Can A1C replace oral glucose tolerance test in the evaluation of patients with impaired fasting glucose?

Abstract

Aim: The aim of this study is to correlate the A1C values with the OGTT in individuals without type 2

Diabetes (DM) but with impaired fasting glucose (IFG) (FPG: 5.6-6.9mmol/l).

Methods: We investigated 119 subjects with IFG divided according to A1C levels (<5.7%; 5.7-6.4%, ≥6.5%) and analyzed the correlation among A1C, FPG and 2-hPG by Pearson's coefficient. Kappa coefficient was used to test agreement between A1C and 2-hPG for the diagnosis of DM.

Results: The average age of the subjects was 54.2 ± 14.6 years, the average BMI was 30.2 ±5.5 and 70.5% were women. While levels of A1C ≥6.5% were associated to alterations in the 2-hPG in 86.7%, only 28.6% of these patients had 2-hPG >11.1mmol/l. Furthermore, 31.6% of the patients with DM diagnosed by the OGTT had A1C levels ≥6.5% and 64.3% of the patients with A1C < 5.7% had a normal OGTT. The Kappa coefficient of reliability between A1C and 2-hPG to diagnose DM was 0.71.

Conclusion: A1C is a useful tool in evaluating IFG patients and correlates better to 2-hPG than to FPG. Yet, the agreement between A1C and OGTT to diagnose DM in this group was moderate (71%). It may be too soon to consider A1C as a substitute exam for OGTT.

Keywords: type 2 diabetes, A1C, oral glucose tolerance test, impaired fasting glucose

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Introduction

According to recent estimates, between 2009 and 2034, the number of people with diagnosed and undiagnosed type 2 diabetes will increase from 23.7 million to 44.1 million. During the same period, annual diabetes-related spending is expected to increase from $113 billion to $336 billion (dollars).[1]

Type 2 diabetes is often asymptomatic in its early stages and can remain undetected for several years. Increasing evidence shows that half of those with type 2 diabetes are not aware that they have the condition and as many as 25% of people with a new diagnosis of type 2 diabetes already have established diabetic retinopathy or microalbuminuria.[2-4] These realities support the critical need to identify diabetes and its precursors more efficiently and earlier.[5]

In 1997, the Expert Committee on Diagnosis and Classification of Diabetes Mellitus examined population data for retinopathy, and noted that for Fasting Plama Glucose (FPG), 2-hour post load glucose during an oral glucose tolerance test (OGTT), and hemoglobin A1c (HbA1c), the diabetes-related complication of retinopathy increased linearly above a certain cut points; for FPG and OGTT, those cut points became the basis for the diagnosis of diabetes.[6] In 2010, it was felt that with the increasing adherence to the National Glycohemoglobin Standardization Program (NGSP), laboratory-based HbA1c is measured in a standardized fashion in the majority of labs in the U.S. Furthermore, the American Diabetes Association (ADA) noted that review of epidemiologic data supported a relationship between HbA1c and the risk of retinopathy similar to what had been shown for FPG and OGTT. Thus, in 2010, the ADA added A1c of 6.5 percent or greater as a diagnostic criterion.[7]

The ADA required that a laboratory-based HbA1c assay method certified by the NGSP be used. This ensures that the assay used is standardized or traceable to the Diabetes Control and Complications Trial. When measured in an NGSP-certified laboratory, a change in A1c of at least 0.5 % is considered both statistically and clinically significant.[8,9] Separately, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) convened a working group in 1995 with the goal of developing a true reference method for A1c. This goal differed from the standardization goal of the NGSP. A consensus statement issued in 2007 by the ADA, the European Association for the Study of Diabetes (EASD) and the International Diabetes Federation (IDF) supports reporting A1C values using both NGSP (%) and IFCC (SI) units.[10]

There is no consensus on the most accurate screening test for the detection of type 2 diabetes. The most widely used screening tests include the fasting plasma glucose (FPG) and the oral glucose tolerance test (OGTT). However, the measurement of both OGTT and FPG require patients to fast overnight for at least 8 hours and diagnosis confirmation using FPG requires the test to be repeated at least twice. Furthermore, studies have shown that FPG sensitivity for diabetes diagnosis is not as high as expected, with nearly one-third of individuals with diabetes remaining undetected.[11] OGTT is also costly, time-consuming and intensive laborious and has low reproducibility that can add confusion and uncertainty to the confirmation of diabetes diagnosis [12].

