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Is HbA1c a good diagnostic test for (pre)diabetes in cardiac rehabilitation patients?

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Increased caloric intake and decreased physical activity in westernised societies, as well as aging of the population, increase people's plasma glucose levels, both fasting and after glucose intake. Hyperglycaemia exists along a spectrum, and the formal diagnosis of diabetes is usually defined by setting a threshold for one or more diagnostic tests along this continuum.

It is essential to realise that we had, and still have, the liberty of defining any threshold that we consider appropriate. If we decide, for example, that a fasting glucose higher than 6.5 mmol/l represents disease, the many people just above this level may indeed progress towards more severe hyperglycaemia, but will usually be asymptomatic, have a low actual risk of hyperglycaemic organ damage, and an uncertain benefit from anti-hyperglycaemic drug treatment. If, on the other hand, the threshold for defining diabetes is set much higher, say above 10 mmol/l, symptoms are more likely, hyperglycaemic damage is a more real risk, and glucose-lowering treatment is usually required. In other words, pre-diabetes and diabetes are not diseases defined by nature, but rather are the result of a man-made classification of glucose levels representing both a spectrum as well as a continuum of risks. Cut-off levels for such hyperglycaemia-associated risks, be it for microvascular disease, macrovascular complications, or overall health outcomes, are arbitrary by definition. The same is true for the need for treatment: lifestyle optimisation is recommended for anyone with glucose in the high to normal range, but drug treatment may not be beneficial until hyperglycaemia is much more pronounced, particularly in elderly patients and those with existing cardiovascular disease, such as cardiac rehabilitation patients.[1]

From this perspective of heterogeneous risk continua, it is no wonder that cut-off levels for glucose defining (pre-)diabetes have changed several times over the years, and differ according to who sets the criteria. Diabetes is traditionally diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-hour plasma glucose (2-h PG) value during a 75 g oral glucose tolerance test (OGTT).[2] In 2011, the American Diabetes Association (ADA) took a major step in the diagnostic approach to (pre-)diabetes.[3] Arguing that: (a) haemoglobin A1c (HbA1c) is a stable marker reflecting glucose levels over a longer period of time; (b) HbA1c correlates with hyperglycaemic complications at least as well as individual glucose levels measured during an OGTT, and potentially better for some, e.g. retinopathy;[4] and (c) clinicians are already highly familiar with HbA1c as a treatment target, they decided that HbA1c was a valid test for defining whether someone has (pre-)diabetes or not. The ADA did so in full awareness of imperfect concordance between various glycaemia tests. In other words: it has always been clear that not just different diagnostic cut-off levels, but also the use of different glycaemic parameters (FPG, 2-h PG and HbA1c), will label different individuals as 'having diabetes' at least near the point of diagnosis. This may seem strange to some, but was considered acceptable simply because there are no good data to indicate that diagnosing, monitoring, or treating hyperglycaemia using any particular glycaemic parameter is associated with better health outcomes than using another.

Elsewhere in this issue, Tutalashvili and colleagues report a study designed to determine whether HbA1c cut-off levels defined by the ADA could allow effective diagnosis of (pre-)diabetes according to OGTT criteria defined by the World Health Organization (WHO), in a cohort entering cardiac rehabilitation after an acute coronary syndrome (ACS).[5] In their study, HbA1c had a sensitivity of 72% and a specificity of 100% for diabetes, and a low sensitivity (64%) and specificity (53%) for pre-diabetes. Also, HbA1c 'overdiagnosed' pre-diabetes (52% vs. 30%). In other words, the

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study by Tutalashvili et al. confirms that, at least based on fixed HbA1c thresholds, HbA1c does not identify the same people as 'having (pre-)diabetes' as do the OGTT results. What should be the consequences of these findings in clinical practice: should we discard HbA1c to diagnose (pre-)diabetes? And is OGTT really the gold standard? We suggest it is not.

HbA1c has several advantages compared with FPG and the OGTT, including greater convenience (fasting not required), greater pre-analytical stability, and less day-to-day variation during stress and illness. Costs, on the other hand, are greater, and HbA1c remains an indirect and imperfect measure of average blood glucose levels. Age, race/ethnicity, and anaemia/haemoglobinopathies may, for example, influence haemoglobin glycation independently of glycaemia.

The study by Tutalashvili et al. is relevant for physicians who, for one reason or another, insist on using the WHO definition of (pre-)diabetes. However, even those colleagues would probably fancy a less cumbersome test than an OGTT, and HbA1c could be just such a test. For them, the analysis of HbA1c could have been more informative if the authors had studied the sensitivity and specificity of several different cut-off levels for HbA1c. HbA1c, like any test with a continuous outcome, has no sensitivity or specificity in itself, only cut-off levels do. As for diabetes, relatively low HbA1c levels virtually excluding diabetes according to WHO criteria, and relatively high HbA1c levels strongly pointing towards WHO-defined diabetes would be identifiable, and cumbersome OGTT tests could at least be avoided in patients below or above such levels. Unfortunately, the study by Tutalashvili et al. does not provide such data. As for pre-diabetes, its identification is mainly relevant for lifestyle interventions and follow-up. However, because the post-ACS population requires such interventions and follow-up anyway, the identification of pre-diabetes by any definition in itself has only limited value in this high-risk population.

The core issue is whether diagnosing, monitoring, or treating dysglycaemia using OGTT data generates better health outcomes than using HbA1c. As said before, such evidence is missing, which was the main reason why the ADA considered HbA1c as a reasonable diagnostic test in the first place. In fact, for fasting glucose, data from a large, community-based prospective cohort study suggested that the glycated haemoglobin level might be a better predictor, especially of cardiovascular disease,[6] a finding confirmed in a recent major meta-analysis of many prospective studies.[7] In addition, HbA1c has been extensively studied in the context of treatment targets, and thus immediately informs the clinician as to which therapeutic strategy is appropriate.

Taken together, although HbA1c may be less appropriate for diagnosing (pre-)diabetes according to strict WHO criteria, it may be at least as good, if not better, for informing the clinician on the implications of dysglycaemia for future risk, therapeutic strategies and follow-up.

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