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REVIEW

Update on pre-diabetes: Focus on diagnostic criteria and cardiovascular risk

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Abstract

Pre-diabetes, which is typically defined as blood glucose concentrations higher than normal but lower than the diabetes threshold, is a high-risk state for diabetes and cardiovascular disease development. As such, it represents three groups of individuals: Those with impaired fasting glucose (IFG), those with impaired glucose tolerance (IGT) and those with a glycated haemoglobin (HbA_{1c}) between 39-46 mmol/mol. Several clinical trials have shown the important role of IFG, IGT and HbA_{1c}-pre-diabetes as predictive tools for the risk of developing type 2 diabetes. Moreover, with regard to cardiovascular disease, pre-diabetes is associated with more advanced vascular damage compared with normoglycaemia, independently of confounding factors. In view of these observations, diagnosis of pre-diabetes is mandatory to prevent or delay the development of the disease and its complications; however, a number of previous studies reported that the concordance between pre-diabetes diagnoses made by IFG, IGT or HbA_{1c} is scarce and there are conflicting data as to which of these methods best predicts cardiovascular disease. This review highlights recent studies and current controversies in the field. In consideration of the expected increased use of HbA_{1c} as a screening tool to identify individuals with alteration of glycaemic homeostasis, we focused on the evidence regarding the ability of HbA_{1c} as a diagnostic tool for pre-diabetes and as a useful marker in identifying patients who have an increased risk for cardiovascular disease. Finally, we reviewed the current evidence regarding non-traditional glycaemic biomarkers and their use as alternatives to or additions to traditional ones.

Key words: Glycated haemoglobin; Cardiovascular risk; Diagnostic criteria; Non-traditional glycaemic markers; Pre-diabetes

Core tip: Pre-diabetes is a high-risk state for diabetes and cardiovascular disease. There are three diagnostic criteria for pre-diabetes: Impaired fasting glucose (IFG),

impaired glucose tolerance (IGT) and glycated haemoglobin (HbA_{1c}) between 39-46 mmol/mol. The concordance between a pre-diabetes diagnosis made by IFG, IGT or HbA_{1c} is scarce and there are conflicting data as to which of these methods best predicts cardiovascular disease. This review focuses on the evidence regarding the ability of HbA_{1c} for pre-diabetes diagnosis and as a marker for cardiovascular risk. Finally, the evidence regarding non-traditional glycaemic biomarkers as alternatives to the traditional ones is reviewed.

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INTRODUCTION

Pre-diabetes is a general term that refers to an intermediate stage between normal glucose homeostasis and overt type 2 diabetes mellitus. As such, it includes three groups of individuals: Those with impaired fasting glucose (IFG), those with impaired glucose tolerance (IGT) and those with a glycated hemoglobin (HbA_{1c}) between 39-46 mmol/mol (Table 1). As underlined by the American Diabetes Association (ADA), a number of previous studies reported that the concordance between pre-diabetes diagnoses made by IFG, IGT or HbA_{1c} is scarce[1]; according with this consideration, in a study conducted on a large population of Caucasian adults the agreement between the three diagnostic criteria was only 10.4% (Figure 1)[2].

The discordance in the identification of individuals with pre-diabetes using three different diagnostic tests is not entirely unexpected given that fasting plasma glucose, 2 h post oral glucose tolerance test (OGTT), and HbA_{1c} probably reflect different aspects of glucose metabolism, and a diagnosis of pre-diabetes based on IFG, IGT, or HbA_{1c} may represent aetiological factors leading to the development of the different prediabetic states[2]. Indeed, subjects with isolated IFG seem to have a reduced hepatic insulin sensitivity, impaired first-phase insulin secretion, and normal/near-normal muscle insulin sensitivity, while subjects with IGT should be characterized by nearly normal hepatic insulin sensitivity and marked reduced peripheral insulin sensitivity combined with defective late insulin secretion[3,4]. In contrast to IFG and IGT, HbA_{1c} is a marker representing blood glucose concentrations over the preceding 2-3 mo and it is affected by both basal and postprandial hyperglycaemia. To date, it is still not clear if these aspects that are strictly bound to the physiopathology of pre-diabetes may have a clinical relevance in view of a possible therapeutic intervention.

