands as a pivotal preventative measure against T2DM. Furthermore, diabetes management and mitigation of its complications are feasible through diet, physical activity, and medication, alongside regular screening and treatment for complications (World Health Organization: WHO & World Health Organization: WHO, 2023).

In 2014, diabetes prevalence among adults aged 18 and older was 8.5%. The year 2019 saw diabetes as the direct cause of 1.5 million deaths, with 48% of all diabetes-related deaths occurring before the age of 70. An additional 460,000 deaths were due to kidney disease caused by diabetes, and elevated blood glucose levels were responsible for approximately 20% of cardiovascular deaths. The period between 2000 and 2019 marked a 3% increase in the age-standardized mortality rate from diabetes. In contrast, the mortality rate due to diabetes in lower-middle-income countries escalated by 13%. In contrast, the probability of dying from one of the four main noncommunicable diseases (cardiovascular diseases, cancer, chronic respiratory diseases, or diabetes) between the ages of 30 and 70 worldwide fell by 22% between 2000 and 2019. This statistical landscape underlies the increasing burden of T2DM on global health ndash; accentuating the necessity for a more unified approach to its management, prevention, and education to ameliorate its toll. The intricate web of genetic, environmental, and lifestyle factors in the pathogenesis of T2DM represents the daunting complexity of managing this increasingly prevalent global health conundrum (World Health Organization: WHO & World Health Organization: WHO, 2023).

METHODOLOGY

The role of omics technologies such as genomics, proteomics, metabolomics, and Transcriptomics in diabetes research was investigated systematically. The role of the omics approaches in identifying biomarkers was explored. A total of 10 studies were selected to conduct the review.

Study Design: Comprehensive analysis of systematic literature

Design: Primary Keywords include Omics, Type 2 Diabetes, Biomarkers, Predictive Biomarkers, Genomics, Proteomics, Metabolomics, Transcriptomics, Integrated Omics, Multi-Omics. Secondary keywords were Bioinformatics, Systems Biology, Precision Medicine, Type 2 Diabetes Mellitus, T2DM, Molecular Markers, and Phenomics. The decided databases Embase, Cochrane, and PubMed were excellent starting points. Each has its strengths and coverage areas, making them complementary in a systematic search. PubMed was used for broad coverage of life sciences, with a focus on biomedicine.

Excellent for all omics-related research. Embase is strong in drug research, medical devices, and clinical guidelines. It complements PubMed well by including conference abstracts and other grey literature. To cover all the high-quality systematic reviews and clinical trials, Cochrane Library was selected because it covers a broad range of data; if it has fewer primary research articles on omics technologies, it is invaluable for reviews on biomarkers and diabetes management.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Studies that focus on omics technologies (genomics, proteomics, metabolomics, Transcriptomics) in the context of type 2 diabetes.
- Studies that identify, validate, or review predictive biomarkers for type 2 diabetes.
- Articles published in the last ten years to ensure the relevance and novelty of the technologies discussed.
- Peer-reviewed articles and systematic reviews.

Exclusion Criteria

- Studies focusing on type 1 diabetes or other non-diabetes conditions.
- Opinion pieces, editorials, and non-peer-reviewed literature.
- Studies not conducted on human subjects.
- Articles not available in English (if language capability is limited).

Search and Selection Strategy

PubMed search strategy:

To maximize the search effectiveness, the keywords can be grouped and combined using Boolean operators.

Integration of Omics Technologies: This is the core concept focusing on the integration aspect (Integrated Omics OR Multi-Omics) AND (Omics).

Specific Omics Fields: To cover all relevant omics areas (Genomics et al., OR Transcriptomics).

Application to Type 2 Diabetes: Ensuring the focus remains on Type 2 Diabetes (Type 2 Diabetes OR T2DM) AND (Biomarkers OR Predictive Biomarkers).

