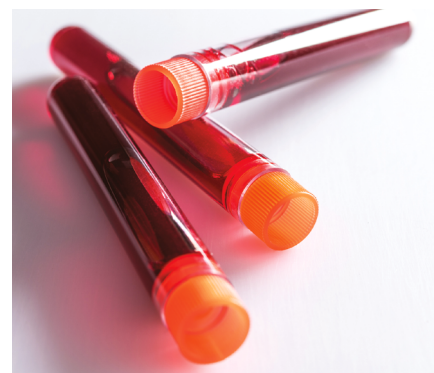


Diagnosis of type 2 diabetes using serial fasting plasma glucose versus HbA1c in the primary care setting



Ashraf Saleh

Background and objective

There are few studies investigating the diagnostic accuracy of type 2 diabetes mellitus (T2DM) by comparing fasting plasma glucose (FPG) with glycated haemoglobin (HbA1c). This proof-of-concept study looked at the correlation between FPG and HbA1c in the early diagnosis of T2DM.

Methods

A case series of 30 consecutive patients met the criteria for T2DM with FPG (>7 mM) or HbA1c (>6.5%), but not both.

Results

Average FPG in patients who met that criterion was $7.57 \text{ mM} \pm 0.53 \text{ mM}$ (average HbA1c $5.81\% \pm 0.37\%$). Average HbA1c in patients meeting that criterion was $6.54\% \pm 0.05\%$ (average FPG $6.18 \text{ mM} \pm 0.8 \text{ mM}$).

Discussion

Serial FPG testing may lead to earlier diagnosis of T2DM than by HbA1c. A higher-powered study could confirm this supposition.

TYPE 2 DIABETES MELLITUS (T2DM) management relies on reliable and accurate diagnostic testing for T2DM. This paper addresses concordance between glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG) as the two most widely used diagnostic tests for T2DM.

The Australian Diabetes Society released position statements in 2012¹ and 2015,² prior to and following Medicare Benefits Schedule rebate of the HbA1c testing of asymptomatic patients for screening of T2DM, respectively.

According to the statements, patients with an initial HbA1c of 6–6.4% should not be retested, whether by HbA1c or by FPG, as they are considered at low risk of microvascular complications. However, many patients with FPG levels consistently greater than 7 mM may still have normal HbA1c levels. These patients are best encouraged to implement diet and lifestyle modifications as soon as practicable as large trials show reductions in microvascular complications in these groups with these interventions.^{3,4}

A systematic review of the Action to Control Cardiovascular Risk in Type 2 Diabetes (ACCORD) trial and the Veteran's Affairs Diabetes Trial (VADT)⁵ showed modest protection against macrovascular disease and myocardial

infarction from tight FPG control in T2DM. Herein lies a potential discord between general practice medicine (primarily preventive in intent) and specialist physician medicine (aimed primarily at secondary and tertiary prevention) in the diagnostic and interventional acumen using FPG and HbA1c tests.

The purpose of this case series is to:

- analyse the sensitivity of FPG in comparison to HbA1c in diagnosing T2DM early in the disease process
- provide a proof-of-concept study for further studies to confirm the presupposition that FPG is the preferred diagnostic test for T2DM in the general practice setting on the basis of the accuracy and practicality of the tests using real-world data.

Materials and methods

Thirty patients registered in a medical centre in Toowoomba, Queensland, who presented in the period May 2017 – April 2018 were identified in two groups using the following criteria:

- FPG group (25 patients)
 - FPG >7 mM in two consecutive readings using formal laboratory test samples (Sullivan and Nicolaidis Pathology)

- HbA1c <6.5% (48 mmol/mol) as an average of the most recent two readings for the respective patient using the same laboratory standards of testing
- HbA1c group (five patients)
 - HbA1c >6.5% (48 mmol/mol) as an average of the most recent two readings for the respective patients using the same laboratory standards of testing
 - FPG <7.0 mM in two consecutive readings using formal laboratory test samples (Sullivan and Nicolaides Pathology).

Both groups only included patients who were not yet diagnosed with T2DM or who were not on treatment for T2DM. These patients were consecutively identified using the PenCAT data extraction tool within the Best Practice software package during the study period, meeting all of the aforementioned criteria.

The limitations of HbA1c have been previously discussed;¹ no subjects in this study had clinical features that would render their HbA1c readings inaccurate.

Ethics approval for this study was granted by the Darling Downs Hospital and Health Services Human Research Ethics Committee (HREC/18/QTDD/58).

Results

The mean age in the FPG group was 65.8 ± 12.8 years. The average FPG for this cohort was 7.57 mM ± 0.53 mM, while the average HbA1c was 5.81% ± 0.37%.

Over two-thirds of the patients exhibited diabetic range FPG with HbA1c <6.5% for over 12 months. The average body mass index (BMI) was 32.1 ± 6.3 kg/m² and average waist circumference was 105.6 ± 14.4 cm.

The mean age of the HbA1c group was 74.4 ± 13.4 years. The average FPG for this cohort was 6.18 mM ± 0.8 mM, while the average HbA1c was 6.54% ± 0.05%. The average BMI was 33.8 ± 10.9 kg/m² and average waist circumference was 99.2 cm ± 10.2 cm.

Figure 1 graphs the average FPG and HbA1c values for all patients in a scatter plot of incident T2DM cases by FPG or HbA1c criteria alone. The difference

between the FPG and HbA1c groups in this preliminary case series was statistically significant ($P < 0.02$ for FPG values and $P < 0.001$ for HbA1c values).

