Journal of Diabetes and Its Complications xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Progression of coronary artery calcification is stronger in poorly than in well controlled diabetes: Results from the Heinz Nixdorf Recall Study

Bernd Kowall [a,*], Nils Lehmann [b], Amir-Abbas Mahabadi [c], Susanne Moebus [d], Thomas Budde [e], Rainer Seibel [f], Dietrich Grönemeyer [g], Raimund Erbel [b], Karl-Heinz Jöckel [b], Andreas Stang [a,h]

[a] Center of Clinical Epidemiology, Institute for Medical Informatics, Biometry and Epidemiology, Medical Faculty, University Duisburg-Essen, Essen, Germany
[b] Institute for Medical Informatics, Biometry and Epidemiology, University Clinic Essen, University Duisburg-Essen, Essen, Germany
[c] West-German Heart and Vascular Center Essen, Department of Cardiology, University Clinic Essen, Essen, Germany
[d] Center for Urban Epidemiology, Institute for Medical Informatics, Biometry, and Epidemiology, University Hospital Essen, Essen, Germany
[e] Alfred Krupp Hospital, Essen, Germany
[f] Diagnosticum, Mülheim, Germany
[g] Department of Radiology and Microtherapy, University Witten/Herdecke, Bochum, Germany
[h] School of Public Health, Department of Epidemiology Boston University, 715 Albany Street, Talbot Building, Boston, MA 02118, USA

ARTICLE INFO

Article history:
Received 15 July 2016
Received in revised form 9 August 2016
Accepted 11 August 2016
Available online xxxx

Keywords:
Type 2 diabetes
HbA1c
Coronary artery calcification
Coronary artery calcium
Glycemic control

ABSTRACT

Aim: To assess associations between HbA1c and progression of coronary artery calcification (CAC) in persons with and without diabetes.
Methods: In the Heinz Nixdorf Recall Study, a population-based cohort study in Germany (N = 3453, aged 45–74 years), CAC was assessed by electron-beam tomography at baseline and at 5-year follow-up. At baseline, participants were divided into five groups: poorly (HbA1c ≥ 7.0%) and well (HbA1c < 7.0%) controlled previously known diabetes (group I/II); no previously known diabetes with HbA1c ≥6.5% (group III), HbA1c 5.7–6.4% (group IV), and HbA1c <5.7% (group V). We fitted linear, logistic and robust Poisson regression models to assess associations between diabetes group and PF_5 (factor by which CAC after 5-year follow-up is larger than baseline CAC), and categories of CAC change, respectively.
Results: Relative to group V, adjusted percentage increase of the geometric mean of PF_5 (95% CI) was: 69.1% (33.9%;113.6%), 15.4% (−5.6%;41.1%), −4.1% (−22.2%;18.2%), 4.2% (−5.4%;14.8%) for groups I–IV, respectively. The corresponding odds ratios for annual CAC increase ≥100 Agatston units (reference: <10) were 10.0 (4.8;20.6), 4.0 (2.1;7.6), 1.5 (0.7;3.2), and 1.1 (0.7;1.8).
Conclusions: In known diabetes, CAC progression was stronger in poor diabetes control. For newly detected diabetes diagnosed by HbA1c ≥6.5%, associations with CAC progression were weak.

1. Introduction

Type 2 diabetes and prediabetes are associated with an increased risk of cardiovascular events (Ford, Zhao, & Li, 2010; Selvin, Steffes, Zhu, et al., 2010; Tabak, Herder, Rathmann, Brunner, & Kivimäki, 2012; The Emerging Risk Factors Collaboration, 2010). In a meta-analysis of more than 700,000 persons from 102 prospective studies, hazard ratios for persons with diabetes as compared to persons without diabetes were 2.00 (95% confidence interval (CI): 1.83–2.19) for coronary heart disease, and 1.84 (95% CI: 1.59–2.13) for stroke after adjustment for age, sex, smoking, BMI and systolic blood pressure (The Emerging Risk Factors Collaboration, 2010).