Cardiovascular disease (CVD) is the leading cause of death among individuals with type 2 diabetes, accounting for 40% to 50% of all deaths[5]. Although type 2 diabetes is frequently associated with other cardiovascular risk factors, such as dyslipidemia and hypertension, it is believed that chronic hyperglycaemia *per se* is an independent risk for macrovascular complications. Currently, it is well established that macrovascular disease starts before the development of diabetes, and the slight increase in plasma glucose levels that characterize pre-diabetes have been shown to be an independent predictor for CVD. Much clinical research has focused on lifestyle or pharmacological intervention to prevent diabetes in these high risk subjects[6]; however, few studies have been conducted with specific focus on CVD prevention in this population. Since many clinical trials have failed to demonstrated a reduction in cardiovascular risk from glucose-lowering interventions in patients with overt type 2 diabetes[7,8], it is noteworthy that several studies have reported benefits in improving cardiovascular risk factors, as well as absolute CVD event rates, in people with pre-diabetes treated with glucose lowering drugs[9-11].

Since the utility of a test for pre-diabetes diagnosis is also defined by its capacity to identify the macrovascular complication risk, an important question is whether subjects with pre-diabetes according to IFG, IGT, or HbA_{1c} have an equivalent cardiovascular risk. To date, cardiovascular risk studies comparing IFG, IGT, and HbA_{1c}-pre-diabetic patients are sparse and the results are still controversial[12-14].

This review highlights recent studies and current controversies in the field. In consideration of the increased use of HbA_{1c} as a marker to detect patients with alterations of glycaemic homeostasis, we thought that it could be interesting, and relevant from the clinical point of view, to evaluate the evidence regarding the ability of HbA_{1c} to identify patients who have increased cardiovascular risk. With this specific aim we focused our attention on HbA_{1c} as a diagnostic tool for pre-diabetes. Finally, we reviewed the current evidence regarding non-traditional glycemic biomarkers and their use as alternatives to or additions to the traditional ones.

COMPARISON OF IFG, IGT AND HBA_{1C}, CRITERIA IN PREDICTING TYPE 2 DIABETES

Subjects with pre-diabetes have shown a high conversion rate to overt diabetes and much clinical research has focused on lifestyle or pharmacological intervention to prevent diabetes in these high risk subjects[6]. Subjects with an isolated alteration of glucose homeostasis (IFG, IGT or HbA_{1c} 39-46 mmol/mol) have an incidence of diabetes of 6% per year, a value that is significantly higher compared with subjects with normoglycemia (0.5% per year)[15]. Progression to overt type 2 diabetes is 30%-40% in the next 3-8 years, with an increase of 10% when two alterations of glucose homeostasis are present[6].

According with these considerations, diagnostic and

Table 1 Diagnostic criteria for categories at increased risk of diabetes

Category	Marker	Diagnostic range
IFG	Fasting plasma glycemia	⩾ 5.6 mmol/L (100 mg/dL) < 6.9 mmol/L (126 mg/dL)
IGT	2-h post-load glycemia	⩾ 7.8 mmol/L (140 mg/dL) < 11 mmol/L (200 mg/dL)
HbA_{1c}-prediabetes	HbA_{1c}	⩾ 39 mmol/mol (5.7%) < 47 mmol/mol (6.5%)

IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; HbA_{1c}: Glycated haemoglobin.

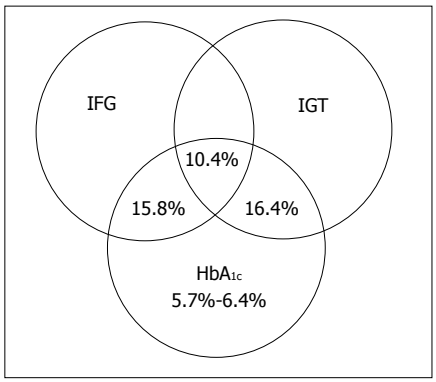

Figure 1 Agreement between glycated haemoglobin pre-diabetes, impaired fasting glucose and impaired glucose tolerance[2]. IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; HbA1c: Glycated haemoglobin.

screening criteria for pre-diabetes have a relevant clinical impact; indeed, it is important to identify individuals at high risk for type 2 diabetes to prevent or delay the development of the disease and its complications.