Diabetic retinopathy is arguably the best criterion from which to compare glycemic measures because it is a specific and early clinical complication usually related to diabetes, and it represents a specific and relevant clinical end point for judging an alternative test.[7-15]

In recent years, the validity of A1C as a screening tool for type 2 diabetes has also been examined, using OGTT as the gold standard and FPG as the comparison. A1C has been suggested as a useful tool for type 2 diabetes screening and diagnosis.[7-14] A1C levels represent a 2–3-month average of blood glucose concentrations and may have several advantages compared to FPG and OGTT.[7-11] Compared with the OGTT, A1C measurement is quicker and more convenient. A1C can be measured at any time of the day regardless of fasting duration or the content of the previous meal.[7-11]

Recommending A1c as a diagnostic test was partly based on its advantages over timed glucose tests, including serving as a better index of overall glycemic exposure and risk for long-term complications, offering less biologic variability and preanalytic instability, and being unaffected by acute perturbations in glucose levels due to an acute illness or stress-related event. In addition, between- and within-subject coefficients of variation have been shown to be substantially lower for A1C than for glucose measurements.[7] Moreover, A1C is relatively unaffected by acute perturbations in glucose level.[7-11]

The International Expert Committee proposed A1C ≥ 6.5% as a diagnostic tool for diabetes in 2009[8] and in January 2010 an intermediate range of A1C 5.7–6.4% (elevated A1C) was proposed by the American Diabetes Association (ADA) with agreement of the Endocrine Society to detect individuals at high risk for developing type 2 diabetes.[7] Although numerous cross-sectional and longitudinal studies indicate that HbA1c is correlated with risk of diabetes and diabetes related co morbidities.[7-19] It is worth noting that not only the of rate of hyperglycemia diagnosed by an oral glucose tolerance test (OGTT) and HbA1c criteria was different but also the overlap between glycemic classification as defined by OGTT and HbA1c criteria was limited in Chinese[20,21] and other populations.[22-26] However, it is still unclear why the prevalence of diabetes and prediabetes between diagnosed by OGTT and HbA1c criteria is substantially discordant.[27,28]

One Chinese population-based study showed that the agreement between HbA1c and OGTT criteria in classifying subjects'glycemia decreased with the increased BMI. Li Jie et al.,[27] observed that the specificity of HbA1c with OGTT as the reference for screening prediabetes, but not newly diagnosed diabetes was significantly lowered in the obese subjects compared with the normal-body weight subjects.[27]

Although, some reports have suggested that A1C may not be a suitable screening test because of low sensitivity and the confounding aspects of assays;[22-26] while some others have suggested the opposite.[29-32] Besides, it should be noted that there will be certain caveats to the use of this test that must be understood by clinicians.[33-36] The aim of this study was to correlate the A1C values with the OGTT in Brazilian individuals without diabetes but with impaired fasting glucose (IFG) and other risk factors for type 2 diabetes.

Subjects

A total of 119 patients recruited at a general endocrine clinic at Felicia Rocho Hospital, Brazil, without known type 2 diabetes, enrolled the research between May 2008 and November 2009. Their mean age was 54.2 ± 14.6 years and 70.5% of them were women. The body mass index (BMI) was 30.2 ±5.5 Kg/m² and the average waist circumference was 98.9 ± 10.2cm for women and 105.4 ± 11.1cm for men.

Materials and methods

A medical interview provided information about their lifestyle, use of medications, gestational diabetes mellitus, nonalcoholic fatty liver disease, polycystic ovary syndrome and personal or familial history of diabetes (on first-degree relatives). Weight and height were measured with subjects lightly clothed, and a tape measure was used around the waist at the smallest circumference between the lower ribs and the iliac crests. Blood pressure was measured by the assistant doctor with a sphygmomanometer with subjects lying at rest for at least 5 minutes.

Glucose tolerance status was defined as proposed by the American Diabetes Association (ADA) as 1) normoglycemia, FPG<5.6 mmol/L (100 mg/dL) and 2-h post challenge glucose (2-hPG)< 7.8 mmol/L (140 mg/dL); 2) impaired fasting glucose (IFG), FPG>5.6 mmol/L (100 mg/dL) and <7.0 mmol/L (126 mg/dl); 3) impaired glucose tolerance (IGT), 2-hPG >7.8 mmol/L (140 mg/dL) and <11 mmol/L (200 mg/dL); and 4) type 2 diabetes, 2-hPG >11.1 mmol/L (200 mg/dL) Patients with previous history of diabetes or FPG ≥ 7.0mmol/L; chronic renal or liver diseases, with known hemoglobinopathies or the presence of anemia (hematocrit < 40% in men or < 35% in women), infected by HIV or hepatitis C virus; in use of glucocorticoids or immunosuppressant in the last three months; with creatinine level above 1.5mg/dL or TSH level >5UI/ml; with other diseases that could interfere with glucose metabolism or pregnancy were excluded.

