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

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by

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TABLE OF CONTENTS

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Abstract

The purpose of this literature 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 data and pooled data analyses, and meta-analyses. Inclusion criteria included human studies, black, white, Hispanic, and Asian populations, studies $\leq$ 10 years old, individuals $\geq$ 15 years of age, fasting plasma glucose in conjunction with OGTT, and subjects without known type 2 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, a 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, and A1c.

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Introduction

In a position statement by the American Diabetes Association (ADA, 2014), diabetes is a collection of metabolic diseases resulting from deficiencies in insulin secretion, action, or both. Variable deficiencies of carbohydrate, fat, and protein metabolism secondary to poor utilization and secretion of insulin can result in marked hyperglycemia. Common symptoms of diabetes include polydipsia, polyuria, polyphagia, weight loss and blurred vision.

According to the ADA, elevated serum glucose levels can cause both acute and chronic complications. Life-threatening consequences of uncontrolled diabetes include hyperosmolar hyperglycemic syndrome and diabetic ketoacidosis. Long-term complications of diabetes include peripheral neuropathy increasing risk of foot ulcers, Charcot deformities, and lower extremity amputations; diabetic retinopathy with possible vision loss; nephropathy and renal disease; and autonomic neuropathies resulting in dysfunctional genitourinary, gastrointestinal, and cardiovascular systems. Additionally, elevated blood glucose increases incidence of hypertension, dyslipidemia, and atherosclerotic, peripheral vascular, and cerebrovascular disease (ADA, 2014).

The ADA (2014) has categorized most diabetes cases into two groups: type 1 and type 2. Type 1 diabetes is initiated by autoimmune destruction of pancreatic beta-islet cells resulting in absolute insulin deficiency. Type 2 diabetes is caused by gradual cellular insulin resistance combined with inadequate compensatory insulin secretion from pancreatic beta-cells. This literature review will focus on type 2 diabetes because this form is most common, accounting for 90-95% of all diabetes cases. Individuals are at increased risk of type 2 diabetes with increasing age, obesity, and lack of physical activity. There is also a strong genetic disposition greater than

type 1 diabetes. Due to its gradual onset, type 2 diabetes may be present for some time prior to its detection. However, abnormalities in carbohydrate metabolism can be recognized by measurement of plasma glucose in a fasting state, challenged oral glucose load, or by hemoglobin A1c.

For decades, diagnostic thresholds have been based on glucose criteria, either fasting plasma glucose or the 75-gram oral glucose tolerance test. These thresholds were revised by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus in 1997 after observing an association between fasting glucose levels and presence of retinopathy. They determined retinopathy as the most important factor to which diagnostic glucose levels and hemoglobin A1c should be determined. The committee found there was little prevalence of retinopathy at a certain cutoff point, and retinopathy would increase in a linear fashion in proportion to glucose and HbA1c levels (ADA, 2014).

The ADA (2014) classified oral glucose tolerance testing (OGTT) as the gold standard for diagnosis of type 2 diabetes with values $\geq$ 200 mg/dL. However, OGTT is time consuming and results only display glucose levels over a single point in time. The test should be repeated prior to diagnosis to rule out a spurious result. Of note, some studies analyzed in this literature review used the term 2-hour plasma glucose (2hPG) rather than OGTT to describe the same diagnostic test but will be referenced as OGTT throughout the review. The ADA also included fasting plasma glucose (FPG) as a second glucose-based method of diabetes diagnosis. It is defined as a serum glucose level $\geq$ 126 mg/dL.

In 2008, the American Diabetes Association began reviewing available literature and discussed use of hemoglobin A1c (HbA1c) as an alternative tool for diabetes diagnosis. In 2010, the ADA concluded a HbA1c $\geq$ 6.5% could be considered a new diagnostic criterion for

diabetes. (Bonora & Tuomilehto, 2011). Bonora and Tuomilehto (2011) also discussed reasons for its inclusion. First, it can assess chronic hyperglycemia over a period of two to three months rather than a single point in time and only one test is required to confirm diagnosis. Second, HbA1c was found to have closer associations with chronic complications compared to fasting serum glucose levels. Third, acute variations such as stress, diet, and fasting status do not affect HbA1c and it may be tested at any time of day. Finally, 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

Despite the American Diabetes Association's approval of HbA1c as a diagnostic indicator of type 2 diabetes, there are known limitations of HbA1c as studied by Radin (2014). First, factors altering age of red blood cells can affect HbA1c, producing both false high and low results. Second, hemoglobin variants affecting hemoglobin glycation challenge the reliability of HbA1c. Finally, Radin noted significant discordance between HbA1c and OGTT within various populations which questions the dependability of HbA1c in relation to true glycemic readings. Based on these limitations, HbA1c's reliably in diagnosis of type 2 diabetes is in question. The goal of this literature review is to improve understanding of the diagnostic utility of HbA1c compared to OGTT in diagnosis of type 2 diabetes.

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?

Methodology

After a thorough literature review, this project investigated the diagnostic utility of HbA1c in reference to OGTT in the diagnosis of type 2 diabetes. The medical research databases ClinicalKey, PubMed, Dynamed, and CINAHL were used to obtain peer-reviewed literature sources within the last ten years. Meta-analyses, cross-sectional studies, population-based studies, secondary data analyses of cross-sectional reviews, pooled analysis, retrospective studies, and survey methodologies were included. *Keywords* include: type 2 diabetes, glucose tolerance test, 2hPG and A1c. PubMed's MESH terms incorporated the words diabetes mellitus, type 2/diagnosis, glucose tolerance test, glycated hemoglobin, and HbA1c. One study by Makaroff and Cavan (2015) was within the reference list of Meijnikman et al. (2017). Inclusion criteria consisted of human studies, black, white, Hispanic, and Asian races, studies $\leq$ 10 years old, adults and adolescents $\geq$ 15 years of age, fasting plasma glucose in conjunction with OGTT, and subjects without known diabetes. It was also important to include studies that used the same diagnostic thresholds for FPG, OGTT, and HbA1c. Studies were excluded if other forms of diabetes such as lipoatrophic, type 1, or experimental diabetes mellitus subtypes were involved. Studies involving animals, 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 were excluded.

