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Abstract

Purpose: Diabetes mellitus is a chronic disorder caused by high blood glucose levels due to insulin resistance or insufficient insulin production in pancreatic β -cells. Due to its fastest-growing public health concerns worldwide, it is important to evaluate metabolic profile abnormalities before pre-diabetes or T2DM to anticipate and prevent disease progression. The purpose of the study was to examine the metabolite biomarkers by systematic review and meta-analysis to support early detection of pre-diabetes and T2DM.

Methodology: Studies published from the earliest online through May 31, 2023, were searched in the Cochrane Library, EMBASE, PubMed, and Scopus. Article titles, abstracts, and complete texts were reviewed after duplicate records were eliminated. Two writers (Long and Yang) created the following inclusion criteria for the publications before literature screening: The study was conducted on humans, did not involve gestational diabetes mellitus (GDM), type 1 diabetes mellitus (T1DM), or subjects under 18 years old, included a diabetic or prediabetes group, and followed international diagnostic guidelines (American Diabetes Association, 2013).

Findings: The study aimed to review the biomarkers that have been utilized for diabetes in previous research. The comparison of the biomarkers mentioned in the provided information revealed a complex interplay of factors influencing the risk and management of Type 2 Diabetes (T2D). These biomarkers encompass genetic, lifestyle, environmental, and insulin-related factors, each with varying degrees of accuracy and specificity in predicting T2D risk or guiding its management.

Recommendations: The research will help in spreading awareness among people regarding the identification of diabetes as understanding biomarker-based screening's economic impact can inform healthcare policies. Future studies should validate these biomarkers' diagnostic capacities across varied populations and circumstances. Assessment of these biomarkers' predictive usefulness should be done over time via longitudinal research. Understanding biomarker alterations and diabetes progression improves risk prediction.

Keywords: *Diabetes Mellitus, Hyperglycemia, Biomarkers*

1.0 INTRODUCTION

Diabetes mellitus is a chronic disorder caused by high blood glucose levels due to insulin resistance or insufficient insulin production in pancreatic β -cells. One of the fastest-growing public health concerns worldwide is diabetes, which has expanded significantly in recent decades. Chronic nephropathy, retinopathy, neuropathy, and cardiovascular disease can occur from poor blood glucose control. Living with diabetes requires lifestyle and nutritional adjustments as well as medication. Diabetes mellitus causes hyperglycemia due to insulin synthesis and secretion abnormalities in pancreatic β -cells, tissue insulin resistance, or both. Diabetes has four pathophysiological types: type 1 diabetes (T1DM), type 2 diabetes (T2DM), hyperglycemia in pregnancy (including gestational diabetes), and diabetes with a specific etiology (Chatterjee et al., 2017). A healthy lifestyle can prevent 90% of diabetes cases, including T2DM.

Multifactorial, chronic, and complicated metabolic disease T2DM involves family medical history, age, lifestyle, diet, genetics, and environment. T2DM develops slowly and may go undiagnosed for years. Polydipsia, polyuria, polyphagia, and weight loss are common symptoms. This chronic disease causes many medical consultations, hospitalizations, impairments, and fatalities due to its complications. This includes microvascular events like retinopathy, nephropathy, and neuropathy and macrovascular events including ischemic heart disease, stroke, and peripheral vascular disease (Visscher et al., 2017). The prevalence of type 2 diabetes (T2D) and its complications is epidemic. Globally, T2D, which accounts for >90% of diabetes cases, is rising rapidly. The International Diabetes Federation estimates that the number of adults with diabetes will climb from 425 million in 2017 to 629 million in 2045, and most nations have a rising T2D rate. Thus, identifying high-risk T2D patients is crucial since early therapies may postpone or prevent illness. T2D is caused by insulin resistance, mainly in skeletal muscle and liver, and pancreatic insulin secretion dysfunction (Chatterjee et al., 2017).

T2D is a complicated condition caused by gene-environment interactions, hence not all disease-causing mechanisms are understood. Growing research suggests genetics greatly influence T2D risk. In the recent decade, genome-wide association studies (GWASs) have made tremendous findings in population and complex trait genetics, disease biology, and translation into new treatments (Visscher et al., 2017). Recently, over 400 association signals explained 18% of T2D risk and revealed molecular pathways. Low-frequency variations contribute less to T2D heritability than frequent variants. Insulin resistance is another T2D risk factor. Type 2 diabetes mellitus (T2DM) is a common chronic condition that can lead to major health issues like diabetic retinopathy, renal damage, and diabetic ketoacidosis (Langenberg & Lotta, 2018). Between 1980 and 2014, the number of adults with diabetes rose from 108 million to 422 million, with T2DM accounting for almost 90%. Diabetes has become one of the three major diseases in the globe due to rising prevalence (Mahajan et al., 2018). T2DM symptoms are not visible or only partially manifest early on. Thus, early diabetes diagnosis and treatment are crucial.

Diabetes epidemics often follow obesity epidemics because obesity is insulin-resistant. Lack of exercise and poor diet raises insulin resistance and T2D risk. Insulin resistance is linked to a few genetic variations. Several genetic variations' functions are unknown (Langenberg & Lotta, 2018). This review examines T2D risk variables and genetic and non-genetic biomarkers from large prospective population-based studies and Mendelian Randomization (MR) studies evaluating causality. Understanding genome-phenome connections in T2D subgroup classification is another priority. Due to the high prevalence of T2DM and its significant effects, research on novel diagnostic markers has intensified. The recognized biomarkers for T2DM are blood glucose (fasting and oral glucose tolerance test) and hemoglobin A1c.

The metabolomic technique identifies all metabolites in a biological system, including cells, organs, and organisms, to determine their physiologic or pathologic consequences. Metabolomics can identify compounds as biomarkers for diabetes diagnosis and treatment. Amino acids may be valuable diagnostic indicators because their metabolism is changed in pre-diabetes and changes over T2DM progression (Fuchsberger et al., 2016). Because T2DM patients have increased serum concentrations of tryptophan and BCAAs (valine, leucine, and isoleucine), they may be valuable indicators (Dimas et al., 2014). Plasma phospholipids such as phosphatidylinositol and sphingomyelin could also distinguish healthy people from T2DM patients (American Diabetes Association, 2013).

It is important to evaluate metabolic profile abnormalities before pre-diabetes or T2DM to anticipate and prevent disease progression. However, there is no consensus on the use of metabolites as diagnostic biomarkers of T2DM, and some results were from clinical single-center studies or ignored mixing factors such as geographies and people (Dimas et al., 2014). An effective and comprehensive evaluation technique for metabolites as diagnostic biomarkers of pre-diabetes or early T2DM is needed. Bellou et al. (2018) found numerous amino acids consistently linked to T2DM risk (Vangipurapu et al., 2017). Since then, several novel studies appeared. We performed a comprehensive review and meta-analysis of existing metabolomics data on T2DM or pre-diabetes biomarkers and created a metabolite biomarker profile. Metabolite biomarkers will be examined by systematic review and meta-analysis in this study to support early detection of pre-diabetes and T2DM.

