The Novel Biomarkers in Diabetes

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Abstract
According to International Diabetes Federation, the worldwide prevalence of impaired glucose tolerance (IGT) in adults is 318 million and is expected to reach 482 million by 2040. With increasing burden of prediabetes and their expectant progression in diabetes has compounded the problem. Now question is that how we can identify the subjects at high risk to develop prediabetic state and among them who will rapidly progress into diabetes? Once a person diagnosed to be a diabetic then there are only few marker which can depict development of diabetes related complications and also to help in preventing such diabetes related complication progression. In this article, we will review several biomarkers used to predict the risk of progression to prediabetes, diabetes states in context to their mechanism of action, sensitivity, specificity, advantages, disadvantages and association with dysglycemia. The risk stratification arising due to insulin resistance by novel biomarker will improve clinical outcome both in prediabetics and diabetics.

Introduction
In coming days diabetes Mellitus will be a major health problem for the world, with its highest impact on newly industrialized, developing nations and minority groups in developed countries.¹ Diabetes will increase from 135 to 300 million worldwide between 1995 and 2025, of which (93-97%) will be type II diabetic patients mounting a 42% increase in diabetes and overall 27% increase in the prevalence globally.² Not only diabetics but the pre diabetics will be compounding the problem. According to Centers for Disease Control one out of three, adults had prediabetes which is an intermediate state and agonizingly, 90% were unaware of their diagnosis.³ In 2015, the International Diabetes Federation estimated that the worldwide prevalence of impaired glucose tolerance (IGT) in adults was 318 million and expected to reach 482 million by 2040.⁴ The subject in question is how can we identify patients with prediabetes early and can we prevent progression to diabetes? Identification of these prediabetes states and risk stratification arising due to insulin resistance by novel biomarker will improve clinical outcome both in diabetics and pre diabetics.⁵ The Finnish Diabetes Prevention Study⁶ ⁷ and the U.S. Diabetes Prevention Program⁸ ⁹ have shown that changes in dietary habits, weight loss, and increased physical activity reduced the risk of progression to diabetes. So, the tools to identify and making an individual aware of his prediabetes state is need of time. Biomarkers for risk stratification, diagnose prediabetes and prevent complication in diabetes. Factors leading to prediabetic state are genetics, peripheral IR, defects in insulin secretion, glucotoxicity, lipotoxicity, impaired incretin release, amylin accumulation, inflammation, oxidative stress, and decreased β-cell mass leading to β-cell dysfunction.¹⁰ ¹¹ Prediabetes includes isolated impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).¹² ¹³ However the differing criteria of WHO and ADA made issue controversial as slight changes in criteria leads of large long term outcome.¹⁴ ¹⁵ Hence review of biomarker will give better understanding of disease course and therapeautic interventions.

Current diagnostic biomarkers and their clinical utility.
Hemoglobin A1c: It’s advantage and disadvantages
A better chronic glycemia estimation is done by HbA1c rather than glucose levels at a single time point. The ADA diabetes criteria cut off are HbA1c ≥6.5% (48 mmol/mol) and 5.7–6.4% (39–46 mmol/mol) for prediabetes.¹⁴ High HbA1c levels were also associated with increased CVD and all-cause mortality in Norfolk prospective study.¹⁵ Advantages of HbA1c over FPG and oral glucose tolerance test (OGTT) includes greater convenience as fasting is not needed, pre-analytical stability not required, and have minimal day-to-day fluctuation during periods of stress and illness.¹⁶ However, there is conflicting evidence regarding the usefulness of HbA1c as it provides moderate sensitivity in diabetes diagnosis when compared to OGTT and FPG.¹⁷ ¹⁸ Moreover OGTT more strongly correlates with IR and insulin secretion than HbA1c.¹⁹ The NHANES and Screening for Impaired Glucose Tolerance studies showed HbA1c levels <5.7% (39 mmol/mol) correlates only 60–70% of subjects having normal glucose tolerance (NGT).²⁰ ²² Additionally HbA1c threshold for prediabetes does not take ethnicity, body mass index (BMI), and age, all of which may significantly alter HbA1c levels under consideration.²³ ²⁵ Changes in the production rate or circulating life span of red blood cells will affect HbA1c levels.²⁶ Falsely low HbA1c occurs in hemolytic anemia, blood loss,²⁷ ²⁸ splenomegaly, and end-stage renal disease.²⁷ Hemoglobin variants, such as HbS, HbC, HbD, and HbE may also result in overestimation or under-estimation of HbA1c.³⁰ So HbA1c alone can be inadequate for diagnosing prediabetes, and more accurate