Literature Review

HbA1c in General Populations

In a secondary data analysis of the 2006-2007 New Hoorn Study by Riet et al. (2010), 2,753 Dutch subjects ages 46-65 years old with varying levels of glucose tolerance were evaluated to explain the association between HbA1c, FPG, and OGTT. They also explored HbA1c's utility in screening and diagnosis of type 2 diabetes. Of note, there was a poor

participation rate (45.4%) leading to potential self-selection and overrepresentation of people with interest in diabetes.

Plasma glucose was analyzed by an automated enzymatic method, and HbA1c was measured using reverse-phase cation exchange chromatography. A diagnosis was made using only one OGTT on all participants, but multiple tests should have been done to confirm the diabetes diagnosis. Spearman correlations were used to assess the relationship between HbA1c, FPG, and OGTT. Receiver operating characteristics (ROC) curves and area under the curve (AUC) including 95% confidence intervals (CI) were used to determine the diagnostic quality of HbA1c. Positive predictive values (PPV) and negative predictive values (NPV) were calculated for every HbA1c cutoff point.

Results showed HbA1c $\geq$ 6.5% had an adequate AUC of 0.895 (95% CI 0.861-0.930). Threshold HbA1c of $\geq$ 6.5% yielded 25% sensitivity and 99% specificity. There were 7% of subjects newly diagnosed with diabetes by a HbA1c threshold of $\geq$ 6.5% who had non-diabetic FPG and OGTT levels according to World Health Organization (WHO) criteria. At a HbA1c threshold of $\geq$ 6.0%, 44% of participants were considered diabetic by serum glucose level criteria. Spearman correlations revealed HbA1c and OGTT in previously undiagnosed diabetics had a moderate association at 0.35 ($p < 0.01$), indicating the diagnostic tests are diagnosing diabetes in different individuals. This was especially noted in the non-diabetic range of glucose tolerance. This may be due to known differences in individual glycosylation rates as observed by Gonzalez et al. (2020).

Gonzalez et al. (2020) analyzed cohorts from two cross-sectional screening reports: Screening for Impaired Glucose Tolerance (SIGT) and Veterans Affairs Screening for Diabetes and Prediabetes. They proposed HbA1c mismatches found within individuals with equivalent

glucose levels would lead to errors in diabetes diagnosis if HbA1c was used alone. 3,106 subjects ages 18 to 87 who did not have a diabetes diagnosis, were not on glucocorticoids or acutely ill were included.

HbA1c was measured with both immunoassays and the high-performance liquid chromatography (HPLC) method which was considered a strength for this study as there may be differences in using one analytic method over another. Serum glucose was determined using two automated enzymatic methods of analysis. ADA criteria was used to diagnose type 2 diabetes with an average of two oral glucose tests as the gold standard to which HbA1c was compared. Completion of multiple OGTTs to confirm diabetes diagnosis was strongpoint of this study. Linear regression modeling was used to predict the association between HbA1c and average glucose of the OGTTs. Then, hemoglobin glycation indices (observed HbA1c subtracted by predicted HbA1c) were categorized into three groups: low, intermediate, and high mismatches.

Of individuals with low mismatches (observed HbA1c was very similar to predicted HbA1c), 0% were diagnosed with diabetes ($p < 0.001$). Of individuals with high mismatches (observed HbA1c was much higher than predicted HbA1c), 10% were diagnosed with diabetes ($p < 0.001$). Gonzalez et al. (2020) concluded HbA1c had a 33% false-positive rate with high mismatches and false-negatives in almost 33% of those with low mismatches. A study by Cavagnolli et al. (2011) attempted to account for these glycation mismatches by excluding patients with conditions known to interfere or lead to misinterpretation of HbA1c such as anemia, hemoglobin variants, and glomerular filtration rate < 60.

This randomized-controlled trial by Cavagnolli et al. (2011) examined 498 test subjects to determine the diagnostic accuracy of HbA1c in diagnosis of type 2 diabetes with reference to FPG and/or OGTT. HbA1c and OGTT were drawn at the same time after an overnight fast. Lab

analysis was completed by an HPLC method and an automated enzymatic method, respectively. Statistical analysis included ROC curves, Cohen's kappa coefficients, and implementation of an algorithm created by the United Kingdom Department of Health. The goal of the algorithm was to validate addition of blood glucose measures to improve HbA1c performance in diagnosis of diabetes.

Sensitivity and specificity of HbA1c $\geq$ 6.5 were 20.0% and 95.3%, respectively. FPG and OGTT were able to identify 23.1% of subjects with diabetes, and HbA1c was able to identify 11.2% of subjects. However, HbA1c diagnosed 5.4% of patients who did not meet FPG/OGTT criteria. There was poor agreement between HbA1c criterion versus glucose measurements ($k = 0.217$, $p < 0.001$). This suggests the two diagnostic methods of diabetes classification identify different patient populations. Another study by Pajunen et al. (2011) supported this result, showing poor concordance between HbA1c diagnosis versus OGTT with a kappa coefficient of 0.11 (95% CI 0.02-0.19).