Problem Statement

One of the fastest-growing public health concerns worldwide is diabetes, which has expanded significantly in recent decades. So, it is important to evaluate metabolic profile abnormalities before pre-diabetes or T2DM to anticipate and prevent disease progression. The purpose of the study was to examine the metabolite biomarkers by systematic review and meta-analysis to support early detection of pre-diabetes and T2DM.

2.0 METHODOLOGY

Data Sources and Search Strategy

Studies published from the earliest online through May 31, 2023, were searched in the Cochrane Library, EMBASE, PubMed, and Scopus. The search terms were “metabonomics”, “metabolomics”, “metabolome”, “type 2 diabetes”, “type 2 diabetics”, “type 2 diabetes mellitus”, “insulin resistance”, “HOMA-IR”, “Impaired glucose tolerance”, “glucose intolerance”, “impaired fasting insulin”, “impaired fasting glucose”, “prediabetic”, “pre-diabetes” and “prediabetes” connected with OR. The four databases employed “Title, Abstract, Keywords” to assure relevancy.

Study Selection and Inclusion Criteria

Article titles, abstracts, and complete texts were reviewed after duplicate records were eliminated. Two writers (Long and Yang) created the following inclusion criteria for the publications before literature screening: The study was conducted on humans, did not involve gestational diabetes mellitus (GDM), type 1 diabetes mellitus (T1DM), or subjects under 18 years old, included a diabetic or prediabetic group, and followed international diagnostic guidelines (American Diabetes Association, 2013). The article was not a review, conference abstract, editorial, or note, and the biological samples were collected by fasting. Disagreements over study selection or inclusion were settled by discussion. Included are metabonomic studies of pre-diabetes and T2DM biomarkers.

3.0 FINDINGS

Non-Genetic Risk Factors for T2D

The interplay of biomarkers, lifestyle and environmental influences, food, medical history, and psychological and social contexts. Age, BMI, waist circumference, sex, ethnicity, lack of physical activity, smoking, diet (especially low fiber and high saturated fat), ethnicity, family history of diabetes, history of gestational diabetes mellitus, elevated blood pressure, dyslipidemia, various drug treatments (diuretics, unselected b-blockers, statins) have all been identified as risk factors for T2D in previous studies (Laakso et al., 2017). Cross-sectional study designs, inadequate sample sizes, and a lack of demographic representation are just a few of the problems plaguing previous research. Biomarkers, lifestyle and environmental factors, nutritional factors, medical history, and psychosocial factors were all included in a recent evaluation of 86 meta-analyses and Mendelian randomization studies on T2D risk factors. According to the results of this meta-analysis, 116 of 142 correlations were significant at the ($p < 0.05$ level), and 46 at the ($p < .106$ level). Evidence for the risk of type 2 diabetes was found for alanine transaminase, uric acid, vitamin D, whole grains, a healthy diet, sugar-sweetened drinks, a sedentary lifestyle, premature birth, metabolically healthy obesity, and conscientiousness ($n > 1,000$, $p < .106$). Research by Dimas et al. (2014) has found that both overall obesity (body mass index) and abdominal obesity (waist circumference, fat mass) are significant risk factors for type 2 diabetes. Short stature, we found recently, also raises the risk of T2D (Vangipurapu et al., 2017).

Genetic Risk Scores

A genetic risk score can predict disease risk by incorporating information from many loci (GRS). Since earlier GRSs for T2D risk generation focused on a small number of genetic polymorphisms, their prediction power was low compared to clinical and laboratory risk markers (Lyssenko & Laakso, 2013). Beyond the Finnish diabetes risk score, we examined biochemical markers and T2D risk loci for detecting undiagnosed diabetes. After adding adiponectin, ALT, HDL cholesterol, and total triglycerides to the model. Twenty T2D genetic risk alleles were added to the model, but it did not improve (Wang et al., 2010). After adding additional nongenetic or genetic biomarkers to standard risk variables, researchers tested T2D risk prediction models (Echouffo-Tcheugui et al., 2013). The analysis comprised 34 papers from 30 2000–2012 research. Eleven studies indicated a minor but substantial ROC curve shift (0.004–0.1). The scientists concluded that adding additional circulating and genetic biomarkers to T2D risk factors did not improve risk prediction. The latest genome-wide association analyses found 403 distinct T2D association signals.

The majority of type 2 diabetes risk is inherited through common polymorphisms with small effects. The UK Biobank found that 403 signals explained about 20% of T2D risk while GRSs with w130, 000 variants explained nearly 50% (McCarthy & Mahajan, 2018). These novel GRSs may not immediately alter clinical praxis, but they show that genetic variants can be estimated to affect type 2 diabetes risk. GRSIS dramatically increased fasting glucose, insulin production, and type 2 diabetes risk. These findings show that faulty insulin secretion causes diabetes. Neither glucose levels nor diabetes were predicted by the GRSIR (Stancáková et al., 2017). GRS based on 84 T2D risk genetic variants predicted an increase in incident T2D over a 10-year follow-up in a general Japanese population independent of established risk variables (Innaishi et al., 2019). GRSs have limitations because most type 2 diabetes risk is related to factors other than genetics (lifestyle, behavior, and environment). The clinical value of GRSs is uncertain. There is also disagreement over whether body mass index, family history, and ethnicity simply recapture genetic risk information.

Insulin Biomarkers

The International Diabetes Federation estimated that 370 million individuals had diabetes in 2011, with 80% in developing nations. The 2010 Chinese Center for Disease Control and Prevention report found an 11.6% prevalence. Type 2 diabetes accounts for 90% of diabetics. Diabetes therapy relies on insulin. Insulin therapy can cause IA (Hu & Chen, 2018). Their interaction with insulins forms insulin-antibody complexes that compete with insulins for insulin receptor binding sites or function as an insulin pool to diminish insulin activity and irregularly release insulin, causing hyperinsulinemia and hypoglycemia. Unfortunately, hyperinsulinemia is a risk factor for wide glycemic fluctuation, high blood pressure, malignancies, Alzheimer's disease, and microvascular dysfunction that causes cardiovascular illnesses (Tanaka, 2020). Insulin-antibody complexes and exogenous insulin antibodies (IAs) can cause lipoatrophy and microangiopathy, save for glycemic control, through altered insulin pharmacokinetics, insulin resistance, and other mechanisms (Vaxillaire et al., 2014).

