Should we continue to use the 75-g OGTT to diagnose diabetes?

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In 2010 the WHO/ADA allowed the use of the HbA1c to diagnose diabetes (Table 1) [1]. Clinicians had long called for the introduction of the HbA1c as a diagnostic tool for diabetes as the 75 g OGTT had started to fall out of favour. The OGTT is a cumbersome test with several conditions required to complete the test satisfactorily; patients are required to be on a stable diet of greater than 150 g of carbohydrate per day for 3 days preceding the OGTT. Patients have to fast overnight, give a fasting blood sample, then ingest the oral 75 g glucose load over five minutes, sit still for 2 h frequently in an already busy GP surgery with a second blood sample

taken at 2 h [2]. The OGTT is altered by an acute episode of stress, illness, or exercise and has a high rate of intra-individual variability with a coefficient of variability (CV) of up to 5.7% of the fasting plasma glucose and 16.7% on the 2-h sample [3]. Therefore, if a patient with glucose intolerance undergoes testing with an OGTT they could be diagnosed with T2DM one day and impaired glucose tolerance (IGT) on another day. It is estimated given the variability in the OGTT that > 12% of patients who undergo OGTT are misclassified as either diabetes or IGT, a confusing situation for both patient and doctor [3].

1. Fasting plasma glucose (FPG) ≥ 7.0 mmol/L OR
 2. 2-h plasma glucose ≥ 11.1 mmol/L during Oral Glucose Tolerance Test (OGTT).
The test should be performed as per the WHO,
using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water OR
 3. HbA1c ≥ 48 mmol/mol (6.5%) OR
 4. In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis,
a random plasma glucose ≥ 11.1 mmol/l
- In the absence of unequivocal hyperglycaemia, results should be confirmed with repeat testing [1].

On the other hand, the HbA1c, glycated haemoglobin, is a random blood test, no fasting overnight is required and in Ireland, using DCCT aligned assays, has a very tight coefficient of variability of < 1%. It is not affected by an acute bout of stress, exercise or illness and, because it is a measure of glucose attached to the N-terminal valine residue of each β -chain of haemoglobin A in the red cell, it gives an indication of glycaemic exposure in the last 2 to 3 months and correlates well with diabetes related complications [3]. The ease of testing and its accuracy has led the HbA1c to become the preferred screening test for diabetes but like any test it has

limitations (Table 2) and the OGTT still has a role to play in screening for diabetes in certain circumstances. Physiological factors such as age and race can elevate the HbA1c. HbA1c concentrations increase by 0.1% per decade after 30 years of age, thought to be partly due to changes in glycation with age [4, 5]. HbA1c concentrations are increased in those of African-American, Hispanic and Latino descent compared to their Caucasian counterparts [4]. Diseases which reduce erythrocyte life span, such as haemolytic anaemias or haemoglobinopathies (such as sickle cell trait/disease), result in a reduced HbA1c [2, 5]. Chronic kidney disease (CKD) and its impact on HbA1c is complicated because of the mixture of iron deficiency anaemia, erythropoietin deficiency and other factors but recent data suggest the HbA1c underestimates glucose control in patients on dialysis. Iron deficiency and pernicious anaemia result in a falsely elevated HbA1c due to reduced erythrocyte turnover [4]. Iron deficiency has the additive effect of increasing glycation which further increases the

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Table 1 Factors which influence HbA1c

Falsely elevated HbA1c	Falsely decreased HbA1c
Physiological factors	Iron supplementation
Increasing age	Chronic liver disease (due to reduced glycation)
Non-Caucasian race	Decreased erythrocyte lifespan
Due to decreased red cell turnover	Pregnancy
Iron deficiency anaemia	Splenomegaly
B12 deficiency anaemia	Haemolytic anaemia
Folate deficiency anaemia	Haemoglobinopathies (HbS and HbC)
Asplenia	Acute or chronic blood loss
Haemoglobinopathies (HbF and HbG)	Chronic kidney disease
Erythropoietin use	
Chronic alcohol intake	
Chronic opioid use	

HbA1c [6]. The HbA1c will underdiagnose diabetes compared to an OGTT and will miss some patients with early beta cell failure but, because the test is so easy to do, it is likely more patients will be screened at a population level for diabetes than would typically be done with an OGTT.