In 2011, the ADA revised the criteria for the diagnosis of type 2 diabetes and the categories at increased risk for diabetes and the use of HbA_{1c} measurement was recommended as another diagnostic test option already including IFG and IGT[1]. Specifically for the categories of increased risk for type 2 diabetes, the new ADA recommendations state that an HbA_{1c} from 39-46 mmol/mol identifies individuals at high risk for diabetes to whom the term pre-diabetes may be applied.

Indeed, both IFG and IGT present some limitations: They require fasting status and are affected by acute perturbations. Furthermore, the OGTT presents some practical difficulties: It is costly, it needs time, and has lower reproducibility compared with the fasting plasma glucose measurement (FPG)[16]. HbA_{1c} is a "picture" of the average blood glucose level over the period of 2-3 mo[17]. HbA_{1c} has higher reproducibility than FPG; indeed, within subject coefficients of variation are 1.7% for HbA_{1c}, and 5.7% for FPG[17,18]. Furthermore, HbA_{1c} does not need fasting status and could better integrate chronic hyperglycaemia than FPG (Table 2). The predictive value of HbA_{1c} for type 2 diabetes has been reported in several studies. Morris *et al*[19] has shown in a metanalysis conducted on 70 studies that the progression rate to type 2 diabetes of patients with HbA_{1c} pre-diabetes was similar to that for ADA-defined IFG and IFG plus IGT. Moreover, the value of HbA_{1c} in predicting type 2 diabetes has been reported four prospective studies[20-23]; of these, one assessed the use of two glycemic parameters (in particular IFG and HbA_{1c}) for predicting the incidence of type 2 diabetes; the authors supported the combined measurement of FPG and HbA_{1c} for predicting diabetes incidence in a 4 year follow-up using receiver operating characteristic curve (ROC) analysis. When the whole population was analysed, the ROC curve of the model including both FPG and HbA_{1c} was greater those including FPG alone or HbA_{1c} alone. Furthermore, the authors reported a weak correlation between HbA_{1c} and FPG at baseline suggesting that HbA_{1c} is not a surrogate marker of FPG[23].

It is necessary to remember that HbA_{1c} between 39-46 mmol/mol seems to have a lower sensitivity in identify population with pre-diabetes compared with IFG and IGT[24,25]. Conversely, the use of HbA_{1c} may also lead to the reclassification of subjects without IFG or IGT as having pre-diabetes[26]. On the other hand, according to the ADA statement, the lower sensitivity of HbA_{1c} for diagnosing pre-diabetes may be offset by its ability to facilitate establishing a diagnosis[27]. Contrary to these considerations, Rosella *et al*[28] recently reported that the prevalence of undiagnosed pre-diabetes in a representative sample of Canadians was significantly higher using HbA_{1c} measures as screening tool compared with plasma glucose diagnostic criteria. The authors hypothesized that this "reverse association" may be due to a number of factors, such as ethnic differences and the increased prevalence of pre-diabetes from 11.6% in 2003 to 35.3% in 2011[29]. Accordingly, in a study conducted in the Mexican population, Kumar *et al*[30] found a higher prevalence of adults with HbA_{1c} pre-diabetes compared with previous studies conducted in the same population[31]. We reported similar findings in a recent study conducted on 380 subjects attending our out-patients clinic for diabetes and cardiovascular risk evaluation; although we did not perform an opportunistic procedure during recruitment, the group with high HbA_{1c} and normal fasting glucose and normal glucose tolerance (NFG/NGT) represented, in this study, approximately 30% of the entire population and is, therefore, not a rare subset[32]. These observations may not be surprising; in fact, although subjects with NFG and NGT have a lower risk of developing diabetes than patients with either IFG or IGT, in several studies a significant percentage (30%-40%) of all individuals who developed type 2 diabetes had NFG and NGT at baseline[33,34]. This indicates that subjects with NFG and NGT experience a lower risk of developing diabetes compared with IFG and IGT in absolute terms; however, among these subjects there is also a subgroup at increased risk of developing diabetes and, consequently, cardiovascular diseases. From these considerations stems the need to add HbA_{1c}, as a diagnostic tool to identify a new category of high-risk individuals[35]. Further epidemiological data are needed to characterize the real percentage of this group

Table 2 Main points supporting/not supporting the use of glycated haemoglobin as diagnostic tool for diagnosis of pre-diabetes

