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Glycated hemoglobin and long-term prognosis in patients with suspected stable angina pectoris without diabetes mellitus: A prospective cohort study

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ABSTRACT

Objective: Associations of glycated hemoglobin A1c (HbA1c) levels to incident coronary and cardiovascular events among non-diabetic patients with coronary artery disease are unclear. We investigated relations of HbA1c to long-term prognosis in such patients.

Methods: A prospective cohort of 2519 patients undergoing elective coronary angiography for suspected stable angina pectoris (SAP) was divided into pre-defined categories according to HbA1c (%) levels (<5.0, 5.0–5.6 (reference), 5.7–6.4), and followed for median 4.9 years. The primary end-point was major coronary events (including non-fatal and fatal acute myocardial infarctions, and sudden cardiac death). Secondary end-points were death from cardiovascular disease (CVD) and all-cause mortality. Hazard ratios (HRs) (95% confidence intervals [CIs]) were obtained by Cox regression.

Results: Median age at inclusion was 62 years, 73% were males, median HbA1c was 5.6% and random plasma-glucose 5.4 mmol/L. After multivariate adjustment, HbA1c levels within the pre-diabetic range were not associated with risk of major coronary events, HR (95% CI): 1.13 (0.79–1.62); $P = 0.49$, death from CVD or all-cause mortality HR (95% CI): 0.95 (0.55–1.66) and 1.04 (0.70–1.53), respectively; $P \geq 0.85$. Similarly, there was no significant association between HbA1c values within the lowest category and risk of study outcomes, ($P \geq 0.18$).

Conclusion: In non-diabetic patients with suspected SAP, there was no overall association between HbA1c levels and prognosis, questioning an independent role of glycemia in the pathogenesis of atherosclerotic complications in these patients.

1. Introduction

Hemoglobin A1c (HbA1c) is a marker of glycemia, reflecting the average plasma glucose concentration over the previous 8–12 weeks [1]. It has been extensively applied for the monitoring and control of diabetes mellitus and was recently introduced as a diagnostic test defining a pre-diabetic state and overt diabetes, at 5.7% and 6.5%, respectively [1].

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The INTERHEART study of multiple ethnicities, showed a strong dose–response relationship between HbA1c and risk of acute myocardial infarction (AMI), independent of the presence of self-reported diabetes [2]. Further, elevated HbA1c levels, even within the pre-diabetic range, have been associated with increased risk of all-cause mortality and cardiovascular disease (CVD) in general populations [3,4]. However, it is not established whether the associations to macrovascular disease reflect glucose levels per se, or is related to the frequent co-occurrence of pre-diabetes with the metabolic syndrome [5]. Interestingly, low HbA1c levels have also been associated with increased risk of mortality [4,6], although results have been inconsistent [7] and underlying mechanisms remain unknown.

The prognostic implications of HbA1c levels in patients without diabetes, but with pre-existent coronary artery disease (CAD) have not been extensively evaluated. Associations of HbA1c to all-cause mortality have been demonstrated in such patients [8], but it is not clear whether the unfavorable prognosis is attributable to CVD [9].

We therefore aimed to evaluate the relations of HbA1c levels with risk of major coronary events, CVD mortality and all-cause mortality in a large cohort of patients without diabetes, referred to coronary angiography for suspected stable angina pectoris (SAP).

2. Methods

2.1. Study population

The source population consists of 4164 adults who underwent elective coronary angiography for suspected SAP in either of two Norwegian university hospitals between 2000 and 2004 [10]. A total of 2573 (61.8%) were originally included in the Western Norway B-Vitamin Intervention Trial (WENBIT; ClinicalTrials.gov Identifier: NCT00354081) [11].

For the present prospective cohort study, 1603 (38.5%) patients with diabetes, defined according to American Diabetes Association criteria [1], and 42 (1.0%) patients with missing HbA1c measurements were excluded, leaving 2519 (60.5%) participants eligible for the final analyses.

The study fulfilled the Declaration of Helsinki and was approved by The Regional Committee for Medical and Health Research Ethics (approval number 2010/1880) and The Norwegian Data Protection Authority. All participants provided written informed consents.