Pajunen et al. (2011) completed a secondary data analysis including 522 high-risk individuals who were part of a randomized-controlled trial called the Finnish Diabetes Prevention Study of 2003. All subjects were between the ages of 40-64, overweight, and with impaired glucose tolerance at baseline. Subjects required two positive OGTTs to establish baseline glucose intolerance, a strength of the study. However, most of these participants were motivated female volunteers which may not be directly applicable to the general population. In addition, HbA1c was analyzed by DCA 2000 rather than the HPLC method. These HbA1c lab methods have strong correlation ($r = 0.923$) but results may be lower with the DCA 2000 analyzer compared to the HPLC method which could inaccurately reduce sensitivity of HbA1c in this study. Sensitivities with 95% CIs were grouped as individuals with HbA1c $\geq$ 6% or $\geq$ 6.5%

at the time of diabetes diagnosed by OGTT over a three-year period. ROC curves and AUC were calculated to determine the predictive performance of baseline FPG, OGTT, and HbA1c on the three-year incidence of diabetes in the control group. The WHO criteria of 1985 were used to diagnose diabetes.

The AUC calculations of three-year incidence of type 2 diabetes defined by OGTT or A1c $\geq$ 6.5 showed no significant differences in predicted performance of the three diagnostic tests. However, different individuals with different characteristics were identified depending on which test was used for diagnosis. For those diagnosed by OGTT, the sensitivity of HbA1c $\geq$ 6.5% was 35% and 47% (female versus male, respectively). Thus, almost half of men and 65% of females were being misdiagnosed by HbA1c levels alone. The individuals correctly identified as diabetic by HbA1c $\geq$ 6.5% were more obese, had higher body mass index (BMI), and larger waist circumference than those diagnosed by OGTT but with A1c < 6.5%. Both Pajunen et. al (2011) and Cavagnolli et. al (2011) showed poor agreement between diagnostic tests but were limited in power secondary to small sample size and use of high-risk but motivated individuals. However, these results were supported in a secondary data analysis by Karnchanasorn et al. (2016) using 5,764 participants from the cross-sectional, population-based National Health and Nutrition Examination Survey (NHANES) from 2005-2010.

Compared to the small sample sizes of Pajunen et al. (2011) and Cavagnolli et al. (2011), Karnchanasorn et al. (2016) had a very large sample size including ethnically diverse individuals with a large age range. Additionally, the population studied was more representative of the population typically screened for diabetes in clinical practice. Subjects included non-institutionalized United States citizens $\geq$18 years old without known diabetes. The aim of this study was to determine the diagnostic effectiveness of HbA1c $\geq$ 6.5% compared to FPG and

OGTT, as well as agreement between blood glucose versus HbA1c in diagnosis of diabetes. The HPLC method was used to analyze HbA1c and an automated enzymatic method was used to analyze plasma glucose levels. ROC curves with 95% CIs were used to examine sensitivity and specificity for HbA1c criterion compared to OGTT standards, and regression analysis was used to examine the relationship of HbA1c compared to FPG and OGTT.

Based on Cohen's kappa coefficient, there was poor agreement between OGTT and HbA1c ($k = 0.386$, 95% CI 0.334 to 0.439) even with a strong correlation between the two (0.5959, $p < 0.000001$). However, the strong correlation was heavily weighted to OGTT levels of < 300 by accounting for over 99% of samples. The AUC for sensitivity and specificity of HbA1c was adequate at 0.8159 with estimated standard of error at 0.0128. The sensitivity of HbA1c $\geq$ 6.5% was 28.1%, with a specificity of 99%. About 72% of patients diagnosed by OGTT were missed by HbA1c criterion. In a clinical setting, HbAlc $\geq$ 6.5% was less likely to detect diabetes than those defined by FPG and OGTT (50% and 30%, respectively). Though this was a strong study showing significant limitations of HbA1c as a diagnostic method, it fails to show clinical significance of missed diagnoses by HbA1c if used alone.

A study by Guo, Mollering, and Garvey (2014) also used NHANES 2005-2010 data to assess ROC curves and regression analysis. However, Guo et al. focused primarily on utility of HbA1c for diagnosis of diabetes by FPG and/or OGTT as it relates to age, gender, and race. Of note, analysis of the NHANES was limited by use of only one OGTT or FPG result to diagnose diabetes. This is because completion of a single glucose-based test to diagnose diabetes is common in clinical practice. Glucose results should be repeated to confirm diabetes.

Inclusion criteria for Guo et al. (2014) was the same as Karnchanesorn et al. (2016) except it included adults $\geq$ 20 years of age versus $\geq$ 18 years of age. It looked at a slightly

smaller population of 5,395 individuals. Guo et al. used the 1985 WHO criteria compared to Karnchanesorn et al. who used the current ADA criteria. The only difference in criteria was a 1-hour decrease in minimum fasting time (> 8 hours instead of > 9 hours, respectively).

Guo et al. (2014) found a strong correlation between HbA1c values ranging between 5-8% compared to FPG and OGTT across age, gender and BMI ($p < 0.001$ for all). Concordance was not evaluated. HbA1c's AUC was excellent at 0.91. It performed best in distinguishing participants who met both FPG and OGTT criteria for diabetes. 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%. In those diagnosed solely by OGTT, sensitivity of HbA1c $\geq$ 6.5% was improved to 55%. Guo et al. concluded if a serum glucose method of diagnosis was not considered, use of HbA1c alone had the potential to inaccurately dismiss the presence of diabetes.