Supporting	Not supporting
HbA_{1c} may better integrate chronic hyperglycaemia than fasting and 2-h post-load glycaemia	HbA_{1c} seems to have a lower sensitivity in pre-diabetes diagnosis
HbA_{1c} predicts microvascular complications (rethinopathy and nephropathy) similarly to fasting and 2-h post-load glycaemia	Standardization of HbA_{1c} assay needs to be improved
HbA_{1c} has a higher predictive value than fasting plasma glucose in predicting cardiovascular disease	Common, and not always known, clinical conditions (haemoglobinophaties, malaria, anaemia, blood loss) may significantly interfere with HbA_{1c} assay
HbA_{1c} has a greater pre-analytical stability than blood glucose	Ethnic differences in HbA_{1c} assay are not well characterized
HbA_{1c} assay does not need fasting status	The low biological variability of HbA_{1c} provides little information on pathophysiological processes involved in pre-diabetes
HbA_{1c} is not affected by acute perturbations (exercize, stress, diet)	Glucose assessment is cheaper thant HbA_{1c} assay
HbA_{1c} biological variability is lower than fasting and 2-h post-load glycemia	
HbA_{1c} may be an attractive option in settings in which OGTT is not used and rarely repeated	

HbA_{1c}: Glycated haemoglobin; OGTT: Oral glucose tolerance test.

in the overall pre-diabetic population.

To date, it is unclear why the prevalence of pre-diabetes diagnosed by OGTT and HbA_{1c} criteria is substantially discordant. The concentration of HbA_{1c} depends on glucose concentrations and on factors affecting the glycation rate such as systemic oxidative stress. Previous studies reported that some characteristics, such as obesity, are associated with increased oxidative stress[36]; thus, HbA_{1c} may not reflect the real concentration of glucose and be disproportionately high in obese subjects. Several studies investigated the effects of phenotypic characteristics such as obesity on the agreement between OGTT and HbA_{1c}. Li *et al*[37] in a recent study conducted on a large cohort of Chinese subjects without a previous diagnosis of diabetes reported a poor agreement between HbA_{1c} criteria and OGTT in patients independently from body mass index. Moreover, different optimal HbA_{1c} cut-off points for pre-diabetes were reported: 38 mmol/mol for normal weight, 39 mmol/mol for overweight, and 42 mmol/mol for obese subjects.

Also other studies recommend a different cut-off point of HbA_{1c} for diagnosis of pre-diabetes. In particular, longitudinal epidemiological studies have reported that demographic and ethnic factors may contribute to complications in using HbA_{1c} for the diagnosis of diabetes, and the optimal diagnostic HbA_{1c} value is debated and varies because of genetic and biological differences. Yan *et al*[38] identified optimal HbA_{1c} cut-off points for pre-diabetes in two diverse population-based cohorts with different ages. The optimal HbA_{1c} cut-off point for pre-diabetes diagnosis was 38 mmol/mol in the young and middle-aged population, whereas, the optimal cut-off for diagnosing pre-diabetes increased to 39 mmol/mol, in the elderly population. Furthermore, many studies have shown that racial disparities affect the performance of HbA_{1c} for diagnosing pre-diabetes[39]. In summary, it is possible that diagnostic tests for glycemic homeostasis should be used and interpreted considering the individual phenotypic characteristics of the patients; further studies are needed to investigate the clinical usefulness of personalized cutoff values.

COMPARISON OF IFG, IGT AND HBA1C, CRITERIA IN PREDICTING CARDIOVASCULAR RISK

The utility of a test for pre-diabetes diagnosis is also defined by its capacity to identify the risk of micro- and macrovascular complications and from this point of view, the high reproducibility and simplicity may make HbA_{1c} dosage an attractive option. Previous observational studies documented that determination of HbA_{1c}, fasting glucose and OGTT significantly predicted the development of retinopathy and nephropathy but no variables had a significant advantage for detecting the incidence or prevalence of either complication[40,41]. However, fasting glycaemia has a low predictive value in terms of cardiovascular disease, while 2-h post-load glycaemia and HbA_{1c} have a higher predictive value for this chronic complication of diabetes[42].