All patients had FPG between 5.6 and 6.9mmol/L and after 12 hours of fasting they were submitted to a standardized OGTT (75g of glucose in 200mL of water) with measurement of plasma glucose 2 hours after over load. A1C, lipid profile, creatinine, uric acid and complete blood cell counts were also determined prior to OGTT. The patients were divided, according to the levels of A1C, in three groups (A1C <5.7; 5.7-6.4; and ≥ 6.5) as American Diabetes Association [ADA] recommends[16] and The Endocrine Society Statement states.

A1C was determined by the automated ion-exchange high-performance liquid chromatography method (Bio-Rad Laboratories; Reference: 4%–6%). The assay has been accredited by the National Glycohemoglobin Standardization Program (NGSP). Total cholesterol, triglycerides, creatinine, uric acid, FPG and 2-hPG were determined by semi automated enzymatic methods (Simens). LDL-c was calculated using the Friedewald equation.

Statistical analysis

We compared the variables using chi-square test and ANOVA. Results are given as means ± SD. The relation between A1C and 2-hPG was evaluated by a Pearson correlation coefficient. We also calculated a Pearson correlation coefficient between A1C and FPG. Kappa coefficient was used to test agreement between A1C values and 2-hPG for type 2 diabetes diagnosis. The SAS 9.0 (SAS Institute Inc., Cary, NC) and BioESTAT 3.0 (Optical Digital Technology, Belem, PA, Brazil) programs were used for all analyses. We considered the P value <0.05 as significant.

Results

Most of our patients were middle aged, obese and 70.5% were women. Twenty eight patients (23.5%) had A1C levels below 5.7%; seventy (58.8%) had them between 5.7-6.4 and twenty-one (17.7%) had A1C ≥ 6.5% (Table 1). A1C levels correlated particularly well with 2-hPG, but also with FPG. The comparison between the third group (A1C> 6.5%) with the two other groups was statistically significant

using ANOVA (P=0.003). There was no significant correlation between the A1C level, age, sex, BMI, waist circumference, red blood cell count, lipids, or uric acid (Table 1).

Sixty four percent of the patients with A1C < 5.7% had a normal OGTT result, but 14.3% of them had levels of 2-hPG >11.1 mmol/L.

The group of patients with A1C between 5.7-6.4% had similar results of OGTT when compared to the group of A1C < 5.7%. Levels of A1C ≥ 6.5% were related to alterations in the OGTT on 85.7% of the cases, but only 28.6% of the patients had 2-hPG >11.1 mmol/L. On the other hand, only 31.6% of the patients with diagnosis of diabetes by the OGTT had A1C levels ≥ 6.5% (Figure 1).

Table1 Participant characteristics by A1C group

| A1C (%)	< 5.7 (A) N=28	5.7-6.4 (B) N=70	≥ 6.5 (C) N=21	P value
2-hPG (mmol/L)	7.5 ± 2.8	7.7 ± 2.5	10.6 ± 2.7	A=B≠C P=0.0001
FPG (mmol/L)	6.1 ± 0.4	6.1 ± 0.4	6.2 ± 0.4	0.15
Age (years)	52.1 ± 18.6	54.4 ± 12.4	56.7 ± 16.1	0.35
BMI (Kg/m²)	29.3 ± 5.8	30.2 ± 5.3	31.3 ± 5.6	0.46
Waist Circumference (cm)	103.2 ± 11.8	100.9 ± 10.4	97.2 ± 11.1	0.29
Hemoglobin (g/dl)	14.2 ± 0.9	14.2 ± 1.2	13.5 ± 1.0	0.12
Total cholesterol(mg/dl)	189.3 ± 36.2	200.6 ± 34.3	194.2 ± 49.6	0.34
HDL-c (mg/dl)	45.1 ± 13.5	48.8 ± 14.1	48.6 ± 10.0	0.49
LDL-c (mg/dl)	114.3 ± 30.1	122.9 ± 30.3	110.6 ± 43.2	0.24
Tryglycerides (mg/dl)	173.3 ± 185.7	149.9 ± 87.8	168.3± 115.5	0.66
Uric acid (mg/dl)	6.3 ± 2.0	5.6 ± 1.4	5.4 ± 2.5	0.2

Data are in means ± SD.
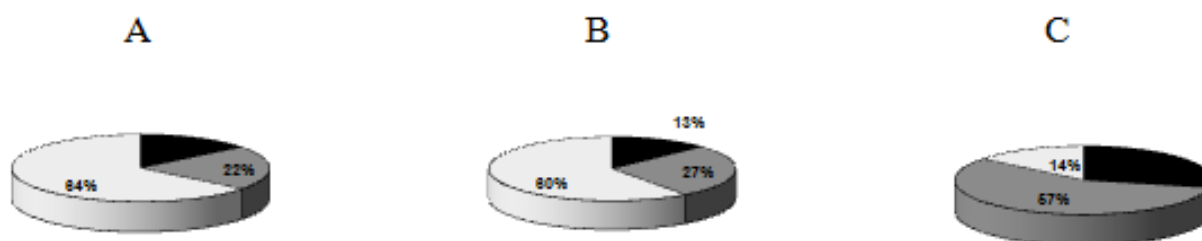
Figure 1 Incidence of normal glucose tolerance ( ), impaired glucose tolerance ( ) and diabetes ( ) (defined by OGTT criteria) in individuals with A1C < 5.7 (A), 5.7-6.4 (B), ≥ 6.5 (C). A=B≠C with P value of 0.003.

