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NEXT-GENERATION DIABETES CARE: INTEGRATING GENETICS, BIOMARKERS, AND PRECISION MEDICINE

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Abstract

Prediabetes represents a critical yet heterogeneous metabolic state affecting more than 100 million individuals worldwide, characterized by elevated glucose levels that fall below the threshold for type 2 diabetes (T2D). Although lifestyle interventions such as dietary modification, physical activity, and weight management significantly reduce T2D incidence at the population level, substantial inter-individual variability exists in both disease susceptibility and response to these interventions. This variability limits the effectiveness of conventional “one-size-fits-all” prevention strategies and highlights the need for a precision-based approach to lifestyle medicine. This review synthesizes evidence from large randomized controlled trials and prospective cohort studies demonstrating that intensive lifestyle modification can reduce T2D risk by approximately 50–60% and delay disease onset by several years. However, the persistence of progression in many individuals despite optimal lifestyle change underscores underlying biological heterogeneity driven by genetic, metabolic, and molecular factors. We examine emerging molecular biomarkers-including microRNAs, metabolites, inflammatory proteins, and lipid species-that offer earlier detection of dysglycemia, stratification of diabetes risk, prediction of therapeutic response, and identification of individuals prone to complications. We further explore advances in genomic medicine, including genome-wide association studies, polygenic risk scores, and pharmacogenomics, which provide insight into individual susceptibility and therapeutic responsiveness. The integration of multi-omics technologies with lifestyle data presents a transformative opportunity to personalize diabetes prevention and management. However, major challenges remain, including biomarker validation, assay standardization, clinical utility, cost-effectiveness, and ethical considerations surrounding genetic data. Overall, lifestyle precision medicine, supported by molecular and genomic profiling, offers a promising pathway to more targeted, effective, and sustainable strategies for preventing and managing type 2 diabetes.

Keywords: Type 2 Diabetes, Prediabetes, Lifestyle Precision Medicine, Molecular Biomarkers, Genomic Medicine.

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INTRODUCTION

Prediabetes, characterized by persistently increased but non-diabetic blood glucose levels, is a significant healthcare concern, impacting over 100 million individuals in Europe alone [1]. The term 'prediabetes' denotes a condition of glucose dysregulation that is likely to deteriorate, with several health organizations emphasizing that those afflicted are at elevated risk of acquiring type 2 diabetes (T2D). Annually, just 5–10%

of individuals with prediabetes will progress to diabetes, whereas 10% will revert to normoglycemia [2]. Furthermore, among individuals who remain prediabetic, there is less evidence that increased, nondiabetic blood glucose levels are directly linked to clinical outcomes; hence, aggressive intervention based merely on glycemia may not be cost-effective. However, if the subgroup(s) of individuals with prediabetes who advance to diabetes could be identified with reasonable accuracy, the argument for early intervention would be persuasive, considering the predominantly unmanageable nature of the disease, primarily due to the degradation of insulin-secreting beta cells, the lack of available beta-cell restorative

therapies, and the severe ramifications of diabetic complications. Type 2 diabetes is mostly a disorder of impaired glucose metabolism, affected by lipid accumulation and metabolism [3]. The disease manifests when the insulin secretory capacity of beta cells diminishes below the body's insulin production requirements, primarily dictated by the influx of glucose from dietary sources or gluconeogenesis in the liver, as well as the rate of glucose utilization and metabolism in tissues and organs. This process is further regulated by peripheral insulin sensitivity, which is affected by intracellular lipid accumulation, and non-insulin-dependent glucose transport, influenced by physical activity. Consequently, it is not unexpected that the underpinnings of a westernized lifestyle (unhealthy food, sedentary behavior, and obesity) constitute the primary modifiable 'exposures' implicated in the etiology of T2D and are the focal points of most non-pharmacological diabetes preventive initiatives. Nonetheless, even the most effective lifestyle changes often postpone the onset of the illness by around three years rather than avoid it altogether [4]. Furthermore, significant inter-individual diversity exists in sensitivity to lifestyle risk factors and in response to therapy. Consequently, there exists a deficiency in the availability of more effective lifestyle interventions. The observable heterogeneity among individuals in susceptibility and responsiveness to lifestyle variables in diabetes has prompted the perspective that customizing lifestyle treatments according to a person's biological traits may enhance diabetes prevention and treatment. This attractive notion has inspired a rapidly growing direct-to-consumer market that aims to align diet and exercise goods and services with the individual's genetic and other omic traits [5]. The main public-sector medical research organizations, namely the NIH and the European Union, are significantly investing in research pertaining to this subject. Nonetheless, much doubt exists about lifestyle precision medicine, especially when marketed; even when biomarkers have been definitively associated with susceptibility and response phenotypes, several obstacles to clinical translation remain. Numerous healthcare organizations promote a lifestyle defined by regular physical exercise, a nutritious food, limited alcohol intake, maintenance of a healthy body weight, robust psychological well-being, and abstention from smoking. certain guidelines derive from extensive epidemiological research and randomized controlled trials (RCTs) demonstrating that certain lifestyle variables reduce the incidence of, or aid in the prevention of, T2D at a population level [6]. The primary risk factor and management focus is excess body weight, since obesity (BMI 30–35 kg/m²) or severe obesity (BMI ≥ 35 kg/m²) presents a 20- to 40-fold heightened relative risk of Type 2 Diabetes compared to those with a lean body mass (BMI < 23 kg/m²) [7]. This document reviews the notion of lifestyle precision medicine in type 2 diabetes. We summarize the published evidence regarding lifestyle risk factors and preventive interventions in T2D,

