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Clinical Significance of Emerging Metabolic Biomarkers in Early Prediction of Insulin Resistance and Type 2 Diabetes Mellitus: A review study

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Abstract

This review outlines the growing clinical importance of emerging metabolic biomarkers to the early detection of insulin resistance (IR) and type 2 diabetes mellitus (T2DM). Due to the long period of T2DM, there is an urgent necessity to identify biomarkers that can identify metabolic derangement at a preclinical stage. The data collected herein shows that lipid metabolic changes, alterations in the amino-acid profile, intermediate metabolites of the energy-generating pathways, and both inflammatory and adipokine signalling changes predetermine the overt hyperglycaemia by a few years. Markers derived by lipidomics, discrete amino-acids, and their metabolites, glucose and mitochondrial energy pathway substrates, and inflammatory mediators all reflect major pathophysiology underlying IR and T2DM, i.e. impaired insulin signalling, pancreatic β-cell dysfunction, gluconeogenic excess of the liver, ectopic lipid accrual, mitochondrial inefficiency, and chronic low-grade inflammation. It is always indicated in prospective cohort studies that these biomarkers significantly add to the risk stratification that is not sufficiently achieved with the conventional clinical determinants, and thus, it is easier to identify people who are at high risk earlier. The review also elaborates on mechanistic interconnections between biomarkers and disease pathogenesis and the issues surrounding the assay normalisation, population heterogeneity, cost-effectiveness, confounding variables, and the ethical issues. Altogether, the evidence supports the promise of multi-omics and metabolite-targeted interventions to transform the paradigm of early detection and preventive in T2DM; however, large-scale, longitudinal, ethnically diverse researches, as well as standardised assays and intervention trials based on biomarkers are all critical requirements before a routine translation into clinical practice.

Keywords: Insulin resistance; Diabetes Mellitus (T2DM); Lipid; Amino acid; Glucose

1. Introduction

Diabetes mellitus is a chronic metabolic disease characterised by chronic hyperglycaemia due to absolute or relative insulin deficiency. The problem is associated with acute complications, such as diabetic ketoacidosis and hyperglycaemic hyperosmolar state that can be lethal in case of no prompt intervention and with chronic outcomes, such as retinopathy, neuropathy, nephropathy, and cardiovascular disease. Its large public-health burden, and the growing prevalence, has led to the classification of the World Health Organization and the International Diabetes Federation as a global epidemic [1]. In 1999, a review of the diabetes epidemic was published by the WHO giving detailed endemic estimates. Further reports and significant interventions have also helped in the impressive reduction of the spread of the disease and increased awareness among the world on the risk factors, clinical presentation and preventive measures. In 2015, the disorder is estimated to affect 415 million adults and this figure is projected to be 642 million by 2040 [1]. The ingrained high prevalence can be explained by the long asymptomatic period and due to the fact that the only effective countermeasures can be implemented at an early stage. Hyperglycaemia, together with insulin resistance is a foremost risk factor. The insulin signalling in target tissues is attenuated in this resistance and leads to the failure to maintain normoglycaemic equilibrium. This consequent decrease in glucose homeostasis triggers

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increased insulin release by pancreatic β-cells, which eventually exhausts them and causes death. Later hyper-insulinaemia and hyperglycaemia are followed by impaired glucose tolerance, prediabetes, and, finally, open diabetes. The problem of diabetes continues being a significant challenge to the health of a population, as the population is constantly growing, urbanisation is becoming increasingly more advanced, and changes in lifestyle and nutrition trends, especially in developing countries [2].

2. Background: Insulin resistance and type 2 diabetes mellitus

Insulin resistance arises when target tissues—mainly liver, muscle, and adipose tissues—exhibit diminished sensitivity to insulin, hampering glucose homeostasis. In response, pancreatic β cells increase insulin secretion; however, when insulin production fails to compensate for insulin resistance, glucose production in the liver and free fatty acid (FFA) release from adipose tissue increase, eventually leading to the metabolic syndrome and type 2 diabetes mellitus (T2DM). T2DM is characterized by a relative insufficiency of insulin, due to defective insulin secretion and/or action, often triggered by β-cell dysfunction. The disease is diagnosed when hyperglycemia occurs or when specific glucose thresholds are surpassed [3]. Epidemiological data show that serum insulin increases before the clinical onset of T2DM. β-cell dysfunction is closely associated with proteinuria, one of the earliest detectable renal complications. These observations suggest that the disease could be diagnosed at the stage of insulin resistance before the appearance of abnormal plasma glucose. For widespread prediction of T2DM and pre-diabetes, measuring plasma glucose is impractical because this test requires fasting and is affected by acute exercise and medication intake. The presence of anti-insulin autoantibodies can also indicate the development of type 1 diabetes [2].