HbA1c and Race

Aviles-Santa et al. (2016) evaluated whether HbA1c differs between Hispanic and non-Hispanic white adults without self-reported diabetes. They retrieved data from a cross-sectional analysis of six Hispanic/Latino heritage groups enrolled in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) from 2008-2011. Data for non-Hispanic white adults were taken from the NHANES 2007-2012 cycles. The study used self-reported racial and ethnic groups which were not ideal for assessing data focused on HbA1c variations seen in different racial populations. There were 13,083 individuals included. The study consisted of adults 18-74 years old, three months or greater post-partum if previously pregnant, did not smoke or perform physical activity prior to testing, and fasted starting at 10:00 p.m. the night prior. Lab analysis of HbA1c was the HPLC method and plasma glucose was measured by an enzymatic method.

Non-Hispanic whites had significantly lower adjusted mean HbA1c ($p < 0.05$) than each individual Hispanic/Latino group, ranging from 0.08 - 0.24% across diabetes status categories. The adjusted mean HbA1c also differed significantly across all six of the Hispanic/Latino groups ($p < 0.001$), ranging from 0.04 - 0.25%. Within all seven groups, the largest difference in mean adjusted HbA1c was seen in the unrecognized diabetes category. Although these numbers are statistically significant, the clinical implications are unknown because clinical HbA1c values only detect levels within one decimal place. However, Karnchanasorn et al. (2016) reported improved HbA1c sensitivity in Hispanics versus non-Hispanic whites at 28.6% and 22.5% respectively which supports the findings of Aviles-Santa et al. (2016). Non-Hispanic whites were also compared to black populations in a study by Ford et al. (2019) which assessed current and optimal HbA1c thresholds.

Ford et al. (2019) performed a secondary data analysis of NHANES data from 2005-2014. A total of 5,324 subjects 18-70 years old, non-pregnant, and fasting $\geq$ 9 hours were included. The HPLC method and an automated enzymatic method were used for lab analysis of HbA1c and plasma glucose levels, respectively. FPG and OGTT were used as reference measures to determine accuracy of HbA1c $\geq$ 6.5%, with false positive and negative rates calculated. Linear regression was used to determine the relationship between black and white race and HbA1c both with and without adjustment for FPG, OGTT, BMI, sex, and age.

Continuous glucose monitoring showed HbA1c levels were 0.3-0.5% higher in blacks compared to whites at the same plasma glucose concentration. Overall, misclassification was not significantly different between blacks and whites (35.4% versus 38.2%, $p = 0.105$). However, the 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%, $p < 0.001$). In another study by

Olson et al. (2010), there were also higher false positives in blacks with higher false negatives in whites.

Olson et al. (2010) performed a secondary data analysis including 4,706 individuals from three studies: SIGT, NHANES III, and NHANES 2005-2006. ROC curves were used to determine the effectiveness of screening. Using ADA criteria, those diagnosed with diabetes by OGTT but missed by HbA1c criteria would have a false negative rate up to 78% of whites and 51% of blacks ($p < 0.05$ for both). The false-positive rate was not significant between the two at 0.3% of whites and 1.8% of blacks ($p = 0.15$). Ford et al. (2019) and Olson et al. suggest that non-Hispanic whites are being misdiagnosed as non-diabetic at a higher rate than blacks. This may be explained by higher hemoglobin glycation mismatches in blacks as they have blood glucose levels lower than expected for any given HbA1c level (Guo et al., 2014). Additionally, 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). A study by Araneta, Grandinetti, and Chang (2010) also examined the sensitivity of HbA1c $\geq$ 6.5% as compared to FPG and OGTT to define type 2 diabetes within in the Filipino American, Japanese American and native Hawaiian populations.

This cross-sectional secondary data analysis included the San Diego Filipino Women's Health Study as an ethnic comparison group to the Rancho Bernardo Study from 1995-1999. They also included a population-based study conducted among native Hawaiians and Japanese Americans from 1997-2000. There were fewer males than females included in this study which may not reflect actual male-female ratios in these populations. HbA1c was measured by the HPLC automated analyzer. ROC curves were used to detect the sensitivity and specificity of HbA1c cutoff points for type 2 diabetes.

Of the 933 subjects included in this analysis, 2.7% did not have diabetes as defined by OGTT but had an HbA1c ≥ 6.5% with an overall specificity of 96.8%. The sensitivity of HbA1c ≥ 6.5% was 40% with an NPV of 89.8%. The AUC of HbA1c ≥ 6.5% as defined by OGTT was not adequate at 0.68. The study also found that two-thirds of Filipino and Japanese American subjects with diabetes would have remained undiagnosed if screening was limited to FPG measures only, rather than including OGTT. However, the poor sample size of this study may be insufficient to accurately evaluate HbA1c measures. A more recent study by Zhou et al. (2018) looked at the diagnostic utility of HbA1c in Chinese populations and had higher power with similar outcomes.

This was a cross-sectional study with 7,909 participants selected from a community-based cohort in Pudong, China in 2013. Subjects were ≥ 15 years of age and without known diabetes. There was a lack of information about participants who may have had hemoglobin glycation alterations affecting HbA1c results. HbA1c was analyzed with HPLC and OGTT with an automated enzymatic method. ADA criteria were used to diagnose type 2 diabetes. ROC curves and AUC were used to determine the HbA1c threshold in diagnosis of diabetes and utility of HbA1c with OGTT as the gold standard.

There were 13.81% of subjects newly diagnosed by HbA1c with an additional 3.2% of participants diagnosed by OGTT but missed by HbA1c. The AUC for diagnosis of diabetes by HbA1c ≥ 6.5% was adequate at 0.798 (95% CI 0.779-0.818, $p < 0.001$). The sensitivity and specificity of HbA1c ≥ 6.5% was 42.3% and 94.5%, respectively (Zhou et al., 2018).