In our study, almost 13% of the patients with IFG (15 of the 119) would only receive the diagnosis of DM by the A1C criteria, if confirmed. On the other hand, a similar number of subjects (13 of 119) had a level of 2-hPG >11.1 mmol/L with A1C levels < 6.5%. The Pearson correlation coefficient between A1C and 2-hPG was 0.335 (P=0.0001). The Pearson correlation coefficient between A1C and FPG was 0.200 (P=0.01). The agreement of the tests (A1C and OGTT) to diagnose or not diabetes was 71% (the Kappa coefficient was 0.71).

Conclusion

In this group of Brazilian obese patients with IFG there was a weak correlation of A1C values with 2-hPG and FPG, what demonstrates that the prevalence of diabetes in some populations may not be the same when diagnosis is based on A1C or glucose measurements. Actually, one method may identify different individuals that were not identified as diabetics by the other.[7,8] In our study, almost 13% of the patients with IFG (15 of the 119) would only receive the diagnosis of DM by

the A1C criteria, if confirmed. On the other hand, in a similar number of subjects (13 of 119), that had a level of 2-hPG >11.1 mmol/L, the diagnosis of DM would have been missed if the screening had relied only on A1C and FPG determinations. In the study conducted by Marini MA, et al with a cohort of adult Italian Caucasians, 48.7% of the individuals with A1C ≥ 6.5% were not classified as diabetic by FPG-only criterion and 35.9% of the individuals with diabetes by FPG-only criterion would be classified as non-diabetic by A1C criterion. Using 2-hPG as criterion, 47.0% of the individuals with A1C ≥ 6.5% were not classified as diabetic by 2-hPG only and 53.4% of the individuals with diabetes by 2-hPG only would be classified as non-diabetic by A1C criterion.[37]

After sorting for A1C ranges, patients with A1C < 5.7% have had normal OGTT results on 64.3% of the tests and levels of A1C ≥ 6.5% were related to alterations in the OGTT on 85.7% of the cases. The degree of reliability between A1C and OGTT, to diagnose or not, diabetes was moderate (kappa coefficient = 0.71). The individuals with IFG are a heterogeneous population that has in common the higher risk to develop type 2 diabetes in the future when compared to individuals with NGT. On our study almost 59% of the patients with IFG had A1C levels between 5.7-6.4 and 17.6% had A1C ≥ 6.5% what reflects some impairment on glucose metabolism in this population. This latter data differs to that found by Fajans et al who have found that, approximately one third of the subjects with early diabetes and IGT, had A1C less than 5.7%[26] That could have been due to the small percentage of subjects in their study with IFG. Marini MA, et al found only modest agreement existed for A1C and 2-hPG criteria for diagnosis of type 2 diabetes (kappa coefficient = 0.427), with 81.8% of individuals classified as not having diabetes by both A1C and 2-hPG criteria, and 6.0% classified as having diabetes by both A1C and 2-hPG criteria.[37]

There have been many studies comparing the performance of A1C as a screening and diagnostic tool for diabetes against OGTT and FPG.[14-37] Little et al.,[29] studied the use of A1C as a screening test in Pima Indian population with high prevalence of type 2 diabetes and found high sensitivity and specificity for detecting diabetes compared to OGTT.[29] Droumaguet et al.,[31] in the Data Epidemiological Study on the Insulin Resistance Syndrome (DESIR), a French cohort study of 2820 people, have found that FPG-defined diabetes risk increased exponentially with baseline A1C and after stratifying on FPG classes, A1C was predictive only in subjects with IFG, with an Odds Ratio of 7.2 (95% CI 3.00 –17.00); thus subjects with IFG and high A1C could be selected for preventive care.[31] Perry et al have demonstrated that a substantial percentage of high-risk individuals with OGTT diagnostic of diabetes, who were not identified on the basis of current FPG criteria, were correctly detected on the basis of an elevated A1C.[32] In another study using an external gold standard, diabetic micro vascular complications, McCance et al.,[14] have showed that A1C was as predictive as FPG and 2-hPG.[14]

