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Original Research

Glycated Hemoglobin, Albuminuria and Surrogate Markers of Macrovascular Disease: The Guangzhou Biobank Cohort Study, Cardiovascular Disease Subcohort

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ABSTRACT

Objectives: To explore the clinical utility of glycated hemoglobin (A1C) levels as an early marker of albuminuria, macrovascular disease and subclinical cardiovascular disease in comparison to fasting and postprandial glucose levels in a well-characterized Chinese population with no history of diabetes.
Methods: The study population consisted of 1223 individuals who were enrolled in the Guangzhou Biobank Cohort Study, Cardiovascular Disease Subcohort, and who had undergone oral glucose tolerance tests. The associations between each glycemic measure and albuminuria, carotid intima-media thickness (CIMT) and CIMT-based presence of carotid plaques and aortic arch calcification were assessed by chest radiographs.
Results: The overall prevalence of albuminuria, carotid plaque and any aortic arch calcification was 20.6%, 22.8% and 25.8%, respectively. All 3 glycemia indices were significantly associated with albuminuria, but only 1 (fasting glucose) was associated with carotid plaques. No significant difference was detected among them in the area under the curve for albuminuria (chi-square test; p=0.84), carotid plaques (p=0.28) or calcifications (p=0.29). In sensitivity analysis, adjusted for age and sex, the above findings remained unchanged.
Conclusions: Although there was evidence suggesting differential associations, the performance of the glycemic indices was similar, and their association with macrovascular disease and albuminuria was modest.

Mots clés :
albuminurie
épaisseur de l'intima-média carotidienne
épidémiologie
dépistage à l'aide de l'hémoglobine glyquée
prédiabète
maladie macrovasculaire
complications du diabète

RÉSUMÉ

Objectifs : Comparer l'utilité clinique des concentrations de l'hémoglobine glyquée (A1c) comme marqueur précoce de l'albuminurie, de la maladie macrovasculaire et de la maladie cardiovasculaire infraclinique aux concentrations de la glycémie à jeun et de la glycémie postprandiale au sein d'une population chinoise bien définie sans antécédents de diabète.
Méthodes : La population faisant l'objet de l'étude était composée de 1223 individus inscrits à la Guangzhou Biobank Cohort Study-Cardiovascular Disease Subcohort qui avaient subi des épreuves d'hyperglycémie provoquée par voie orale. Les associations entre chacune des mesures de la glycémie et l'albuminurie, l'épaisseur de l'intima-média carotidienne (ÉIMC) et la présence de plaques carotidiennes en fonction de l'ÉIMC et la calcification de l'arc aortique étaient évaluées au moyen de radiographies pulmonaires.
Résultats : La prévalence globale de l'albuminurie, de la plaque carotidienne et des calcifications de l'arc aortique était respectivement de 20,6 %, 22,8 % et de 25,8 %. Les 3 indices glycémiques étaient significativement associés à l'albuminurie, mais seulement 1 (la glycémie à jeun) était associé aux plaques carotidiennes. L'aire sous la courbe pour l'albuminurie (test du chi carré; p=0,84), les plaques carotidiennes (p=0,28) ou les calcifications (p=0,29) ne montrait aucune différence significative entre elles. À l'analyse de sensibilité, ajustée selon l'âge et le sexe, les résultats ci-dessus demeuraient inchangés.

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Conclusions : Bien que des données probantes indiquaient des associations différentielles, la performance des indices glycémiques était similaire, et leur association à la maladie macrovasculaire et à l'albuminurie était modeste.

Introduction

Current diagnostic criteria for diabetes mellitus are based on the observation that microvascular complications occur above a threshold level of hyperglycemia that can be used to differentiate people with and without diabetes (1). Those criteria were derived from cross-sectional epidemiologic studies that examined diabetes-specific retinopathy across a range of glycemic levels (2). Glycated hemoglobin (A1C) levels have been introduced as alternative diagnostic criteria for diabetes diagnosis (conditional recommendation) on the basis of evidence suggesting their association with diabetes-specific retinopathy as well as favourable measurement characteristics, namely, reproducibility, independence from the fasting state and reflection of glycemia over the course of the past 3 months (3).

However, it has been advocated that A1C may not be associated only with microvascular (4) but also with macrovascular outcomes (5). A1C levels have been found to be independent predictors of cardiovascular mortality and disease in individuals without diabetes (6,7) and were associated with the risk for cardiovascular disease, in contrast to fasting glucose levels, in a community-based population of adults without diabetes (5). Furthermore, describing the association between A1C levels and microalbuminuria, a relatively underreported outcome of microvascular disease compared to retinopathy, is thought to be clinically relevant, especially in light of evidence suggesting that microalbuminuria is a strong predictor of mortality (8) and cardiovascular outcomes in type 2 diabetes (9). Despite this, it remains uncertain whether A1C levels are more informative, in terms of micro- and macrovascular complications and measures of dysglycemia, than fasting or postload glucose levels, and whether they accurately reflect processes relevant to vascular damage in response to glycation (10); in other words, subclinical cardiovascular disease (CVD).

