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Comparison of Oral Glucose Tolerance and Hemoglobin A1c as an Initial Indicator of Type 2 Diabetes

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Abstract

The purpose of this review was to evaluate the diagnostic utility of hemoglobin A1c (HbA1c) compared to oral glucose tolerance testing (OGTT) for diagnosis of type 2 diabetes. Databases ClinicalKey, PubMed, Dynamed, and CINAHL withdrew a total of 17 peer-reviewed cross-sectional and retrospective studies, secondary and pooled data analyses, and meta-analyses. Inclusion criteria included human studies, studies ≤ 10 years old, individuals ≥ 15 years of age, fasting plasma glucose in conjunction with OGTT, and subjects without known diabetes. Exclusion criteria included alternative forms of diabetes, screening and diagnosis of prediabetes, comparisons in relation to specific medical conditions such as heart disease, pregnancy, and gestational diabetes, prior diabetes diagnosis, and children <15 years old. Discrepancies with sole utilization of HbA1c when used to screen and diagnose type 2 diabetes mellitus were found when compared to OGTT standards. Current literature proposes race, gender, age, and obesity may be related to inaccurately low HbA1c compared to OGTT standards in patients who have not been diagnosed with diabetes. Of those, race and metabolic profiles appear to have the greatest impact in reduction of HbA1c's sensitivity. An alternative to sole utilization of HbA1c may be increasing utilization of OGTT, especially in those with risk of erroneously low HbA1c and high risk for type 2 diabetes. Longitudinal data is needed to strengthen findings noted in this literature review.

Keywords: type 2 diabetes, glucose tolerance test, 2hPG, A1c.

Introduction

Type 2 diabetes is caused by gradual cellular insulin resistance combined with inadequate compensatory insulin secretion from pancreatic beta-cells. Risk factors include increasing age, obesity, and a sedentary lifestyle. Type 2 diabetes may be present for some time prior to its detection by measurement of plasma glucose in a fasting state, challenged oral glucose load, or by hemoglobin A1c.

The ADA classified oral glucose tolerance testing (OGTT) as the gold standard for diagnosis of type 2 diabetes at values ≥ 200 mg/dL. Fasting plasma glucose (FPG) was included as a second glucose-based method of diabetes diagnosis defined as a serum glucose level ≥ 126 mg/dL. In 1997, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus discussed inclusion of HbA1c after increasing prevalence of retinopathy at a certain HbA1c cutoff point which was determined at ≥ 6.5% (ADA, 2014).

Bonora and Tuomilehto (2011) also discussed reasons for its inclusion.

- It can assess chronic hyperglycemia over a period of two to three months rather than a single point in time
- Only one test is required to confirm diagnosis.
- HbA1c was found to have closer associations with chronic complications compared to fasting serum glucose levels.
- Acute variations such as stress, diet, and fasting status do not affect HbA1c and it may be tested at any time of day.
- HbA1c can be used to monitor diabetes progression over time and as a means of establishing metabolic control with implementation of various treatment methods.

Statement of the Problem

There are known limitations of HbA1c as studied by Radin (2014).

- Hemoglobin variants alter rates of hemoglobin glycation
- Many factors alter age of red blood cells, producing both false high and low HbA1c values
- There is significant discordance between HbA1c and OGTT within various populations

Based on these limitations, HbA1c's reliably in diagnosis of type 2 diabetes is in question.

Research Question

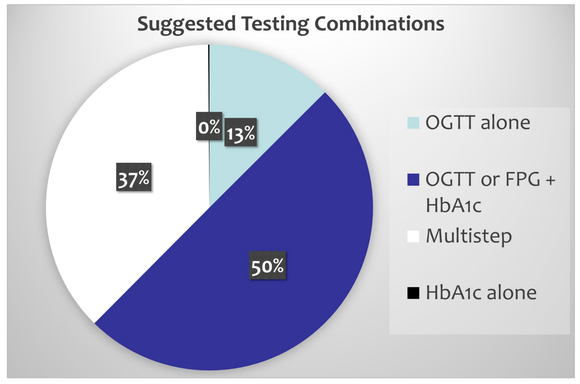
Is oral glucose tolerance testing more reliable in diagnosis of type 2 diabetes compared to hemoglobin A1c within the general population and as a factor of race, gender, age, and body mass index?