In a recent work, we showed that arterial stiffness and carotid intima-media thickness were altered in subjects with higher HbA_{1c} levels and similar as that observed in subjects with new onset type 2 diabetes[43]. Furthermore, when we analyzed our population including only subjects with NFG/NGT we found that the NFG/NGT subjects with HbA_{1c} 39-46 mmol/mol showed an alteration of subclinical markers of cardiovascular risk compared with NFG/NGT with lower HbA_{1c} and no significant differences were found compared with IGT and type 2 diabetic patients (Figure 2). According to these data, a reproducible and simple marker such as HbA_{1c} seems to identify subjects at high cardiovascular risk that would be considered normal according to fasting glycaemia and glucose tolerance. Other studies have shown similar data reporting a positive association between the pre-diabetic stage, echogenic plague and progression of coronary artery calcification[44,45]. A recent study has analysed the routine use of HbA_{1c} for diagnosis of pre-diabetes in patients with ST-segment elevation myocardial infarction. The study showed a similar in-hospital and long-term mortality in these patients with pre-diabetes as those with known diabetes. The authors discussed that the

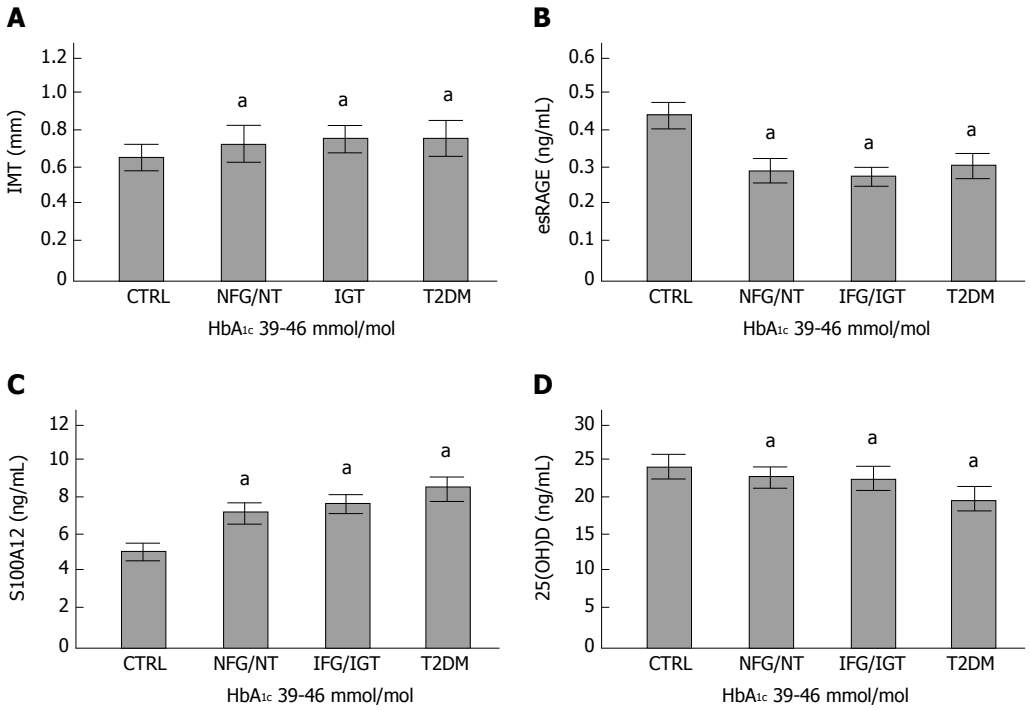

Figure 2 Intima media thickness, endogenous receptor for advanced glycation end-products, S100A12 and 5-hydroxyvitamin D according to glucose tolerance and glycated haemoglobin levels. A: IMT, $^{a}P < 0.05$ *vs* CTRL; B: esRAGE, $^{a}P < 0.05$ *vs* CTRL; C: S100A12, $^{a}P < 0.05$ *vs* CTRL; D: 25(OH)D, $^{a}P < 0.05$ *vs* CTRL. IMT: Intima-media thickness; esRAGE: Endogenous receptor for advanced glycation end-products; 25(OH)D: 25-hydroxyvitamin D; NFG: Normal fasting glucose; NGT: Normal glucose tolerance; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; T2DM: Type 2 diabetes mellitus; HbA1c: Glycated haemoglobin.

difficulty in performance and the presence of stress hyperglycaemia in an acutely ill patient with myocardial infarction make OGTT a rarely used diagnostic test in this setting. The use of a simple, one-time HbA1c test allowed them to identify a substantial proportion of patients with previously undiagnosed diabetes or pre-diabetes who could be targeted for risk factor modification with lifestyle interventions and tailored medical therapy[46].