3. Emergent metabolic biomarkers: definitions and measurement

Emergent biomarkers can be mechanistically linked to insulin resistance (IR) and T2DM. Insulin resistance (IR), defined as reduced responsiveness to insulin in target tissues, is the earliest defect in the pathophysiology of type 2 diabetes mellitus (T2DM). Over time and depending on additional genetic and environmental factors, individuals may develop T2DM, which is currently diagnosed on the basis of fasting glucose ≥ 7.0 mmol/L, 2-hour glucose ≥ 11.1 mmol/L in an oral-glucose-tolerance test (OGTT), or glycated hemoglobin (HbA1c) ≥ 6.5% (≥ 48 mmol/mol). The risk factors associated with T2DM include family history, physical inactivity, obesity, gestational diabetes, and polycystic ovary syndrome. Globally, the number of people with T2DM is expected to increase from 463 million in 2019 to 700 million by 2045, with the prevalence increasing steeply, particularly in low- and middle-income countries [1,4,5].

3.1. Lipidomics-derived markers

A targeted lipidomics approach has identified specific lipid biomarkers in plasma that are independently associated with insulin resistance, representing a major advance in disease mechanistic comprehension [6]. For example, diacylglycerol (DAG) 38:5 is associated with insulin resistance regardless of the assay used to quantify glucose metabolism. Plasma lipidomics can elucidate the relationship between metabolic fingerprints and dietary interventions [7]. Ample longitudinal studies on several cohorts show that systemic lipid profiles differ before the onset of type 2 diabetes. All these observations indicate that targeted plasma lipid analysis can assist in identifying those individuals with increased risk of developing the disease, thus influencing measures to prevent its progression to the clinical stage. picosecond chromatography-mass spectrometry enables high-throughput profiling of 696 lipid species across 33 classes from human serum, facilitating this analysis. Circulating lipids play influential regulatory roles in various metabolic processes and are tightly linked to insulin resistance [8]. Systematic lipidomic studies using large cohort populations can therefore further increase understanding of the disease. Lipid classes including sphingomyelins, phosphatidic acid, lysophosphatidylcholine, diacylglycerol, and triacylglycerol differ significantly between individuals with impaired glucose tolerance and those with normal glucose tolerance. Triacylglycerol species associated with insulin resistance are concentrated in the mid- and long-chain subgroups, while triacylglycerols with saturated fatty acids in full-length 18-carbon chains or longer are negatively associated. Up-regulated sphingomyelins exhibit stronger correlation with more severe insulin resistance and higher fasting blood glucose level [9].

3.2. Amino acid and their derivatives

Insulin-resistant cells exhibit impaired macromolecule metabolism with diminished lipid consumption and greater reliance on glutamine and branched-chain amino acids (BCAA). Reduction in BCAA catabolism due to obesity impairs insulin signaling, leading to beta-cell hypersecretion and increased risk of type 2 diabetes. BCAA and their catabolites associate with relevant dysmetabolic pathways. Aromatic amino acids (AAA) share similar characteristics. AAA accumulate in obesity and correlate with hepatic insulin resistance and lipotoxicity; cotreatment with glucagon also elevates plasma AAA levels [9]. Arterial plaques in atherosclerosis and fatty liver these feeds through two distinct stages

during the initiation of type 2 diabetes. In the specific case of type 2 diabetes predicted through insulin resistance measured with homeostasis assessment model assay II the BCAA is promoted both directly and indirectly through both a direct increased production and by promoting the secretion of triglycerides in very low density lipoprotein [1].

