Impact of Polycystic Ovarian Syndrome and body mass index on the accuracy of hemoglobin A1c in detecting severe insulin resistance

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Background

Insulin resistance (IR), a key early feature in the pathogenesis of type 2 diabetes mellitus, is found in over half of women with polycystic ovary syndrome (PCOS).[1] Early detection of IR is critical to instituting timely interventions to prevent disease progression. Hemoglobin A1c (HbA1c), a test that estimates average blood glucose over the preceding 2-3 months, is commonly used to screen for prediabetes or diabetes. Because it can be obtained without fasting, HbA1c is often used as a convenient indicator of overall metabolic health. However, the extent to which a normal HbA1c value excludes the presence of severe insulin resistance remains uncertain. Further, it is not known whether the relationship between HbA1cand insulin resistance differs between individuals with and without PCOS or across varying BMI categories.

Objective

To evaluate the impact of PCOS status and BMI on the diagnostic accuracy of HbA1c for detecting severe insulin resistance as measured by the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR).

Methods

- Cross-sectional analysis of overweight/obese individuals with and without PCOS
- Presented for initial visit at Allara Health between January 1 and December 31, 2024
- BMI categorized as: (1) 25-30, (2) ≥30, and (3) ≥40 kg/m²
- HOMA-IR calculated as (fasting insulin x fasting glucose)/22.5]. Severe IR defined as HOMA-IR ≥ 4
- Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for HbA1c thresholds (normal <5.7%, prediabetes 5.7-6.4%, diabetes ≥6.5%), stratified by BMI and PCOS status.
- Logistic regression models with three-way interaction terms evaluated whether HbA1c performance varied across subgroups.
- ROC curves compared categorical versus binary HbA1c models.
- Chi-square tests and likelihood ratio tests assessed statistical significance.

Results

Table 1. Patient Characteristics

	No PCOS (n=2, 415)	PCOS (n=2,130)	p-value
Age (years), mean ± SD	36.5 ± 6.9	33.2 ± 5.6	<.001
BMI Category, n (%)			<.001
BMI 25-30	1,169 (48.4)	717 (33.7)	
BMI ≥30 kg/m²	1,010 (41.8)	988 (46.3)	
BMI ≥40 kg/m²	236 (9.8)	425 (20.0)	
HbA1c (%), mean ± SD	5.44 ± 0.43	5.49 ± 0.54	<.001
HOMA-IR, mean ± SD	3.16 ± 3.19	4.45 ± 5.21	<.001
Severe IR (HOMA-IR ≥4), n (%)	506 (21.0)	787 (36.9)	<.001

SD = standard deviation; HOMA-IR = homeostatic model assessment of insulin resistance. BMI category distribution: Pearson $\chi^2(2) = 163.07$, $p < 0.001$.

Figure 1. Severe IR Prevalence by HbA1c Category % of women with severe IR

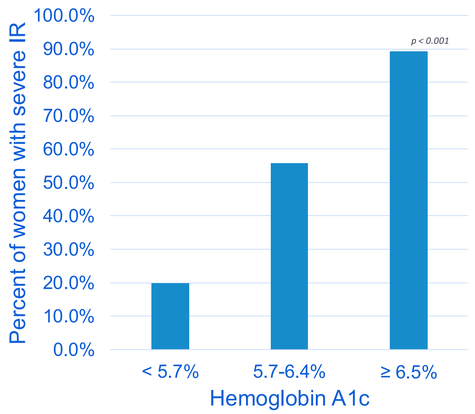

Table 2. Diagnostic performance of HbA1c ≥5.7% for detecting Severe IR

Metric	Value
Sensitivity	45.6%
Specificity	87.2%
PPV	58.5%
NPV	80.1%
AUC	0.742

AUC = area under the curve; NPV = negative predictive value; PPV = positive predictive value; IR = insulin resistance (HOMA-IR ≥4). Categorical model significantly outperformed binary classification (LR χ^2=22.6, p<0.001).

Table 3. Diagnostic performance HbA1c ≥5.7% by BMI and PCOS status

Subgroup	Sensitivity	Specificity	PPV
Stratified by BMI			
BMI 25–30	28.7%	90.7%	22.7%
BMI ≥30	42.2%	84.4%	58.9%
BMI ≥40	57.4%	75.9%	82.3%
Stratified by PCOS status			
No PCOS	45.5%	87.3%	48.6%
PCOS	45.7%	87.0%	67.3%

Three-way interaction HbA1c×BMI×PCOS: χ^2=7.54, p=0.023. HbA1c ≥5.7% binary cutoff used throughout.

Conclusions

The prediabetic HbA1c threshold of 5.7% was unable to detect over half of the cases of severe IR for both PCOS and non-PCOS patients. HbA1c performance varied substantially across BMI-PCOS subgroups and was least sensitive in non-obese patients, detecting only one in every three patients with severe IR.
These findings suggest that HbA1c, when used in isolation, may provide false reassurance regarding underlying metabolic health. Incorporating direct measures of insulin resistance, such as fasting insulin or HOMA-IR, may improve early identification of at-risk women, particularly those with PCOS and lower BMI, who might otherwise be missed using HbA1c alone.

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References:
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