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diagnosis may require confirmation with other biomarkers.\textsuperscript{31}

**Fructosamine: Is it a better glycemic marker?**

Fructosamine (FA) is used as an alternate glycemic marker for diabetes screening and it is also useful to diagnose prediabetes. It reflects mean blood glucose level of previous 1–4 weeks.\textsuperscript{39} FA is also useful in conditions which affects hemoglobin levels. This method is cost effective and convenient to perform.\textsuperscript{52,53} It have high variability within the subject and in a state of rapid albumin turnover such as nephrotic syndrome and chronic liver disease resulting in falsely low levels.\textsuperscript{54} FA is also a good indicator of the risk for microvascular complications.\textsuperscript{35} But few studies deny it to be useful, for prediabetes screening.\textsuperscript{28,29,31-36,38} In conclusion, conditions where HbA1c is inaccurate FA can be used as a valuable complementary marker.

**Glycated albumin: Why and when to prefer over FA?**

Although it is similar to FA, glycated albumin (GA) is definitely better indicator of glycemic control than HbA1c in individuals having renal failure, hemolytic anaemia, and blood transfusions cases.\textsuperscript{31,33} As GA quantify the ratio of GA to total albumin,\textsuperscript{39} so GA is a preferable choice to FA in clinical conditions like nephrotic syndrome, chronic liver disease, and thyroid disorders.\textsuperscript{39} However the combination of GA with HbA1c have better sensitivity to predicts prediabetes than HbA1c alone.\textsuperscript{38} drawback is that, sometimes GA may be artificially low in individuals having increased BMI, body fat mass, and high visceral fat.\textsuperscript{40} Still the mechanism for variation in GA quantification in these conditions is poorly understood.\textsuperscript{41}

1,5 Anhydroglucitol (1,5 AG): Is it better postprandial hyperglycemia and complication predictor?

1,5 Anhydroglucitol, is a monosaccharide, identified as a prediabetes marker. Renal Proximal tubules have relatively greater affinity for glucose than 1, 5 AG, so hyperglycemia prevents 1, 5 AG reabsorption leading to increased 1,5 AG urinary concentration. So, plasma 1,5 AG concentrations lowers as plasma glucose increases as reflected in healthy control, prediabetes and diabetes groups.\textsuperscript{42} alike FA, 1,5 AG is a better biomarker as it reflects glucose levels within 2 weeks.\textsuperscript{43} Other advantages are it is stable, reproducible, and cost effectiveness than other glycemic diagnostic tests.\textsuperscript{43} It is better used in identifying postprandial glycemic excursions and those having risk of complications in context to retinopathy and microvascular and macrovascular episodes in diabetes. However, its level fluctuates in individuals on renal replacement therapy or receiving SGLT 2 inhibitor.\textsuperscript{44,45} On contrary few studies do not recommends use of 1,5 AG as a prediabetes screening tool.\textsuperscript{46,44}