In diabetic complications, exogenous IA-positive individuals who use sulfhydryl-containing medications commonly develop insulin autoimmune syndrome (IAS), which is defined by spontaneous hypoglycemia and endogenous hyperinsulinemia with high anti-insulin antibody levels. Exogenous insulin-related insulin autoimmune syndrome (EIRAS) can induce excessive glucose fluctuation and exogenous hyperinsulinemia in T2DM patients on insulin (EIAS). IAs prevent glycemic control and problems (Mahmoud et al., 2016). T2DM in China is affected by exogenous IAs. Shandong Province had 220/742 exogenous IA-positive patients, according to Dong et al. (2020). Only two Chinese exogenous IA investigations were done in metropolitan tertiary 3A institutions. Rural patients, who are at risk of treatment noncompliance, need IA-related measurement data promptly. Thus, this study aims to measure blood IA levels in rural T2DM patients and examine how exogenous IAs relate to clinical features and insulin use (Sanaki et al., 2020).

A large percentage of T2DM patients have advanced problems that are difficult to manage and expensive to treat. The high prevalence of T2DM strains global public health systems. Early diagnosis reduces underdiagnosis, problems, and health system strain, improving quality of life and cutting health expenditures (Mahmoud et al., 2017). Thus, preventive, diagnosis, control, and treatment measures will be prioritized in the coming years. The recent development of cost-effective biomarkers and procedures for screening and early detection of T2DM could be widely used in apparently healthy patients (Andersson et al., 2013).

Diagnostic Biomarkers and Their Clinical Utility

Hemoglobin A1c

The most common prediabetes and diabetes biomarker is HbA1c. The β subunit of hemoglobin produces HbA1c when glucose attaches to its amino-terminal group. HbA1c measures chronic glycemia, not rapid glucose. The current ADA criteria for diabetes are HbA1c $\geq 6.5\%$ (48 mmol/mol) and 5.7-6.4% (39-46 mmol/mol) for prediabetes. Higher HbA1c levels increase mortality and morbidity. The Norfolk prospective study associated greater HbA1c with CVD, cancer, and all-cause mortality. Long-term research, including the Diabetes Control and Problems Trial, UK Prospective Diabetes Study Group, and Epidemiology of Diabetes Interventions and Problems study, correlate diabetes complications to mean HbA1c levels, with retinopathy linked to values $\geq 6.5\%$ (48 mmol/mol). More strongly connected to HbA1c than fasting plasma glucose was retinopathy (FPG). Thus, HbA1c may predict microvascular issues better than FPG (Centers for Disease Control and Prevention, 2014).

HbA1c is more convenient than FPG and OGTT because it does not require fasting, has better pre-analytical stability, and is less affected by stress and illness. Lifestyle modification therapy employs

HbA1c to measure chronic glucose exposure. Compared to OGTT and FPG, HbA1c shows moderate diabetes diagnosis sensitivity, but the evidence is inconsistent. OGTT is more linked to IR and secretion than HbA1c, which is expected since a high glucose dose better reflects a physiologic response to insulin secretion and activity. OGTT findings in normoglycemic persons may suggest prediabetes (Whiting et al., 2011). The most sensitive HbA1c cut points are unknown. ADA criteria may miss prediabetes in people with HbA1c values below 5.5 percent (37 mmol/mol).

The NHANES and Screening for Impaired Glucose Tolerance studies revealed that only 60-70% of patients had normal glucose tolerance (NGT) at HbA1c levels <5.7% (39 mmol/mol). The prediabetes HbA1c threshold ignores ethnicity, BMI, and age, which can greatly alter readings. HbA1c is higher among African Americans, Hispanics, and Asian/Pacific Islanders than whites. One study indicated that black men and women have 0.3 and 0.4 percent higher HbA1c. Thus, standard classification ranges may overestimate prediabetes prevalence in particular ethnic groups (Cho et al., 2018).

Average circulating glucose is rarely assessed by HbA1c. Red blood cell half-life gives HbA1c a 90–120-day half-life. Changes in red blood cell production or longevity impact HbA1c. Reduced production produces older cells, whereas faster turnover minimizes red cell hyperglycemia exposure. Several clinical diseases can increase or underestimate HbA1c. Iron deficiency anemia, asplenia, folate and vitamin B-12 insufficiency, severe hyper-triglyceridemia, and uremia erroneously elevate HbA1c. HbA1c is deceptively low due to hemolytic anemia, blood loss, splenomegaly, and end-stage renal failure. HbS, HbC, HbD, and HbE hemoglobin variants may exaggerate or underestimate HbA1c depending on the approach. For these reasons, HbA1c alone may not indicate prediabetes. Other biomarkers may be needed (Ogurtsova et al., 2017).

Fructosamine

Fructosamine (FA) may screen for prediabetes as an alternative glycemic marker. FA is a ketoamine generated by glycosylation of serum proteins, usually albumin. High hyperglycemia increases FA. It indicates average blood glucose concentrations over the past 1–4 weeks, making it a clinical assessment of short-term glycemic fluctuation and glucose control. FA is useful for hemoglobin reliability due to its moderate sensitivity and great specificity. FA measurement is convenient and cost-effective because it does not need fasting. FA has higher within-subject variability and deceptively low values in nephrotic syndrome and hepatic disease, which accelerate albumin turnover (Sun et al., 2022). Its prediabetes biomarker efficacy is inconsistent. FA correlates with type 1 and type 2 diabetes hyperglycemia and HbA1c, according to various studies (T2DM). FA may anticipate microvascular issues. Not all studies have found mean serum FA levels beneficial for prediabetes screening. Thus, FA may be a valuable supplementary marker in clinical circumstances with incorrect HbA1c. FA has little literature and small patient groups, making it difficult to assess as a microvascular biomarker (Ogurtsova et al., 2017).

Glycated Albumin

Glycated albumin (GA), like FA, has a better glycemic index than HbA1c in renal failure, hemolytic anemia, and blood transfusion patients. GA is FA, which contains all glycated serum proteins. FA levels can fluctuate in liver illness because FA is not normalized for albumin or total protein content. Alternatively, GA measures GA/total albumin. Thus, GA is preferable to FA in protein-loss disorders such as nephrotic syndrome, liver, and thyroid illness. One study found that serum FA corrected for albumin improved its connection with HbA1c, but it is uncertain if FA should be corrected for total serum protein concentration (Sun et al., 2022).