HbA1c and Gender

Chatzianagnostou et al. (2019) assessed the concordance between HbA1c and OGTT with an emphasis on possible gender related differences. There were few total participants with

949 individuals enrolled as outpatients at two Italian hospitals. All were considered high-risk for diabetes secondary to being overweight or obese which may limit its applicability to a more generalized population. ADA criteria were used to diagnose diabetes. HbA1c was analyzed by the HPLC method while serum glucose was measured by an automated enzymatic method. Linear regressions and Spearman coefficients were used to determine concordance between OGTT and HbA1c. Regression analysis was used to assess the relationship between continuous variables.

Like Riet et al. (2010), this study observed moderate correlation between OGTT and HbA1c in the overall population ($r = 0.46$, $p < 0.001$). 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 (Chatzianagnostou et al., 2019). Several studies also showed poor concordance between HbA1c and OGTT within the United Kingdom, United States, and Finland (Cavagnolli et al., 2011; Karnchanasorn et al., 2016; Pajunen et al., 2011).

However, several studies suggest HbA1c of $\geq$ 6.5% performs better in males compared to females. Individuals with HbA1c < 6.5% but meeting OGTT standards were more likely to be female (53%) compared to 32.2% of males ($p = 0.008$). Thus, males with a positive OGTT reached a HbA1c $\geq$ 6.5% threshold more often than females (Karnchanasorn et al., 2016). In addition, hemoglobin glycation values in males were more closely related to true glucose levels than females, $p < 0.001$ (Gonzalez et al., 2020). Further, Pajunen et al. (2011) found the sensitivity of HbA1c $\geq$ 6.5% was higher in males at 47% (95% CI 0.51-0.82) compared to females at 35% (95% CI 0.24-0.47). However, when assessing AUC values, the overall

adequacy of HbA1c at any given threshold performed better in females than males at 0.64 and 0.70 ($p<0.001$), respectively (Guo et al., 2014).

HbA1c and Age

Kramer, Araneta, and Barret-Connor (2010) compared the sensitivity and specificity of HbA1c and OGTT diagnosed by ADA measures in the elderly population. A total of 2,107 community-dwelling adults 69.4 $\pm$ 11.1 years of age without known diabetes were assessed through a secondary data analysis of the cross-sectional Rancho Bernardo Study. HbA1c was analyzed using the HPLC method. ROC curves were used to assess sensitivity and specificity of HbA1c cutoff points. The Kappa coefficient was used to determine agreement between HbA1c and diabetic status.

There was poor agreement between OGTT and HbA1c ($k = 0.112$) which was similar to general populations (Cavagnolli et al., 2011; Karnchanasorn et al., 2016; Pajunen et al., 2011). Kramer et al. (2010) also found 85% of elderly subjects with HbA1c $\geq$ 6.5% were considered non-diabetic by OGTT criteria, and 34% of subjects meeting OGTT diagnostic criteria had a HbA1c of < 6.5%. The ROC curve HbA1c threshold of 6.5% had a sensitivity of 44% and specificity of 79%. Several studies (Cavagnolli et al., 2011; Guo et al., 2014; Karnchanasorn et al., 2016; Riet et al., 2010) reported similar sensitivities but higher specificities ranging from 95.3% to 99.5% in general populations.

When assessing AUC values, 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). This was also noted by Zhou et al. (2018), with lower AUCs in subjects > 60 years old than that of subjects $\leq$ 60 years old, becoming statistically significant in patients < 50 years of age. In general populations, adequate to excellent AUCs of HbA1c were noted, ranging from

0.81 to 0.91 (Karnchanasorn et al., 2016; Guo et al., 2014; Riet et al., 2010). Guo et al. (2014) also stratified their results by ages (20-39, 40-59 and ≥ 60 years old), finding increasing age reduces the AUC by statistically significant quantities. A study by Joung et al. (2018) looked at ways to improve AUC values of HbA1c and found including OGTT to the HbA1c criteria improved the AUC to 0.96 (95% CI 0.93-0.989) in older adults.

This retrospective study by Joung et al. (2018) examined the differences in diagnostic rates of diabetes according to various criteria in different age groups and evaluated the efficacy of each criterion for screening older patients. There was a total of 515 participants included from the Korean Diabetes Center of Chungnam National University Hospital. This urban tertiary teaching hospital may have caused selection bias, especially with low subject numbers included in the study. All were ≥18 years old, without history of diabetes, and divided into < 65 or ≥ 65 years of age once a new diabetes diagnosis was established by the 2015 ADA criteria. HbA1c was analyzed by the HPLC method and serum glucose was measured using an automated blood chemistry analyzer. ROC curves were plotted for older patients diagnosed with diabetes and AUCs were calculated. Youden indices were used to determine various cutoff points for HbA1c.

Prevalence rate of diabetes using HbA1c criterion was significantly different in adults < 65 years old compared to adults ≥ 65 years of age at 81% and 61.5%, respectively ($p < 0.001$). Prevalence of diabetes by OGTT was not significantly different by age groups. Zhou et al. (2018) also noted a difference in prevalence rates by HbA1c criteria in younger populations compared to those ≥ 70 years of age, with younger populations having higher diagnostic HbA1c prevalence ($p = 0.003$ in 15-39 year age group, and $p < 0.001$ in the 40-49 year age group). Similar results were noted by Karnchanasorn et al. (2016), finding HbA1c < 6.5% with a positive OGTT were more likely to be older (64 ± 15 versus 60 ± 15, $p = 0.01$).

