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COMMENTARY

HbA_{1c} in type 2 diabetes diagnostic criteria: addressing the right questions to move the field forwards

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Abstract This commentary aims to move the debate regarding the adoption of HbA_{1c} for diagnosis of type 2 diabetes forwards by highlighting the need to avoid addressing irrelevant questions, in particular, comparison of individuals diagnosed with different diagnostic criteria. Instead, we provide a list of important future questions, including whether adoption of HbA_{1c} as the primary diagnostic test improves uptake of diabetes screening, with resultant earlier diagnosis and improvement in outcomes.

Keywords Cardiovascular · Diagnosis · HbA_{1c} · OGTT · Prediction

Abbreviations

DETECT-2	Evaluation of Screening and Early Detection Strategies for Type 2 Diabetes and Impaired Glucose Tolerance
FPG	Fasting plasma glucose

Much has been written and debated on the benefit of introducing measurement of HbA_{1c} as a diagnostic tool for type 2 diabetes. With an accumulation of supportive data addressing factors such as assay accuracy and linkage to clinical outcomes, many shortcomings have been resolved. Yet, certain issues still cause significant concern amongst some researchers, clinicians and laboratory specialists. To move the debate forwards these issues need to be directly addressed while being mindful that the crucial requirement for a diagnostic tool for diabetes is its ability to identify individuals at risk of future microvascular disease.

One of the most common reasons the role of HbA_{1c} as a diagnostic tool is questioned is that it does not identify the same individuals as conventional glucose-based criteria, and a considerable number of studies on this issue continue to be published [1, 2]. However, this concern assumes that glucose-based criteria, in particular the OGTT, represent the gold standard for diagnosing diabetes. This assumption is frankly incorrect. There is no gold standard for diagnosing diabetes, and whilst many are swayed by the argument that the OGTT must be best, given that it represents a 'dynamic' test of glucose handling, there are major limitations inherent in the duration, correct conduct and very poor reproducibility of the test in clinical practice [3, 4]. Furthermore, the results of the important Evaluation of Screening and Early Detection Strategies for Type 2 Diabetes and Impaired Glucose Tolerance (DETECT-2) collaboration, which compared the three diagnostic candidates (HbA_{1c}, fasting plasma glucose [FPG], 2 h glucose) with presence of retinopathy in 44,623 participants, suggest that 2 h glucose levels are not strongly associated with microvascular risk [5]. By contrast, FPG and HbA_{1c} in particular showed much sharper inflections points (at 6.5 mmol/l and 6.5% [48 mmol/mol], respectively), above which the prevalence of retinopathy clearly rose. While the DETECT-2 analyses were admittedly cross-sectional, older glucose-based diagnostic criteria are themselves largely based on cross-sectional data. Of course the aforementioned poor results for 2 hour glucose may be linked to its considerable intra-individual variance in real-life settings but, as this weakness cannot be easily addressed, the data suggest that the OGTT should be removed from diabetes diagnostic criteria.

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Some readers may worry that the different diagnostic criteria differentially associate with risk for macrovascular disease, but this concern is misplaced. Diabetes diagnostic criteria are correctly aligned to microvascular, not cardiovascular, risk. It is now clear that cardiovascular risk in newly diagnosed diabetes patients (irrespective of the criteria used for diagnosis) is, on average, below the widely touted 'myocardial infarction risk equivalence' level [6, 7] but, even so, statins continue to be widely recommended. As a result, current treatment algorithms for cardiovascular risk reduction are benefiting diabetic patients, including those newly diagnosed before they necessarily reach the 20% cardiovascular risk threshold, a policy that is unlikely to change given their high long-term risk. A question more pertinent to the debate is whether any glycaemia measurement meaningfully enhances cardiovascular risk reclassification beyond established risk scores in those without diabetes. Of all three glycaemia measures in the non-diabetic range, HbA_{1c} appears most strongly associated with cardiovascular events [8] and so is the most likely of the three to improve cardiovascular risk reclassification, with some preliminary supportive evidence [9, 10].

Based on the recognition that, over time, all three glycaemia measures will rise together in most individuals (leading, in turn, to differential diagnostic groups coalescing), we strongly recommend that researchers cease comparing diagnostic criteria in cross-sectional analyses. Such practice does not address a relevant clinical question but instead leads to unnecessary confusion (see text box). A more fruitful avenue of research is to address whether introduction of HbA_{1c} may help diagnose individuals with diabetes earlier than is seen with glucose-based criteria in usual clinical practice. In Scotland in 2008, the average HbA_{1c} within 1 year of diagnosis was about 8.0% (64 mmol/mol) [11], suggesting considerable room for earlier diagnosis. Diagnosing diabetes earlier in its course offers the potential advantage of better uptake of lifestyle measures. Although the recently reported Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care (ADDITION-Europe) trial, which compared intensive risk factor and glucose control with usual care in 3,057 patients with screen-detected diabetes, did not address this point directly, the relative stability of both HbA_{1c} (about 6.5% [48 mmol/mol]) and BMI achieved over 5 years in participants in the control arm (routine clinical care) was notable [12]. Wider application of HbA_{1c} offers the possibility of earlier diagnosis of diabetes, a hypothesis that can and must be addressed in due course.