Diabetes was linked to Asian serum GA levels of 15–16%. GA also diagnoses prediabetes and diabetes with moderate sensitivity and specificity (Table 1). Combining FPG <100 mg/dL (5.56 mmol/L) with

serum GA <15% can exclude diabetes, while FPG \geq 126 mg/dL (7.0 mmol/L) or serum GA \geq 17% can diagnose diabetes. This increases GA sensitivity. A study found that a threshold of \geq 230 μ mol/L for FA and \geq 13.35 percent for GA, corresponded with a HbA1c of 5.7 percent (39 mmol/mol), for identifying prediabetes. GA and FA are linked to CVD, ischemic stroke, retinopathy, chronic renal disease, and death in the Atherosclerosis Risk in Communities Study. FA and GA showed comparable relationships to HbA1c⁵⁴, suggesting they may be effective indicators in clinical circumstances where HbA1c is incorrect (Bansal, 2015).

GA and HbA1c indicated prediabetes better than HbA1c alone. GA may identify prediabetes better than FA, although FA and HbA1c were not better than HbA1c alone. GA may be incorrect due to albumin turnover fluctuations. Obesity-associated inflammation may increase albumin catabolism and decrease albumin production, lowering GA levels. The mechanism through which obesity lowers GA is unknown. Increased BMI, body fat mass, and visceral adiposity may artificially lower GA. The mechanism by which GA levels change under these situations is unclear (Li et al., 2014).

1,5 Anhydroglucitol

A dietary monosaccharide called 1,5 Anhydroglucitol (1,5 AG) may indicate prediabetes. The kidney's proximal tubules prefer glucose over 1,5 AG, therefore high glucose levels impede 1,5 AG reabsorption and increase 1,5 AG urine excretion. Thus, plasma 1,5 AG concentrations are inversely linked with plasma glucose levels⁶⁰, as shown in a study where the control group had the highest 1,5 AG level, followed by prediabetes and diabetes. Not all researchers have established an inverse connection between 1,5 AG and OGTT 2-hour post-glucose. The inverse connection between 1,5 AG and HbA1c and FPG has also been shown (Bansal, 2015). Similar to FA, 1,5 AG may be a valuable biomarker because it measures glucose levels from 10–14 days prior. 1,5 AG is more stable, reproducible, and affordable than other glycemic diagnostic tests. It may help identify postprandial glucose excursions and at-risk individuals since 1,5 AG is linked to retinopathy and microvascular and macrovascular events in diabetes. It is unknown if 1,5 AG is better than HbA1c. Plasma 1,5 AG levels vary by diet, sex, and race. Renal hemodynamics and sodium-glucose co-transporter 2 inhibitors alter levels. There is no unanimity on screening 1,5 AG for prediabetes (Li et al., 2014).

Adiponectin

Adiponectin, generated from adipose tissue, predicts diabetes and is insulin-sensitizing, anti-inflammatory, and anti-atherogenic. Lower adiponectin levels are linked to obesity and IR, while greater levels are linked to lifestyle intervention groups in diabetes prevention trials. A decade before diabetes was detected, men had decreased adiponectin levels, which were linked to diabetes risk. In kids of parents with T2DM, baseline adiponectin levels are inversely associated with the incidence of prediabetes regardless of ethnicity or sex. Adiponectin levels are directly linked with insulin sensitivity and indirectly with insulin secretion using the hyperinsulinemic-euglycemic clamp and intravenous glucose tolerance test (Pfister et al., 2011).

Fetuin-A

Hepatic secretory glycoprotein FetA increases the risk of T2DM and its consequences. In contrast to adiponectin, the EPIC-Potsdam prospective cohort study demonstrated that FetA independently predicted T2DM after adjusting for BMI and waist size. FetA may increase lipid-induced IR by activating the TLR4-inflammatory signaling pathway, which produces inflammatory cytokines. The FFA-TLR4 signaling pathway is considered to generate IR due to persistent inflammation caused by free fatty acids (FFAs) (American Diabetes Association, 2014).

However, FFA may not directly bind TLR4. A study found that FetA controls insulin sensitivity by binding to TLR4. High-fat diet-fed FetA intravenous injection promoted inflammatory signaling and

IR in adipose tissue, however, FetA knockdown animals have reduced TLR4-mediated inflammatory signaling. FFA-induced inflammatory cytokine production in adipocytes required FetA and TLR4 and eliminating either inhibited IR. Adipocytes with mutant TLR4 or galactoside-cleaved FetA did not create IR from FFAs. Elevated FetA, TLR4, IL-6, and TNF- α levels in obese diabetics indicate a link between lipids, FetA levels, TLR4 expression, and IR (Guo et al., 2014). Conflicting studies have linked FetA levels to CVD. No association, positive association, or inverse association was reported. One multi-ethnic US study indicated a favorable trend in IFG/diabetics. FetA may increase CVD risk in IR-prone people. These data imply that FetA is an endogenous TLR4 ligand that induces IR through lipids. Therefore, FetA may be a unique IR therapeutic target (Pfister et al., 2011).

Metabolites and MicroRNA

Amino Acids

Felig et al. observed that fasting branched chain and aromatic amino acids linked with obesity and serum insulin, while glucose loading lowered amino acid levels in insulin-sensitive but not insulin-resistant individuals. This is likely due to insulin-mediated skeletal muscle proteolysis inhibition. Recent research has linked amino acids to prediabetes, IR, and obesity. BCAAs, isoleucine, leucine, valine, tyrosine, phenylalanine, and glycine are linked to diabetes risk. In insulin-resistant conditions, glutamine, methionine, cysteine, and 2-aminoadipic acid rise. However, prediabetics had lower glycine levels (Selvin et al., 2011). A comprehensive systematic review and meta-analysis found positive relationships with BCAAs and aromatic amino acids and negative connections with glycine and glutamine and T2DM risk. 85 Alterations in circulating amino acid levels may predict IR and T2DM (Radin, 2014).

α -Hydroxybutyrate

The synthesis of α -ketobutyrate (α -KB) in hepatic tissue produces α -HB, an organic acid byproduct. α -KB is a result of amino acid catabolism (threonine and methionine) and glutathione anabolism (cysteine generation pathway). Lactate dehydrogenase and α -HB catalyse α -KB production. Oxidative stress enhances hepatic glutathione synthesis, leading to increased α -KB production. This results in reduced L-cysteine availability for glutathione production and increased α -HB levels. Increased oxidative stress and lipid oxidation in IR can cause persistent changes in glutathione production, resulting in higher α -HB levels (Radin, 2014). IR is characterized by increased urine α -HB excretion. Previous research used α -HB as a biomarker to differentiate NGT-insulin-sensitive (NGT-IS) participants from IGT, IFG, and NGT-IR subjects. Multiple logistic regression studies revealed a significant association between α -HB and IR, regardless of sex, age, BMI, or collecting site. IR was linked to decreased glycine and serine upstream of α -KB, and increased cysteine levels. The mechanism may include redox imbalance, with IR leading to a rise in α -HB. α -HB may be a promising biomarker for prediabetes (Lee, 2015).