briefly addressing the limitations of current approaches that emphasize lifestyle interventions for T2D prevention, and examine how the utilization of biomarker technologies may enhance these strategies. We provide evidence of varied responses to lifestyle interventions influenced by distinct genetic characteristics, together with functional data supporting the biomolecular foundation of these responses. We delineate contemporary omics technologies applicable for identifying and stratifying populations according to an individual's distinct genotype [8].

PUBLISHED EVIDENCE OF LIFESTYLE IN T2D RISK AND PREVENTION

The review highlights numerous well-conducted RCTs that demonstrate the significant effect of lifestyle changes in reducing the risk of T2D. Notably, the Diabetes Prevention Program (DPP) involved 3,234 participants and showed that an intensive lifestyle intervention was more effective than metformin in lowering diabetes incidence during a 2.8-year follow-up; specifically, there was a 58% reduction in the lifestyle group compared to 31% in the metformin group relative to placebo [9]. Long-term studies further confirmed the lasting impact of lifestyle interventions, with 10-year follow-ups indicating a delay in the development of T2D by approximately 4 years for the lifestyle group and 2 years for the metformin group compared to placebo. The Finnish Diabetes Prevention Study (DPS), which had 522 participants, also reported a 58% decrease in diabetes incidence through similar lifestyle modifications aimed at overweight or obese individuals [10]. In addition, the review cites various other studies across different demographics and settings that observed comparable, albeit less pronounced, reductions in diabetes incidence, reinforcing the findings from the DPP and DPS trials. Prolonged evaluations have shown that the benefits of intensive lifestyle changes can last up to 20 years. Cohort studies, such as the Kailuan prospective trial (50,656 participants) and the Finnish Twins Study (20,487 participants), illustrated strong correlations between lifestyle factors and T2D risk [11]. Physical activity positively impacted T2D risks even among genetically similar individuals, highlighting lifestyle choices' significance in disease prevention. Furthermore, Yates et al. conducted a thorough review of RCTs focused on dietary and exercise interventions for T2D prevention. The results indicated that lifestyle modifications could reduce diabetes risk by approximately 50% during the trials, and follow-up studies maintained these findings over 10 to 20 years [12]. Despite challenges in delineating the distinct impacts of diet versus exercise due to the reliance on self-reported data, interventions emphasizing high-volume exercise and specific dietary patterns demonstrated notable benefits in improving glucose tolerance and reducing diabetes risk. The review acknowledges potential biases in lifestyle RCTs, particularly difficulties in blinding treatment

assignments, which may obscure the causal relationships. Nonetheless, epidemiological research supports various modifiable lifestyle factors as being closely related to T2D onset. Socioeconomic conditions further complicate this relationship, whereby disadvantaged social environments contribute to increased risks of obesity and diabetes. Research exploring environmental factors, such as pollution and dietary patterns (e.g., coffee intake and red meat consumption), reflects mixed results regarding their association with T2D [13]. For instance, while some studies have failed to identify strong causal links with pollutants, others have indicated a correlation between traffic-related pollution and T2D incidence. Additionally, the review posits that the interindividual variability in response to lifestyle interventions underscores the need for tailored approaches, particularly concerning genetic predispositions and lifestyle interactions. Effective interventions should not only address standard guidelines but also consider genetic and environmental factors that influence responses to lifestyle modification. Recent analyses have begun integrating genetic data with lifestyle factors related to T2D, with limited studies focusing on gene-lifestyle interactions specifically related to diabetes risk. Overall, while comprehensive, the literature's reliance on average outcomes may underestimate the complexity of individual susceptibility and response to lifestyle interventions.