3.3. Metabolites of glucose and energy pathways

The energy input–output equilibrium of an organism is a well-established risk factor for multiple metabolic diseases including obesity and T2D. Such balance can be assessed through systematic measurement of energy fluxes in various forms. In glycolytic pathway, glycerol and glucose has been reported as potential biomarkers to identify T2D risks [1]. Fumarate, malate, succinate and citric acid in TCA cycle are noted as key T2D markers where these metabolites levels shown to elevated in pre-diabetic and diabetic patients [5]. Analysis of glucose and energy pathway metabolomics, therefore, allows an insightful prediction of T2D risks during prediabetic stages.

3.4. Inflammatory and adipokine profiles

The progression of insulin resistance and the subsequent transition to Type 2 Diabetes Mellitus (T2DM) are typically accompanied by the onset of a low-grade chronic inflammatory state associated with obesity. Proinflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), and C-Reactive Protein (CRP), along with a number of adipokines and chemokines, rise in blood concentrations [9]. Increased hepatic production of CRP appears tied to augmentations of free fatty acid and triglyceride fluxes, resulting in the induction of c-Jun N-terminal kinase (JNK) , sterol regulatory element-binding protein 1c (SREBP-1c), and lipotoxic metabolites that all promote insulin resistance. Similarly, the remaining enrichment of lipogenic factors pertaining to the SREBP-1c signaling pathway was connected to the secretion of potent anti-inflammatory adipokines such as Leptin (LEP) and Angiopoietin-like protein 4 (ANGPTL4). The concentration of leptin in circulation is thus related to hepatic destination lipotoxicity and organ-selective insulin resistance [10].

4. Biomarker evidence in early prediction

Emerging metabolic biomarkers improve early prediction of insulin resistance and type 2 diabetes compared with traditional risk factors [11]. Prospective studies clearly demonstrate that multiple cohorts have yielded a spectrum of markers associated with preclinical disturbance of lipid, amino acid, and energy metabolism [1]. Several risk models incorporating biomarkers outperform those based on clinical factors alone, and biomarkers confer substantial incremental value beyond such factors [2]. These findings indicate that metabolites capture physiologic derangements linked to the disease before overt clinical signs become apparent and highlight the potential to define pre-diabetes and related conditions at a much earlier stage. Prospective studies across diverse cohorts have consistently identified metabolic signatures associated with the preclinical onset of type 2 diabetes mellitus (T2DM). Considerable evidence indicates that, in contrast to traditional clinical risk factors, biomarker-based information contributes incrementally to risk stratification models. Multiple longitudinal investigations have established that biomarkers accurately indicate future progression of prediabetes years prior to conventional diagnostic thresholds. Comprehensive statistical evaluations have further confirmed that biomarker data provides significant performance enhancement relative to traditional variables [12].

4.1. Prospective cohort findings

Persistent elevation of fasting glucose or impaired glucose tolerance are hallmarks of progression from insulin resistance to type 2 diabetes. Progression is often accompanied by increased secretion of circulating triglycerides (TG). A 5-year multi-population study of non-diabetic patients revealed significant risk associations, analyzed along with classic risk factors. Along with additional information on the occurrence of new diabetes cases, several studies monitored alterations of individual biomarkers correlated with diabetes incidence in prospective cohorts. In a 8-year cohort study of French adults aged 30 to 55, a panel of 10 metabolic markers measured on a single blood specimen at baseline could significantly discriminate a progressive 8-year pre-diabetes state with an area under the ROC curve of 0.86, a specificity of 83%, and positive predictive value of 20%. Further studies correlated metabolic biomarkers with changes in hepatic and muscle fat accumulation, insulin signaling, and plasma lipids; pathways in turn correlated with changes observed during the temporal evolution of insulin resistance and β-cell failure leading to overt diabetes and consequently linked to the intermediate-type biomarkers [12]. In the aforementioned cohort study, a metabolomic analysis across 10,520 baseline samples from the Framingham Heart Study Offspring Cohort in the USA indicated the importance of 24 serum metabolites associated with the risk of developing type 2 diabetes over 8 years 2. A logistic regression analysis carried out on the Framingham data set analyzed a multi-ethnic European sample and identified a panel of 6 strongly linked metabolites [11].

