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ORIGINAL RESEARCH

Diagnostic accuracy of tests for type 2 diabetes and prediabetes: systematic review and meta-analysis - Evidence review

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1. ABSTRACT

The analyzed study is a systematic review with meta-analysis of 37 studies on adults without previously diagnosed diabetes. It compared glycated hemoglobin (HbA1c) and fasting plasma glucose with the oral glucose tolerance test, used as a reference. At an HbA1c value of 6.5%, specificity was found to be very high, while sensitivity was more limited. The authors estimated that a threshold of 6.03% would have increased case identification, with a reduction in the ability to exclude false positives.In the narrative of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the study contributes to the concept that the 6.5% value prioritizes diagnostic confirmation over the early interception of all cases. Meta-analysis and independent population studies confirm the same trade-off between sensitivity and specificity, but also indicate that the test's performance and the seemingly more balanced threshold can change according to the population and comparison standards. The conclusion is therefore moderately supported for screening, not for defining an alternative universal threshold.

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MISSION

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Through articles, reviews, in-depth analyses and expert contributions, the Journal champions evidence-based medicine and science, fostering a correct interpretation of scientific data and countering misinformation. Every piece of content is developed with the aim of translating the complexity of research into understandable, useful and applicable information, while keeping intact the principles of accuracy, transparency and scientific independence.

Free from political, industrial and commercial influence, the journal stands as an authoritative and independent editorial space, dedicated to promoting scientific culture, professional development and the growth of health awareness among the public.

2. ANALYZED STUDY

The research question was whether common blood tests can reliably identify type 2 diabetes and prediabetes in apparently undiagnosed adults. The hypothesis was that the performance of glycated hemoglobin, or HbA1c (the percentage of hemoglobin that has bound glucose, reflecting glycemic exposure over the previous weeks), would change according to the chosen threshold value.The relevance to the book's section is precise: the research does not demonstrate that a value below 6.5% should replace international diagnostic criteria, but it documents that the 6.5% threshold is highly selective. In practice, when the result exceeds this threshold, it is rare to incorrectly classify a person as diabetic who is not according to the reference test; however, a significant portion of cases identified by the oral glucose tolerance test remains below the 6.5% HbA1c threshold.The study can estimate diagnostic accuracy compared to the oral glucose tolerance test, but it cannot prove that lowering a threshold improves health outcomes, prevents complications, or is appropriate for every population. The choice of a threshold depends, in fact, on the goal: confirming a diagnosis with few false positives or identifying potentially affected individuals earlier.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The authors conducted a systematic review with meta-analysis of diagnostic accuracy, registered in the PROSPERO database. They searched for studies published from the inception of the databases until March 9, 2020, across seven bibliographic archives, supplementing the search with checks of bibliographies and institutional websites.Studies on adults recruited from the community, without a previous diagnosis of type 2 diabetes, were included, in which all participants had performed both the test under evaluation and the reference test. The tests evaluated included HbA1c, fasting plasma glucose, random blood glucose, and certain capillary blood measurements. The primary reference was the 75-gram oral glucose tolerance test, or venous blood glucose two hours after the load.Of the 8,713 records initially retrieved, 37 peer-reviewed articles were included in the review. Twenty-one studies evaluated HbA1c and ten evaluated fasting plasma glucose for diabetes at different thresholds. Methodological quality was assessed using QUADAS-2, a tool that examines the risk of bias in participant selection, test execution, and timing. To combine sensitivity and specificity, the authors used a bivariate random-effects model; to estimate the thresholds with the best statistical balance, they used data from multiple threshold values reported in the studies. Analyses for prediabetes were not performed due to a lack of comparable studies.

4. RESULTS

The key finding is that an HbA1c of 6.5% showed high specificity but limited sensitivity. Sensitivity indicates the proportion of people with diabetes according to the reference test that a screening test is able to identify; specificity, on the other hand, indicates the proportion of people without diabetes that the test correctly classifies as negative.For an HbA1c of 6.5%, across 17 studies and 64,928 participants, the pooled sensitivity was 50.2% (95% confidence interval: 41.7–58.8%) and the specificity was 97.3% (95%: 95.3–98.4%). This means that, compared to the oral glucose tolerance test, the 6.5% threshold identified approximately one in two people with undiagnosed diabetes, but correctly excluded almost all people without diabetes. The positive likelihood ratio was 18.33, a value that makes a positive result much more likely in the presence of diabetes; the negative likelihood ratio was 0.51, a value indicating only a partial ability to rule out the disease after a negative result.In the model estimating the best purely statistical compromise, the HbA1c threshold was 6.03%. At this value, the pooled sensitivity increased to 73.9% (95%: 68.0–79.1%), while the specificity decreased to 87.2% (95%: 82–91%). In practical terms, lowering the threshold would have identified more cases, but it would also have increased the number of people without diabetes who would have required further testing.Fasting plasma glycemia showed the same pattern. At the diagnostic threshold of 126 mg/dL, the pooled sensitivity was 59.4% and the specificity was 98.8%; at the statistically optimal threshold of 104 mg/dL, the sensitivity rose to 82.3% and the specificity fell to 89.4%. The authors judged the certainty of the evidence regarding the 6.03% HbA1c threshold to be of moderate quality, primarily due to limitations in the

selection of participants in the included studies.