MOLECULAR BIOMARKERS

The management of diabetes is crucial for controlling blood sugar levels and preventing severe complications such as cardiovascular disease, neuropathy, nephropathy, and retinopathy. Current standard biomarkers for diabetes management include hemoglobin A1c (HbA1c), fasting blood glucose, and the oral glucose tolerance test, which are vital for diagnosing and monitoring the disease [14]. HbA1c, in particular, provides insights into average blood glucose levels over the preceding two to three months by reflecting the long-term exposure to glucose and assists in guiding treatment plans to optimize blood sugar control. Additionally, fasting blood glucose, measured after an 8-hour fast, and the oral glucose tolerance test, assessing glucose levels before and two hours after a glucose intake, are fundamental in diagnosing prediabetes and diabetes based on established American Diabetes Association criteria [15]. The C-peptide biomarker further differentiates between type 1 and type 2 diabetes, as levels are undetectable in type 1 diabetes due to the loss of insulin-producing beta cells, while they can be normal or even elevated in type 2 diabetes due to insulin resistance. Furthermore, emerging molecular biomarkers, such as microRNAs (miRNAs), metabolites, and proteins, are gaining interest for their potential in enhancing diabetes management. miRNAs, like miRNA-204, have been identified as specific to type 1 diabetes and offer insight into gene regulation affecting insulin secretion and biosynthesis. Similarly,

metabolites are being explored as indicators of metabolic dysfunction, with altered patterns linked to diabetes progression and insulin resistance. Notably, branched-chain amino acids and other lipid species have shown relationships with diabetes complications and disease progression. Proteins, including inflammatory markers, have also demonstrated correlations with insulin resistance and pancreatic dysfunction. Elevated levels of proteins such as IL-6, TNF- α , and CRP are indicative of diabetes-related inflammation, while markers reflecting vascular dysfunction can aid in early detection of diabetic complications [16]. Overall, the integration of these molecular biomarkers could herald the future of precision medicine in diabetes, facilitating earlier interventions and personalized treatment strategies while requiring further validation and standardization for clinical applications. Molecular biomarkers present several significant advantages over traditional clinical biomarkers in the context of diabetes care. Firstly, they enable a precision medicine approach by providing personalized data that helps tailoring treatment according to the individual patient's unique molecular profile. Profiling specific molecules, including microRNAs, metabolites, and proteins, offers insights into the active pathological processes in a patient. For example, certain microRNA signatures can inform clinicians about likely reduced therapeutic responses to oral hypoglycemic medications, such as miR-103/107 indicating a poor response to metformin, and let-7 miRNA suggesting decreased efficacy of sulfonylureas. Furthermore, biomarkers like miR-21, miR-29a/b, and miR-146a are associated with insulin resistance, impacting the effectiveness of insulin therapy [17]. This detailed molecular understanding can lead to the reconsideration of treatment strategies to enhance patient outcomes. In addition to individualized therapy, molecular biomarkers facilitate earlier diagnosis and screening for diabetes. Traditional methods, reliant on glucose tests, only identify diabetes once certain clinical thresholds are met. Conversely, molecular biomarkers can uncover early indicators of biological processes linked to impaired insulin secretion and glucose homeostasis, such as abnormal levels of branched-chain amino acids and lipid metabolites that appear before overt diabetes develops. This capability opens doors for earlier interventions to prevent disease progression and allows for targeted screening within high-risk populations for timely diagnosis and management. Another critical advantage of molecular biomarkers is their ability to provide deeper insight into an individual's risk of diabetic complications and disease progression, as opposed to merely tracking overall blood glucose control. Biomarkers related to vascular dysfunction and inflammation can predict the likelihood of developing cardiovascular, renal, and neurovascular complications, enabling healthcare providers to implement more intensive monitoring and therapeutic responses based on specific biomarker data. Lastly, molecular biomarkers enhance the monitoring of