The links between alteration of glucose homeostasis and vascular damage in this population is still unclear, however, several studies have emphasized that the interaction of advanced glycation end products (AGE) with their cell-surface receptor (RAGE) is implicated in triggering inflammatory processes strictly connected with cardiovascular disease[47]. A RAGE soluble form termed endogenous secretory RAGE (esRAGE) may contribute to the removal of circulating ligands, thus competing with cell-surface RAGE for ligand binding[48]. Low levels of esRAGE have been associated with cardiovascular disease and, in a recent study, we found that subjects with pre-diabetes showed low esRAGE plasma levels suggesting a decreased scavenger capacity of these subjects (Figure 2). Further analysis conducted on mononuclear cells isolated from peripheral blood samples of these patients revealed a decreased esRAGE mRNA expression[32]. The regulatory mechanism for alternative splicing to generate esRAGE remains unclear, and environmental or genetic factors may be involved. Further examinations of the molecular mechanism underlying esRAGE regulation will provide potential targets for the prevention and/or treatment of cardiovascular disease.

Our research team has further investigated the characterization of the population with HbA1c pre-diabetes (39-46 mmol/mol) also investigating other markers closely associated with metabolic abnormalities and cardiovascular risk; in a previous study we highlighted a reduced insulin response in combination with impaired suppression of glucagon secretion in subjects with pre-diabetes according to HbA1c undergoing isoglycaemic intravenous glucose infusion[49]. Other data published in 2014 indicated that the presence of pre-diabetes according to HbA1c is associated with hepatic steatosis and with an alteration in the lipid profile known to be predisposing to cardiovascular and liver diseases[50]. Moreover, we showed that the levels of 25 hydroxyvitamin D are reduced and associated with vascular damage in subjects with pre-diabetes by HbA1c with NFG/NGT (Figure 2)[51]. Based on these data, we suggest that among subjects with NFG and NGT, HbA1c may identify subjects with different cardiovascular and glycometabolic risks.

These considerations are, furthermore, supported by previous studies. Indeed, it is important to remember that many authors have documented a significant increase in the incidence of cardiovascular events with HbA1c values substantially lower than those used for diagnosis of diabetes[12]. A recent meta-analysis of six prospective cohort studies in subjects without diabetes mellitus showed a linear association of HbA1c levels with primary cardiovascular events. The observed effect estimates for increased HbA1c levels and was strongly attenuated by adjustment for cardiovascular risk factors but remained statistically significant for primary car-

diovascular events, cardiovascular mortality and all-cause mortality[52].

The majority of randomized controlled trials in non-diabetic subjects with increased HbA_{1c} failed to observe significant effects when aiming to reduce the cardiovascular risk and mortality of these individuals. In the recent IRIS trial, which involved patients without diabetes but with a recent history of ischemic stroke or transitory ischemic attack and who had insulin resistance, the rate of the primary outcome (fatal or non-fatal stroke or fatal or non-fatal myocardial infarction) was lower in the pioglitazone group compared with placebo[11]. These results, although in contrast, at least in part, with other trials conducted on patients with type 2 diabetes (BARI-2D and Pro-active), are of great interest suggesting a favourable effect of pioglitazone on the progression of subclinical atherosclerosis[53,54]. The mechanism that was responsible for the lower rates of stroke and myocardial infarction in the pioglitazone group remains unclear. A recent meta-analysis of prospective, randomized clinical trials has shown a non-significant trend towards reduced risk of fatal and non-fatal myocardial infarction, and fatal and non-fatal stroke were only reduced to borderline. However, the short average follow-up time of 3.75 years was a limitation of previous trials and further RCTs, with a larger sample size and longer follow-up, are required to explore the efficacy of non-drug and drug based approaches to reduce the cardiovascular risk of non-diabetic subjects with increased HbA_{1c}[55].

Other studies have reported similar findings suggesting the role of HbA_{1c} as an early marker of cardiovascular risk; however, it is pertinent to recognize that the determinants of cardiovascular risk in subjects with metabolic alterations are complex and multiple, and individual's cardiovascular risk can't be identified by a single laboratory test[56].

