Asian Journal of Medical Research & HealthSciences, Vol2, Issue-1,2024;p05-08, doi:10.5455/AJMRHS.1107202300018,

ISSN:2583-7761

Original Article

The classical Biomarkers to Predict Diabetes Mellitus-

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Article Received 12-Dec-2023 Accepted 1-JAN-2024 Published 4-MAR-2024

ABSTRACT

Diabetes mellitus is metabolic disorders; depicted by elevated blood glucose levels ascribed to a futile, scanty or sojourns production of insulin. Enduring complications of the disease have been related to peripheral vascular problems, steering to cardiovascular diseases, stroke, diabetic retinopathy, nephropathy and foot. Precise monitoring of these complications and early therapy stages will allow improvement in prevention and treatment approaches. The availability of measurable, accurate and reproducible biomarkers allow the patient to receive timely enactment of personalized therapies and circumventing harmful blood sugar fluctuations that ultimately progress to life-threatening impediments. Profound knowledge of these biomarkers released by extracellular vesicles in metabolic diseases and other disease condition may guide the development of novel therapeutic approaches to restore the affected pathogenesis, rather than merely treating the symptoms.

With advent of method that can isolate (ultracentrifugation, affinity-based capture, size exclusion chromatography/filtration, polymer precipitation) and characterize (protein quantification, transmission electron microscopy, atomic force microscopy, ELISA, nanoparticles tracking analysis, flow cytometry, western blot) from body fluids have become a major diagnostic and prognostic biomarkers not only in diabetes, in other conditions like cancer, neurodegradative disease.

Keywords: Biomarkers, diabetes mellitus, blood glucose, metabolic diseases.

Introduction

Diabetes Mellitus will be a significant medical issue for the world in the coming days, with its greatest impact in developed countries on newly industrialized, developing nations and minority groups [1]. Diabetes will escalate from 135 to 300 million worldwide by 2025, of which 93-97%) patients will be with type II diabetes. Centers for Disease Control, data indicates that 1 in 3 adults have prediabetes which is an intermediate stage and, 90 percent of people were unaware of their condition. In 2019, the International Federation for Diabetes reported that the worldwide prevalence of impaired glucose tolerance (IGT) in adults was 318 million and predicted to exceed 482 million by 2040 [2, 4]. The main concern is how can we identify prediabetes patients early, and how can we prevent diabetes progression. Identification of these prediabetes states and risk stratification resulting from novel biomarker insulin resistance will improve both diabetic and pre-diabetic clinical outcomes [3]. Diabetes Prevention Program has illustrated that changes in dietary habits, weight loss, and exercise reduce the risk of diabetes progression [5]. So the tools to identify and raise awareness of an individual's prediabetes state require more time [6, 7].

Biomarkers are used to diagnose prediabetes for clinical assessment and prevent chronic conditions in diabetes [8, 9]. Genetics, peripheral insulin resistance, insulin secretion defects, lipotoxicity, glucotoxicity, amylin accumulation, impaired incretin release inflammation, oxidative stress, and decreased β-cell mass resulting in β-cell dysfunction are factors leading to prediabetic state [10-12]. Prediabetes includes impaired isolated fasting glucose (IFG) or impaired tolerance glucose (IGT) [13]. This chapter will thus enable a better idea of the course of diabetes and therapeutic interventions.

Handy Novel Biomarkers

Adiponectin

It is a protein and adipokine, is developed from adipose tissue, has insulin-sensitizing, anti-inflammatory, and anti-atherogenic functions and is proven to be an independent diabetes predictor [14]. Adiponectin concentrations are inversely related to insulin resistance (IR), cardiovascular disease and obesity [15]. Lower adiponectin concentrations were determined even a decade before diabetes developed, or its problems notably in men. The levels of adiponectin in children of diabetic parents are inversely associated with risk of prediabetes and this effect is observed in either sex or ethnicity. Hyperinsulinemic clamp and intravenous glucose tolerance (IGT) test showed a direct correlation of the adiponectin levels [15].

Fetuin-A

Fetuin-A (FetA) is a liver-secreted glycoprotein, that is associated with an elevated risk of T2DM incidence [16]. FetA enhances lipid-induced Insulin resistance via the toll-like receptor 4 (TLR 4 is a transmembrane protein) an inflammatory signaling pathway resulting in inflammatory cytokine production. High-fat diet-fed and FetA knock-down animal module has less TLR4-mediated signaling in adipose tissue causing IR, in this model, FetA injection induces inflammatory signals and IR [17].

Inflammatory cytokine expression in adipocytes was induced by the presence of FetA and TLR4 both required for FFA (free fatty acid). Higher FetA correlates also with the risk of cardiovascular disease in IR-susceptible candidates. In conclusion, FetA acts as an endogenous ligand to TLR4 for lipid IR induction. ThereforeFetA can serve as a novel therapeutic target for IR [18].

Amino acids:

Studies have shown a correlation between amino acids and Prediabetes, Insulin resistance, and obesity. Branched-chain and aromatic amino acids are associated to obesity as well as serum insulin, and the loading of glucose decreases amino acid levels in individuals sensitive to insulin but not in individuals resistant to insulin [19-23]. This is because proteolysis suppression in skeletal muscles is mediated by insulin. A variety of metabolic impairments are associated with high fasting levels of branched-chain amino acids (BCAAs: valine, isoleucine, leucine, and other aromatic amino acids such as phenylalanine, tyrosine) in venous blood, including increased risk of type 2 diabetes (T2D). These different concentrations of circulating amino acids can be considerable predictive biomarkers for IR and T2DM [24-29].