patient responses to various therapies, such as insulin and metformin. This timely assessment allows for quick identification of ineffective treatment regimens, guiding necessary adjustments to medications. For instance, low levels of miR-424 may predict poor responses to DPP4 inhibitors in Type 2 Diabetes Mellitus (T2DM), while increased expressions of miR-126 and miR-155 are tied to improved glycemic control with thiazolidinedione medications [18]. Overall, molecular biomarkers promote more timely, evidence-based decisions in diabetes care, ensuring that treatments are optimized for each patient's unique needs.

CHALLENGES/LIMITATIONS IN DEVELOPING MOLECULAR BIOMARKERS

Although molecular biomarkers possess significant potential for advancing healthcare, their application in clinical settings faces considerable obstacles. One major challenge is the necessity for extensive research involving large cohorts to discover and validate new biomarkers [19]. This process includes establishing and confirming the correlations between biomarkers and health outcomes, which is inherently time-consuming. Additionally, biomarkers must not only demonstrate associations with diseases but also provide incremental benefits over existing clinical assessments. Validation in diverse populations is crucial to ensure generalizability. A vast number of candidates must typically be tested before identifying those suitable for clinical application, underscoring the need for sufficient funding and resources to support the rigorous research demanded [20]. Currently, there is a notable limitation in the availability of standardized molecular biomarker tests for diabetes. Although research efforts may yield promising candidates, transforming these into standardized assays suitable for clinical laboratories poses a significant challenge. Inconsistencies in sample handling, processing protocols, reference ranges, and reporting formats compromise the reliability of tests. Substantial efforts are thus required to enhance and standardize laboratory-developed tests, analytic methodologies, and quality control procedures essential for implementing molecular biomarkers effectively. Moreover, issues related to adoption and reimbursement significantly impede the integration of novel molecular biomarkers into clinical practice. For clinical uptake to occur, there must be compelling evidence demonstrating the cost-effectiveness of these new tests compared to traditional methods [21]. However, evaluating and validating biomarkers can incur substantial costs. Without appropriate insurance coverage and financial incentives, healthcare providers may be reluctant to order innovative, specialized tests. Lack of reimbursement options also serves as a barrier to the commercial development of these biomarkers. Addressing these financial and logistical challenges is essential for the effective clinical translation of molecular biomarkers into practice.

GENOMIC INTERVENTIONS

Genomic medicine is a progressive field that utilizes genomic information to inform health decisions and personalize care, focusing on the unique DNA sequence variations of individuals. This innovative approach is revolutionizing how diseases, particularly complex conditions like diabetes, are understood and managed, offering insights into disease susceptibility, precise diagnostics, tailored treatments, and the development of new drugs. The rapid advancements in DNA sequencing technology and the growing understanding of genetic factors in diseases are fostering a shift towards genomic medicine. Diabetes mellitus, which includes both monogenic and polygenic disorders affecting glucose metabolism, benefits from genomic insights. Type 1 diabetes arises from the autoimmune destruction of insulin-producing cells, while type 2 diabetes is primarily linked to obesity and insulin resistance, with considerable genetic risk factors also identified. Genome-wide association studies (GWAS) have revealed over 400 genetic loci associated with the risk of developing type 2 diabetes, and more than 60 rare variants have been associated with hereditary forms like neonatal diabetes [22]. This genetic understanding enhances diagnostic accuracy, particularly for atypical cases, and facilitates early identification of individuals at high risk for diabetes, aiding in targeted prevention strategies. Genomic medicine opens new avenues for intervention, integrating pharmacogenomics, gene editing, and epigenetic therapies to combat the disease's underlying mechanisms. The personalization of treatment based on genetic profiles promises to optimize efficacy while reducing adverse effects. However, practical implementation faces challenges, including the need for robust evidence supporting genetic interventions, healthcare provider education on genomics, and ethical considerations regarding genetic information. GWAS has significantly contributed to our understanding of the genetic architecture of type 2 diabetes by identifying common variants that have modest effects on disease risk [23]. The findings from GWAS have implications for predicting diabetes susceptibility and developing polygenic risk scores that combine various genetic variants to better assess an individual's risk. Next-generation sequencing has further characterized rarer variants that may significantly impact disease risk, emphasizing the importance of integrating both common and rare genetic variants into risk assessments. Efforts to leverage genetic insights for prevention and treatment include developing genetic risk scores to identify individuals who may benefit from early interventions, potentially enhancing resource allocation compared to universal screening methods. Additionally, pharmacogenomics focuses on optimizing diabetes medication by tailoring treatment plans based on genetic factors that influence drug responses, effectively personalizing medical care. Innovations in gene editing and gene silencing techniques, such as CRISPR/Cas9, offer promising strategies for directly modifying disease-related genes,