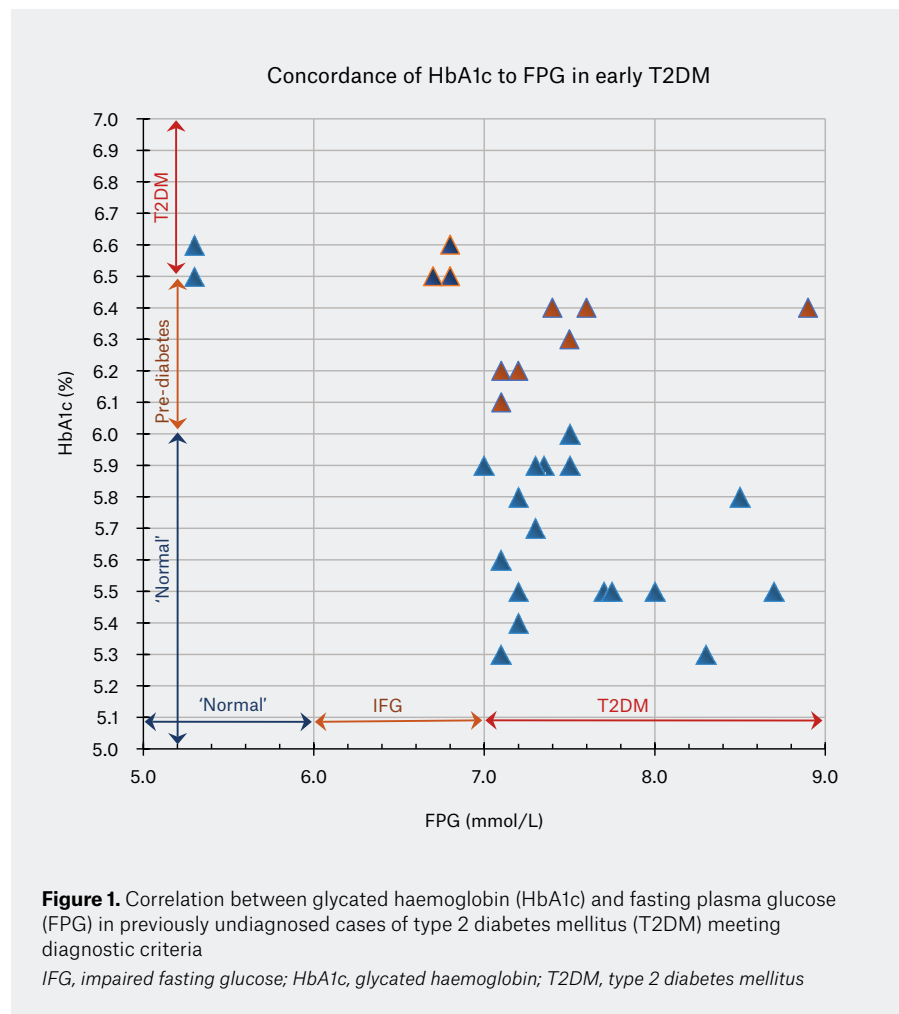
To provide statistical significance in determining a difference between testing modalities, an a priori computation of sample size was conducted, given a 1 mM difference in mean FPGs comparing the two groups in a Student's *t*-test (7.5 mM vs 6.5 mM ± 0.8 mM, effect size $d = 1.25$, $\alpha = 0.05$). This power calculation produced a required sample size of 18 in each group, using the same study design as in this proof-of-concept study.

and mortality,⁶ and 'pre-diabetes' – defined as impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or HbA1c in the 6–6.5% range – has been recently found to be associated with an increased risk of CVD.⁷ The health risk was shown to start increasing in people with an FPG from 5.6 mM, or from an HbA1c of 5.8%. There is a slightly different pathophysiology between IGT and IFG; however, the clinical effect of both is similar. IFG is due to preferential resistance of glucose production to suppression by insulin, whereas IGT results chiefly from peripheral insulin resistance.⁸

In primary care, it is not uncommon to see patients with pre-diabetes with no other CVD risk factors. Since weight loss and cardiovascular fitness reduce the progression of T2DM,⁹ as well as all-cause

Discussion

T2DM is a strong and independent risk factor for cardiovascular disease (CVD)



mortality,¹⁰ it is helpful for general practitioners (GPs) to identify the patients with pre-diabetes and encourage them to participate in these types of programs.

A typical patient from this study with early T2DM by FPG criteria but a normal HbA1c, who has no family history of T2DM, is a non-smoker, eats two serves of fruit every day, and exercises with moderate intensity activities more than 30 minutes per day scores 21 (high) on the Australian type 2 diabetes risk assessment (AUSDRISK) calculator. By this conservative measure, at least one in three such people will have T2DM, all of whom may be missed using HbA1c as a diagnostic test for T2DM.

Indeed, a 2002 analysis of the Diabetes Control and Complications Trial (DCCT)¹¹ found HbA1c had a 42% sensitivity for diagnosing T2DM against a reference standard of FPG using the current diagnostic criteria. In comparison, the free-to-administer AUSDRISK questionnaire has a sensitivity of 74% for identifying incident T2DM.¹²

The diagnostic lag of HbA1c may reduce its reliability for primary care doctors, and should be further studied in higher-powered studies to confirm this phenomenon. It is proposed that serial FPG is primary care physicians' preferred modus operandi as a cost-effective, sensitive and relatively easy test to perform for the diagnosis of T2DM.

Conclusion

A significant proportion of patients with early T2DM may be missed using HbA1c as a diagnostic test, which warrants further investigation. In the general practice setting, serial FPG is proposed to be a more accurate test for identifying early T2DM for early intervention.

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