Supporting Technologies and Approaches: Incorporating bioinformatics and systems biology for a comprehensive search (Bioinformatics et al.).

Combining All Aspects: To encapsulate the full breadth of your research topic ((Integrated Omics OR Multi-Omics) AND (Genomics OR Proteomics OR Metabolomics OR Transcriptomics) AND (Type 2 Diabetes OR T2DM) AND (Biomarkers OR Predictive Biomarkers)) AND (Bioinformatics et al.).

The advanced search strategy was:

((Integrated Omics[Title/Abstract] OR Multi-Omics[Title/Abstract]) AND (Genomics[Title/Abstract] OR Proteomics[Title/Abstract] OR Metabolomics[Title/Abstract] OR Transcriptomics[Title/Abstract]) AND (Type 2 Diabetes[Title/Abstract] OR T2DM[Title/Abstract]) AND (Biomarkers[Title/Abstract] OR Predictive Biomarkers[Title/Abstract])) AND (Bioinformatics[Title/Abstract] OR Systems Biology[Title/Abstract] OR Precision Medicine[Title/Abstract])

Embase Search Strategy

Embase is particularly strong in its coverage of drug research, pharmacology, and biomedical literature, offering a wide array of indexed journals not found in other databases. For your topic, it is crucial to incorporate Emtree terms (Embase's controlled vocabulary) along with keywords to ensure a comprehensive search.

A comprehensive search string in Embase might look like this:

('genomics'/exp OR 'proteomics'/exp OR 'metabolomics'/exp OR 'transcriptomics'/exp OR 'Integrated Omics' OR 'Multi-Omics') AND ('Type 2 diabetes mellitus'/exp OR 'Type 2 Diabetes' OR 'T2DM') AND ('biomarker'/exp OR 'Predictive Biomarkers') AND ('Bioinformatics' OR 'Systems Biology' OR 'Precision Medicine').

Cochrane Library Search Strategy

The Cochrane Library, with its focus on evidence-based medicine, is an excellent resource for systematic reviews and clinical trials. While it may not have the same breadth of biomedical literature as Embase, its strength lies in high-quality

studies on interventions and outcomes.

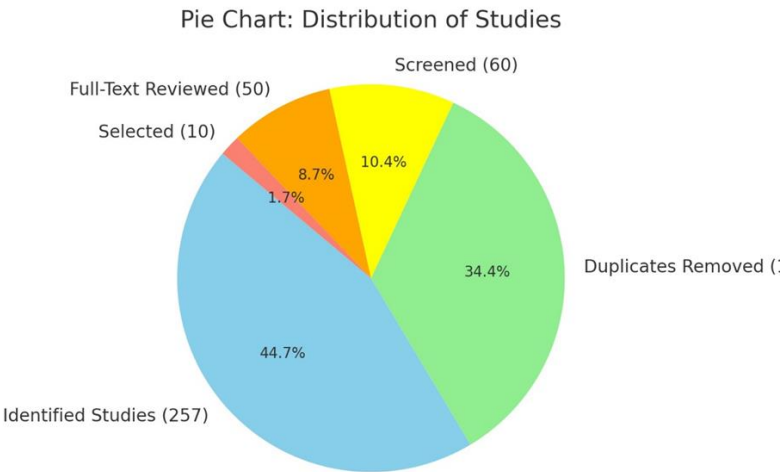
Targeted search might include: "Omics Technologies" AND "Type 2 Diabetes" AND "Biomarkers" AND (Genomics OR Proteomics OR Metabolomics OR Transcriptomics) AND "Predictive Biomarkers."

Selection Process

In the initial stage of our comprehensive literature review, a total of 257 studies were identified through database searches that met the preliminary criteria based on titles and abstracts. The first step involved duplicates removal, which resulted in 198 unique studies.