BEYOND TRADITIONAL DIAGNOSTIC CRITERIA: THE ROLE OF NON-TRADITIONAL GLYCAEMIC MARKERS IN PREDICTING DIABETES AND CARDIOVASCULAR RISK

As previously explained, the traditional markers of glucose homeostasis are not definitive, and their use in clinical practice may be biased by a number of clinical and analytical factors. For these reasons, there is growing interest in new serum biomarkers of hyperglycaemia to be used as alternatives or in conjunction with traditional measures. In this review, we will provide a brief overview of the properties and of the existing literature linking these emerging biomarkers with micro- and macro-vascular complications.

One-hour post-load plasma glucose

Recently, an increasing body of evidence has focused on subjects with a plasma glucose concentration of at least 8.6 mmol/L at 1-h during OGTT. In 2008, Abdul-Ghani *et al*[57] demonstrated for the first time that the 1-h post-load plasma glucose concentration may be a clinical indicator that can be used to identify subjects with high risk for type 2 diabetes. These observations were confirmed in other recent studies showing that the incidence rate to type 2 diabetes over a period of 5 years in subjects with NGT and 1-h post-load glycaemia > 8.6 mmol/L was 16.7%[58]. Furthermore, a 1-h post-load glycaemia value > 8.6 mmol/L was strongly associated with different predictors for future cardiovascular events[59,60]. In conclusion, it seems that this glucose value may identify subjects with an intermediate cardiometabolic risk profile between NGT and IGT[57,61]. This has been observed and confirmed in populations of different ethnicities such as Mexican-American, Scandinavian Caucasian, and Asian Indian[59,61,62]. Why 1-h post-load glucose is a good indicator of cardiometabolic risk is still an open question; to date it is known that chronic hyperglycaemia promotes the formation of advanced glycation end products and reactive oxygen species.

One hour post-load glycaemia provides physiopathological information since it is dependent on insulin sensitivity in skeletal muscles and beta-cell function[63].

These data might underline the importance of obtaining intermediate plasma glucose levels during oral glucose tolerance test[59,64]. However, from the clinical point of view, 1-h post-load glycaemia requires, in any case, an OGTT, and, to date, strict lifestyle modification is the only therapy recommended from guidelines for subjects with pre-diabetes, independently from their physiopathologic profile. Furthermore, a study conducted on subjects with HbA_{1c} pre-diabetes reported that most patients with HbA_{1c} in the 39-46 mmol/mol range have a 1-h glucose $\geqslant$ 8.6 mmol/L; these data lead to the consideration that HbA_{1c} may be the most practical tool to identify subjects with impaired glucose homeostasis[43].

Fructosamine and glycated albumin

Fructosamine and glycated albumin are both ketoamines formed from the binding of fructose to total serum protein, mostly albumin, through glycosylation. The fructosamine assay is cheaper and easier to perform than the HbA_{1c} assay and it measures total glycated serum protein, whereas glycated albumin is reported as the proportion of total albumin[65]. Fructosamine and glycated albumin are short-term markers of glucose homeostasis; indeed, they provide information on blood glucose levels over the previous 2-3 wk[66]. This depends on the rapid turnover of glycated proteins, that in contrast to HbA_{1c}, is independent from the turnover of red blood cells or hemoglobin characteristics. Similar to HbA_{1c}, blood for fructosamine dosage can be obtained in any moment of the day, without regard to recent food intake. Both fructosamine and glycated albumin are associated with future risk of diabetes, independently from fasting glucose and HbA_{1c}[67,68]. Another recent study explored the ability of HbA_{1c}, fructosamine and glycated albumin to detect pre-

diabetes and whether there would be added diagnostic value in combining HbA_{1c} with fructosamine or glycated albumin. The study, conducted on United States Africans, showed that HbA_{1c}, fructosamine and glycated albumin detected almost 50% of Africans with pre-diabetes; however, combining HbA_{1c} with glycated albumin (but not with fructosamine) made it possible to identify nearly 80% of Africans with pre-diabetes, as reported in previous studies[69]. Furthermore, the authors reported that pre-diabetic patients identified by glycated protein were younger and with a lower BMI, as previously reported. It is still not clear why glycated plasma proteins are inversely related to body size, however, this observation could be of clinical relevance and it may support the use of glycated albumin to enhance the detection of pre-diabetes in specific populations, such as the non-obese.