Our study included patients of several ages, ranging from twelve to ninety years. We did not make distinction of the subjects by race or ethnicity. There was no correlation between A1C level and age, contrary to what has been found by Pani et al whose study demonstrated that A1C levels appear to increase with age.[34]

Furthermore we did not find any correlation between A1C levels, sex, BMI, waist circumference, red blood cell count, lipids, or uric acid. Jie Li et al.,[27] evaluated whether obesity affected the performance of HbA1c in diagnosing diabetes and prediabetes against a standard

OGTT, which was partly mediated by oxidative stress, and to identify the optimal HbA1c cutoffs in normal body weight (BW), overweight, and obese population in a large cross-sectional study in Harbin, China.[27] And they found that the HbA1c cutoff values for diagnosing prediabetes increased with BMI (5.6% in normal BW, 5.7% in overweight, and 6.0% in obese subjects) corresponding to 80% specificity. Although the HbA1c cutoff values for diagnosing diabetes remained relatively stable in every BMI classification corresponding to 97.5% specificity.[27]

Patients with A1C ≥ 6.5% had a 2-hPG value statistically higher when compared to the other two categories of A1C. The group with A1C ≥ 6.5% had a higher number of patients with IGT or type 2 diabetes. A1C ≥ 6.5% had a sensitivity of 28.5% and specificity of 85.7% to diagnose type 2 diabetes according to the OGTT result, what was similar to that found by other reports.[5,25,26,37] For example Marini MA, et al using 2-hPG ≥ 200 mg/dl criterion as the reference standard, diagnosis of diabetes by the A1C criterion had 46.6% sensitivity, 93.9% specificity, 53.0% positive predictive value and 93.9% negative predictive value.[37]

In our study, we found a weak correlation between A1C and 2-hPG (Pearson correlation coefficient of 0.335). There was an even weaker correlation between A1C and FPG (Pearson correlation coefficient of 0.200), showing that A1C value correlated better with the 2-hPG than FPG. Peters et al have performed a meta-analysis in which they compared the relationship of FPG and OGTT results with A1C levels, and found that A1C levels above 6.5% occurred only with FPG ≥ 7.8mmol/L.[30] We believe that this could be the reason why we found a weak correlation between A1C and FPG since the population we studied had FPG between 5.6 and 6.9mmol/L. The Pearson correlation coefficient between A1C and FPG at inclusion of DESIR Study conducted by Droumaguet et al. was 0.38, what was higher than ours, probably because of the much higher number of subjects studied by Droumaguet (3,854 subjects) compared to ours.[31]

The agreement of the tests (A1C and OGTT) on our study to diagnose, or not, diabetes was 71% (the kappa coefficient was 0.71). This former data differs to what has been found on The Rancho Bernardo Study, conducted by Kramer et al.,[25] that studying community dwelling adults without known diabetes by an OGTT and A1C measured on the same day. They have found a lower agreement between OGTT and A1C (cut point of 6.5%) to diagnose type 2 DM (Kappa coefficient was 0.119).[25] This difference could be explained by distinct population characteristics; in our study all the subjects were younger and have had IFG contrary to the Rancho Bernardo Study.[25] Besides, all the subjects from our study had the A1C measured on a single laboratory and by the same method. Recently, Vega-Vásquez et al.,[38] on a cross-sectional analysis of 1342 participants, free of diagnosed diabetes that were recruited for the San Juan Overweight Adult Longitudinal Study (SOALS) found an overall agreement between plasma glucose criteria (PGC) and HbA1c criteria was 55.1%. Kappa for diabetes was 0.57 and for prediabetes was 0.22. To investigate whether the percent agreement between the PGC and HbA1c varies according to weight, they stratified the population among overweight and obese participants. The overall percent agreement of the tests remaining similar among overweight was 56.4% and 54.3% for the obese participants.[38]

Despite this high correlation between A1C and OGTT, the tests were not often concordant. Even though some reports propose that HbA1c is useful as a diagnostic criterion of diabetes,[7,8,11,39] others suggest that

its diagnostic usefulness is inferior to standard testing because of a low sensitivity (26, 40-42). Our study showed that only 28.6% of the patients with levels of A1C ≥ 6.5% had 2-hPG >11.1 mmol/L. On the other hand, only 31.6% of the patients with DM diagnosed by the OGTT had A1C levels ≥ 6.5%. This discordance among the tests was also found in other studies. In the Rancho Bernardo study, 85% of participants with A1C ≥ 6.5% were not classified as diabetic by ADA criteria and one-third of the participants with diabetes by ADA criteria would be classified as normoglycemic by A1C, i.e., a significant proportion of misclassification.[25] Analysis of U.S. National Health and Nutrition Examination Survey (NHANES) data revealed that 50–60% of patients with FPG ≥ 7 mmol/l had A1C < 6.5%, suggesting that A1C might reduce the number of people diagnosed as having diabetes compared to the current glycemic criteria in use.[28,43]