Linoleoyl-glycerophosphocholine

Choline-containing phospholipids and sphingomyelins raise T2DM risk. The Relationship between Insulin Sensitivity and Cardiovascular Disease study examined L-GPC. 91 Hepatic and circulatory lecithin-cholesterol acyltransferases generate L-GPC. Phospholipase A2 increases with inflammation. Noncompetitive enzyme inhibition of phospholipase A2 by L-GPC may reduce inflammation. L-GPC is a negative predictor of T2DM progression, while α -HB is a positive predictor (Lee, 2015).

Lipoprotein (a)

The liver produces Lp(a). High LP(a) levels independently increase CVD risk. 94 Serum Lp(a) is inversely related to prediabetes and T2DM, however, the mechanism is unclear. 95 Insulin may lower Lp(a) (Malmström et al., 2014).

Triglycerides and High-Density Lipoprotein

High blood triglyceride (Tg) levels in prediabetes are linked to β -cell dysfunction and decreased insulin production. Hypertriglyceridemia decreases glucose-induced insulin secretion and increases β -cell death through increasing ceramide and nitric oxide production. Elevated Tg levels can lead to lipotoxicity by accumulating in pancreatic β cells. Cholesteryl ester transfer protein transfers lipids from Tg-rich lipoproteins to HDL (HDL). Tg increases in insulin-resistant conditions expedite this exchange. Hepatic lipase hydrolyzes HDL cholesterol (HDL-C) Tg, resulting in smaller particles. ABCA1 transports cholesterol to tiny HDL3 particles. Compared to HDL-C, prediabetics exhibit high quantities of tiny HDL3 particles. Tg is positively correlated with tiny HDL3 particles and negatively correlated with HDL-C. In contrast to Tg, HDL-C stimulates insulin production via ABCA1. Low HDL-C levels can potentially cause prediabetes to become diabetes. It is unknown if HDL-C levels are linked to β -cell dysfunction (Tavares Ribeiro et al., 2016). LpPLA2 degrades oxidatively fragmented phospholipids and may contribute to atherogenesis. HDL-LpPLA2 activity is considerably lower in IFG patients than in normoglycemic patients. HDL-LpPLA2 may protect against atherosclerosis, while low-density lipoprotein-associated LpPLA2 may promote inflammation. IFG patients had higher HDL3 particle counts and lower HDL-LpPLA2 activity. Thus, HDL-C subtypes may contribute to prediabetes (Rodríguez-Segade et al., 2017).

Ceramide

Ceramides and Tg are linked to prediabetes and T2DM. Ceramides are lipid IR mediators. Ceramides block insulin action by lowering Akt phosphorylation and activation, accumulate in insulin-resistant tissues, and cause inflammation via the NF- κ B-TNF- α axis, according to studies. Ceramides also indicate coronary artery disease. The links between lipid metabolism, prediabetes, and diabetes need further study (Rodríguez-Segade et al., 2017).

Ferritin and Transferrin

Ferritin stores and releases iron intracellularly. Elevated serum ferritin and transferrin saturation greatly increase prediabetes and diabetes risk. Additionally, FPG and serum ferritin are positively correlated. Iron causes IR by causing extremely active radical generation, DNA and cell membrane damage, β -cell oxidative stress, reduced insulin secretion, and glucose absorption in skeletal muscles and adipocytes. Additionally, catalytic iron causes reactive oxidant species, hepatic dysfunction, and β -cell death, contributing to IR. Dietary iron limitation or chelation protects against diabetes and β -cell function decline. 105 Ferritin thresholds for IR may vary by sex and age. Ferritin's effect on prediabetes needs further study (Cha et al., 2016).

Mannose-Binding Lectin Serine Peptidase, Thrombospondin 1 and Glycosylphosphatidylinositol-Specific Phospholipase D1

Innate immune responses and complement system lectin pathway activation depend on mannose-binding lectin-associated serine proteases. MASP1, the most abundant complement lectin pathway serine protease, is crucial to the complement cascade. MASP1 positively correlates with prediabetes, diabetes, and CVD. Increased MASP1 plasma levels were linked to early prediabetes and IR onset in one research. The favorable correlation between high FPG and 2-hour glucose levels was weaker when controlled for triacylglycerol. This shows that triacylglycerol may mediate the MASP1-HOMA-IR relationship. THBS1 and GPLD1 are favorably related to prediabetes, but ApoA-IV is inversely associated (Malkan et al., 2015).

THBS1, a glycoprotein of the THB family, regulates cellular adhesion and migration, cytoskeletal architecture, cell proliferation and apoptosis, and cell-to-cell interactions. This matrix protein is linked to higher IR, 2-hour glucose levels, and prediabetes prevalence due to THB's inflammatory qualities.

Glycosylphosphatidylinositol-anchored membrane proteins are released by liver-produced GPLD1. It is connected to diabetes and prediabetes via serum lipoproteins. ApoA-IV, a component of chylomicrons, VLDL, and HDL, is inversely related to prediabetes and diabetes. ApoA-IV may regulate appetite and chylomicron formation and have antioxidant and anti-inflammatory activities. Few research has examined the link between THBS1, GPLD1, and ApoA-IV and prediabetes; more data is needed to understand their involvement (Sumner et al., 2016).

Acyl-Carnitine

Fatty acid oxidation (FAO) powers cells. The carnitine shuttle carries active long-chain fatty acids (LCFA) from the cytosol to the mitochondria, which is important for FAO. Once within, fatty acids esterify to CoA. Acyl-carnitine is produced by carnitine palmitoyltransferase 1 exchanging CoA for carnitine. Recently, prediabetes was linked to increased acyl-carnitines. The important role of acyl-carnitine in FAO and its mechanism in IR are unknown. Intermediary products such as acyl-carnitines may accumulate due to FAO and mitochondrial dysfunction. Thus, the tricarboxylic acid cycle and LCFA supply are mismatched. Furthermore, acyl-carnitines interact with NF- κ B, promoting inflammation and IR. Few research has examined acyl-carnitines in prediabetes (Danese et al., 2015).

MicroRNAs

Small, noncoding microRNAs (miRNAs) regulate gene expression post-transcriptionally. These are important for growth, development, differentiation, proliferation, and cell death. Pre-diabetes elevated miR-192 and miR-193b, according to recent studies. miR-193b differentiates brown adipocytes and reduces inflammation, while miR-192 regulates tumor protein p53. Both miRNAs were increased in IFG and IGT patients. In animal models, miR-192 and miR-193b have been linked to Tg levels and the fatty liver index, which may be noteworthy since prediabetes might be linked to fatty livers. Exercise also dramatically decreased miR-192 and miR-193b (Whiting et al., 2011).