4.2. Risk stratification models incorporating biomarkers

Emerging metabolomic biomarkers significantly enhance early prediction of insulin resistance and type 2 diabetes compared to traditional risk factors. Risk stratification models demonstrate that a small number of biomarkers combined into simple scores improve identification of incident diabetes cases, particularly in individuals poorly recognized by classical clinical risk factors.These analyses reveal that early metabolic derangements accompany clinically silent states of borderline glucose intolerance and are therefore of prime importance in the design of prevention strategies. Measurements of 1,5-anhydroglucitol (1,5-AG) and dehydroepiandrosterone sulfate (DHEA-S) score high in stability over a 6-year period and are thus prime candidates for use in large-scale, low-cost risk prediction [2]. Early prospective studies indicate that certain metabolic biomarkers predict the onset of type 2 diabetes years in advance of clinical diagnosis . A large cohort study of healthy subjects identified a panel of twelve metabolites whose baseline concentrations were associated with diabetes progression over a follow-up of approximately 10 years. These metabolic measures significantly enhanced risk prediction when combined with standard clinical factors. Machine learning approaches revealed that diabetes-associated metabolic changes already occurred at an intermediate stage, long before the condition was clinically recognized. Five metabolites—glucose, mannose, α-hydroxybutyric acid (α-HB), α-tocopherol, and alcohols—were among the greatest such predictors [11].

4.3. Incremental value beyond traditional risk factors

In untreated patients, beta-cell function and/or insulin action remain relatively stable early in the progression of impaired glucose homeostasis, and thus, fasting plasma glucose (FPG) and/or 2-h plasma glucose (2hPG) levels do not deteriorate noticeably. Nevertheless, hepatic glucose production and/or beta-cell function begin to deteriorate appreciably at the stage of metabolic syndrome. Initiation of treatment to prevent the incidence of type 2 diabetes could thus be framed a few years before the value of impaired glucose homeostasis shifts towards the clinical diagnosis of diabetes [2,11]. Emerging metabolic biomarkers selected based solely on their association with the progression to impaired glucose homeostasis have been demonstrated to significantly enhance the early prediction of non-diabetic individuals at high risk. Net reclassification improvement (NRI) shows the greatest gain in risk prediction performance, followed by integrated discrimination improvement (IDI). Multivariate models incorporating selected metabolic biomarkers also exhibit superior predictive capability over models containing only fasting or 2-h glucose alone [13].

5. Mechanistic insights linking biomarkers to pathogenesis

Emergent biomarkers are mechanistically linked to the pathogenesis of insulin resistance (IR) and Type 2 Diabetes Mellitus (T2DM). Key metabolic and biochemical pathways underpinning their association to glycaemia regulation are summarised below. Biomarkers derived from lipidomics, amino acid profiles, glucose and energy metabolites, as well as inflammatory and adipokine signals provide information on different aspects of metabolic dysregulation and pathology, which can affect the progression to T2DM [1]. Accumulation of biomarkers associated with ectopic fat deposition, mitochondrial dysfunction, and oxidative stress reflect a second pathway contributing to the transition from IR to besity and T2DM. Analysis highlights that these widespread metabolic dysregulations accompany early developments of IR, before the emerging metabolic “need” for a deeper dysregulation of such pathways, in agreement to the observed temporal changes of these bioindicators through the pathology [11].

5.1. Insulin signaling and beta-cell function

Insulin acts on target tissues through specific signalling mechanisms for the regulation of nutrient metabolism.Deterioration of insulin action and signalling is an incipient and pivotal factor in the gradual evolution of type 2 diabetes. Therefore, laboratory parameters reflecting the status of insulin action, signalling, and target-cell sensitivity are closely intertwined with the progression of glucose intolerance and insulin point towards developing multiple parameters for monitoring insulin action and signalling without needing elaborate and time-consuming clamp procedures [3,12]. The pancreas secretes insulin in response to glucose and other stimuli. The glycaemic-dependent pancreatic response is readily measured in an isoglycaemic clamp or during tests of glucose tolerance. Consequently, potential laboratory parameters of the performance capacity of the secretion machinery are formulated based on analysis of these pilot studies. A variety of metabolic and signalling abnormalities gradually develop in the glucostat and participate strongly in glucose metabolism prior to the onset of glucose intolerance [13].

