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Agreement Between Glycated Haemoglobin and Fasting Plasma Glucose in Screening for Diabetes

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ABSTRACT

Fasting plasma glucose and glycated haemoglobin (HbA1c) are the two blood tests most often used to screen for diabetes, and since 2009 both have carried an agreed diagnostic threshold. They are not interchangeable. Glucose reports a single moment after a night without food; HbA1c reflects glycation of red-cell haemoglobin over the preceding weeks and is therefore exposed to everything that changes red-cell biology. This narrative review asks how well the two tests agree, why they sometimes do not, and what disagreement means for screening. It draws on published diagnostic-criteria documents, population surveys, laboratory-standardisation work, studies of ethnic and haematological influences, and prospective studies of risk, and it reports no new measurements. Across settings the tests identify overlapping but different groups of people, and the direction and size of the difference depend on age, ancestry, anaemia and iron status, haemoglobin variants, assay quality and the threshold chosen. Agreement statistics are also easy to over-read, because kappa and correlation are sensitive to prevalence and to range. Evidence that screening itself improves outcomes at population level remains limited. The review concludes that HbA1c and fasting glucose are best treated as complementary, that a discordant result is information and not an error, and that studies of agreement should report methods, populations and sample handling in full.

Keywords: HbA1c; Fasting plasma glucose; Diabetes screening; Diagnostic agreement; Prediabetes; Narrative review

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Article Class: Narrative Review

1. Introduction

Diabetes is one of the commonest chronic conditions in the world, and published estimates of its prevalence have climbed

with each revision (1). Much of the burden is silent: glucose can be raised for years before any symptom appears, and complications may already be under way



at diagnosis (2, 3).

For most of the late twentieth century the fasting plasma glucose (FPG) measurement carried that role, with a diagnostic threshold of 7.0 mmol/L (126 mg/dL) adopted in 1997 (4, 5). In 2009 an international expert committee recommended that HbA1c be used as well, with a threshold of 6.5% (48 mmol/mol) (6), and the American Diabetes Association adopted the recommendation the following year (7). The appeal was that a sample could be drawn at any time of day, without fasting, and summarised exposure over weeks and not a single morning (8, 9).

The two tests, however, do not measure the same thing, and in practice they do not always flag the same people. Agreement is not a single quantity: it depends on the threshold, the population, the sample handling and the statistic chosen. No local clinic data are reported here, and no figure from any single study is offered as typical. The aim is simple enough: to describe where the two tests agree, where they part company, and why that matters.

2. Literature Review

2.1 What Each Test Captures

Fasting glucose is a snapshot. It describes the concentration in plasma after an overnight fast and so says little about how the body handles a meal. The DECODE analysis showed that post-load and fasting glucose identify partly different people, each with their own information about later mortality (10, 11).

HbA1c is formed when glucose attaches to haemoglobin inside red cells, and the proportion rises with the average glucose to which the cell has been exposed. Because red cells circulate for roughly four months, the result is weighted towards recent weeks (8). The relationship with average glucose is close enough to be

expressed as an estimate, though with scatter around it. Table 1 sets the two tests side by side.

Table 1. Fasting plasma glucose and HbA1c compared as screening tests.

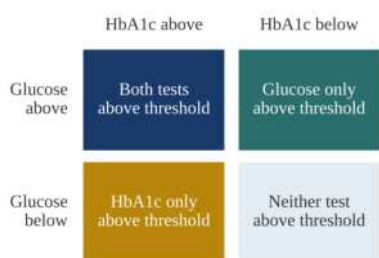
Attribute	Fasting glucose	HbA1c
Reflects	One moment, after an overnight fast (12, 13)	Average glycation over weeks (8)
Patient burden	Fasting; early-morning visit	No fasting; any time of day (9)
Day-to-day variation	Relatively large (12, 13)	Smaller within a person (12)
Sample handling	Glycolysis must be controlled (14)	Stable once collected
Standardisation	Long established	Improved but later (15, 16)
Main weakness	Misses post-meal abnormality (10)	Affected by red-cell factors (17, 18)

Note: Qualitative comparison based on the cited literature; no test characteristics are quoted because they depend on population and threshold.

2.2 How the Diagnostic Criteria Developed

The 1997 criteria lowered the fasting threshold and introduced impaired fasting glucose, a category the American Diabetes Association later widened by lowering its lower boundary (4, 5). Early concern was already on record that the revised fasting criteria might misclassify people when set against HbA1c (19); earlier population work had already asked whether HbA1c could screen at all (20).

HbA1c became a candidate diagnostic test once the assay was standardised (15) and evidence on retinopathy accumulated (21, 22). Some commentators argued that the change traded one set of problems for another (23, 24). Figure 1 shows the four outcomes that result when both are applied to the same people, and Figure 2 places the main milestones on a single timeline.