HbA1c in Overweight and Obese Populations

Meijnikman et al. (2017) assessed performance of OGTT versus HbA1c in 1,241 overweight or obese individuals ≥ 18 years of age, without history of diabetes or use of diabetic medications, and without factors known to falsely alter HbA1c values. All subjects were middle-aged white females, so results may not be valid in other populations. HbA1c was analyzed by the HPLC method while serum glucose was measured by an enzymatic method. One-way analysis of variance was used to compare non-diabetic and newly diagnosed diabetic populations. ROC curves and AUC were used to consider the relationship between sensitivity and specificity of HbA1c in addition to its accuracy. ADA criteria was used to diagnose diabetes.

The study found that 5.6% of the 11.9% of subjects newly diagnosed with diabetes had positive OGTT results but HbA1c was < 6.5%. In contrast, 1.9% of the 11.9% of subjects diagnosed had negative OGTT results but HbA1c was ≥ 6.5%. Concordance between OGTT and HbA1c was not assessed. However, another study found poor concordance of the two diagnostic tests in subjects that were overweight or obese (Chatzianagnostou et al., 2019).

Meijnikman et al. (2017) found the sensitivity of HbA1c ≥ 6.5% was 53% with a specificity of 97%. The AUC of HbA1c was adequate at 0.87 (95% CI 0.84-0.91). Subjects that did not meet HbA1c criteria but tested positive for diabetes by OGTT standards were found to have lower BMI, lesser waist circumference, less visceral, subcutaneous and total fat, and lower FPG levels compared to those with HbA1c ≥ 6.5% ($p < 0.5$ for all). Pajunen et al. (2011) also studied a high-risk population consisting of middle-aged, overweight individuals with impaired glucose tolerance at baseline. Those with HbA1c < 6.5% with positive OGTT were found to be leaner. Those with HbA1c ≥ 6.5% were more obese, had higher BMI, larger waist circumference, and higher FPG compared to those not meeting HbA1c criterion. In addition,

HbA1c sensitivity found by Pajunen et al. was slightly lower at 41% compared to 53% noted in Meijnikman et al. (2017). In general populations results were similar. Individuals with HbA1c < 6.5% but with positive OGTT had leaner body profiles (BMI 29.7 $\pm$ 6.1 versus 33 $\pm$ 6.6, p = 0.00005) compared to HbA1c $\geq$ 6.5% (Karnchanasorn et al., 2016).

Suggested HbA1c Diagnostic Thresholds

A meta-analysis was performed by Hoyer, Rathmann, and Kuss (2018) that included nine cross-sectional studies from two systematic reviews. This analysis did not consider whether non-glycemic factors affecting HbA1c values were removed from the test population, and no studies used HbA1c as the standard to which glucose-based tests were compared. Instead, optimal HbA1c thresholds for populations-based screening of diabetes were compared to OGTT, the gold standard. All patients underwent an OGTT to determine true disease status and used those values to determine HbA1c's accuracy. Individuals were divided into four categories: number with diabetes, number without diabetes, and test positives and negatives for each HbA1c threshold reviewed. This meta-analysis used all available observations of the reported thresholds of the individual studies which allowed for estimation of full summary ROC curves of HbA1c, a strength of the study. In addition, a four-dimensional logistic regression model was used to estimate parameters. Sensitivity and specificity were predicted for arbitrary thresholds, and Youden index was used as the sum of sensitivity and specificity reduced by one.

The sensitivity and specificity of HbA1c $\geq$ 6.5% was 68.4% (95% CI 0.466-0.843) and 95.9% (95% CI 0.854-0.989), respectively. Maximal Youden index of 0.68 (95% CI 0.47-0.89) was determined at a HbA1c of 6.2%, with sensitivity of 80.4% (95% CI 0.624-0.910) and specificity of 87.5% (95% CI 0.637-0.966). Thus, Hoyer et al. (2018) suggested the HbA1c threshold should be lowered based on maximum values calculated by Youden's index of the

reconstructed ROC curves. Other studies followed a similar approach, using the ROC curves to determine the HbA1c threshold with optimal sensitivity and specificity. Cavagnolli et al. (2011) found the HbA1c cutoff point of maximal sensitivity and specificity (62.9% and 64.1%, respectively) was lower than current HbA1c standards. The study felt a HbA1c threshold of 5.9% should be considered diagnostic when compared to OGTT as reference criteria. Olson et al. (2010) agreed with a HbA1c diagnostic threshold of 5.9%.

In the meta-analysis completed by Hoyer et al. (2018), differences were found between ethnic groups (primarily in Asian populations) suggesting the HbA1c cutoff should be 5.7%. This is supported by the findings of Araneta et al. (2010) who looked at Filipino, Hawaiian, and Japanese American individuals. The suggested cutoff point was 5.8% which is also lower than what was suggested in the general population. However, in Chinese populations, the HbA1c threshold was similar to general population thresholds at 6.0% (Zhou et al., 2018). When discriminating diabetes versus prediabetes, Ford et al. (2019) found the HbA1c threshold with greatest accuracy among white individuals was 6.3%, compared to black individuals with a threshold significantly higher than current HbA1c standards at 6.9% (accuracies of 91.8% and 92.5%, respectively).

Age may also impact suggested HbA1c thresholds as a diagnostic standard. Zhou et al. (2018) was able to represent adolescents, middle-aged and older individuals within the Chinese population. They found a threshold of HbA1c $\geq$ 6.1% was acceptable for adults age 15-49 and 60-69 year age group. The exception was the 50-59 year age group with a suggested cutoff of 5.8%. In adults $\geq$ 70 years old, the cutoff proposed was HbA1c $\geq$ 6.0%. Kramer et al. (2010) assessed the HbA1c threshold of older individuals ages 58-80 years of age, finding a cutoff point of HbA1c $\geq$ 6.1% was more appropriate than current standards. However, there would still be

one-third of older adults with a missed diagnosis, and another one-third with false positive results secondary to a significant reduction in specificity (Kramer et al., 2010).