5.2. Hepatic glucose production and lipid metabolism

Insulin acts chiefly on the liver to suppress glucose output. Unchecked hepatic glucose production is therefore a major cause of fasting hyperglycemia in type 2 diabetes (T2D). Glucose released by the liver during the postprandial period further contributes to disease progression. Hepatic glucose production is in turn regulated by multiple metabolic signals, as well as by availability of fuel substrates. Perturbations in glucose metabolism that lead to increased hepatic

glucose production thus represent a critical abnormality in T2D pathogenesis [14]. Dietary carbohydrates are converted to glucose in the intestine and subsequently enter the liver via the portal circulation. In addition, free-glucose can traverse the blood–brain barrier and reach the liver indirectly through the brain. Upon entering the liver, glucose can be phosphorylated to glucose-6-phosphate (G6P) by glucokinase (GK) or hexokinase I–III (HK I–III), where it is trapped in the liver for further metabolism. G6P can subsequently enter glycolysis for ATP generation or enter glycogen synthesis for storage through glycogen synthesis pathway for energy reserve. In situations of excess caloric intake, G6P can be used as a precursor in the production of triglycerides; it can subsequently convert to pyruvate and further into acetyl-CoA. As a result, glucose metabolism is thereby compartmentalized for different purposes according to the energetic state, feeding status, and other systemic requirements [15].

5.3. Ectopic lipid deposition and mitochondrial function

Abnormal lipid distribution and impaired mitochondrial functioning is associated with the ectopic lipid deposition in insulin-resistant phenotypes. Certain metabolic biomarkers are positively associated with ectopic lipid deposition measured with the help of imaging, including magnetic resonance spectroscopy, positron emission tomography, or computed tomography. Moreover, these biomarkers reveal an inverse relationship with mitochondrial activity, as estimated through the metabolic elimination of exogenous deuterated glucose, and thus provides mechanistic support that ties these biomarkers to increased ectopic adiposity and impaired mitochondrial efficiency [15-17].

6. Clinical translation and implementation considerations

Early identification of those at risk of developing insulin resistance and type 2 diabetes allows medical practitioners to take interventions in time to prevent or delay the development of diseases, which would minimize the morbidity of the disease. The development of insulin resistance is however hindered with an insidious onset and a long asymptomatic course which hinders identification. Traditional methods of risk assessment use anthropometry indices, and the existence of the metabolic syndrome, but these parameters are not sensitive enough to identify the disease at an early stage. Metabolic biomarkers hold a prospective good ground in improving early detection of type 2 diabetes by addressing underlying metabolic derangements. The ability to measure a large variety of metabolic parameters such as lipids, amino acids and other small molecules in one biological sample helps form predictive models that incorporate a broader range of metabolic data [2,5].

6.1. Assay standardization and reproducibility

The lack of standardization remains the major impediment to clinical translation of metabolic biomarker assays, significantly limiting their broader adoption . Addressing this challenge through interlaboratory verification and harmonization of metabolic biomarker panels would expand their utility in clinical screening and epidemiological studies. This process begins with the definition of the biomarker itself, followed by characterization of metabolic pathways and fluxes, their interconnections, and identification of accessible tissue compartments; selection of measurement technology; and development of materials for method performance evaluation. The most relevant steps toward standardizing and validating metabolic biomarker assays in diverse biological matrices are summarized here, supported by practical examples and indications of the relevance of each feature to the biomarkers mentioned in this review [18].

6.2. Population diversity and generalizability

Prediction of insulin resistance and type 2 diabetes risk using metabolic biomarkers has been primarily evaluated in European, American, Chinese, and Indian populations, along with a few smaller cohorts targeting specific populations; however, broader representation is still lacking . In particular, cohorts investigating risk prediction in other regions or countries with an increasing incidence of diabetes—such as South Korea, Southeast Asia, Africa, South America, or Eastern Europe—are desirable. Alternatively, the capability of these biomarkers might be tested in diverse populations characterized by significant environmental, ethnic, genetic, or lifestyle factors. Differences in convenience store entrepreneurs (CSEs) workplaces led to varying insulin resistance levels: CSEs in regions with limited high-sugar and high-fat foods or those restricted to selling goods with low sugar and fat accumulated less visceral fat than those in other regions. Comparison of metabolic biomarkers across these diverse groups could support adjustments for region-based influences on insulin resistance or enhance the understanding of the pathophysiological mechanisms underlying markers influencing progression to type 2 diabetes [2].