Schematic, not data; cell sizes carry no counts

Figure 1. Four possible outcomes when both tests are applied to the same people (schematic, not data).

2.3 Measurement Quality

A threshold is only as good as the measurement behind it. Glucose in a tube left unspun continues to be consumed by the blood cells, so that a delay before centrifugation lowers the result, and laboratory guidance accordingly sets out how samples should be collected and processed (14). Fasting glucose also varies from day to day within a person (12, 13), so a threshold will sort some people differently on another morning.

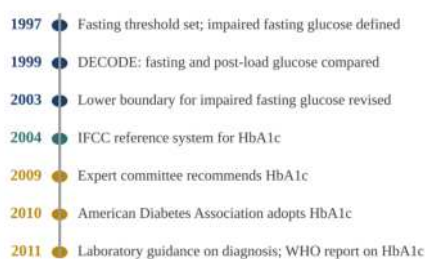


Figure 2. Milestones in the diagnostic use of glucose and HbA1c (schematic timeline, not data).

HbA1c has its own history of imprecision. Methods once differed from laboratory to laboratory, and bringing results into line took an international reference system (15); progress has been real but uneven (16). When agreement between the tests is reported without naming the assay or the way the sample was collected, the reader cannot tell how much of the disagreement belongs to the biology and how much to the laboratory. It is a habit worth keeping even when the answer seems obvious.

2.4 Biological Reasons for Discordance

Because HbA1c depends on red cells, anything that changes red-cell behaviour can move the result. Iron deficiency is the best-known example: in a national survey of adults without diabetes, iron deficiency was associated with higher HbA1c values (18). Differences in red-cell survival between healthy people are sufficient, on their own, to shift the result for a given glucose exposure (17). Haemoglobin variants add a further problem, because some assay methods are affected by them.

Ancestry is the most contested factor. Studies in the United States found that, at similar levels of glycaemia, HbA1c differed between black and white participants and between other groups (25, 26), and a later review judged that glucose alone could not explain this (27). The explanation is still unsettled (28). Table 2 collects the main factors that are known to loosen the link between HbA1c and glucose.

Table 2. Factors that can move HbA1c away from the glucose it is meant to reflect.

Factor	Likely effect on HbA1c	Source of concern
Iron deficiency	Tends to read higher (18)	Older red cells
Ancestry	Differences at equal glucose (25, 26)	Biology not fully explained (27, 28)
Red-cell lifespan	Varies between people (17)	Glycation time differs
Haemoglobin variants	Assay-dependent	Method interference (14)
Assay quality	Bias between laboratories	Calibration (16)

Note: Direction is described qualitatively; magnitude varies between individuals and studies.

3. Materials and Methods

3.1 Scope

This is a narrative review of published literature on agreement between HbA1c



and fasting plasma glucose in screening for diabetes. It follows the general approach described for narrative reviews (29), one of the review types catalogued in the methodological literature (30). It is not a systematic review.

3.2 Literature Assembly

Sources were gathered by purposive reading, not by a protocol-driven search: criteria documents, population surveys, laboratory guidance and prospective studies were chosen for their influence and for their coverage of different populations, and reference lists were then followed outwards. Neither step is complicated, though both are easy to skip. No database was searched systematically and no study was excluded on a stated rule. Only work published up to the year of this issue is cited.

3.3 Appraisal Framework

Each source was read against a short set of questions: who was tested, which assay and sample handling were used, whether the threshold was fixed in advance, and what reference standard was applied. The reporting guidance for diagnostic-accuracy studies supplied the checklist (31), and the common summaries of agreement were read with their known limits in mind (32, 33). The appraisal is qualitative. Table 3 lists the summaries met most often.

4. Results

4.1 Overlap and Disagreement in Population Surveys

Where both tests have been applied to the same national sample, the finding is consistent in kind: the two criteria identify overlapping but not identical groups. In United States surveys, each criterion flagged people the other did not (34, 35). A systematic review of HbA1c as a screening test found that sensitivity and specificity depended heavily on the cut-off chosen

(36). This is why the same pair of tests can look well matched in one report and poorly matched in the next. Figure 3 outlines how guidelines handle the commonest situation, in which only one test is above its threshold.

Table 3. Common ways of summarising agreement between two tests.

Summary	Asks	Caution
Correlation	Do values rise together?	Ignores systematic offset (32)
Limits of agreement	How far apart are paired values?	Needs one scale (32)
Kappa	Do labels agree beyond chance?	Depends on prevalence (33)
Sensitivity, specificity	Does one find what the other finds?	Needs a reference (31)
Overlap table	Who is flagged by one test only?	Threshold-specific (34)

Note: Each summary answers a different question; none of them replaces a look at the cross-tabulation.