**Now the Novel Biomarkers**

**Adiponectin: A helper from fat tissue**

Adiponectin, is formed from adipose tissue, it has insulin-sensitizing, anti-inflammatory, and anti-atherogenic functions and it is shown to be independent predictor of diabetes.\textsuperscript{47} Concentration of adiponectin are inversely related to IR (insulin resistance) and obesity.\textsuperscript{47} Lower level of adiponectin was observed even a decade prior to development of diabetes or its complications specially in men.\textsuperscript{37} In offspring of diabetic parents, the baseline adiponectin levels are inversely related to the risk of prediabetes and it is independent of sex or ethnicity.\textsuperscript{48} Hyperinsulinemic euglycemic clamp and intravenous glucose tolerance test, showed that adiponectin levels were directly correlated with higher insulin sensitivity and indirectly with insulin concentration.\textsuperscript{48}

**Fetuin-A**

Fetuin-A (FetA) is a glycoprotein secreted from liver, it correlates with increased risk of T2DM incidence and it’s complications.\textsuperscript{49} Importantly, unlike adiponectin, the EPIC-Potsdam prospective cohort study establish, FetA as a independent risk maker after normalization of the BMI and waist circumference for T2DM.\textsuperscript{49} FetA promotes lipid-induced IR through the toll-like receptor 4 (TLR4)-inflammatory signaling pathway leading to production of inflammatory cytokines.\textsuperscript{50} Pal et al showed that FetA binds to TLR4, and regulates insulin sensitivity through this interaction.\textsuperscript{50} High-fat diet-fed FetA knock down animal module have less TLR4-mediated signaling in adipose tissue causing IR, with FetA injection in this model induces inflammatory signaling and IR. Presence of FetA and TLR4 both needed for FFA (free fatty acid) induced inflammatory cytokine expression in adipocytes. Higher FetA is also correlating with risk of cardio vascular disease in candidates susceptible IR.\textsuperscript{51} In conclusion FetA acts as an endogenous ligand for TLR4 for induction of IR by lipids. Hence FetA may therefore serve as a novel therapeutic target for IR.

**Metabolites and amino acid: The hidden catalyst**

Amino acids. Branched chain amino acids (BCAAs).: The good one and the bad one for diabetes Isoleucine, leucine, valine, tyrosine, aromatic amino acid phenylalanine and glycine have been significantly associated with development of diabetes.\textsuperscript{52,53-56} Glutamine, methionine, cysteine, and 2-aminoacidic acid are increased in initial insulin-resistant states.\textsuperscript{57-59} Contrarily glycine levels are lower in prediabetic individuals.\textsuperscript{60,62} These changes in circulating amino acid levels may prove to be significant predictive biomarker for IR and T2DM.

**α-Hydroxybutyrate (α-HB).**

α-Hydroxybutyrate (α-HB) is a catabolic by product of threonine , methionine and glutathione anabolism (cysteine formation) in hepatic tissue.\textsuperscript{63} Increased oxidative stress and lipid oxidation leads to chronic shifts in glutathione synthesis resulting in elevated α-HB levels in individuals of IR.\textsuperscript{63,64} It is reflected by increased urinary α-HB excretion in IR.\textsuperscript{64} α-HB can be used as a biomarker to distinguish NGT-insulin-sensitive (NGT-IS) individuals from IGT and IFG individuals and NGT-IS individuals from those with NGT-IR individuals.\textsuperscript{65} Hence it can be an effective and promising biomarker for prediabetes.\textsuperscript{63,65}

**Lipoprotein(a)**

Lipoprotein(a) is synthesized by liver. Elevated levels of LP(a) is proved to be independent risk factor for development of CVD.\textsuperscript{66} Serum Lp(a) and the prevalence of prediabetes and T2DM have inverse relationship.\textsuperscript{68} Although the mechanism is not clear higher insulin may play a role in reducing Lp(a) concentration.\textsuperscript{66}

**Triglycerides and high-density lipoprotein.**

In prediabetics significant increment in levels of small HDL3 particles compared to HDL-C levels have been observed.\textsuperscript{69} Small HDL3 particles is
positively relates with triglyceride and negatively relates with HDL-C. HDL-C induces insulin secretion and low HDL-C promotes progression of prediabetes to diabetes however, it is not clear whether HDL-C levels plays a role in β-cell dysfunction or not.70