Because the measurements of glucose levels and A1C reflect different aspects of glucose metabolism, this was already expected. Thus, FPG may mostly reflect hepatic insulin resistance and a dysfunction in early phase of insulin secretion whereas post-challenge hyperglycemia may predominately reflect muscle insulin resistance and defects in early-phase and late-phase insulin secretion.[44] By contrast, A1C may represent chronic exposure to basal and postprandial hyperglycemia and may reflect a combination of metabolic defects underlying type 2 diabetes.[7,45]

Besides, the A1C cut point of 6.5% emphasizes specificity rather than sensitivity, thus the use of A1C ≥6.5% identifies substantially fewer individuals as having diabetes than do FPG or OGTT.[7]

We believe that the patients with A1C levels ≥ 6.5% and OGTT not diagnostic of type 2 diabetes should be examined for diabetic microvascular complications. Sabanayagam C et al.,[46] found that higher levels of A1C were associated with microvascular complications. They support the use of an A1C cut-off point between 6.6 and 7.0% in diagnosing diabetes. Cut-off points in this range were best for the identification of individuals with mild and moderate retinopathy.[46] Recently, Costa B and colleagues recommend that that all people attending primary healthcare facilities should be screened for diabetes risk using the FINDRISC. And a shift from the glucose-based diagnosis to the A1C-based diagnosis would significantly reduce not only the estimated diabetes prevalence but also the FINDRISC capability to screen for glucose abnormalities. Consequently, it is desirable that new adaptations of this score consider the real possibility of diagnosing by the A1C.[47]

The value of OGTT in diagnosing diabetes lies in the close relationship of 2hPG with the risk of diabetic complications. Elevated HbA1c level has also been linked to a higher risk of diabetic retinopathy,[48] nephropathy,[49] cardiovascular diseases[50,51] and premature death.[52,53] Other studies must be done to establish the best cut point of A1C that correlates with specific diabetic microvascular complications, especially when the diagnostic tests are discordant.

To our knowledge, this is the first report that compares the relationship of A1C levels with the results of OGTT and FPG on a group of Brazilian subjects with IFG that willingly presented to an endocrinologic check-up. Nevertheless, our study has some limitations. First, the small sample size and the low number of incident cases of type 2 diabetes diminishing the statistical power. Second, we took a single measurement of A1C, which could potentially misclassify chronic glucose exposure. We did not make hemoglobin electrophoresis to definitely exclude hemoglobinopathies. We did not correlate our finding with diabetic microvascular complications. Our

results apply only to patients without known hemoglobinopathies, pregnancy, anemia or chronic renal disease.

In summary, considering the use of A1C and OGTT to diagnose type 2 diabetes in patients with IFG, the agreement between them was moderate (71%). On our study, some patients with IFG (15 of the 119) would only receive the diagnosis of DM by the A1C criteria, if confirmed. On the other hand, a similar number of subjects (13 of 119), that had a level of 2-hPG >11.1 mmol/L could miss the diagnosis of DM by reliance the screening only on A1C and FPG determinations. These findings demonstrate that one method may identify different individuals than the other. Maybe, it is too soon to consider A1C as a substitute exam for OGTT and there is yet no single assay related to hyperglycemia that can be taken as the "gold standard".

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Conflicts of interest

The author declares there is no conflict of interest.

References

1. Huang ES, Basu A, O'Grady M, et al. Projecting the Future Diabetes Population Size and Related Costs for the U.S. *Diabetes Care*. 2009;32(12):2225–2229.

2. Harris MI. Undiagnosed NIDDM: clinical and public health issues. *Diabetes Care*. 1993;16(4):642–652.

3. Harris MI, Klein R, Welborn TA, et al. Onset of NIDDM occurs at least 4–7 yr before clinical diagnosis. *Diabetes Care*. 1992;15(7):815–819.

4. Thompson TJ, Engelgau MM, Hegazy M, et al. The onset of NIDDM and its relationship to clinical diagnosis n Egyptian adults. *Diabet Med*. 1996;13(4):337–340.

5. Saudek CD, Herman WH, Sacks DB, et al. A new look at screening and diagnosing diabetes mellitus. *J Clin Endocrinol Metab*. 2008;93(7):2447–2453.

6. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 1997;20(7):1183–1197.

7. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care*. 2009;32(7):1327–1334.

8. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care*. 2010;33(Suppl 1):S11–S61.

9. National Glycohemoglobin Standardization Program.

10. Sacks DB. Measurement of Hemoglobin A1c. *Diabetes Care*. 2012;35(12):2674–2680.

11. Bennett CM, Guo M, Dharmage SC. HbA(1c) as a screening tool for detection of type 2 diabetes: a systematic review. *Diabet Med*. 2007;24(4):333–343.