Evidence derived from prospective studies regarding the link between non-traditional markers and micro and macrovascular complications are limited. Data from the Atherosclerosis Risk in Communities (ARIC) Study have shown that glycated albumin predicted chronic kidney disease over two decades of follow-up with a similar magnitude to those observed for HbA_{1c}[69]. Other evidence has come from cross-sectional studies. A recent analysis from the ARIC Study has shown an association between glycated albumin and retinopathy, with a pattern of association very similar to that observed for HbA_{1c}[69]. Furthermore, in other studies conducted on adults without diagnosed diabetes, glycated albumin was associated with subclinical atherosclerosis, kidney and cardiovascular disease[70].

A potential limitation to the clinical use of these markers may be that, to date, there is no established clinical cut-off points and the assays are not standardized across instruments. Particular caution should be used in pathological conditions that can impact albumin metabolism including anaemia, malnutrition, nephrotic syndrome and liver cirrhosis.

To date, fructosamine and glycated albumin are not incorporated in clinical guidelines, however, they may be useful complements to HbA_{1c} in clinical practice, mainly when HbA_{1c} testing is inaccessible or when the result might not be reliable.

1,5-anhydroglucitol

1,5-anhydroglucitol (1,5-AG) is a monosaccharide primarily derived from dietary sources and is a non-traditional biomarker of hyperglycaemia. During euglycaemia, serum 1,5-AG is typically maintained at a constant concentration (12-40 μg/mL). It is freely filtered from the glomeruli and a small amount, dependent on dietary intake, is excreted with the urine. The remaining amount is reabsorbed in the renal tubule. In conditions of hyperglycaemia (> 8.9-10 mmol/L) glucose blocks renal tubular reabsorption of 1,5-AG resulting in a drop in 1,5-AG serum levels; therefore, an inverse association exists between hyperglycaemia and 1,5-AG. Clinically, 1,5-AG may be used as a marker of short-term glycaemic variability, reflecting hyperglycaemic episodes over 1-2 wk. 1,5-AG is a non-fasting test and it may include information about glycaemic excursion that is not included in HbA1c dosage.

Previous studies found a significant association between 1,5-AG and the subsequent development of diabetes with a magnitude that was significant but weaker compared with fructosamine and glycated albumin[68]. However, consistent with its pathophysiology, 1,5-AG was no longer associated with incident diabetes among people with a normal fasting glucose < 5.6 mmol/L or HbA_{1c} < 39 mmol/mol, suggesting a limited usefulness for 1,5-AG in the setting of normal glucose and HbA_{1c} levels. According to this data 1,5-AG seems to be a biomarker suitable for detecting glycaemic variations in patients with HbA_{1c} between 53-64 mmol/mol (for example, to monitor a patient's response to changes in medication) rather than in subjects with pre-diabetes.

Few studies have assessed the relationship of 1,5-AG with micro and macrovascular complications. Cross-sectional studies have reported associations between 1,5-AG serum levels, subclinical atherosclerosis, prevalent retinopathy and coronary heart disease in subjects with and without diabetes[71,72]. A recent study observed a threshold effect, with little evidence of risk for cardiovascular events at the "non-diabetic" 1,5-AG concentration of 10-15 μg/mL. However, most of the study group were diabetic subjects, and in the categorical analysis the association with the clinical outcomes was largely confined to the subjects with diabetes[73].

CONCLUSION

The measurement of HbA_{1c} appears to be a reliable diagnostic approach to identify patients at high risk for diabetes and cardiovascular disease; it seems to provide several advantages, especially in settings where OGTT is rarely used and never repeated as a confirmatory test, and eliminates a long series of biological and analytical limits. In most conditions HbA_{1c} could became the reference method, provided that its assay is aligned with international standards. The budget/cost benefit of replacing glucose with HbA_{1c} remains unclear and it is necessary to acquire additional information.

Finally, alternative biomarkers of glucose homeostasis may have a clinical use in identifying subjects at risk for diabetes and cardiovascular disease (mostly 1-h post-load glycaemia) and for short-term evaluation of glucose homeostasis in settings in which HbA_{1c} may present some bias (fructosamine, glycated albumin and 1,5-AG). It is possible that one or more of these biomarkers may be of clinical usefulness, however, long-term prospective studies are needed to demonstrate whether their clinical use may be useful to improve outcomes and patient care.

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are reported. Purrello F is the guarantor of this work and takes responsibility for the integrity and the accuracy of the manuscript. All authors approved the final version. We wish to thank the Scientific Bureau of the University of Catania for language support.

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