5. INTERPRETATION

For a non-technical reader, the message is simple: a higher threshold acts as a stricter filter. It reduces the likelihood of assigning a diagnostic label to those who do not meet the reference test criteria, but it may leave out people whom the oral glucose tolerance test classifies as diabetic. Conversely, a lower threshold widens the net: it increases case identification at the cost of a higher number of positive results not confirmed by the reference test.The segment of the book's narrative that is effectively documented is therefore: HbA1c at 6.5% very high specificity and lower sensitivity lower ability to intercept all undiagnosed cases compared to a lower threshold. The publication does not prove that 6.5% was chosen exclusively to prioritize diagnostic certainty, nor does it establish that 6.03% should become a new universal clinical criterion. This value derives from a statistical synthesis of heterogeneous studies and requires clinical, organizational, and economic evaluations before any potential application in screening programs.This interpretation is consistent with the paragraph from "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, provided that the phrase "one in two diabetic subjects might not be identified" is read in the context of the standard adopted in the meta-analysis, i.e., the oral glucose tolerance test, and the population of adults without a previous diagnosis.

6. INDEPENDENT CONFIRMING EVIDENCE

An independent meta-analysis conducted on Chinese adults compared an HbA1c of 6.5% with the oral glucose tolerance test across nine studies, involving a total of 25,932 participants. The combined sensitivity was 51.8%, while the specificity was 95.6%. The authors estimated that the 6.5% HbA1c criterion would fail to identify 48.7% of newly diagnosed diabetes cases defined by the oral glucose tolerance test. This directly confirms the central point of the narrative: the 6.5% threshold is highly specific but lacks sufficient sensitivity to capture all cases during screening. The main limitation is that it concerns a specific national population and does not establish which threshold is preferable in other contexts [1].An independent cross-sectional study of 1,370 Palestinian Arab adults without known diabetes compared HbA1c with fasting plasma glycemia. A value of 6.3% offered the best observed balance, with a sensitivity of 65.6% and a specificity of 94.5%; by raising the threshold to 6.5%, specificity increased to 97.1%, while sensitivity dropped to 57.4%. This direction of effect is consistent with the analyzed study: raising the threshold reduces case identification but increases the ability to avoid unconfirmed positives. However, the comparison standard was fasting glycemia, not the oral glucose tolerance test, so the confirmation is relevant but not directly comparable [2].A further systematic review with meta-analysis compared the performance of HbA1c in Arabs and Europeans. At the 6.5% threshold, the combined sensitivity was 42% and the specificity was 97%; no statistically significant difference in the area under the curve emerged between the two populations. This data reinforces the conclusion that 6.5% selects for highly reliable positives but does not identify all cases defined by glycemic measures. The review also observed variations in sensitivity and specificity at lower thresholds, a factor that supports caution when transferring an apparently optimal value from one population to another [3].

7. CONFLICTING EVIDENCE

No directly conflicting evidence of sufficient relevance has been identified; this does not prove the absence of contrary results.The available evidence does not contradict the fact that a lower HbA1c threshold generally increases sensitivity and reduces specificity. However, it shows that the extent of this trade-off varies depending on the population studied, the reference test, and pre-analytical conditions. In particular, one study may compare HbA1c with the oral glucose tolerance test, while another compares it with fasting glycemia: these tests do not necessarily identify the same individuals. For this reason, threshold values observed in different studies should not be interpreted as perfectly interchangeable results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the study under review from independent publications used to evaluate the same diagnostic narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Systematic review and meta-analysis of diagnostic accuracy	37 studies on adults without known diabetes; comparison with oral glucose tolerance test	HbA1c 6.5%: sensitivity 50.2% and specificity 97.3%; estimated threshold 6.03%: sensitivity 73.9% and specificity 87.2%	biologically consistent evidence	moderate
[1]	Meta-analysis	9 studies, 25,932 Chinese adults; HbA1c compared with oral glucose tolerance test	HbA1c 6.5%: sensitivity 51.8% and specificity 95.6%; estimated failure to identify 48.7% of cases	direct confirmation	moderate
[2]	Cross-sectional observational study of diagnostic accuracy	1,370 Palestinian Arab adults without known diabetes; HbA1c compared with fasting glycemia	HbA1c 6.3%: sensitivity 65.6% and specificity 94.5%; at 6.5% sensitivity 57.4% and specificity 97.1%	indirect confirmation	moderate
[3]	Systematic review and meta-analysis	3 Arab and 16 European populations; 51,007 total participants	HbA1c 6.5%: sensitivity 42% and specificity 97%; performance varies by threshold and population	direct confirmation	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The systematic review clearly shows that an HbA1c of 6.5% is associated with very high specificity and lower sensitivity in screening for previously undiagnosed diabetes. The idea that a threshold near 6.03% would capture more cases is supported by statistical estimation and consistent independent evidence regarding the trade-off between case identification and false positives. However, it is not proven that this value should universally replace 6.5% in clinical practice. The narrative is moderately supported for screening and requires local validation, clinical assessment, and integration with other glycemic tests.

Aggiornato al 17/11/2026. Questo contenuto riflette una sintesi divulgativa delle evidenze scientifiche al momento della pubblicazione e non sostituisce il parere medico.

10. TRANSPARENCY AND SCIENTIFIC RESPONSIBILITY

Artificial Intelligence was used solely as a tool for editorial and documentary support. All content, interpretations, bibliographic citations and conclusions have been verified, reviewed and approved by the author, who assumes full scientific responsibility for them.

The manuscript was also subjected to independent peer review prior to publication.

To ensure the greatest transparency, the complete history of the article, including the dates of submission, revision, acceptance and publication, as well as information on the peer

review process, is available on the dedicated Article History page.

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