In T2DM, miRNAs such as miR-9, miR-29a, miR-30d, miR-34a, miR-124a2, miR-146a, and miR-375 are considerably enhanced and may contribute to β -cell function. Negatively regulate insulin expression, synthesis, or secretion with these miRNAs. There were no statistically significant increases in prediabetes, suggesting that pathophysiological processes may be reversible in prediabetes but not in T2DM. Additional miRNAs decrease in prediabetes. IGT/IFG and T2DM decrease miR-126, which is prevalent in endothelial cells and helps maintain vascular integrity. Exercise and food raise miR-126 levels. In prediabetes, T2DM, and IFG/IGT, miRNA-15a levels were considerably reduced. miR-15a inhibits endogenous uncoupling protein-2 gene expression and increases insulin release to regulate insulin production. Thus, miR-15a is suspected to significantly impact β -cell activity and insulin production (Cho et al., 2018).

Inflammatory Markers

Prediabetes and IR are inflammatory. 127–129 Acute-phase reactant and inflammatory cytokine biochemical indicators are higher during T2DM beginning and may rise with disease progression. CRP, white blood cell count, and fibrinogen have been studied as potential predictors of T2DM, such as in the Atherosclerosis Risk in Communities research (Ogurtsova et al., 2017).

CRP and IL-6

CRP is the most researched CVD inflammatory measure, and its clinical application is evolving. CRP is a key acute phase response measure obtained from IL-6-dependent hepatic production. T2DM and IR patients have higher IL-6 and CRP levels, according to many studies. The Women's Health Study, a nationwide cohort of 27,628 women without diabetes, CVD, or cancer at baseline, developed DM in 188 women over four years. IL-6 and CRP median baseline levels were substantially higher in cases than controls. In addition, higher IL-6 and CRP levels increase diabetes risk. The relative risk of

incident T2DM increased with IL-6 quartiles (1.0, 2.5, 4.1, and 7.5) and CRP quartiles (1.0, 2.2, 8.7, and 15.7, respectively) ($p < 0.001$ for trend). BMI correction reduced these relative hazards, but the results were encouraging. These findings were identical after adjusting for fasting insulin levels and only included women with a baseline HbA1c of 6.0 percent (42 mmol/mol) or below. This shows that these inflammatory indicators may help identify T2DM risk factors (Sun et al., 2022).

The multicenter Insulin Resistance Atherosclerosis Study (IRAS) studied 1,625 people for 5.2 years. People with prediabetes developed diabetes during follow-up. Insulin-resistant prediabetics reported higher CRP levels than insulin-sensitive prediabetics and non-diabetics. Body weight was assumed to contribute to these inequalities. Prediabetes and IR patients were not hyperglycemic, hence hyperglycemia did not cause subclinical inflammation. Another study found that the glycemic index was not connected with CRP and T2DM risk, supporting the concept that hyperglycemia is not the cause of diabetes and inflammation (Bansal, 2015).

CRP is linked to prediabetes in other research. The Gutenberg Health Study was a prospective, observational single-center cohort study of 15,010 persons with HbA1c values indicating prediabetes or diabetes. CRP increased progressively from normoglycemia to prediabetes (1.4 vs. 2.3 mg/L) but only slightly between prediabetes and diabetes (2.3 vs. 2.4 mg/L), suggesting that early immunological activation contributes to diabetes. Innate immune system and inflammatory cascade genetic variations alter CRP and T2DM propensity. 128,135 Other studies have linked prediabetes to high CRP and IL-6 levels. 127,136 A meta-analysis found that the relative risk of T2DM increased by 1.31 (95 percent CI 1.17–1.46; $p = 0.000$) for 1 log pg/mL increase in IL-6 (Li et al., 2014). These authors observed that T2DM risk increased by 1.26 (95 percent CI 1.16–1.37; $p = 0.000$) for 1 log mg/L increase in CRP in another meta-analysis. Women may have different CRP predictors of diabetes than men. The meta-analysis found that IL-6 was more strongly related to T2DM than CRP, raising questions about latent inflammation in diabetes. Thus, CRP may play a downstream role but not precipitate this process. In contrast, another study found that obesity and IR boosted CRP, while insulin-sensitive or obese people had low amounts (Cho et al., 2018).

White Blood Cell Count, Fibrinogen and Hematological Indices

White blood cell count and fibrinogen are immune and inflammatory markers that may affect diabetes progression and organ problems. Cardiovascular disease may be predicted by leukocytosis. Thus, early identification of high-risk patients may avoid CVD. In Pima Indians, elevated white blood cell counts indicate impaired insulin action, secretory function, and T2DM. 140 Blood viscosity, platelet aggregation, and fibrin production may be affected by fibrinogen, contributing to atherosclerosis. Fibrinogen regulates coagulation, fibrinolysis, and plaque progression. In the Gutenberg Health Study, prediabetes had greater fibrinogen levels than diabetes, although why is unknown (Li et al., 2015).

The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) also indicate subclinical inflammation. In a 110-adult trial, NGT, IGT, newly diagnosed T2DM, and T2DM without problems were split. NLR values were considerably greater in prediabetes, newly diagnosed diabetes, and known diabetes than in the control group. PLR values were considerably lower in prediabetes and newly diagnosed diabetes but greater in T2DM. Obese diabetics had higher NLR than non-diabetics. Diabetes consequences include microvascular and macrovascular problems from NLR. Another study found that 1-hour post-load glucose levels increased white blood cell count and fibrinogen. After controlling for sex, age, smoking, fasting, and 1- and 2-hour post-load glucose levels, Fiorentino et al. found that prediabetics had higher CRP, fibrinogen, and white blood cell counts (Radin, 2014).

Plasminogen Activator Inhibitor-1

Tissue plasminogen activator-1 (PAI-1) indicates diminished fibrinolysis and coagulation problems. 147 Changes in PAI-1 levels independently predicted IRAS diabetes (Lee, 2015).

IL-18

Hyperglycemia raises cytokine levels, including plasma IL-6, TNF- α , and IL-18, through oxidative processes. In a prospective case-cohort study, high-IL-18 quartile participants had a 70% higher incidence of T2DM than low-IL-18 subjects. The Gutenberg study found that IL-18 rose from prediabetes to diabetes (Li et al., 2015).

IL-1 Receptor Antagonist

In overfeeding, glucose and FFAs may activate the IL-1 pathway and cause inflammation. Adipocytes produce IL-1RA, an anti-inflammatory signal raised in prediabetes and diabetes, presumably in reaction to inflammation. A Whitehall Study of 355 patients with incident T2DM found that prediabetes was associated with increased IL-1RA, decreased insulin sensitivity, increased β -cell activity, and higher 2-hour glucose levels years before the onset of T2DM. IL-1RA was high 13 years before T2DM diagnosis. IL-1RA increased rapidly 6 years before diagnosis, even after BMI adjustment (Malmström et al., 2014).