Literature Review

- Gonzalez et al. (2020) found HbA1c had a 33% false-positive rate in individuals with high Hb glycation mismatches and false-negatives in almost 33% of those with low mismatches.
- Karnchanasorn et al. (2016) reported the sensitivity of HbA1c ≥ 6.5% was 28.1%, with a specificity of 99%. About 72% of patients diagnosed by OGTT were missed by HbA1c criterion.
- Guo et al. (2014) found when both FPG and OGTT results were available, diagnosis by HbA1c alone had a false-negative rate of 75.1% (sensitivity of 24.9%) and false-positive rate of 0.6%.
- Ford et al. (2019) reported HbA1c's rate of false positives was significantly more common in blacks (17.6% versus 6.3%, $p < 0.001$), and false negatives were higher in whites (34.0% versus 19.8%, $p < 0.001$)
- HbA1c performed poorly in both Hispanic and non-Hispanic white populations compared to blacks with sensitivities of 28.6%, 22.5%, and 51.2%, respectively (Karnchanasorn et al., 2016).
- Chatzianagnostou et al. (2019) found, in both genders, there was poor concordance between the two diagnostic tests and no significant differences were found between males and females ($r = 0.44$, $p < 0.001$ and $r = 0.47$, $p < 0.001$), respectively.
- When assessing AUC values in elderly populations, a poor value of 0.65 was observed, suggesting HbA1c has limited ability for HbA1c to distinguish diabetic from non-diabetic elderly patients. (Kramer et al., 2010)
- Individuals with HbA1c < 6.5% but with positive OGTT had leaner body profiles (BMI 29.7 ± 6.1 versus 33 ± 6.6, $p = 0.00005$) compared to HbA1c ≥ 6.5% (Karnchanasorn et al., 2016)

Discussion

- There was a moderate to strong correlation between HbA1c and OGTT. As HbA1c increased, blood glucose levels also increased (Guo et al., 2014; Karnchanasorn et al., 2016; Riet et al., 2010).
- There was poor concordance of HbA1c and OGTT indicating the diagnostic tests were diagnosing diabetes in different individuals (Cavagnolli et al., 2011; Karnchanasorn et al., 2016; Pajunen et al., 2011).
- The sensitivity of HbA1c ≥ 6.5% ranged from 20-55% with a specificity of 99% or greater (Cavagnolli et al., 2011; Guo et al., 2014; Karnchanasorn et al., 2016; Pajunen et al., 2011; Riet et al., 2010)
- Proposed HbA1c Thresholds:
  - General Populations: 5.9-6.2%
  - Race
    - Non-Hispanic Whites: 6.3%
    - Blacks: 6.9%
    - Asians: 5.7-6.0%
  - Age
    - 15-49 years: 6.1%
    - 50-59 years: 5.8%
    - > 59 years: 6.1%
  - Male/Female: 6.0%



Conclusion

Discrepancies with sole utilization of HbA1c when used to screen and diagnose type 2 diabetes mellitus are expected when compared to OGTT standards. These inconsistencies are likely to involve additional factors associated with falsely low HbA1c readings, such as non-glycemic variations of HbA1c. Current literature proposes race, gender, age, and obesity may be related to inaccurately low HbA1c compared to OGTT standards in patients who have not been diagnosed with diabetes mellitus. Of those, race and metabolic profiles appear to have the greatest impact reducing the sensitivity of HbA1c. An alternative to sole utilization of HbA1c may be increasing utilization of OGTT, especially in those with risk of erroneously low HbA1c and high risk for type 2 diabetes.

Applicability to Clinical Practice

The aim of this review was to evaluate the diagnostic utility of HbA1c compared to OGTT for diagnosis of type 2 diabetes. There was significantly poor concordance between HbA1c and OGTT indicating these tests are diagnosing diabetes in different individuals at different rates. A person's race may also impact the reliability of HbA1c with black populations being over-diagnosed and white, Hispanic, and especially Asian populations being underdiagnosed. Increasing age reduced HbA1c's sensitivity and AUC to an unsatisfactory level which could be reducing diagnosis rate . Females may be more prone to wider variations in glucose levels in relation to falsely low HbA1c values resulting in more missed cases if HbA1c alone was used. Individuals who are leaner also have a higher chance of being missed by current HbA1c thresholds.

It is recommended that HbA1c diagnostic thresholds as low as 5.8% should be considered, especially in Asian populations. For white and Hispanic populations, a threshold of around 6.3% would be more accurate, and black populations up to a diagnostic cutoff of 6.9% could be considered. Recommended HbA1c thresholds as a factor of age and gender fell between 6.0-6.1%.

In those at high risk for diabetes or to verify a HbA1c result, consider OGTT in addition to or in conjunction with HbA1c to avoid missed cases of type 2 diabetes and consequential delays in its management.

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