Additional concerns that do require consideration include the greater laboratory cost of HbA_{1c} analysis compared with FPG. Given that FPG seems to perform well in categorising risk for microvascular disease (based on DETECT-2 data [5]), why not simply recommend its use alone? The arguments against this option are twofold. First, this option necessarily requires fasting, which

HbA_{1c} for diagnosing diabetes: important and unimportant questions for future research

Important questions	Unimportant questions
Which glycaemia measurement is the best predictor of microvascular disease? (See DETECT-2 data.)	Does HbA_{1c} diagnose the same group of patients as glucose-based criteria?
Does use of HbA_{1c} as a diagnostic measure lead to earlier diagnosis of type 2 diabetes and thereby improve clinical outcomes?	How does the cardiovascular risk factor profile differ in individuals identified by various diabetes diagnostic criteria in cross-sectional studies?
In which patients should HbA_{1c} measurement be combined with fasting glucose?	Should oral glucose tolerance testing be part of future diagnostic algorithms?
What is the impact of using HbA_{1c} for diabetes diagnosis on laboratory costs and what are the potential savings elsewhere?	
How best can diabetes and cardiovascular risk screening be combined?	

crucially limits opportunities for testing. The overall cost to the economy of time away from work and the need for additional appointments to conduct fasting sampling (and repeat this if not fasted properly) is unknown. Furthermore, to conduct diabetes risk assessment with cardiovascular risk screening, a policy now being considered within the UK, also necessitates that diabetes screening can be performed any time of the day. For cardiovascular risk screening, blood lipids measured in the non-fasting state are acceptable in view of their equivalent ability to predict vascular risk compared with fasting lipids [13]. Thus, only the flexible measurement conditions afforded by HbA_{1c} dovetail perfectly with cardiovascular risk screening, whereas FPG requirements will limit opportunities for, and thus conduct of, combined risk assessment. Second, screening for diabetes alone (which, at best, occurs in a piecemeal fashion at present) does not make good clinical sense. Rather, parallel cardiovascular and diabetes risk screening appears the best way forward in most individuals, recognising that there is some overlap between cardiovascular and diabetes risk in some, but also that individuals without one condition may still have risk for the other and thus require lifestyle advice and pharmacotherapy. If we accept this argument, we next need to ask whether HbA_{1c} should be conducted on all individuals undergoing cardiovascular risk assessment or whether it can be restricted to those at highest risk of diabetes as calculated from simple risk scores. We have recently argued the case for the latter [14], and supportive analyses of the value of this approach are beginning to emerge [15]. One valid concern is that HbA_{1c} may not be a suitable diagnostic tool for a minority of patients with haemoglobinopathies or with alterations in red cell turnover, such as those encountered in patients with advanced renal impairment or on dialysis [16]. In addition, HbA_{1c} can be mildly elevated in iron deficiency anaemia, leading to concerns that use of HbA_{1c} may be problematic in women. However, in a study of 6,666 mostly premenopausal women in NHANES (1999–2006), while 14% were iron deficient and 4% had iron deficiency anaemia, the presence of iron deficiency was not associated with a greater odds of having HbA_{1c} ≥6.5% (48 mmol/mol) in an adjusted model (only 32 women had both iron deficiency and HbA_{1c} ≥6.5% [48 mmol/mol]) [17]. We would argue that with good education and sensible guidelines, an approach of combined measurement of FPG and HbA_{1c} in patients with or at high risk of such conditions can overcome major problems. Importantly, the higher cost of HbA_{1c} vs FPG assays must be borne in mind, as there is likely to be a need to redirect cost savings in other clinical services towards laboratories. Moving forwards, HbA_{1c} measurement costs should decline together with increasing choice of available analytical platforms.

In summary, this short commentary aims to move the HbA_{1c} debate forwards by highlighting the need to avoid addressing irrelevant questions, in particular comparison of individuals diagnosed with diabetes based on differing diagnostic criteria. Rather, we suggest the adoption of HbA_{1c} into diagnostic criteria, which will facilitate combined cardiovascular and diabetes screening. In addition, future research should be directed towards important questions, including whether this improves uptake of screening, with resultant earlier diagnosis and improvement in outcomes.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement The two authors jointly conceived the idea for this commentary and co-wrote the first and subsequent drafts. Both authors approved the final version of the manuscript.

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