Thus, the primary aim of the present study was to explore the clinical utility of A1C levels as early markers of albuminuria, macrovascular disease (aortic arch calcifications) and subclinical CVD (carotid intima media thickness) (CIMT) in comparison to other glycemic indices. We used data from a well-characterized, homogeneous population.

Methods

Study population

The Guangzhou Biobank Cohort Study is an ongoing collaboration among the Guangzhou Number 12 Hospital, Guangzhou, China; the University of Hong Kong, Hong Kong; and the University of Birmingham, Birmingham, United Kingdom. The Guangzhou Biobank Cohort Study: Cardiovascular Disease Subcohort consists of subjects who have been intensively phenotyped for a range of surrogate markers of vascular disease as well as coagulatory and inflammatory markers (11). The study participants were recruited from a community welfare network of 107,000 members on a voluntary basis, after the exclusion of those with life-threatening diseases. A total of 1996 potentially eligible subjects in the Guangzhou Biobank Cohort Study: Cardiovascular Disease Subcohort were initially considered for the study. To exclude the confounding effects of anemia and chronic kidney disease on A1C values (12), the subjects with evidence of significant anemia (A1C levels <11 g/dL for females or <12 g/dL for males) or impaired renal function (serum creatinine >100 μmol/L for females or ≥120 μmol/L for males) were not included in the study population. Subjects with known histories of diabetes mellitus were also excluded. Because of financial constraints, from a total of 1834 potentially eligible subjects phenotyped for vascular disease during phase III of the original study, oral glucose tolerance tests (OGTTs) were performed in a random sample of 1232 of the participants, and all 3 glycemia measures were available for 1223 individuals, who constituted the study population. The measurements of both independent (i.e. A1C levels) and dependent variables (i.e. albuminuria) were conducted concurrently.

Criteria and definitions

Microalbuminuria was defined as an albumin-creatinine ratio of 31 to 220 mg/g (3.5 to 25 mg/mmol) in women and of 22 to 220 mg/g (2.5 to 25 mg/mmol) in males. Macroalbuminuria was defined as an albumin-creatinine ratio of 220 mg/g or greater (≥25.0 mg/mmol). Albuminuria was defined by the presence of either micro- or macroalbuminuria. On the basis of the fasting plasma glucose (FPG) and postprandial glucose (2hPG) levels, patients were diagnosed with diabetes if FPG levels were 7.0 mmol/L (126 mg/dL) or above or if 2hPG levels were 11.1 mmol/L or above (200 mg/dL), they were diagnosed with impaired glucose tolerance (IGT) if 2hPG levels were between 7.8 and 11.1 mmol/L (140 to 199 mg/dL), with impaired fasting glucose (IFG) levels if FPG levels were between 5.6 and 7.0 mmol/L (100 to 26 mg/dL) and with normal glycemia if FPG and 2hPG levels were below 5.6 and below 7.8 mmol/L, respectively, according to the criteria of the American Diabetes Association. On the basis of the association's criteria for the interpretation of A1C measurements, subjects were classified into 3 states: diabetes (≥6.5%), impaired A1C levels (5.7% to 6.4%) or normal glycemia (<5.7%). The quantitative insulin-sensitivity check index (QUICKI) was calculated as 1/log (fasting insulin in μU/mL) + log (FPG in mg/dL).

Measurements

A1C levels were measured using ELISA (DiaSTATHemoglobinA1C Program; Bio-Rad Laboratories, Hercules, California, United States), and all other fasting parameters, including fasting FPG, microalbuminuria, insulin, lipid panel and high-sensitivity C-reactive protein, were measured in the Clinical Laboratory of the Guangzhou Number 12 Hospital using standardized procedures (11). The standardized 2-hour protocol for the OGTT was followed, using 75 grams of anhydrous dextrose dissolved in 250 to 300 mL of boiled water, after an overnight fast.

CIMT was measured by a B-mode ultrasound using an ATL HDI-3000 mainframe with a high-resolution, linear phased array ultrasound transducer (frequency 5 to 12 MHz) (13). Three scanning angles were used, with the image focused on the posterior wall, and the images were recorded from the angle showing the greatest distance between the lumen-intima interface and the media-adventitia interface. All scans were analyzed by the same investigator, who was blinded to the subjects' identities. The total plaque areas were summed for areas of all plaques observed. The presence of carotid plaques was defined by a CIMT value of 1.2 mm or more. To detect the presence of any aortic arch calcification, all participants were given posterior-anterior plain chest x-ray radiographs obtained during deep inspiration in a standing position by using a Toshiba