International Journal of Cardiology 266 (2018) 250–253

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Impact of optimal glycemic control on the progression of coronary artery calcification in asymptomatic patients with diabetes

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ARTICLE INFO

Article history:
Received 31 October 2017
Received in revised form 19 February 2018
Accepted 23 March 2018

Keywords:
Diabetes mellitus
Optimal glycemic control
Coronary artery calcification

ABSTRACT

Background: Data on the impact of optimal glycemic control (OGC) on the progression of coronary artery calcification, an important marker for future adverse cardiovascular events in individuals with diabetes are limited.
Methods: We investigated 1637 asymptomatic adults with diabetes (56 ± 8 years, 88.8% men) and no history of coronary artery disease or stroke, who underwent serial coronary artery calcium (CAC) screening. The median inter-scan period was 3.0 (2.0–4.4) years. The change in CAC was compared base on OGC status. OGC was defined as a follow-up hemoglobin A1C (HbA1C) of <7.0%, and CAC progression was defined by a square root (√) transformed difference between the baseline and follow-up CAC scores (Δ √transformed CAC) of ≥2.5.
Results: Despite no significant difference in the baseline CAC scores, the incidence of CAC progression was lower in the OGC group than in the non-OGC group (45.4% vs. 51.7%; $p < 0.013$). The two groups differed in the Δ √transformed (OGC, 3.8 ± 6.4; non-OGC, 4.7 ± 6.9; $p = 0.016$) and annualized Δ √transformed CAC (OGC, 1.1 ± 2.4; non-OGC, 1.4 ± 2.6; $p = 0.010$) scores. Subgroup analysis showed that OGC significantly reduced the risk of CAC progression in patients aged <65 years and in: smokers, and patients with a body mass index of <25 kg/m^2, dyslipidemia, and baseline CAC scores between 1–100 and >400. In multivariate regression analysis, OGC was independently associated with a reduced risk of CAC progression (odds ratio, 0.745, 95% confidence interval, 0.601–0.924; $p = 0.007$).
Conclusion: OGC attenuated the progression of coronary artery calcification in asymptomatic patients with diabetes.

1. Introduction

Diabetes is strongly associated with an increased risk of cardiovascular (CV) morbidity and mortality worldwide. It is associated with a two- to three-fold increase in the risk of coronary artery disease [1,2]. Previous epidemiologic data have indicated that poor glycemic control is associated with an increased risk of major CV events [3–5]. Recently, several long-term follow-up studies on patients with diabetes have reported that intensive glucose control is effective for reducing adverse CV outcomes [6,7]. Thus, in clinical practice, the significance of optimal glycemic control (OGC) is emphasized in patients with diabetes.

Coronary artery calcium (CAC) is closely associated with coronary atherosclerotic burden and CV events [8–10]. Moreover, CAC progression has an additive predictive value for mortality compared with baseline CAC scores and traditional CV risk factors [11]. However, limited data are available on the impact of OGC on CAC progression in patients with diabetes. Therefore, the present study aims to evaluate the impact of OGC on CAC progression in asymptomatic patients with diabetes by using serial cardiac computed tomography (CT).

2. Methods

2.1. Study population and design

Data from the Korea Initiatives on Coronary Artery Calcification (KOICA) multicenter registry were analyzed. This is a retrospective, single-ethnicity, multicenter observational registry in a self-referral setting for patients who underwent health checkups at six healthcare centers in South Korea. In total, 93,707 patients were enrolled in the KOICA

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https://doi.org/10.1016/j.ijcard.2018.03.112
0167-5273/