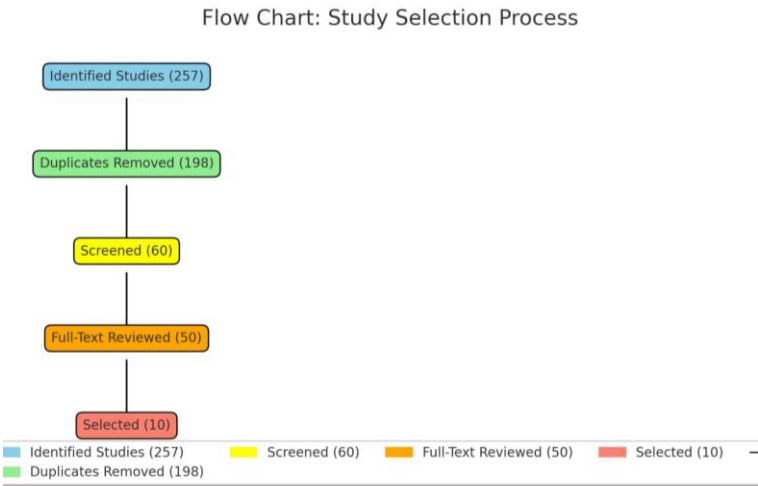
Titles and abstracts of these 198 studies were screened for relevance to the integration of omics technologies for identification of predictive biomarkers for Type 2 Diabetes, leading to the removal of 138 studies that did not meet the inclusion criteria, or were unrelated to the research question, and leaving 60 potentially relevant studies. These 60 studies then underwent full-text review, during which each study was subjected to rigorous evaluation of its methodological quality and relevance to our research objective, as well as of the specificity of their findings with respect to predictive biomarker identification in Type 2 Diabetes. As a result, 50 studies were excluded due to lack of information on omics data integration, absence of predictive biomarker focus, or methodological limitations. These included observational studies, intervention studies and review papers. This strenuous selection process yielded 10 high quality studies that were directly aligned with our research objective. These studies cover a range of omics technologies—genomics, proteomics, metabolomics and microRNA Transcriptomics—and provide a holistic representation of the current landscape of predictive biomarker identification for Type 2 Diabetes through integrated omics approaches. The funneling of 257 initial studies to the final 10 identified ones underscores the strict criteria and methodological rigor employed to ensure the relevance and quality of the evidence included in our analysis.

Figure 1. Distribution of the studies



Note: The chart is describing how studies are distributed among different stages, facilitating a quick grasp of the study selection's progression

Figure 2. Study selection process



Note: The diagram visually conveys the systematic and rigorous methodology employed in the selection of studies

RESULTS AND DISCUSSION

Omics Technologies in T2DM Compared to Conventional Technologies

Recent advances in high-throughput technologies have piqued interest in omics-based approaches in biological research. Omics-based techniques, which include genes, RNAs, proteins, and metabolites on a universal scale, collectively called systems biology, aim to understand molecules comprehensively and their dynamic interactions in physiological and disease processes rather than rely on measuring a few molecules based on a hypothesis, which is the focus of classical methodologies (Dai & Shen, 2022). Omics technologies offers the possibility to explore molecular changes in various conditions, including in disease states.

Genomics and Type 2 Diabetes Biomarkers

Genomic research engages in a comprehensive investigation of the structure, function, and expression of genetic material in cells or organisms. It is data-intensive, and focuses on genetic variations, such as single nucleotide polymorphisms (SNPs), and chromosomal aberrations, being key to understanding disease. These variations are implicated in susceptibility to disease, response to particular therapies, and prognosis. Genotype microarrays and next-generation sequencing for whole-genome and exome sequencing (the portion of the genome that codes for protein), have been developed for uncovering genetic markers of diseases, e.g. Type 2 Diabetes (T2D) or Gestational Diabetes Mellitus (GDM). TCF7L2, ABCC8, CAPN10, GLUT2, IRS1, GCK, PRAG, HNF1A, KLF14 and GCCR all contribute to the disease process of T2D (Tabackman, 2023). Huge progress has been made in identifying the many genes that have been linked to a vulnerability to T2D, establishing the genetic basis for this disease. Numerous genes are known for GDM, revealing that much remains to be understood. Nevertheless, both T2D and GDM share pathophysiological characteristics and genetic origins (Yahaya et al., 2020). Consequently, genes like, CDKAL1, KCNQ1, and CDKN2A/B, have been strongly associated with T2DM. Their SNPs have been found in blood, as well as in tissue of diabetic targets, linking them with possible blood-based biomarkers for these different types of diabetes (Fadheel et al., 2022).