Following renal transplantation OGTT remains the gold-standard for identifying diabetes mellitus, owing to improved detection, identification of impaired glucose tolerance and lack of reliability of the HbA1c, especially in the early post-transplant period [7]. Alteration of glycation and red cell turnover in cystic fibrosis related diabetes (CFRD) also preclude the use of HbA1c as a screening tool and the OGTT is preferred [8]. However, there is emerging evidence of the use of the HbA1c at a lower threshold of 40 mmol/mol to diagnose glucose intolerance in this group, as an attempt to reduce the burden of the OGTT in these patients [9]. Use of the HbA1c may also miss the diagnosis in patients with acute hyperglycaemia where the duration of high blood glucose levels is too short to as yet affect the HbA1c. Pregnancy is a state of increased red cell turnover in the second and third trimester and therefore HbA1c is not a suitable test to diagnose diabetes in pregnancy [1]. Specifically gestational diabetes is a relatively acute condition and a HbA1c may not accurately reflect hyperglycaemia given it reflects the previous 3 months of glycaemia, therefore currently the recommendation to diagnose gestational diabetes is the OGTT [10].

Clinicians need to be aware of the limitations and concerns with the individual diagnostic tests available to diagnose diabetes. The application of continuous glucose monitoring

systems (CGMS) to diagnose diabetes seems to be a next logical step but, expense may inhibit its widespread use. CGMS provides information on fasting, postprandial glucose levels as well as glucose excursions and variability. This provides the diabetologist with information on glucose levels at multiple time-points and facilitates early diagnosis of impaired glucose tolerance or dysglycaemia [11]. Early reports of CGMS as a diagnostic tool show promising results, with superiority to OGTT and HbA1c [11] and particularly in gestational diabetes CGMS would give the clinician and patient a much better picture of foetal glucose exposure than an OGTT.

The HbA1c is increasingly been used to diagnose diabetes and the simplicity of a random blood test will hopefully translate into more patients been screened for diabetes but like every test there are limitations and so the OGTT still has a role to play in certain circumstances to diagnose diabetes.

References

1. American Diabetes Association. 2 (2018) Classification and diagnosis of diabetes: standards of medical care in diabetes. Diabetes Care 41(Supplement 1):S13–S27. <https://doi.org/10.2337/dc18-S002>
2. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia; World Health Organization/International Diabetes Federation 2006. Accessed from: https://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf. [Accessed on 10/10/2019]
3. Sacks D (2011) A1c versus glucose testing: a comparison. Diab Care 34(2):518–523
4. Welsh K, Kirkman M, Sacks D (2016) Role of glycosylated proteins in the diagnosis and management of diabetes: research gaps and future directions. Diab Care 39:1299–1306
5. Campbell L, Pepper T, Shipman K (2019) HbA1c: a review of non-glycaemic variables. Journal of Clinical Pathology 72:12–19
6. Sodi R, McKay K, Dampetla S, Pappachan JM (2018) Monitoring glycaemic control in patients with diabetes mellitus. BMJ 363: k4723
7. Sharif A, Hecking M, de Vries APJ, Porrini E, Hornum M, Rasoul-Rockenschaub S, Krebs G, Berlakovich M, Kautzky-Willer A, Scherthaner G, Marchetti P, Pacini G, Ojo A, Takahara S, Larsen JL, Buddle K, Eller K, Pascual J, Jardine A, Bakker SJL,

Table 2 Conditions which favour FPG/OGTT testing

Conditions which favour diabetes screening with FPG/OGTT
Chronic kidney disease stages 4/5
New-onset diabetes after transplant
Gestational Diabetes Mellitus or diabetes in pregnancy
Cystic-fibrosis related diabetes
Acute onset of diabetes
Diseases and conditions which alter the HbA1c

- Valderhaug TG, Jenssen TG, Cohnen S, Saemann MD (2014) Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. *Am J Transplant* 14(9):1992–2000
8. Godbout A, Hammana I, Potvin S, Mainville D, Rakel A, Berthiaume Y, Chiasson J-L, Coderre L, Rabasa-Lhoret R (2008) No relationship between mean plasma glucose and glycated haemoglobin in patients with cystic fibrosis-related diabetes. *Diabetes Metab* 34(6):568–573
9. Burgess J, Bridges N, Banya W, Gyi KM, Hodson M, Bilton D, Simmonds NJ (2016) HbA1c as a screening tool for cystic fibrosis-related diabetes. *J Cyst Fibros* 15(2):251–257
10. Siricharoenthai P, Phupong V (2019) Diagnostic accuracy of HbA1c in detecting gestational diabetes mellitus. *J Matern Fetal Neonatal Med*. 11:1–4
11. Soliman A, DeSanctis V, Yassin M, Elalaily R, Eldarsy NE (2014) Continuous glucose monitoring system and new era of early diagnosis of diabetes in high risk groups. *Indian J Endocrinol Metab*. 18(3):274–282

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