2.2. Baseline data

Information on medical history, cardiovascular risk factors and current medication were provided through a self-administered questionnaire completed by each patient, as previously reported [11]. Trained study personnel validated completed questionnaires against medical records. Fasting referred to not having ingested any food or beverage 6 h prior to blood sampling. Left ventricular ejection fraction, angiographic extent of CAD and smoking status was assessed as previously described [10]. Body mass index (BMI) was calculated by dividing weight by height squared (kg/m^2).

2.3. Biochemical analyses

Standard blood laboratory parameters were analyzed in fresh samples according to routine protocols at the referring hospitals. Study specific samples were collected together with routine blood samples before coronary angiography, and stored at −80 °C until analysis. Reagent kits of type Tina-quant® were used for measurement of apolipoprotein A-I and apolipoprotein B. C-reactive protein (CRP) (latex, high sensitive assay) were obtained from Roche Diagnostics (GmbH, Mannheim, Germany) and serum measurements on these parameters were done on the Hitachi 917 system (Roche Diagnostics). HbA1c was determined by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry [12] and plasma cotinine by liquid chromatography/tandem mass spectrometry at BEVITAL AS, Bergen, Norway [13]. We measured serum cardiac troponin T using a high sensitive cardiac troponin T assay on Modular E170 (Roche Diagnostics), with 3 ng/L as the lower detection limit. Cobalamin was measured using a microbiological assay [14]. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [15].

2.4. Follow-up and clinical end-points

Information on study end-points was collected as described previously [16]. The primary end-point was major coronary events, which included non-fatal and fatal AMIs, and sudden cardiac death (diagnoses coded I21, I46 and R96 according to the International Statistical Classification of Diseases, 10th version [ICD-10]). Secondary end-points were CVD mortality (causes of death coded I00–I99 according to the ICD-10 system), and all-cause mortality.

Patients were followed up until they experienced an event, or throughout December 31, 2006.

2.5. Statistical analyses

The total cohort was divided into pre-defined categories according to HbA1c levels (%): <5.0, 5.0–5.6 and 5.7–6.4 [17]. Baseline continuous and categorical variables are listed as median (25th, 75th percentile) and counts (%), respectively. The linear trends across HbA1c categories were tested by median quantile regression models [18] for continuous variables and logistic regression for categorical variables.

The associations between HbA1c and risk of study outcomes were explored by Cox proportional hazard regression with the HbA1c range 5.0–5.6% as the reference category. In addition, generalized additive modeling was performed to assess potential risk associations on a continuous scale. The simple model included age and sex as independent variables. Additional covariates for the multivariate model were selected on the basis of clinical relevance and included: current smoking (dichotomous), hypertension (dichotomous), number of significantly stenosed coronary arteries (0–3), left ventricular ejection fraction (continuous), revascularization following angiography (none, percutaneous coronary intervention or coronary artery bypass graft surgery: 0–1), previous AMI (dichotomous), eGFR (continuous), CRP (continuous), BMI (continuous), apolipoprotein A-I (continuous), apolipoprotein B (continuous), and treatment with statins or aspirin (both dichotomous). Additional adjustments for circulating levels of hemoglobin, cobalamin, alanine aminotransferase and aspartate aminotransferase, self-reported weekly alcohol consumption and use of beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor-blockers did not appreciably alter the results and were not included in the final model. We performed log–log plots and plotted Schoenfeld residuals [19] to ensure that the assumption of proportional hazards was not violated.

Statistical power was assessed on the basis of a two-tailed χ^2 test comparing an HbA1c of ≥5.7% versus <5.7% (SamplePower 2.0, SPSS Inc., Chicago, IL). At $\alpha = 0.05$, a power of 97% was obtained for an increase in event rate from 10% to 15% (relative risk 1.5) for the primary end-point major coronary events.

All probability values are two-tailed, with a 5% significance level. Statistical analyses were performed with R 3.0.2 (The R-Foundation for Statistical Computing, Vienna, Austria) [20], the R-packages 'survival' [21] and 'quantreg' [22], and IBM SPSS Statistics 21 (SPSS IBM, NY, USA).