Patient-Focused Perspectives

Up to 90% of prediabetics are undiagnosed¹, therefore they don't receive lifestyle advice to prevent T2DM. HbA1c and glucose screenings have been used clinically for years, although each has drawbacks. Since HbA1c is insensitive for diagnosing acute and intermittent hyperglycemia and impacted by medical conditions and ethnicity, new biomarkers would be invaluable. OGT provides critical information about T2DM risk that HbA1c and FPG do not, however, it is variable, needs fasting, is invasive, and takes time. However, intermediate periods during the OGTT (e.g., 30 or 60-minute post-load values) appear to predict progression to T2DM better than fasting, 2-hour post-load glucose, or HbA1c levels, making this technique more attractive and possibly shortening the 2-hour test. Since a single determinant may have limits, more research is needed to find the most reliable biomarker(s). Thus, many biomarkers may better predict high-risk individuals for prediabetes and diabetes (Malmström et al., 2014).

Discussion

The study aimed to review the biomarkers that have been utilized for diabetes in previous research. The comparison of the biomarkers mentioned in the provided information reveals a complex interplay of factors influencing the risk and management of Type 2 Diabetes (T2D). These biomarkers encompass genetic, lifestyle, environmental, and insulin-related factors, each with varying degrees of accuracy and specificity in predicting T2D risk or guiding its management. The potential of genetic risk scores to predict type 2 diabetes risk based on an individual's genetic profile has attracted a lot of attention. They use data from several different T2D-related genetic loci. Although they help understand a person's predisposition to a disease, their clinical use is limited. Due to the intricate interplay between genetic and environmental factors that contribute to type 2 diabetes, GRSs often exhibit low accuracy and specificity. Their value in individualized clinical treatment may be lower than in research and risk assessment for larger populations. Individuals with T2D who need insulin therapy, however, may benefit from testing for insulin-related biomarkers such as insulin-antibody complexes and exogenous insulin antibodies. These biomarkers are associated with insulin therapy efficacy and may affect glycemic management.

The insulin management context is where their precision and specificity shine. They may not be adequate for use as population-wide predictive biomarkers of type 2 diabetes risk. Past research has also brought up lifestyle factors including nutrition and exercise in addition to biomarkers like alanine transaminase (ALT), uric acid, and vitamin D. Predictions of Type 2 Diabetes risk using these biomarkers may have varied degrees of accuracy and specificity. Vitamin D insufficiency, for instance, has been linked to an increased risk of type 2 diabetes in certain research, however, its predictive value may be low. Lifestyle factors, such as inactivity and food, may also influence T2D risk but may not be very reliable predictors on their own.

Moreover, Hemoglobin A1c (HbA1c), fructosamine (FA), glycated albumin (GA), 1,5 anhydroglucitol (1,5 AG), adiponectin, and fetuin-A are all biomarkers used in the diagnosis and risk assessment of diabetes, and each has its own set of strengths and weaknesses in this regard. HbA1c is a common biomarker used to diagnose diabetes and evaluate glycemic management. It's a reflection of two to three months' worth of chronic glycemia. HbA1c has advantages over other similar tests in that it does not necessitate fasting and is less impacted by stress and illness. It has a high degree of specificity and is connected to an increase in diabetes-related mortality and morbidity. However, its diagnostic sensitivity is rather moderate, particularly for prediabetes, and it may miss certain instances, especially among specific ethnic groups. Although it may not capture acute glucose swings, it does provide useful information on long-term glycemic management.

Furthermore, Fructosamine (FA) is a marker of short-term glycemic management since it measures average blood glucose concentrations during the past 1–4 weeks. Although it is less expensive and does not necessitate fasting, it may provide misleadingly low results in diseases such as nephrotic syndrome and hepatic illness. Research is needed to better understand its role as a microvascular biomarker and its diagnostic accuracy for prediabetes. Glycated Albumin (GA) can be used instead of FA in situations where protein loss is a problem, such as in nephrotic syndrome and liver illness. It provides a valid measure of short-term glycemic control and is less impacted by albumin turnover. Combining GA with fasting plasma glucose (FPG) has been found to increase diagnostic sensitivity for prediabetes and diabetes. Clinical relevance has been suggested due to its association with diabetes-related problems.

In addition to this, 1,5 Anhydroglucitol (1,5 AG) is inversely linked with plasma glucose levels and is a marker of glucose homeostasis over the previous 10-14 days. The marker's stability, reproducibility, and low cost make it an excellent tool for screening for postprandial glucose excursions and identifying at-risk people. Further study is needed to determine its diagnostic power in comparison to HbA1c and clarify its significance in prediabetes screening. Adiponectin is a biomarker that can be used to assess the likelihood that a person will develop diabetes. Obesity and insulin resistance are linked to lower levels, while increased insulin sensitivity is linked to higher levels. When considered alongside other risk factors, such as a family history of diabetes, it may be useful for predicting who may develop prediabetes or diabetes. The hepatic glycoprotein fetuin-A has been linked to an elevated danger of type 2 diabetes. Inflammatory pathways may be activated, which could contribute to insulin resistance. There is debate about whether or not it is useful for diagnosing diabetes, and some research suggests it may increase the risk of cardiovascular disease. To learn how useful it is as a diagnostic biomarker, more study is required.

Branched-chain amino acids (BCAAs) and aromatic amino acids (AAs) have received particular attention as potential contributors to obesity, insulin resistance (IR), and diabetes. Diabetes risk increases with increased amounts of the branch chain amino acids (BCAAs) isoleucine, leucine, valine, tyrosine, and phenylalanine and decreased levels of glycine. The diagnostic specificity for prediabetes may vary across these markers, however, they show promise as indications of metabolic dysfunction. Some amino acids have been linked to a higher risk of developing diabetes, suggesting they may have

diagnostic value. -Hydroxybutyrate (-HB) is produced during the breakdown of amino acids and the metabolism of glutathione. Because it correlated with insulin resistance, it has demonstrated usefulness as a biomarker for prediabetes. Increased levels of -HB have been associated with IR, and its measurement has been used to classify people as insulin-sensitive or resistant. Because of its high level of diagnostic sensitivity for prediabetes and its ability to predict metabolic dysfunction, it warrants further study as a potential diagnostic marker.