Coronary artery calcification (CAC) is a measure of subclinical atherosclerosis, and, moreover, is a strong risk factor of cardiovascular events (Erbel, Möhlenkamp, Moebus, et al., 2010; Joshi, Patel, Blaha, et al., 2016; Kara, Mahabadi, Berg, et al., 2014; Möhlenkamp, Lehmann, Moebus, et al., 2011; Zeb & Budoff, 2015). Moreover, CAC progression was shown to be associated with incident coronary heart disease (Budoff, Young, Lopez, et al., 2013). As increased calcification of the coronary arteries may be one of the mechanistic steps between diabetes and CVD, it is appealing to investigate associations between diabetes and presence or progression of CAC. CAC prevalence and CAC progression, respectively, were larger in persons with diabetes defined by fasting glucose and 2-hour glucose tolerance test in the Framingham Offspring Study and in the Multiethnic Study of Atherosclerosis (Meigs, Larson, D'Agostino, et al., 2002; Wong, Nelson, Granston, et al., 2012). Moreover, prediabetes defined by impaired fasting glucose was shown to be associated cross-sectionally with CAC in the German Heinz Nixdorf Recall Study in adjusted analyses (Moebus, Stang, Möhlenkamp, et al., 2009). In two further

Conflict of interest: The authors declare no conflict of interest.

* Corresponding author at: Center of Clinical Epidemiology, c/o Institute of Medical Informatics, Biometry and Epidemiology (IMIBE), Hufelandstraße 55, 45147 Essen, Germany. Tel.: +49 201 92239 295; fax: +49 201 92239 333.
E-mail address: bernd.kowall@uk-essen.de (B. Kowall).

http://dx.doi.org/10.1016/j.jdiacomp.2016.08.011
1056-8727/

cross-sectional studies, associations between impaired fasting glucose and presence of CAC were either small or disappeared after statistical adjustment (Rutter, Massaro, Hoffmann, O'Donnell, & Fox, 2012; Xing, Neeland, Odette Gore, et al., 2014).

Associations between hemoglobin A1c (HbA1c) and CAC have rarely been examined although HbA1c has a double function: first, it is an established indicator of long-term glycemic control in patients with diabetes (American Diabetes Association, 2016a), and it is of interest whether good glycemic control has a positive impact on CAC progress. Second, HbA1c has now been recommended as a diagnostic criterion of diabetes (American Diabetes Association, 2016b; World Health Organization, 2011; International Expert Committee, 2009). There is no gold standard for defining diabetes, and a diagnostic criterion for the definition of diabetes is only meaningful when subjects who meet the criterion are at a higher risk of diabetes complications (International Expert Committee, 2009). So far, it has not yet been examined whether subjects who meet the new 6.5% HbA1c criterion show stronger CAC progression than those with lower HbA1c levels. Besides cross-sectional studies on the association between HbA1c and CAC (Chang, Yun, Jung, et al., 2013; McNelly, McClelland, Bild, et al., 2009; Xing et al., 2014), there are only few prospective studies (Anand, Lim, Darko, et al., 2007; Budoff, Yu, Nasir, et al., 2005; Carson, Steffes, Carr, et al., 2015). In the two prospective studies on persons with diabetes, one uses a categorical but no continuous criterion for CAC progression (Anand et al., 2007) and the other shows results of unadjusted analyses (Budoff et al., 2005), so there is still need for further analyses.

Our aim was twofold: For persons without previously known diabetes, we assessed how strongly diabetes newly diagnosed by the 6.5% HbA1c criterion is associated with progression of CAC. For persons with previously known diabetes, we assessed how well poor glucose control (measured by HbA1c ≥ 7.0%) is associated with CAC progression.

2. Subjects, materials, and methods

2.1. Study population

The Heinz Nixdorf Recall Study (HNRS) is a population-based prospective cohort study conducted in three large adjacent cities (Bochum, Essen, Mülheim) in the Ruhr-region in Germany. The study rationale and design have been described in detail elsewhere (Schmermund, Möhlenkamp, Stang, et al., 2002). In brief, the cohort comprises a total of 4814 participants (49.8% men, aged 45–76 years). The baseline visits were performed between 2000 and 2003, the 5-year follow-up visits between 2005 and 2008, with a median follow-up of 5.1 years. The 5-year follow-up response was 90.2%. Data assessment at baseline and 5-year follow-up included a self-administered questionnaire, face-to-face interviews, and a physical examination including among others anthropometric measurements and comprehensive laboratory tests.