Thus, the gene CDKAL1 located on chromosome 6p22.3 has been associated with impaired insulin secretion in both T2D and type 1 diabetes. This defect correlates with deficiencies in cAMP-induced insulin production and in particular with the miscoding of the Lys-coding codon in proinsulin, which in turn results in the diminution of proinsulin synthesis and increased endoplasmic reticulum stress. Because CDKAL1's function is the synthesis of tRNA^{Lys}, which deciphers Lys residue translation in proinsulin, its importance in the pathology of diabetes is apparent. Similarly, the KCNQ1 gene located on chromosome 11p15.4 encodes the Kv7.1 α -subunit of potassium voltage-gated channels. Variants in this gene are thought to affect insulin secretion and glucose tolerance without impacting pancreatic β -cell maturation. The gene's involvement in β -cell action potentials and insulin exocytosis underscores its importance in diabetes. The CDKN2A/B genes, located on chromosome 9p21.3, encode proteins regulating cell cycle progression and have implications in tumorigenesis, senescence, and ageing. Specifically, the p16INK4A protein, expressed in pancreatic β -cells, plays a vital role in cell proliferation and insulin secretion. SNPs within these genes are linked to reduced β -cell mass and function, presenting a risk for T2D (Kong et al., 2016).

Metabolomics in Type 2 Diabetes Mellitus Research

Metabolomics is the comprehensive analysis of small molecules, known as metabolites, within cells, tissues, or organisms under specific conditions. These metabolites – which include amino acids, fatty acids, and carbohydrates – are the intermediates and byproducts of cellular metabolism, and thus serve as windows to metabolic dysregulation caused by diseases, such as Type 2 Diabetes Mellitus (T2D). The field employs advanced analytical techniques, primarily mass spectrometry (MS) and nuclear magnetic resonance (NMR), to identify metabolic alterations that deviate from the norm, offering a window into the disease's metabolic signature (Qiu et al., 2023). Tam et al. suggested metabolic perturbations in T2D that cause insulin resistance, have been extensively studied through metabolomics. This approach has proven effective in discovering diagnostic biomarkers across various human biological samples like serum, saliva, skin, and urine. Notable biomarkers identified include 1,5-Anhydroglucitol (1,5-AG) and 5'-Methylthioadenosine (5'-MTA) and their levels either increasing or decreasing in relation to T2D pathogenesis (Tam et al., 2017).

1,5-AG is a stable blood compound and it decreases in T2D patients, inversely correlating with blood glucose levels and this level down is attributed to glucose's competition with 1,5-AG for renal reabsorption. As a diagnostic marker, 1,5-AG demonstrates high sensitivity and specificity, outperforming another glycemic indicator. However, its effectiveness as a marker for Gestational Diabetes Mellitus (GDM) remains limited. Saliva, an essential component of oral physiology, reflects biochemical changes, including glucose levels, in diabetic patients. Metabolomics studies have shown that saliva 1,5-AG levels correlate with those in blood, inversely related to blood glucose levels. This makes saliva 1,5-AG a potential non-invasive biomarker for T2D diagnosis (Migała et al., 2022). In urine, metabolites such as 5'-MTA have shown significant changes in late-onset T2D compared to non-diabetic individuals, suggesting their potential as validated biomarkers for T2D. Breath