Gender was also considered in suggested HbA1c thresholds. Two studies found a threshold of HbA1c $\geq$ 6.0% was adequate, with no difference between males and females (Pajunen et al., 2011; Zhou et al., 2018).

Suggested Testing Combinations

A pooled-analysis of data including 331,288 participants from 96 population-based health examination surveys in different world regions was completed by Makaroff and Cavan (2015). This study assessed different diagnostic definitions of diabetes based on prevalence within the population. They also evaluated classification of previously undiagnosed individuals who had diabetes versus those who did not. To note, few studies were available from some regions including south Asia, sub-Saharan Africa, Middle Eastern, north African and central and eastern European areas. Available data was organized by the Non-Communicable Disease Risk Factor Collaboration (NCD-RisC) and was considered representative of community, subnational, and nationwide populations. Subjects were $\geq$ 18 years of age, not pregnant, fasted for > 6 hours, and diabetics were excluded from the sensitivity and specificity of HbA1c secondary to use of pharmacologic treatments affecting biomarkers used to diagnose diabetes. Standardized assays were used for lab analysis. However, HbA1c measures can vary between laboratories and instruments, also noted by Gonzalez et al. (2020). Diabetes was defined as HbA1c $\geq$ 6.5%, a history of diabetes, or use of insulin or oral hypoglycemic drugs compared with to either FPG or OGTT definitions. The analysis was unable to exclude non-glycemic factors that could affect HbA1c. Also, it could not guarantee individuals were following all requirements of glucose testing, such as fasting, activity, and smoking. Further, only single OGTTs were recorded

secondary to the nature of health-examination surveys. For a true clinical diagnosis, repeated positive OGTTs should be recorded.

The large number of studies and age-sex groups within each study applied regression analysis to compare prevalence of diabetes. The random-effects model was used to pool results of sensitivity and specificity from each survey. Meta-regressions were used to assess sources of heterogeneity of sensitivity. Finally, univariate R^2 and semipartial R^2 measured how much variance could be explained by each independent variable, and how it contributed to the total explained variance.

When HbA1c was compared to OGTT, the sensitivity of HbA1c $\geq$ 6.5% was 37.16% (95% CI 0.351-0.393) and specificity was 99.84% (95% CI 0.9979-0.9989). Diabetes prevalence was highest when diabetes was defined by either FPG or OGTT and was lowest when based on HbA1c alone. The most important determinant of variation between the two prevalence rates was age, with some effect from BMI, national income, year of survey, and which population the survey represented.

Many other studies also suggest a glucose-based method of diagnosis in conjunction with HbA1c to improve diagnosis rate of diabetes (Cavagnolli et al., 2011; Gonzalez et al., 2020; Guo et al., 2014). In comparison, Joung et al. (2018) suggested OGTT alone provides the highest diagnostic rate of diabetes, and addition of HbA1c did not improve sensitivity of diabetes diagnosis. Ford et al. (2019) felt all three diagnostic tests should be completed for a true diagnosis. Other studies took a multi-step approach, suggesting an OGTT should be completed only to verify diabetes diagnosis if HbA1c results were in doubt, or if the individual was high risk but with HbA1c $\leq$ 6.5% (Karnchanasorn et al., 2016; Meijnikman et al., 2017; Riet et al., 2010).

Future Research

Diabetic complications. Further research has been considered in determining whether differences in HbA1c thresholds relate to differences in development of microvascular and macrovascular complications associated with type 2 diabetes (Ford et al., 2019). Makaroff and Cavan (2015) questioned HbA1c's ability to predict prevention rate of diabetic complications associated with the current HbA1c criteria. In comparison, Riet et al. (2010) felt HbA1c's cost effectiveness and practicality could be related to lower risk in development of future complications. Studies assessing potential improvement of risk scores in relation to HbA1c were also considered. This would be associated with calculation of mortality and cardiovascular morbidity in individuals with increased risk of diabetes (Pajunen et al., 2011).

HbA1c as the gold standard. Two studies concluded further research is warranted using HbA1c as the gold standard to which OGTT was compared. Hoyer et al. (2018) included studies only using OGTT as the gold standard but discussed a way to account for a varying gold standard test and suggested including another covariate for that variable. This would allow an analysis of how different study characteristics influence diagnostic accuracy and optimal HbA1c thresholds. Additionally, optimal HbA1c thresholds could be determined by future studies investigating whether sensitivity or specificity of HbA1c is more important (Ford et al., 2019).

Underlying pathophysiologic mechanisms of HbA1c and OGTT. Chatziagnostou et al. (2019) recommended further studies should address the pathophysiologic processes involved with the diagnostic accuracy of HbA1c and OGTT. More specifically, phenotypic factors potentially affecting the relationship between HbA1c and OGTT should be considered (Makaroff & Cavan, 2015). Aviles-Santa et al. (2016) suggested consideration of non-glycemic factors affecting HbA1c and inclusion of those factors into the interpretation of HbA1c are necessary.

Further, studies determining the cause of hemoglobin glycation mismatches should be considered using continuous glucose monitoring to establish red blood cell age (Gonzalez et al., 2020). Future studies could include other diagnostic tests such as a 1-hr 50-gram OGTT or random glucose since these tests are more easily obtained in clinical settings (Olson et al., 2010).

Longitudinal data. Meijnikman et al. (2017) concluded longitudinal data must be gathered to determine the clinical impact of implementing variable HbA1c cutoffs for race, age, gender, and BMI. When considering individuals ≥ 65 years of age, more studies should be completed to confirm if increasing HbA1c is associated with age, especially with increased prevalence of diabetes in elderly populations (Joung et al., 2018; Zhou et al., 2018).