Subjects with definitive coronary heart disease at baseline (n = 327) were excluded. Of the remaining, only subjects with information on CAC at baseline and follow-up (n = 3675) were eligible for the present analysis. Because stents, bypass surgery and balloon angioplasty may lead to artifacts in CAC measurement, these persons were excluded during 5-year follow-up (n = 154). Moreover, we excluded persons outside the study age range (45–74 at baseline, 50–79 at 5-year follow-up, n = 12), with missing information on covariates (n = 28), and with missing HbA1c values (n = 28). Thus, 3453 subjects form the analysis set. Among these 3453 persons, 1243 had CAC = 0 at baseline. This subgroup of the whole study population was used for analyses with CAC onset as the dependent variable. A flow diagram is shown in the Supplementary material.

The study was approved by the Ethical Committee of the Medical Faculty of the University Clinic Essen. All participants gave their written informed consent.

2.2. Assessment of CAC

CAC was assessed from non-contrast enhanced electron-beam computed tomography (EBCT) scans, performed with a C-100 or C-150 scanner (GE Imatron, South San Francisco, CA, USA) at baseline and follow-up using identical scanning protocols (Erbel, Lehmann, Churzidse, et al., 2014). Prospective ECG-triggering was performed at 80% of the RR-interval. Contiguous 3-mm thick slices from the pulmonary bifurcation to the apex of the heart were obtained in both scans at an image acquisition time of 100 ms. CAC was defined as a focus of at least 4 contiguous pixels with a CT density ≥ 130 Hounsfield Units. The CAC Agatston score was computed by summing the CAC scores of all foci in the epicardial coronary system. The CAC score at baseline was neither communicated to the participants nor to their treating physician.

We implemented a reassessment of CAC scoring as quality control when extreme progression or regression from baseline to 5-year examination was found (CAC at baseline (CAC_BL) ≤10 Agatston units to CAC at the 5-year examination (CAC_5Y) >50 Agatston units, CAC_BL >20 to CAC_5Y ≤10, or, otherwise, >30% or <−7% annual change, accounting for the reproducibility correction factor given by Detrano (Detrano, Anderson, Nelson, et al., 2005). In these cases (n = 244), a reader with several years of experience in evaluation of cardiac EBCT, who was blinded to the risk factor profile of the participants, performed a second reading of CAC score.

2.3. Baseline measurement of HbA1c and covariates

HbA1c was measured using immunonephelometry at 340/700 nm (BNII nephelometer, Dade-Behring, Deerfield, IL, USA). Previously known diabetes was stated if subjects gave a self-report of physician's diagnosis or took antidiabetic drugs (ATC code A10). Data on weight were collected with measuring systems of the company 'seca' (seca gmbh & co. kg, Hamburg, Germany). Body mass index (BMI) was calculated as a participant's weight in kilogram divided by the height squared in meters. Blood pressure was determined from the mean value of the 2nd and 3rd of three measurements taken at least three minutes apart (Omron 705_CP, OMRON, Germany) and classified according to JNC-VII threshold values (Stang, Moebus, Möhlenkamp, et al., 2006). Triglyceride and cholesterol serum concentrations were measured with an automatic analyzer (ADVIA 1650, Siemens Medical Solutions, Erlangen, Germany). Alcohol consumption, smoking status, school education, use of statins (ATC code C10AA), and use of antihypertensives (ATC code C02) were gathered from interviews at baseline examination. Average pure ethanol intake in g/day was estimated from frequencies of drinking beer, wine, sparkling wine, and spirits. Smoking was grouped into three categories (current, former, never smoker) (Jöckel, Lehmann, Jaeger, et al., 2009). School leaving certificates were categorized as low, intermediate and high according to the three school types at secondary level in the three-tiered German school system.

2.4. Statistical analyses

For all regression models, the following categories of HbA1c were used: previously known diabetes with HbA1c ≥7.0%; previously known diabetes with HbA1c <7.0%; no previously known diabetes with HbA1c ≥6.5%; no previously known diabetes with HbA1c 5.7–6.4% which is the new category of increased risk of diabetes in addition to fasting impaired glucose and impaired glucose tolerance as suggested by the American Diabetes Association, (2016b); no previously known diabetes with HbA1c <5.7% (reference category).

In all regression analyses, three models were fitted: a crude one; an age-sex adjusted one; a model adjusted for age, sex, BMI, smoking (never /former/current), alcohol consumption (g/day), school education (low/intermediate/high), systolic blood pressure, diastolic blood

Please cite this article as: Kowall, B., et al., Progression of coronary artery calcification is stronger in poorly than in well controlled diabetes: Results from the Heinz Nixdor..., *Journal of Diabetes and Its Complications* (2016), http://dx.doi.org/10.1016/j.jdiacomp.2016.08.011