12. Barr RG, Nathan DM, Meigs JB, et al. Tests of glycemia for the diagnosis of type 2 diabetes mellitus. *Ann Intern Med*. 2002;137(4):263–272.

13. McCance DR, Hanson RL, Pettitt DJ, et al. Diagnosing diabetes mellitus: do we need new criteria? *Diabetologia*. 1997;40(3):247–255.

14. McCance DR, Hanson RL, Charles MA, et al. Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. *BMJ.* 1994;308(6940):1323–1328.

15. Engelgau MM, Thompson TJ, Herman WH, et al. Comparison of fasting and 2–hour glucose and HbA1c levels for diagnosing diabetes. Diagnostic criteria and performance revisited. *Diabetes Care.* 1997;20(5):785–791.

16. Cheng YJ, Gregg EW, Geiss LS, et al. Association of A1C and Fasting Plasma Glucose Levels with Diabetic Retinopathy Prevalence in the U.S. Population. *Diabetes Care.* 2009;32(11):2027–2032.

17. Vistisen D, Colagiuri S, Borch Johnsen K, et al. Bimodal distribution of glucose is not universally useful for diagnosing diabetes. *Diabetes Care.* 2009;32(3):397–403.

18. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med.* 2010;362(9):800–811.

19. Pradhan AD, Rifai N, Buring JE, et al. Hemoglobin A1c predicts diabetes but not cardiovascular disease in nondiabetic women. *Am J Med.* 2007;120(8):720–727.

20. Yuqian B, Xiaojing M, Huating Li, et al. Glycated haemoglobin A1c for diagnosing diabetes in Chinese population: cross–sectional epidemiological survey. *BMJ.* 2010;340(7757):2249c.

21. Zhou X, Pang Z, Gao W, et al. Performance of an A1C and fasting capillary blood glucose test for screening newly diagnosed diabetes and pre–diabetes defined by an oral glucose tolerance test in Qingdao, China. *Diabetes Care.* 2010;33(3):545–550.

22. Picón MJ, Murri M, Muñoz A, et al. Hemoglobin A1c versus oral glucose tolerance test in postpartum diabetes screening. *Diabetes Care.* 2012;35(8):1648–1653.

23. Pinelli NR, Jantz AS, Martin ET, et al. Sensitivity and specificity of glycated hemoglobin as a diagnostic test for diabetes and prediabetes in Arabs. *J Clin Endocrinol Metab.* 2011;96(10):E1680–E1683.

24. Saukkonen T, Cederberg H, Jokelainen J, et al. Limited overlap between intermediate hyperglycemia as defined by A1C 5.7–6.4%, impaired fasting glucose, and impaired glucose tolerance. *Diabetes Care.* 2011;34(10):2314–2316.

25. Kramer CK, Araneta MR, Barrett–Connor E. A1C and Diabetes Diagnosis: The Rancho Bernardo Study. *Diabetes Care.* 2010;33(1):101–103.

26. Fajans SS, Herman WH, Oral EA. Insufficient sensitivity of hemoglobin A1C determination in diagnosis or screening of early diabetic states. Metabolism. 2010;60(1):86–91.

27. Li J, Ma H, Na L, et al. Increased Hemoglobin A1c Threshold for Prediabetes Remarkably Improving the Agreement Between A1c and Oral Glucose Tolerance Test Criteria in Obese Population. *J Clin Endocrinol Metab.* 2015;100(5):1997–2005.

28. Bloomgarden ZT. A1C: Recommendations, Debates, and Questions. *Diabetes Care.* 2009;32(12):141–147e.

29. Little RR, England JD, Wiedmeyer HM, et al. Glycated haemoglobin predicts progression to diabetes mellitus in Pima Indians with impaired glucose tolerance. *Diabetologia.* 1994;37(3):252–256.

30. Peters AL, Davidson MB, Schriger DL, et al. A clinical approach for the diagnosis of diabetes mellitus: an analysis using glycosylated hemoglobin levels. Meta–Analysis Research Group on the Diagnosis of Diabetes Using Glycated Hemoglobin Levels. *JAMA..* 1996;276(15):1246–1252.

31. Droumaguet C, Balkau B, Simon D, et al. Use of HbA1c in predicting progression to diabetes in French men and women: data from an epidemiological study on the insulin resistance syndrome (DESIR). *Diabetes Care.* 2006;29(7):1619–1625.

32. Perry RC, Shankar RR, Fineberg N, et al. HbA1c measurement improves the detection of type 2 diabetes in high–risk individuals with nondiagnostic levels of fasting plasma glucose: The early diabetes intervention program (EDIP). *Diabetes Care.* 2011;24(3):465–471.