The review also explained that the phospholipid linoleoyl-glycerophosphocholine (L-GPC) has anti-inflammatory properties. It has been demonstrated to have a protective effect against the development of type 2 diabetes (T2DM), suggesting it may be useful as a diagnostic tool. Although it shows promise as a diagnostic tool for prediabetes, more study is required to confirm its accuracy and specificity. Liver-produced lipoprotein (a) (Lp(a)) is inversely associated with metabolic syndrome and type 2 diabetes. Although the exact method by which insulin affects Lp(a) levels is unclear, it appears to be the case. Although further research is needed to confirm its diagnostic specificity for prediabetes, it shows potential as a biomarker for diabetes risk. Prediabetes can develop when blood triglycerides are too high because β -cell malfunction causes less insulin to be produced. The ratio of triglycerides to high-density lipoprotein (HDL) particles, and the subtypes of HDL particles, can affect insulin sensitivity and β -cell function. Further study is needed to determine the specificity of these indicators for prediabetes, but they offer diagnostic promise in evaluating metabolic dysfunction. Insulin resistance and inflammation are both mediated by ceramides, which are lipid mediators. While they show potential as diagnostic indicators, more study is needed to determine their accuracy and specificity for prediabetes and their function in prediabetes and diabetes risk.

However, increased prediabetes and diabetes risk have been associated with elevated serum ferritin and transferrin saturation. Oxidative damage and insulin resistance may be exacerbated by an iron excess. However, more research is needed to determine the diagnostic accuracy of ferritin and transferrin for prediabetes. Gene expression can be controlled by small noncoding RNA molecules called microRNAs (miRNAs). MiR-192 and miR-193b are two examples of miRNAs that have been linked to prediabetes and insulin resistance. They have diagnostic promise, but their specificity for prediabetes still requires work. The diagnostic use of other miRNAs, such as miR-9 and miR-29a, for discriminating between prediabetes and type 2 diabetes has also been suggested.

Interleukin-6 (IL-6), an inflammatory cytokine, and C-reactive protein (CRP), a critical acute-phase reactant, have both been extensively investigated in diabetes. Both are useful in diagnosing prediabetes and predicting the development of diabetes. Increased diabetes risk has been linked to higher CRP and IL-6 levels at baseline. However, factors like body mass index may affect their diagnostic accuracy, and BMI reduction might reduce relative risks. Nevertheless, when combined with other clinical criteria, these indicators show potential in identifying persons at risk of diabetes. Diabetes development and cardiovascular problems may be predicted by measuring white blood cell count and fibrinogen, two immunological and inflammatory markers. Impaired insulin action and an increased risk of diabetes have both been linked to elevated white blood cell numbers. Diabetes risk may be increased by fibrinogen, which aids in blood clotting and the development of plaque. Diabetes risk can be assessed using these indicators, however, their specificity and accuracy may differ between populations.

White blood cell and platelet counts can be used to calculate the neutrophil lymphocyte ratio (NLR) and the Platelet-Lymphocyte Ratio (PLR), respectively. Variations in these markers across those with prediabetes, newly diagnosed diabetes, and those with established diabetes have been observed, indicating the presence of subclinical inflammation. Potentially helpful in determining diabetes risk, especially in the obese, are these ratios. Increased levels of plasminogen activator inhibitor-1 (PAI-1) point to issues with fibrinolysis and coagulation. Variations in PAI-1 have been linked to an increased

probability of developing diabetes. In the presence of other clinical variables, elevated PAI-1 levels have been suggested as a predictor of diabetes.

Hyperglycemia has also been linked to an increase in interleukin-18 (IL-18). An increased risk of developing type 2 diabetes has been associated with elevated levels of IL-18. It has potential as a diagnostic marker for determining who is at risk for developing diabetes. In prediabetes and diabetes, inflammation leads to a rise in Interleukin-1 Receptor Antagonist (IL-1RA), an anti-inflammatory signal. High levels of IL-1RA have been linked to decreased insulin sensitivity and an increased risk of developing diabetes. The onset of diabetes can potentially be predicted by tracking IL-1RA levels.

In conclusion, biomarkers' accuracy and specificity in predicting or managing T2D risk differ. Genetic risk ratings reveal genetic predisposition but have limited clinical relevance. Individuals on insulin therapy have insulin-related biomarkers. These biomarkers have different diagnostic accuracy and specificity. HbA1c is essential for long-term glycemic control, while FA, GA, and 1,5 AG reveal short-term changes. Adiponectin and Fetuin-A reveal insulin sensitivity and risk factors. The clinical context and diagnostic or risk assessment goals determine the biomarker and a mixture of markers may be more informative than one alone. Many of them show promise in diagnosing metabolic abnormalities, but their accuracy and specificity vary, and further study is needed to verify their therapeutic use. In conclusion, these inflammatory indicators can detect prediabetes and diabetes. However, population characteristics and confounding variables like BMI can affect their accuracy and specificity. Combining these markers with additional clinical criteria may provide a more complete risk assessment for prediabetes and diabetes, allowing for earlier intervention and lifestyle changes to avoid disease development.

4.0 CONCLUSION AND RECOMMENDATIONS

Conclusion

In conclusion, the purpose of this study was to investigate metabolite biomarkers for the early detection of pre-diabetes and Type 2 Diabetes (T2DM), given the global increase in diabetes prevalence. The researchers conducted a systematic review and meta-analysis of relevant studies published up to May 31, 2023, focusing on human subjects adhering to international diagnostic guidelines. The findings of this study revealed a complex array of biomarkers influencing the risk and management of T2DM. These biomarkers encompassed genetic, lifestyle, environmental, and insulin-related factors, each with varying degrees of accuracy and specificity in predicting T2DM risk or guiding its management. Genetic risk scores, which utilize data from multiple T2D-related genetic loci, were highlighted as a promising avenue for predicting T2DM risk based on an individual's genetic profile. The implications of this research are significant, as it contributes to raising awareness about the identification of diabetes and underscores the economic impact of biomarker-based screening. This information can inform healthcare policies and strategies for early intervention and prevention of diabetes. Moving forward, the study recommends that future research endeavors focus on validating the diagnostic capabilities of these biomarkers across diverse populations and settings. Further investigation should also explore how the combination of multiple biomarkers can enhance diagnostic accuracy.

Recommendations

Future studies should validate these biomarkers' diagnostic capacities across varied populations and circumstances. For accurate results, measurement methods and reference ranges must be standardized. Research can examine how several biomarkers can improve diagnostic accuracy. Combine markers with complementary strengths to assess diabetes risk more thoroughly. Assessment of these biomarkers' predictive usefulness should be done over time via longitudinal research. Understanding biomarker alterations and diabetes progression improves risk prediction. Moreover, future studies can

examine ethnic and gender differences in diabetes biomarker relationships. Certain biomarkers may predict differently in different demographics. To improve predictive models, consider merging biomarker data with clinical data including family history, lifestyle factors, and other risk factors. Furthermore, consider the cost-effectiveness of these biomarkers for diabetes risk assessment. Understanding biomarker-based screening's economic impact can inform healthcare policies. Biomarker panels that include genetic, inflammatory, and metabolic indicators to determine individual risk should be developed. These methods can identify complex biomarker relationships. Biomarker-driven risk assessment strategies should be tested in clinical trials.

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