Discussion

HbA1c in General Populations

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). All AUCs for HbA1c were adequate to excellent, ranging from 0.74 to 0.90 (Cavagnolli et al., 2011; Guo et al., 2014; Karnchanasorn et al., 2016; Riet et al., 2010).

HbA1c and Race

HbA1c's sensitivity was poor in all studies at 22.5%, 28.6%, 40%, 42.3% and 51.2% in whites, Hispanics, Filipino, Japanese, and Hawaiian, Chinese, and black populations,

respectively (Araneta, et al., 2010; Karnchansorn et al., 2016; Olson et al., 2010; Zhou et al., 2018).

HbA1c and Gender

In both genders, there was poor concordance between OGTT and HbA1c with no significant differences found between males and females (Cavagnolli et al., 2011; Chatzianagnostou et al., 2019; Karnchanasorn et al., 2016; Pajunen et al., 2011). Yet, several studies suggest HbA1c of $\geq$ 6.5% performed better in males compared to females. Males reached a HbA1c threshold $\geq$ 6.5% more often than females (Karnchanasorn et al., 2016), had a higher sensitivity (Pajunen et al., 2011) and had hemoglobin glycation values more closely related to true glucose levels (Gonzalez et al., 2020). However, the overall adequacy of HbA1c at any given threshold performed better in females than males (Guo et al., 2014).

HbA1c and Age

Concordance between HbA1c and OGTT was not dependent on age, performing poorly overall (Kramer et al., 2010). Prevalence of diabetes did not change with increasing age by OGTT criterion but did increase with increasing age by HbA1c criterion (Karnchanasorn et al., 2016; Joung et al., 2018; Zhou et al., 2018). Increasing age also lowered the AUC for HbA1c to inadequate levels (Guo et al., 2014; Kramer et al., 2010; Zhou et al., 2018). Lastly, the specificity of HbA1c $\geq$ 6.5% decreased with increasing age (Kramer et al., 2010).

HbA1c and BMI, Overweight, and Obese Categories

All studies examining HbA1c as it relates to BMI, overweight, and obese individuals concluded leaner subjects were more likely to be missed by HbA1c compared to those with poorer metabolic profiles (Chatzianagnostou et al., 2019; Karnchanasorn et al., 2016; Meijnikman et al., 2017; Pajunen et al., 2011).

Proposed HbA1c Thresholds

HbA1c thresholds in the general population. Hoyer et al. (2018) analyzed nine cross-sectional studies to determine an estimated summary of ROC curves for HbA1c. The maximal sensitivity and specificity of HbA1c was found at a threshold of 6.2%. Other studies followed a similar approach and found a cutoff of 5.9% should be considered when compared to OGTT standards (Cavagnolli et al., 2011; Olson et al., 2010). Therefore, in general populations, it is suggested the HbA1c threshold for diagnosis of type 2 diabetes should be between 5.9 – 6.2%.

HbA1c thresholds and race. HbA1c diagnostic cutoffs varied widely between different racial groups and subgroups. In Asian populations, Filipino, Hawaiian, and Japanese populations, and Chinese populations, the suggested HbA1c cutoff was 5.7%, 5.8% and 6.0%, respectively. (Araneta et al., 2010; Hoyer et al., 2018; Zhou et al., 2018). White population's recommended HbA1c cutoff was closer to the current standard at 6.3%, while black population's proposed HbA1c threshold was greater than the standard at 6.9% (Ford et al., 2019). There were no HbA1c thresholds recommended for Hispanic populations.

HbA1c thresholds and age. A HbA1c threshold of 6.0% to 6.1% was recommended for individuals > 59 years old by Kramer et al. (2010) and Zhou et al. (2018). A similar cutoff of 6.1% was noted for individuals ages 15-49 years old with an exception for individuals ages 50 to 59 with a proposed cutoff of 5.8% (Zhou et al., 2018). It appears age variations do not significantly alter proposed HbA1c thresholds. However, at any age, HbA1c is more closely associated with OGTT at lower thresholds than current ADA standards.

HbA1c thresholds and gender. Pajunen et al. (2011) and Zhou et al. (2018) recommended a HbA1c threshold of 6.0% for both male and female populations.

Suggested Testing Combinations

Numerous studies agree a glucose-based method of diabetes diagnosis should be utilized due to HbA1c's low diagnostic prevalence rates compared to OGTT and FPG. However, the method to which this is done varies greatly between studies. Variations include: sole use of OGTT (Joung et al., 2018), OGTT or FPG in conjunction with HbA1c (Cavagnolli et al., 2011; Gonzalez et al., 2020; Guo et al., 2014; Makaroff & Cavan, 2015), or a multistep approach using OGTT only if HbA1c results were in doubt, to verify results, or if the individual was high risk but had a HbA1c $\leq$ 6.5% (Karnchanasorn et al., 2016; Meijnikman et al., 2017; Riet et al., 2010). There were no studies that felt HbA1c should be used as a lone method of diabetes diagnosis.

Future Research

There is a significant amount of research that must be done to clarify the utility of HbA1c compared to OGTT. First, the prevalence and significance of diabetic complications in relation to newly proposed HbA1c thresholds must be determined. Further, longitudinal data is needed to determine the clinical impact of these proposed diagnostic cutoffs. Other research is needed employing HbA1c as the gold standard to which OGTT is compared. Lastly, the underlying pathophysiologic mechanisms of HbA1c and OGTT potentially affecting their relationship must be further contemplated.

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 literature 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 which indicates these tests are diagnosing diabetes in different individuals at different rates. If either HbA1c or OGTT is solely utilized to diagnose diabetes, cases may be missed. 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 and increasing rate of complications associated with a missed diagnosis. 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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