6.3. Cost-effectiveness and feasibility in screening programs

Screening programs targeting pre-diabetes and diabetes have been shown to be cost-effective. Cost-effectiveness was estimated for an adult population without diabetes from the time of screening in the 20s until treatment was initiated

upon the diagnosis of diabetes. Such an approach allows the consideration of all the costs incurred before the initiation of treatment . The incremental cost per quality-adjusted life-year (QALY) gained, over an unrestricted policy of screening in the 30s and 40s after a 10-year diabetes-free interval would remain attractive if screening in the 20s were saved for those who subsequently developed diabetes before age 50. The estimated costs of the diagnostic interventions for the selected emergent metabolic biomarkers for a combination of prospective cohort studies found emerged biomarkers that can predict incident diabetes can be assessed as low cost screening without any need for separate collection of specimens at additional cost [2,19].

7. Risks, challenges, and limitations

Emergent metabolic biomarkers hold promise for improving the early prediction of insulin resistance and type 2 diabetes mellitus. However, the integration of these novel tools into clinical practice faces significant risks, challenges, and limitations attributed to both the biomarkers themselves and their implementation. These problems need to be understood to guide future research and development in the field. Most of the biomarkers have predictive evidence that mostly represents associative but not causal relationships, and this makes such findings especially prone to confounding. Various numbers of variables can have an effect on biomarker profiles without necessarily having any effect on the underlying pathophysiology. It is therefore very necessary that researchers put these variables into consideration when designing a study; considerations include age, dietary patterns, comorbid ailments and medication patterns among others. The temporal disconnect between illness onset and when the specimen was collected(which can be several years), only adds to the difficulty of establishing a time-related relationship between risk factors and clinical diagnosis [19]. The excitement surrounding emerging biomarkers may reflect a research signal rather than a decisive clinical utility signal. In the absence of collectively validated prognostic thresholds, the information they confer weighs heavily on early identification alongside conventional risk factors rather than on actionable intervention decisions. Such an understanding is important for both laboratories and clinicians to avoid overselling their practical usefulness [17].

7.1. Confounding factors and temporal dynamics

Biomarkers are subject to fluctuations during life, such as those due to circadian rhythms. Additional factors, including diet, socioeconomic status, lifestyle, and drug usage, also play a role. Several studies showed that significant changes in profiles of amino acid-derived metabolites oriented metabolomic analyses towards predicting alterations in physique and age . Causality is often difficult to establish with reliable confidence. For example, the consumption of certain foods triggers their catabolism, therefore mere identification of their presence in the blood would indicate that they had been eaten shortly before taking the measurement rather than suggesting some concentration equilibrium that would hint at any systemic status [11].

7.2. Clinical utility versus research signal

Emerging metabolic biomarkers improve early prediction of insulin resistance and type 2 diabetes compared with conventional risk factors. The evidence of these biomarkers, however, is not yet sufficient to support routine clinical use. Specific metabolic biomarker combinations show modest, replicable associations with prospective development of insulin resistance and type 2 diabetes, in addition to conventional clinical risk factors . Such biomarker combinations may allow the identification of at-risk individuals who would not otherwise qualify for intervention based on standard measures. These findings may have substantial public health implications, given the relatively few populations that have been studied and the poorly characterized human population at large. Nevertheless, the precisive mechanisms through which the indicated biomarkers relate to insulin resistance and type 2 diabetes pathogenesis remain largely unknown [11].

7.3. Ethical and privacy considerations

Emerging metabolic biomarkers are offering new possibilities for predicting the risk of developing insulin resistance and type 2 diabetes. The focus of this section is on ethical and privacy considerations in the rapid adoption of novel diagnostic methodologies. For the implementation of predictive algorithms to be sustainable, relevant regulatory frameworks must accompany authorization at the pre-marketing stage [2]. At present, a major unresolved question is the ownership of biological data, in particular the extent to which it is deemed proprietary following measurements undertaken by a third party. Furthermore, the law is ill-equipped to address individuals' rights to withdraw their consent subsequently. The likelihood of incidental findings poses additional challenges, especially when abnormal data potentially point to a serious clinical condition, and no appropriate follow-up is possible [13]. Emerging metabolic biomarkers are offering new possibilities for predicting the risk of developing insulin resistance and type 2 diabetes. Biomarker-driven assessment opens the door to a more extensive re-evaluation of risk than the conventional

examination of core variables such as body mass index or family history. The desirable aim should be the formulation of a risk classification tool based on a multi-omics approach including some metabolite screening, rather than a simple panel of biomarkers [19].