thus addressing diabetes risk [24]. These techniques aim to provide greater specificity than traditional pharmaceutical approaches but also come with challenges, including potential off-target effects and delivery methods. Despite these advancements, barriers remain that hinder the widespread adoption of genomic medicine in diabetes care. The lack of demonstrated clinical utility and cost-effectiveness for many genomic interventions necessitates large-scale studies to validate their effectiveness. Moreover, addressing the ethical and privacy concerns surrounding genetic information is crucial for promoting equitable access to genomic advancements. Ongoing research is essential to expand applications of genomic medicine across diverse populations, refine predictive tools, and enhance clinical guidance, ultimately leading to more effective and personalized diabetes care.

FUTURE RECOMMENDATIONS

Future strategies for the prevention and management of T2D should move decisively toward a precision-based lifestyle medicine framework that integrates molecular, genetic, and behavioral data. Large-scale longitudinal studies are needed to validate multi-omics biomarkers-including genomic, epigenomic, metabolomic, proteomic, and microbiome signatures-for identifying individuals with prediabetes who are most likely to progress to T2D [25]. These biomarkers should be incorporated into standardized, clinically actionable panels that complement traditional measures such as HbA1c and fasting glucose. Precision-guided randomized controlled trials must be designed to test whether genetically and metabolically stratified individuals benefit differentially from specific dietary patterns, physical activity regimens, and weight-loss strategies, rather than relying on population-average effects. The integration of polygenic risk scores into routine screening could enable earlier identification of high-risk individuals and allow targeted allocation of intensive preventive resources. Digital health technologies, including wearable devices and continuous glucose monitoring, should be combined with artificial intelligence to dynamically adapt lifestyle recommendations in real time based on individual metabolic responses [26]. Importantly, future research must include ethnically diverse and socioeconomically underrepresented populations to ensure equity and global applicability of precision-based interventions. Health-economic evaluations will be essential to demonstrate the cost-effectiveness of biomarker-guided lifestyle interventions compared with conventional approaches. Finally, robust ethical, legal, and data-governance frameworks, together with enhanced training of healthcare professionals in genomics and biomarker interpretation, will be crucial for the safe and effective translation of lifestyle precision medicine into routine diabetes care.

CONCLUSION

Type 2 diabetes represents one of the most pressing global health challenges, driven by complex interactions between genetic susceptibility, metabolic dysfunction, and lifestyle factors. Although large randomized controlled trials and epidemiological studies clearly demonstrate that lifestyle modification-particularly weight management, diet, and physical activity-can substantially reduce the risk of diabetes, these benefits are highly variable across individuals. This heterogeneity highlights the limitations of uniform prevention strategies and underscores the need for a more precise and biologically informed approach. Advances in molecular biomarkers, including microRNAs, metabolites, inflammatory proteins, and lipid species, provide powerful tools to identify early metabolic disturbances, predict disease progression, and guide therapeutic decisions. In parallel, genomic medicine has revealed hundreds of genetic loci associated with diabetes risk, enabling improved risk prediction through polygenic scores and facilitating pharmacogenomic tailoring of therapies. When combined, these molecular and genomic insights offer a framework for lifestyle precision medicine that can more effectively target interventions to those most likely to benefit. However, substantial challenges remain in standardization, validation, cost-effectiveness, and clinical implementation. Overcoming these barriers through rigorous research, technological integration, and ethical governance will be essential to translate precision-based strategies into routine care. Ultimately, integrating lifestyle interventions with molecular and genomic profiling holds the promise of transforming diabetes prevention and management, shifting from generalized recommendations to truly personalized, evidence-driven healthcare.

CONFLICT OF INTEREST

Conflict of interest declared none

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