Agreement statistics add complication: a correlation can be high while two tests sit on different scales, and kappa can look poor merely because most people in a low-prevalence sample are negative on both (32, 33). A reader of any agreement study needs an answer to a plain question: who, exactly, was tested, and how?

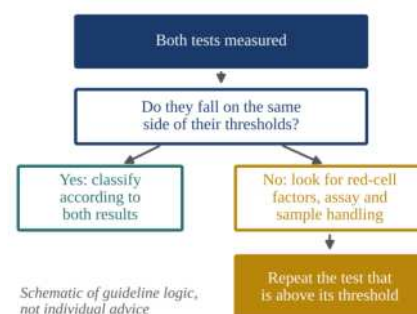


Figure 3. A guideline-style route for a discordant pair of results (schematic, not individual advice).

4.2 Population and Ethnic Patterns

Studies from Asia show that the question of agreement cannot be settled with a single universal number. A cross-sectional



survey in China examined HbA1c against glucose-based diagnosis and suggested that a somewhat different threshold gave the best balance (37). Work in India asked similar questions in community samples (38, 39). Ethnic differences in HbA1c at the same glucose suggest that part of the regional variation may be biological (27, 28). Such differences look small in a single person, yet across a screened population they accumulate.

4.3 Prognosis and Complications

Agreement between tests is less important than what each test says about the future. In a large cohort of adults without diagnosed diabetes, HbA1c predicted cardiovascular events and death at least as well as fasting glucose (40). A systematic review found risk of future diabetes to rise continuously across the A1C range, with no sharp boundary (41), in line with meta-analyses of progression from the prediabetic categories (42, 43). Prediabetes is better thought of as a gradient of risk than as a single state (44), and retinopathy studies point the same way (21, 22).

4.4 Evidence on Screening Programmes

Whether finding diabetes earlier improves outcomes is a separate question. A cluster-randomised trial of screening in the United Kingdom reported no clear reduction in mortality at ten years (45). Modelling work shows that the age at which screening begins and how often it is repeated matter for cost-effectiveness (46).

5. Discussion

5.1 Interpretation

The literature supports a restrained reading. HbA1c and fasting glucose are correlated, and each predicts later disease, but they are not two versions of the same measurement. Where they disagree, the explanation may lie in timing, assay, red-cell biology or the threshold, and often

in more than one. Treating a discordant pair as an error discards what it may reveal about post-meal glucose, red-cell turnover or simple measurement noise. Read this way, disagreement between the tests is not the same as absence of information. The guidance that a discordant result should lead to repetition of the test above its threshold is sensible for just this reason (7).

Using both tests together identifies more people than either alone, at the price of more follow-up; whether that pays depends on what happens to them, and the trial evidence is thin (45). That is a modest claim, but it is the one the literature will bear. Nothing here argues against using HbA1c; it argues for knowing what it measures.

5.2 Limitations

The review has the limits of its method. Sources were chosen by judgement, so selection bias is possible, and North American and European work may be overrepresented. Cross-sectional agreement cannot show which test is closer to the truth, and assay methods improved over the period covered. The point is not that a study is poor, only that its result travels less far than its abstract suggests. Because nothing was pooled numerically, the review cannot say how large any difference is. Reviews of this kind are more useful when they say where the evidence ends than when they smooth it over.

5.3 Future Work

Three needs stand out. First, agreement studies should state the assay, the sample handling and the population in full, following established reporting guidance for diagnostic studies (31). Second, studies should tabulate who is flagged by one test and not the other, and follow them for outcomes. Third, screening models should



compare strategies built on both tests with those built on one. These points apply equally to any biomarker adopted as a diagnostic test, not only to HbA1c.

6. Conclusion

HbA1c and fasting plasma glucose agree well enough to be used for the same purpose and poorly enough that they cannot be treated as interchangeable. The agreement a study reports depends on the threshold, the population, the assay and the statistic chosen.

For the reader the message is practical: check how a study defined agreement and who it included, and treat a discordant result as information. For the researcher, the opportunity lies in complete reporting and in following discordant groups long enough to learn what their results mean.

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9. Conflict of Interest

The authors declare no conflict of interest.

10. Author Contributions

G.S. conceived the review and wrote the sections on measurement and laboratory aspects. J.P. wrote the sections on population surveys and prognosis. A.G. wrote the sections on screening programmes and methods. All authors revised the manuscript and approved the final version.

11. Ethics Statement

This is a review of published literature. No participants were recruited and no ethical approval was required.

12. Data Availability

No new data were generated. All sources are cited in the reference list.

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