8. Future directions and research priorities

Integration of several 'omics' analytical platforms and large population studies has great potential for developing precision risk scores, combining different risk factors into a single score with stronger predictive power than individual markers. Future studies should emphasise external validation in subgroups and in other urban and rural Chinese populations. Longitudinal studies routinely measuring emerging metabolic biomarkers over time, together with monitoring of established risk factors, may facilitate dynamic evaluation of insulin resistance and individualised risk assessment for type 2 diabetes. Biomarker-guided intervention trials are also needed to determine whether improving specific pathways directs the trajectory of insulin resistance and type 2 diabetes and ultimately reduces clinical incidence [17]. Recent studies have shown that multiple metabolic biomarkers produced by different 'omics' platforms measured in a single screening can improve early prediction of insulin resistance, provide mechanistic links to its underlying pathogenesis, and enhance individualised risk stratification for the development of type 2 diabetes within 3-5 years. Early prediction of type 2 diabetes is considered more clinically meaningful than prediction of insulin resistance, and the detection of early disease is especially helpful for patients with type 2 diabetes [15].

8.1. longitudinal profiling and dynamic risk assessment

Early identification of individuals at risk of developing overt type 2 diabetes mellitus (T2DM) is crucial for preventive intervention, and emerging evidence has demonstrated the ability of metabolite profiling to greatly enhance prediction beyond established clinical risk factors 2. Specific biomarkers such as 1,5-anhydroglucitol (1,5-AG), dehydroepiandrosterone sulfate (DHEA-S), glycine, isoleucine, and γ-glutamylvaline demonstrate strong independent associations with the risk of incident T2DM and are stable over periods of months to years, thereby facilitating early and ongoing identification of at-risk individuals, particularly in populations where conventional risk factors have limited or even opposing predictive capacity. Serial assessments of such metabolites with periodic follow-up can enable estimation of individual trajectories towards T2DM, thus yielding dynamic insights into pathological progression and informing time-sensitive interventions to slow, halt, or reverse deterioration [13]. Longitudinal profiling of biomarker trajectories further allows refinement and individualization of prognostic signal and risk assessment. The estimated risk for abnormal glucose metabolism is rarely constant over the life course; age remains a well-known yet imperfect surrogate. Serial measurement of metabolic biomarkers linked to glucose homeostasis during maturation towards midlife when insulin resistance and β-cell dysfunction typically accelerate can better characterize temporal evolution of these underlying physiological processes. Thus, characterization of biomarker trajectories, together with isolated longitudinal readings, can assist in accurately gauging individual risk and determining optimal timing for preventive intervention [18].

8.2. Intervention trials guided by biomarker targets

Intervention trials designed around biomarker targets enable the early identification of intervention opportunities to prevent progression to insulin resistance and type 2 diabetes. Metabolic biomarkers such as α-tocopherol, bradykinin hydroxyproline, and X-13435 are linked to lower risk of disease development, whereas glucose, mannose, and α-hydroxybutyrate associate with elevated risk. An effective predictive model incorporates five metabolites that forecast disease progression independently of conventional risk factors, including physical activity, medications, and cardiovascular events. Models based on preclinical metabolomics data further substantiate the prognostic value of glucose, mannose, α-hydroxybutyrate, and α-tocopherol and support their use in targeting experimental preventive trials [11].

9. Conclusion

Evidence summarized in this review demonstrates that alterations in lipidomic profiles, amino acid metabolism, energy pathway intermediates, and inflammatory and adipokine markers precede overt disturbances in glucose homeostasis by several years. These biomarkers reflect key mechanisms such as impaired insulin signaling, β-cell dysfunction, hepatic glucose overproduction, ectopic lipid accumulation, mitochondrial inefficiency, and low-grade chronic inflammation, all of which contribute to disease progression.

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