α-Hydroxybutyrate (α-HB)

In the liver α-Hydroxybutyrate (α-HB) is an oxidative product of amino acids like threonine, methionine, and glutathione [30].

Induced metabolic stress and lipid oxidation result in persistent shifts in glutathione synthesis leading to elevated levels of α-HB in insulin-resistant individuals [31, 32]. It is represented by increased excretion of the urinary α-HB in Insulin-resistant people. α-HB would be used as a biomarker to distinguish normal glucose tolerance insulin sensitive (NGT-IS) individuals from impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) and NGT-IS individuals from individuals with normal glucose tolerance insulin resistant (NGT-IR) [33]. Thus the α-Hydroxybutyrate (α-HB) can be a promising and useful biomarker for prediabetes.

Lipoprotein(a)

Lipoprotein(a) synthesizes through the liver. Elevated levels of LP(a) are a risk factor for coronary heart disease development. Serum LP(a) has an inverse relationship with the prevalence of prediabetes and T2DM. The higher insulin levels may be responsible for reducing lipoprotein(a) levels in the body [34, 35].

Triglycerides and high-density lipoprotein

Elevated serum triglyceride (Tg) levels have been associated with□□-cell dysfunction and reduced insulin secretion in prediabetes [36]. Significant increases in levels of small, high-density lipoprotein 3 (HDL3) particles were noticed in prediabetics compared to HDL-C levels. HDL-C induces insulin secretion and low HDL-C promotes prediabetes progression to diabetes [37].

Ceramide

I R. mediate Ceramidealipid molecules [38, 39]. It acts by diminishing phosphorylation by inhibiting the insulin action. It accumulates further in insulin-resistant tissues and induces inflammation by activating TNF-α. Studies have also shown that ceramide spreads coronary artery disease [39-41].

Ferritin and transferring

The storage and release of iron is regulated by an intracellular protein ferritin. High serum ferritin and transferrin saturation association with elevated risk of prediabetes and diabetes [42, 43]. The catalytic iron mechanism promotes the synthesis of superoxide radicals molecules that cause hepatic dysfunction, and β-cell apoptosis that contributes to IR. Dietary iron restriction prevents diabetes from developing, and β-cell function loss [44, 45]. The ferritin threshold levels that correlate with IR, however, are not certain.

Mannose-binding lectin serine peptidase and thrombospondin-1

MASP1 high levels discovered in prediabetes, diabetes, and CVD. Elevated levels of FPG and 2-hour glucose were associated positively with higher levels of MASP1. Other prediabetes markers, such as thrombospondin1(THBS1) and glycosylphosphatidylinositol-specific phospholipase D1 (GPLD1), are also increased [46]. Thrombospondin has inflammatory properties and contributes to the increased prevalence of prediabetes.

Acyl-carnitine

In prediabetes, serum levels of acyl-carnitine are elevated. However, it is not clear what role acylcarnitine plays in Fatty acid oxidation (FAO) and its mechanism in IR. An abnormal FAO and mitochondrial function has been postulated to lead to the accumulation of intermediate products such as acyl-carnitines that promote inflammation and IR [47, 48].

MicroRNAs: The hidden player

MicroRNAs (miRNAs) are small, noncoding RNAs participating in post-transcriptional gene expression. These are involved in many biological processes such as growth, development, differentiation, proliferation, and cell death [49-51]. Recently, miRNAs have been studied in pre-diabetes and found to be strongly correlated especially high levels of miR-192 and miR-193b. In animal studies, increased levels of both miRNAs i.e., miR-192 and miR-193b were observed with IFG and IGT, and directly linked with Tg levels and the fatty liver index [52]. It's quite significant since prediabetes can be correlated with a fatty liver.

Some miRNAs significantly enhanced in T2DM are miR-9, miR-29a, miR-30d, miR-124a, miR-146a, and miR-375, all of which play an important role in dysfunction of the β cells [53-55]. Such miRNAs adversely regulate insulin expression and secretion.

Inflammatory markers: The universal culprits

The high percentage of IL-6 and CRP is associated with a greater risk of developing diabetes. These inflammatory markers help to identify people at greater risk of developing T2DM. Changes to the tissue plasminogen-1 (PAI-1) activator are an independent predictor of diabetes incidence [56-57].

In the Gutenberg study, IL-18 levels increased in line with the advancement from prediabetes to diabetes. IL-1RA levels were found to be significantly bumped up even thirteen years before diabetes was diagnosed, and it starts to rise more extremely quickly approximately 6 years before diagnosis. The Whitehall research reported an increase in prediabetes IL-1RA in tandem with reduced insulin sensitivity, increased β-cell function, and 2-hour glucose levels, all occurring years before T2DM developed [58,59].

White blood cell count, fibrinogen, and hematological indices

Subtle measure an elevated WBC counts for worsening insulin action, insulin secretion, and the risk of diabetes among Pima Indians. The neutrophil-lymphocyte ratio (NLR) has also been associated with increased incidence of both microvascular and macrovascular diabetes [60-64].

Conclusions and Prospective

Dysglycemia is a pathophysiological process that continues. It is explicitly underreported and poses a threat to a large number of people. It has been late in the evolution of T2DM, leading to micro macrovascular complications. β-cell function reduced significantly on the higher side of the "normal glycemic range," leading to exponentially rising glucose levels.

To predict progression to diabetes at the earliest, there is a vital need to identify and use delicate, accurate biomarkers. Interference at an early stage could be more responsible for the reconfiguration of the way of living and antidiabetic drugs. The well-identified list of biomarkers in medical care may offer forecasting of prediabetes and chronic conditions of diabetes greater sensitivity and accuracy.

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