Ceramide
Ceramide a lipid molecules mediate IR.71,72 It acts through inhibiting insulin action by decreasing phosphorylation, further it accumulates in insulin-resistant tissues and induce inflammation through activation of TNF-α.72,73 Studies also showed, ceramide propagates coronary artery disease.74

Ferritin and transferring
Storage and iron release are regulated through an intracellular protein ferritin. There is a association of high serum ferritin and transferring saturation with increased risk of prediabetes and diabetes.75,76 Mechanism being the catalytic iron induces formation of reactive oxidative molecules causing hepatic dysfunction, and β-cell apoptosis, which contribute to IR.77,78 Dietary iron restriction prevents the development of diabetes and loss of β-cell function.77 However the threshold levels of ferritin which correlate with IR is not certain.

Mannose binding lectin serine peptidase and thrombospondin 1
High levels of MASP1 found in prediabetes, diabetes, and the CVD. Even onset of prediabetes and IR occurred earlier in those with higher MASP1 plasma levels.79 Elevated FPG and 2-hour glucose levels have positive association with higher levels of MASP1.79 Other markers like thrombospondin 1 (THBS1) and glycosylphosphatidylinositol-specific phospholipase D1 (GPLD1) are also increased in prediabetes. Thrombospondin have inflammatory properties, and contributes to higher prediabetes prevalence.79

Acyl-carnitine
Serum levels of acyl-carnitines have been shown to be elevated in prediabetes. Although the role of acyl-carnitine in FAO and its mechanism in IR are not clear. It has been postulated that abnormal of FAO and mitochondrial function leads to accumulation of intermediary products such as acyl-carnitines which promotes inflammation and IR.80,81

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. Recently, miRNAs have been studied in pre-diabetes and found to be strongly correlated.82,83 In particular miR-192 and miR-193b high levels observed in prediabetics. miR-193b plays critical roles in differentiation of brown adipocytes and inflammation reduction in IR. Elevated levels of both miRNAs i.e., miR-192 and miR-193b were observed with IFG and IGT and it also correlated with Tg levels and the fatty liver index in animal models.83 It is quite significant as a fatty liver can be associated with prediabetes.84 Other miRNAs significantly elevated in T2DM are miR-9, miR-29a, miR-30d, miR-124a, miR-146a, and miR-375, all of these play a role in β-cell dysfunction. These miRNAs negatively regulate insulin expression and secretion. Few miRNAs levels are low in prediabetes, of these microRNA-126, miRNA-15a is found in endothelial cells and it is quite low in IGT/IFG and T2DM.87 miR-15a is thought to regulate and promote insulin formation by inhibiting endogenous uncoupling protein-2 gene expression and increasing insulin secretion.88 So, miR-15a have a significant role in β-cell function and insulin synthesis..

Inflammatory markers: The universal culprits
IL-6 and CRP higher concentration is associated with a greater risk of diabetes development. These inflammatory markers are useful in identifying individuals at higher risk of developing T2DM.86 Tissue plasminogen activator-1 (PAI-1) changes is an independent predictor of incidence of diabetes.87 IL-18 level increased parallel to progression from prediabetes to diabetes in the Gutenberg study.88 Levels of IL-1RA were found to be significantly elevated even 13 years prior to the diagnosis of diabetes and it raises more rapidly about 6 years prior to diagnosis even after adjusting for obesity.89 The Whitehall Study, showed an increase in IL-1RA in prediabetes in parallel with decreasing insulin sensitivity, increasing β-cell function, and 2-hour glucose levels, all of which occurred altogether years before the development of T2DM.92

White blood cell count, fibrinogen, and hematological indices: Subtle indicator
A high WBC count predicts worsening insulin action, insulin secretion, and diabetes development in Pima Indians. The neutrophil-lymphocyte ratio (NLR) has also been associated with both microvascular and macrovascular complications in diabetes.93-96