33. Rohlfing C, Wiedmeyer HM, Little R, et al. Biological variation of glycohemoglobin. *Clin Chem.* 2002;48(7):1116–1118.

34. Pani LN, Korenda L, Meigs JB, et al. Effects of aging on A1C levels in individuals without diabetes. *Diabetes Care.* 2008;31(10):1991–1996.

35. Radin MS. Pitfalls in Hemoglobin A1c Measurement: When Results may be Misleading. *J Gen Intern Med.* 2013;29(2):388–394.

36. Zhang X, Gregg EW, Williamson DF, et al. A1C Level and Future Risk of Diabetes: A Systematic Review. *Diabetes Care.* 2010;33(7):1665–1673.

37. Marini MA, Succurro E, Arturi F, et al. Comparison of A1C, fasting and 2–h post–load plasma glucose criteria to diagnose diabetes in Italian Caucasians. *Nutr Metab Cardiovasc Dis.* 2012;22(7):561–566.

38. Vega–Vázquez MA, Ramírez–Vick M, Muñoz–Torres FJ, et al. Comparing glucose and hemoglobin A1c diagnostic tests among a high metabolic risk Hispanic population. *Diabetes Metab Res Rev.* 2017;33(4):2874e.

39. Santos–Rey K, Fernández Riejos P, Mateo J, et al. Glycated hemoglobin vs. the oral glucose tolerance test for the exclusion of impaired glucose tolerance in high□risk individuals. *Clin Chem Lab Med.* 20101;48(12):1719–1722.

40. Khoo J, Tay TL, Foo JP, et al. Sensitivity of A1c to diagnose diabetes is decreased in high□risk older Southeast Asians. *J Diabetes Complications.* 2012;26(2):99–101.

41. Bianchi C, Miccoli R, Bonadonna RC, et al. Pathogenetic mechanism and cardiovascular risk differences between HbA1c and oral glucose tolerance test for the diagnosis of glucose tolerance. *Diabetes Care.* 2012;35(12):2607–2612.

42. Kim HJ, Choi EY, Park EW, et al. The utility of HbA1c as a diagnostic criterion of diabetes. *Korean J Fam Med.* 2011;32(7):383–389.

43. Pajunen P, Peltonen M, Eriksson JG, et al. HbA$_{1c}$ in diagnosing and predicting Type 2 diabetes in impaired glucose tolerance: the Finnish Diabetes Prevention Study. *Diabet Med.* 2010;28(1):36–42.

44. Nathan DM, Davidson MB, DeFronzo RA, et al. Impaired fasting glucose and impaired glucose tolerance. Implications for care. *Diabetes Care.* 2007;30(3):753–759.

45. Giaccari A, Sorice G, Muscogiuri G. Glucose toxicity: the leading actor in the pathogenesis and clinical history of type 2 diabetes e mechanisms and potentials for treatment. *Nutr Metab Cardiovasc Dis.* 2009;19(5):365e77.

46. Sabanayagam C, Liew G, Tai ES, et al. Relationship between glycated hemoglobin and microvascular complications: is there a natural cut–off point for the diagnosis of diabetes. *Diabetologia.* 2009;52(7):1279–1289.

47. Costa B, Barrio F, Piñol JL, et al. Shifting from glucose diagnosis to the new Hba1c diagnosis reduces the capability of the Finnish Diabetes Risk Score (FINDRISC) to screen for glucose abnormalities within a real–life primary healthcare preventive strategy. *BMC Med.* 2013;21:11–45.

48. Xin Z, Yuan MX, Li HX, et al. Evaluation for fasting and 2–hour glucose and HbA1c for diagnosing diabetes based on prevalence of retinopathy in a Chinese population. *PLoS One.* 2012;7(7):40610e.

49. McCarter RJ, Hempe JM, Gomez R, et al. Biological variation in HbA1c predicts risk of retinopathy and nephropathy in type 1 diabetes. *Diabetes Care.* 2004;27(6):1259–1264.

50. Xu L, Chan WM, Hui YF, et al. Association between HbA1c and cardiovascular disease mortality in older Hong Kong Chinese with diabetes. *Diabet Med*. 2012;29(3):393–398.

51. Khaw KT, Wareham N, Bingham S, et al. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Intern Med.* 2004;141(6):413–420.

52. Kerr D, Partridge H, Knott J, et al. HbA1c 3 months after diagnosis predicts premature mortality in patients with new onset type 2 diabetes. *Diabet Med.* 2007;28(12):1520–1524.

53. Zoungas S, Chalmers J, Ninomiya T, et al. Association of HbA1c levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds. *Diabetologia.* 2012;55(3):636–643.