analysis, exploring volatile organic compounds (VOCs) derived from metabolic processes, has emerged as a promising non-invasive diagnostic method. Acetone, a ketosis byproduct, has been identified with high sensitivity and specificity in breath tests for diabetes. Signals on prediabetes and T2D overlap significantly; thus, early diagnosis in cure development for these diseases has led to sensor advances. These sensors include 1-butyl-3-methylimidazolium tetrafluoroborate [C4mim][BF₄]-based flexible sensors that integrate with waste and human health management the e-skin & monitoring system; these have exhibited photosensitivity for sensitivity and selectivity of 9.58% and 11.35% towards acetone, one of several VOCs that could signal diabetes on breath (Tao et al., 2017). Quartz crystal microbalance sensors are being developed for stringently detecting acetone among ppb-level VOCs with 96% sensitivity and 99% specificity for diabetes (Rodríguez-Torres et al., 2023).

In an illustrative breath test case of ¹³C-enriched foods for prediabetes and T2D diagnosis, breath tests were 87% sensitive and 76% specific with a 65% accurate positive predictive value and 86% accurate negative predictive value for detecting altered CO₂ breath AUC among controls and diabetics was 0.81 with clinically acceptable accuracy overall; significantly ($p=0.02$) greater at 0.94 among control vs. diabetic alveolar air measurements. These can translate in well-controlled studies for clinical development of similar technologies as early noninvasively. Consequently, precise breath monitoring of circuits closed with the lung BRM to manage waste and human health can guide early diabetes diagnosis for cure development (Wang, 2021).

Metagenomics and Its Role in Type 2 Diabetes Mellitus Research

The intricate relationship between gut microbiota and T2D was revealed in part by the metagenomics approach. This field examines the DNA of various microbial communities taken straight from the environment through the Next-generation sequencing technique of 16S rRNA. These sophisticated sequencing techniques provide researchers with clues about the nature and characteristics of specific types of microbes and the pathways in which they function as biomarkers for disease like T2D. The researchers presented data showing that T2D patients had higher levels of sulfate-reducing bacteria such as *Desulfovibrio spp.* These are microorganisms associated with an increased metamorphosis process of sulphur, the raw material for life and popper inside rocks! Furthermore, T2D patients exhibited increased numbers of pathogenic bacteria including *Eggerthella lenta* and *Escherichia coli*, implying a disturbed gut environment. Although vital for maintaining gut health and metabolic balance, a significant decrease in butyrate-producing bacteria such as *Clostridia Eubacterium Faecalibacterium* and *Roseburia* was also observed in T2D patients (Chen et al., 2017). T2D patients exhibit enrichment in metabolic pathways related to the membrane transport of sugars and branched-chain amino acid (BCAA) transport, indicating altered nutrient absorption and amino acid metabolism (Vanweert et al., 2022). There is also an increase in methane metabolism, indicated by a rise in methane-producing microbes like *Methanobrevibacter spp.*, and a decrease in bacterial chemotaxis and flagellar assembly, reflecting a reduction in motility-associated bacteria. Enhanced pathways for xenobiotics degradation and metabolism highlight the microbiota's increased ability to process foreign compounds in T2D (Gan et al., 2019). These shifts not only suggest a decrease in beneficial metabolic functions such as butyrate biosynthesis and vitamin metabolism, potentially affecting the nutritional and metabolic health of T2D patients, but also offer early indicators of metabolic changes preceding T2D development, as seen in the microbial diversity shifts in prediabetic states. The crucial point to note is that gut microbiota profiling could be a good way to diagnose T2D and to use it in therapy, pointing the way forward for individual nutrition solutions and microbiota modulation. However, putting this knowledge into clinical practice will require more research and trials to confirm that these biomarkers are really working or applicable to different people with diabetes disorder, i.e. personalized medicine. Therefore, there is still much research yet to be done to determine if this southern Turkish community indigenous with T2D subjects could use glycemic index foods safely (Bakır-Güngör et al., 2021).