Conclusions and Prospective
Dysglycemia is a continuous pathophysiologic process. It is overtly underestimated and puts large number of individuals at risk for full blown disease state. With development of hyperglycemia it is already late in the evolution to T2DM leading to uninhabitable microvascular complications. β-cell function markedly reduced leading to progressively rising glucose levels, on higher side of “normal glycemic range”.97 So there is a vital need to identify and use sensitive precise biomarkers to predict progression to dysglycemia at the earliest, when β-cell function is optimally functional. Interference at this stage may be more responsive to lifestyle modification and pharmacological agents. A well identified set of biomarkers in a clinical practice will give better sensitivity and specificity in prediabetes and diabetes complication prediction. Comparative studies of biomarkers will help to ascertain their clinical utility. Furthermore, genetic studies assessing mutations will also provide additional insight into associations with metabolic deregulation.98

Abbreviations
HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; BMI, body mass index; FA, fructosamine; GA, glycated albumin; OGTT, oral glucose tolerance test; IR, insulin resistance; 1, 5 AG, 1, 5 anhydroglucitol; FetA, fetuin-A; TLR4, toll-like receptor 4; T2DM, type 2 diabetes mellitus; α-HB, alpha-hydroxybutyrate; α-KB, α-ketobutyrate; L-GPC, L-alpha glycerylphosphorylcholine; Lp(a), lipoprotein(a); HDL-C, high-density lipoprotein cholesterol; HDL-LpPLA2, HDL-associated lipoprotein-associated phospholipase A2; MBL, mannose binding lectin; CVD, cardiovascular disease; THBS1, thrombospondin 1;
GLP1R, glucosedephytidylinositol-
specific phosphatase D1; NF-Kβ, nuclear factor-κB; mRNA, microRNA; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; CRP, C-reactive protein; IL, interleukin; WBC, white blood cell; NLR, neutrophil-
lymphocyte ratio; PAI-1, plasminogen activator inhibitor-1; IL-1RA, IL-1 receptor antagonist; SGLT2, sodium-
glucose co-transporter 2.

References

Enhancing Medication Adherence through Improved Patient-Provider Communication for Chronic Disorders in Indian Health Settings

Introduction

It is well-established that suboptimal medication adherence precludes the diagnosis and treatment of diabetes mellitus and pre-diabetes. It is thus estimated that nearly half of all patients with diabetes do not take their medication as prescribed. This is a major public health challenge especially in non-western settings, like the developing world, where lack of health care infrastructure and support from all available resources especially family support, (A)nticipating and (P)redicting risk, are key elements for adequate patient-provider communication. We identified strategies for enhancing adherence for diabetes mellitus and pre-diabetes.

Public-health facilities in the developing world often experience a high patient burden, low doctor-patient ratio, drug stock-outs and the lack of avenues for patient-provider communication. Various strategies to augment patient-provider communication through a review of the literature are reported. We identified strategies for enhancing medication adherence for chronic disorders in Indian health settings for diabetes mellitus and pre-diabetes. We conclude with a discussion on the need for a patient-centered health care system which will improve the population health and sustainable economic losses.

Methods

We conducted a literature search using keywords: diabetes, medication adherence, patient-provider communication, diabetes mellitus, pre-diabetes, chronic disorders, Indian health settings, and interventional studies. We reviewed English language articles published between 2000 and 2019. The search was limited to articles published in English language journals. The search was conducted using PubMed, Embase, and Google Scholar. The search strategy included a combination of keywords related to diabetes, medication adherence, patient-provider communication, diabetes mellitus, pre-diabetes, chronic disorders, Indian health settings, and interventional studies.

Results

Enhancing Medication Adherence through Improved Patient-Provider Communication

We identified strategies for enhancing medication adherence for diabetes mellitus and pre-diabetes. We identified strategies for enhancing medication adherence for diabetes mellitus and pre-diabetes. We concluded with a discussion on the need for a patient-centered health care system which will improve the population health and sustainable economic losses.

Discussion

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References