registry from December 2012 to August 2016. Self-reported medical questionnaires were used to obtain information about patients' medical history. All data were obtained during the healthcare center checkup visit. Among the 93,707 patients from this registry, 1637 patients with established diabetes and available follow-up HbA1C level data, and who underwent at least two CAC CT scan examinations, were included in the present study. All patients were categorized into two groups based on a HbA1C cut-off value of 7.0%. Diabetes mellitus (DM) was defined by a fasting glucose level of ≥126 mg/dL, HbA1C level of ≥6.5%, referral diagnosis of DM, or currently receiving antidiabetic treatment [12,13]. OGC was defined as a follow-up HbA1C of <7.0%. Body mass index (BMI) was calculated as weight (kg) ÷ height (m^2). All blood samples were obtained after a minimum of 8-h fast and analyzed for triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and glucose levels. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or treatment with antihypertensive agents. Dyslipidemia was defined as total cholesterol ≥240 mg/dL, LDL ≥130 mg/dL, HDL ≤40 mg/dL, and triglycerides ≥150 mg/dL and/or treatment with lipid-lowering agents. The appropriate institutional review board committees for each healthcare center have approved the study protocol. CAC progression was defined as the square root (√) transformed difference between the baseline and follow-up CAC scores (Δ √transformed CAC score) of ≥2.5, considering inter-scan variability [14]. In all centers, CAC scans were obtained using a >16-slice multi-detector CT scanner (GE 64-slice Lightspeed, Philips Brilliance 256 iCT, Philips Brilliance 40 channel MDCT, and Siemens 16-slice Sensation). All centers utilized standard prospective or retrospective methods. The CAC score was evaluated based on the scoring system from a previously described method [15].

2.2. Statistical analysis

Continuous variables are expressed as means ± standard deviations. Categorical variables are presented as absolute values and proportions. Continuous variables were compared using Student's *t*-test. Categorical variables were compared using the χ^2-test or Fisher's exact test, as appropriate. To identify the impact of OGC on CAC progression, subgroup analysis was performed. Univariate logistic regression analysis was performed to identify the significant clinical factors for CAC progression. Then, multivariate logistic regression analysis was performed to identify the independent predictors for CAC progression after adjusting for all independent variables in the univariate analysis. All statistical analyses were performed using the Statistical Package for the Social Sciences version 19 (SPSS, Chicago, IL), and $p < 0.05$ was considered significant for all analyses.

3. Results

3.1. Baseline characteristics

The mean age of the patients in this study was 56 ± 8 years, and 1453 (88.8%) patients were men. Among them, 1036 (63.3%) and 601 (36.7%) were categorized into OGC and non-OGC groups. In addition, 825 (79.6%) and 380 (63.2%) participants were initially under the same condition in OGC and non-OGC group, respectively. Table 1 describes the baseline characteristics of patients. At enrollment in the present study, the mean ages, BMIs, waist circumferences, and triglyceride levels were significantly higher in the non-OGC group than those in the OGC group. However, the incidence of hypertension was significantly higher in the OGC group than that in the non-OGC group.

3.2. Change in CAC according to OGC status

Table 2 presents the baseline and follow-up CAC scores on OGC status. The median inter-scan period was 3.0 (2.0–4.4) years. The baseline CAC score and categorical CAC score were not significantly different between the two groups. The incidence of CAC progression was significantly lower in the OGC group than that in the non-OGC group (OGC, 45.4%; non-OGC, 51.7%; $p = 0.013$). Both the Δ √transformed (OGC, 3.8 ± 6.4; non-OGC, 4.7 ± 6.9; $p = 0.016$) and annualized Δ √transformed CAC score (OGC, 1.1 ± 2.4; non-OGC, 1.4 ± 2.6; $p = 0.010$) were different between the two groups. The annualized Δ CAC score was also significantly lower in the OGC group than that in the non-OGC group (OGC, 31 ± 108; non-OGC, 44 ± 139; $p = 0.048$). In the OGC group, the incidence of CAC progression was significantly higher in patients with initial HbA1C of ≥7.0% than in those with initial HbA1C <7.0%. However, no significant difference in the incidence of CAC progression was observed in the non-OGC group (Supplementary Fig. 1).

Table 1
Baseline characteristics.