Transcriptomics

The focus of transcriptomics is the all-around analysis of RNA, which includes coding RNAs and noncoding RNAs. This makes it extremely important in understanding the mechanisms behind T2D at a molecular level. This field uses skills such as RNA microarray technology and RNA sequencing with Polymerase Chain Reaction (PCR) techniques to accurately and quantitatively assess the cells and tissues containing one or more types of RNA expressed there. These studies represent an effort to understand what role these RNAs have in structure and regulation, as elucidated in (Bury et al., 2021).

In T2D, transcriptomics shows that microRNAs (miRNAs) play an important role in the regulation of genes associated with insulin resistance. For instance, miR-7, identified in plasma, acts as a negative regulator impacting blood glucose and triglyceride levels. Its overexpression is linked to reduced glucose-stimulated insulin secretion and a decrease in pancreatic β -cell mass (Wan et al., 2017). Similarly, miR-802 targets the expression of the hepatocyte nuclear factor 1 β gene in liver cells, leading to glucose intolerance and insulin resistance by promoting hepatic gluconeogenesis (Grieco et al., 2022). A wide range of miRNAs found in peripheral blood mononuclear cells (PBMCs) of T2D patients, including miR-140-3p, miR-199a-3p, miR-222, and others, have been identified through techniques like qRT-PCR followed by miRNA sequencing or miRNA microarray. Among these, miR-181c-3p and miR-148a-5p have been specifically linked to T2D pathways. Additionally, miR-503 is downregulated in T2D and obesity, while miR-126 correlates with major cardiovascular events, showcasing the diverse

roles of miRNAs in T2D and its comorbidities (Afsharmanesh et al., 2023). The expression profiles of these miRNAs in plasma reveal distinct patterns of upregulation and downregulation, with miRNAs such as miR-7, miR-802, and miR-143-3p being upregulated, whereas miR-126 and miR-503 are among those downregulated. These expression patterns provide insights into the molecular landscape of T2D, offering potential biomarkers for diagnosis and treatment. Beyond blood samples, saliva has emerged as a promising non-invasive source for T2D biomarkers. Transcriptomic diagnostics have identified specific mRNAs in saliva, such as those of KRAS and SAT1, that are upregulated in T2D patients. Conversely, EGFR and PSMB2 mRNAs are downregulated. The combined detection of these mRNAs in saliva can achieve a high sensitivity and specificity for T2D diagnosis, presenting a compelling alternative to traditional blood samples (Siegl et al., 2022).

Table 1. Transcriptomics Biomarkers for T2DM

Biomarker (Gene)	Sensitivity (%)	Specificity (%)
KRAS (K-Ras)	84.6	69.2
SAT1 (Spermidine/Spermine N1-Acetyltransferase 1)	69.2	76.9
SLC13A2 (Solute Carrier Family 13, Member 2)	69.2	84.6
TMEM72 (Transmembrane Protein 72)	46.2	100
PSMB2 (Proteasome Subunit Beta Type-2)	69.2	76.9
EGFR (Epidermal Growth Factor Receptor)	100	46.2

Note: Own elaboration based on the specialized literature

The variability in specificity and sensitivity among various biomarkers is vividly displayed in this table. For example, EGFR's sensitivity rate climbs to 100% but its specificity is at only 46.2% stopping short of a "perfect score." This implies that while the test can reliably pick out T2D sufferers, it will likely give a false positive for some. In contrast, TMEM72 shows a perfect 100% sensitivity to match its unparalleled specificity. But with a sensitivity of only 46.2%, it rarely misidentifies non-T2D cases as T2D showing T2D rather than non-T2D as a rule--though it may also miss a T2D diagnosis in some people (Gan et al., 2019). The variability in these biomarkers' performance highlights the complex nature of T2D diagnosis using saliva mRNAs. While some biomarkers like KRAS and SAT1 offer a balanced sensitivity and specificity, making them potentially useful for preliminary screenings, others like TMEM72 could serve as confirmatory tests due to their high specificity. The combination of these biomarkers could enhance diagnostic accuracy, allowing for a non-invasive, efficient screening tool for T2D. However, the critical analysis underscores the need for further validation and research to optimize the use of saliva mRNA profiles in clinical settings, ensuring they complement existing diagnostic methods effectively (Gan et al., 2019).

Proteomics

Proteomics provides a fine-grained approach to biomarker detection in type 2 diabetes mellitus (T2DM), utilizing methods of protein arrays and mass spectrometry to analyze the abundance, structure, function, and interactions of proteins. Though classical autoantibodies such as ZnT8A, IA-2A, GADA, and IAA are found in T2DM patients they are not useful for interim diagnosis because they are shared with type 1 diabetes and only have a limited linkage to complications specific to T2DM. Recent advancements have identified novel serum proteomic biomarkers, such as complement C3f fragments and kininogen one isoform one precursor, which demonstrate notable diagnostic accuracy. Proteins like PPARG2 and UBE2M autoantibodies have shown potential in distinguishing T2DM patients from controls, with improved diagnostic sensitivity and specificity observed when combined. Additionally, proteins such as leptin, retinol-binding protein 4, and betatrophin have been linked to T2DM pathophysiology, offering new avenues for biomarker discovery. Salivary proteins like alpha-2-macroglobulin (A2MG) present a non-invasive marker option, correlating with glucose levels. Furthermore, the study of metabolic disorder markers such as MCP-1 has revealed its association with insulin resistance and T2DM risk, underscoring the therapeutic and diagnostic potential of proteomics in T2DM management (Gan et al., 2019).

Table 2. Categorized Biomarkers for Type 2 Diabetes Across Different Omics Technologies

Sample Type	Omics Technology	Biomarker Type	Biomarkers	References
Blood	Genomics (SNPs)	Risk	PPARG, FTO, CDC123, TCF7L2, CDKAL1, WFS1, KCNJ11, SLC30A8, ADAMTS9, IGF2BP2, TSPAN8, JAZF1	(Gan et al., 2019)
	Transcriptomics (mRNA)	Diagnostic	IL-6, IL-8, TTP	(Bell et al., 2021)
	DNA Methylation	Diagnostic, Prognostic	ABCG1, PHOSPHO1, SOCS3, SREBF1, TXNIP	(Dayeh et al., 2016)
	microRNA	Diagnostic, Prognostic, Pharmacodynamic/response	hsa-miR-126, hsa-miR-146a, hsa-miR-150, hsa-miR-192, and others	(Padilla-Martínez et al., 2021)
Saliva	DNA Methylation	Prognostic	ADCY5, ABCC8, PDX1, TCF7L2, IGF2BP2, IRS1, SLC30A8	(Prasad & Groop, 2015)
	microRNA	Diagnostic	hsa-miR-146a, hsa-miR-146b, hsa-miR-155, hsa-miR-203	(Al-Rawi et al., 2020)
Urine	Genomics (SNPs)	Prognostic	KCNJ11, TCF7L2, HNF1A, HNF1B, PPARG, SLC30A8, CDKAL1	(Rabby et al., 2023)
	DNA Methylation	Prognostic	SMTNL2, G6PC	(Padilla-Martínez et al., 2021)
	microRNA	Prognostic	hsa-miR-126, hsa-miR-29a, hsa-miR-133b, hsa-miR-342, hsa-miR-30a, and others	(Lee et al., 2023)

Note: Own elaboration based on the specialized literature

Table 2 structure simplifies the extensive data presented, making it accessible for readers to understand the current landscape of T2D biomarker research. Categorized applications can be found alongside the biomarker names. The table structure provides a clear and concise overview of the biomarkers identified for T2D across different sample types and omics technologies.