	OGC ($n = 1036$)	Non-OGC ($n = 601$)	*p*
Age, yrs	56 ± 8	55 ± 8	0.003
Male, *n* (%)	916 (88.4)	537 (89.4)	0.564
BMI, kg/m^2	25.1 ± 2.9	25.5 ± 2.9	0.018
Waist circumference, cm	89 ± 8	90 ± 8	0.002
Systolic blood pressure, mmHg	123 ± 16	122 ± 16	0.456
Diastolic blood pressure, mmHg	76 ± 10	76 ± 11	0.326
Hypertension, *n* (%)	613 (60.0)	292 (50.3)	<0.001
Dyslipidemia, *n* (%)	790 (76.3)	456 (75.9)	0.862
Non-smoking, *n* (%)	259 (27.0)	139 (25.7)	0.596
Initial laboratory findings			
Total cholesterol, mg/dL	189 ± 36	190 ± 38	0.683
Triglycerides, mg/dL	146 ± 81	170 ± 116	<0.001
HDL cholesterol, mg/dL	52 ± 17	49 ± 15	<0.001
LDL cholesterol, mg/dL	114 ± 34	115 ± 32	0.492
Calcium, mg/dL	9.1 ± 0.4	9.2 ± 0.4	0.157
Phosphate, mg/dL	3.3 ± 0.6	3.4 ± 0.6	0.283
Creatinine, mg/dL	1.0 ± 0.2	0.9 ± 0.2	0.065
Fasting glucose, mg/dL	119 ± 27	145 ± 40	<0.001
HbA1C, %	6.4 ± 0.9	7.5 ± 1.2	<0.001

Values are given as mean ± standard deviation or number (%).
BMI = body mass index; HbA1C = hemoglobin A1C; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OGC = optimal glycemic control.

3.3. Subgroup analysis for the impact of OGC on CAC progression

Fig. 1 shows the subgroup analysis of the estimated odds ratio (OR) of OGC for CAC progression. OGC was significantly associated with a reduced risk of CAC progression in patients aged <65 years (OR, 0.788; 95% confidence interval [CI], 0.634–0.978; $p = 0.031$) and smokers (OR, 0.769; 95% CI, 0.602–0.984; $p = 0.036$), as well as those with a BMI of <25 kg/m^2 (OR, 0.650; 95% CI, 0.483–0.874; $p = 0.004$), dyslipidemia (OR, 0.791; 95% CI, 0.628–0.997; $p = 0.047$), and baseline categorical CAC scores of 0–100 (OR, 0.736; 95% CI, 0.585–0.926; $p = 0.009$) and > 400 (OR, 0.397; 95% CI, 0.182–0.866; $p = 0.020$).

3.4. Association between clinical factors and CAC progression

Univariate logistic regression analysis showed that age (OR, 1.027; 95% CI, 1.015–1.039; $p < 0.001$), male sex (OR, 1.732; 95% CI, 1.260–2.381; $p = 0.001$), and baseline CAC scores of >100 (OR, 1.678; 95% CI, 1.329–2.119; $p < 0.001$) were associated with an increased risk of CAC progression. However, OGC (OR, 0.774; 95% CI, 0.633–0.947; $p = 0.013$) was associated with a reduced risk of CAC progression. In multivariate logistic regression analysis, age (OR, 1.032; 95% CI, 1.018–1.047;

Table 2
Change in CAC according by glycemic control status.

	OGC ($n = 1036$)	Non-OGC ($n = 601$)	*p*
Baseline			
CAC score	109 ± 313	112 ± 326	0.843
Categorical CAC score			0.714
0–100	798 (77.0)	466 (77.5)	
101–400	168 (16.2)	90 (15.0)	
>400	70 (6.8)	45 (7.5)	
Follow-up			
CAC score	212 ± 393	244 ± 467	0.166
Categorical CAC score			0.091
0–100	615 (59.4)	348 (58.0)	
101–400	262 (25.3)	136 (22.7)	
>400	159 (15.3)	116 (19.3)	
Δ CAC score	103 ± 283	132 ± 297	0.060
Annualized Δ CAC score	31 ± 108	44 ± 139	0.048
Δ √transformed CAC score	3.8 ± 6.4	4.7 ± 6.9	0.016
Annualized Δ √transformed CAC score	1.1 ± 2.4	1.4 ± 2.6	0.010
CAC progression, *n* (%)	470 (45.4)	311 (51.7)	0.013

CAC was defined as Δ √transformed CAC score ≥ 2.5, considering inter-scan variability.
CAC = coronary artery calcium; OGC = optimal glycemic control.