The systematic review presented in the article sheds light on the transformative role of omics technologies in understanding and managing Type 2 Diabetes Mellitus (T2DM). Diabetes, particularly T2DM, has emerged as a significant global health challenge, with its prevalence steadily increasing over the past few decades. Omics technologies, encompassing genomics, proteomics, metabolomics, and transcriptomics, have revolutionized our approach to studying T2DM by providing comprehensive insights into its underlying molecular mechanisms. Through these advanced techniques, researchers have been able to explore the intricate genetic, protein, metabolic, and gene expression profiles associated with T2DM, offering unprecedented opportunities for early diagnosis, personalized treatment, and targeted interventions.

One of the notable findings highlighted in the review is the identification of predictive biomarkers for T2DM. Omics studies have revealed a myriad of genetic variations, protein alterations, metabolic dysregulations, and gene expression patterns that are closely linked to the development and progression of T2DM. For instance, genomic research has identified several genetic loci and single nucleotide polymorphisms (SNPs) associated with T2DM susceptibility, providing valuable insights into the genetic basis of the disease. Similarly, metabolomics studies have uncovered distinct metabolic signatures and biomarkers indicative of T2DM, offering potential diagnostic and prognostic tools for clinicians.

Moreover, the review underscores the importance of integrating multiple omics datasets to gain a comprehensive understanding of T2DM pathophysiology. By combining genomics, proteomics, metabolomics, and transcriptomics data, researchers can unravel complex molecular networks and identify novel therapeutic targets for T2DM management. This holistic approach towards precision medicine holds promise for improving patient outcomes and addressing the multifaceted nature of T2DM.

Furthermore, the article discusses the clinical implications of omics-derived biomarkers in T2DM management. Early detection of T2DM risk through predictive biomarkers can enable timely interventions, lifestyle modifications, and targeted therapies to prevent or delay the onset of the disease. Additionally, personalized treatment strategies based on individual molecular profiles can optimize therapeutic efficacy and minimize adverse effects, paving the way for more tailored and effective diabetes care.

CONCLUSIONS

This review highlights a milestone in the field due to the huge impact of omics technologies in the exploration of diabetes, identifying biomarkers and unraveling the complexity of molecular mechanisms of type 2 diabetes. Integration of genomics, proteomics, Transcriptomics, metagenomics and metabolomics represents a comprehensive approach to decipher the complicated picture of T2D pathology. By analyzing disease phenotypes and the characteristics of participating individuals, omics technologies hold promises for increased precision in prediction, diagnosis, and personalized treatment of this disease. Current research will need to be validated through advanced clinical investigations, to integrate omics data for development of new diagnostic tools, and to use it in combination with other information sources to design new therapeutic strategies.

Main limitations of the study and future research

While the systematic review argues for the importance of omics technologies in understanding type 2 diabetes mellitus (T2DM), several limitations require consideration. First, the review relies on published literature, and in so doing, there may be a possibility of publication bias that would exclude certain types of data that are more likely to be found in unpublished studies or non-English language articles. Besides, the mentioned studies would be considered at different levels of granularity in methodology, sample size, and population demographic. Further research should try and resolve these inconsistencies by the incorporation of diverse study populations, standardized methodologies, and multi-omics approaches towards completely elucidating the molecular pathways in the pathogenesis of T2DM. Additionally, temporal dynamics of omics biomarkers are critical in clarifying disease progression and response to treatment and are key in creating more effective personalized therapeutic approaches. Integrating omics data with clinical parameters, along with leveraging advanced machine learning algorithms, may better the predictive accuracy of biomarkers regarding T2DM risk stratification and prognosis.

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B. data research and statistical analysis:	20%	20%	20%	20%	20%
C. elaboration of figures and tables:	20%	20%	20%	20%	20%
D. drafting, reviewing and writing of the text:	20%	20%	20%	20%	20%
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