Original Article

Correlation between prediabetes, coronary artery calcification and cardiovascular risk factors: A 5-year retrospective case study

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Received 15 June 2021; revised 21 March 2022; accepted 28 March 2022
doi:10.46475/aseanjr.v23i1.136

Abstract

Objective: To evaluate the correlation between prediabetes, Hemoglobin A1c (HbA1c) 5.7 to 6.4%, cardiovascular risks (determined by Framingham Risk Score: FRS) and the coronary artery calcium score (CACS), by the retrospective analysis of 5 year data documents on PACS, Jan 2015 to Dec 2020.

Materials and Methods: There were 1,639 eligible cases, reviewed by certified radiologists via Picture Archiving and Communication System (PACS), with an asymptomatic condition in the check-up center, divided into two groups: - (1) the prediabetes group, with 756 cases and (2) the non-diabetes group, with 883 cases. The results of vital signs, BMI, CACS, blood test, HbA1c, fasting blood sugar (FBS), lipid profiles, and serum uric acid of all eligible cases were reviewed.

THE ASEAN JOURNAL OF RADIOLOGY
ISSN 2672-9393

Linear regression, t-test, chi-square, and Adjusted Odd ratio were used analyzed the significance and correlation between variables.

Results: (1) Most of the prediabetes participants (456 cases, 60.31%) had an intermediate risk of Framingham Risk Score (FRS). While most of the non-diabetes participants (665 cases, 75.31%) had a low risk of FRS., with a statistical difference (Chi-square, $P < 0.05$), (2) The prediabetes cases were significantly associated with coronary calcification at 2.38 times to the non-diabetic cases [Adjusted Odds Ratio = 2.38 [95% CI (1.98 – 14.98)]., (3) The intermediate cardiovascular risk (FRS) was associated with positive coronary artery calcification at 2.36 times to the low cardiovascular risk [Multivariate adjusted OR = 2.36 (95% CI (1.06 – 5.46)]., and (4) The high cardiovascular risk (FRS) was associated with positive coronary artery calcification at 8.64 times to the low cardiovascular risk [Multivariate adjusted OR = 8.64 (95% CI (2.65 – 18.58)]. Moreover, we found a significant higher serum uric acid in the prediabetes group than the non-diabetes group.

Conclusion: Subclinical prediabetes, among 47 to 62-year-old individuals, with an intermediate risk of FRS was significantly associated with positive coronary calcification (atherosclerosis). The combination of CACS screening with a safety low dose radiation protocol and FRS are of complementary together to evaluate the potential risk of Atherosclerotic Cardiovascular Disease (ASCVD). The benefits of combining CACS and FRS are used for decision making of the statin therapy, according to the ACC/AHA primary prevention guidelines (2019). Moreover, a high serum uric acid (UA) is a new challenging ASCVD risk factor in the present that we found it in prediabetes. The association of UA, cardiometabolic disease, and coronary atherosclerosis needs further studies.

Keywords: Prediabetes, Coronary Artery Calcium Score, Framingham Risk Score.

Introduction

According to the American Diabetes Association [1], prediabetes is a metabolic stage between normal glucose homeostasis and diabetes, by HbA1c value of 5.7 – 6.4%. It can develop diabetes and atherosclerotic cardiovascular disease (ASCVD) in the future. The continuing increase in the prevalence of diabetes mellitus and prediabetes in the general population is predicted to result in a higher incidence of coronary artery disease (CAD), ischemic heart disease (IHD) and Atherosclerotic Cardiovascular Disease (ASCVD).

In 2019, the American Heart Association guideline [2] suggests that coronary artery calcium (CAC) testing may be considered in adults of 40 -75 years of age without diabetes mellitus and with the LDL-C level > 70 to 189 mg/dL at a 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 7.5% to 20%.

In the present, subclinical prediabetes have been increasing in general population which has lifestyle dealing with high glycemic food, high sugar intake, fast foods, oxidative stress, inadequate exercise, and no available time for health checkup.

The benefit of combination of CACS screening with the safety low dose radiation protocol and FRS is an early detection of coronary atherosclerosis and evaluation of the potential risk of Atherosclerotic Cardiovascular Disease (ASCVD). This is an important state of the art for the statin therapy and lifestyle modification, according to the ACC/AHA primary prevention guidelines (2019).

Research objective

The objective the study was to evaluate the correlation between prediabetes (HbA1c 5.7 to 6.4%), cardiovascular risks (determined by Framingham Risk Score: FRS) and coronary artery calcium (CAC), by a retrospective analysis of 5 year data documents, Jan 2015 to Dec 2020.

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ISSN 2672-9393

Materials and methods

Study design, data collection and participants

The participants were asymptomatic cases of a check-up center who were identified by reviewed medical records in PACS (Picture Archive and Communication System) and HIS (Hospital Information System) of Kasemrad International Hospital, Thailand, during Jan 2015 to December 2020. All cases of CACS received scan by a 256-slice iCT scanner Philips with the standard protocol of CACS. All cases of CACS were interpreted by certified radiologists. This research was approved by the Human Research Ethics Review Board of Dhurakij Pundit University since March 24, 2021.

Inclusion criteria were cases of the check-up center with CACS, during January 2015 to December 2020, who had less HbA1c than 6.5% and less fasting blood sugar (FBS) than 126 mg/dL and had a blood test of lipid profiles and uric acid.

Exclusion criteria were known cases of ischemic heart disease, coronary balloon, coronary stent, diabetes mellitus, hypertension, autoimmune disease, gout, cancer, advanced renal disease (GFR < 40 ml/minutes), liver disease, statin therapy, antihypertensive therapy, steroid therapy, and received bisphosphonates.

Participants were classified into two groups: (1) non-diabetic group: HbA1c < 5.7% and FBS < 100 mg/dL and (2) prediabetes group: HbA1c 5.7 to 6.4% and FBS < 126 mg/dL

The CT coronary calcium (CAC) score was classified into four levels, as follows: level 1 CAC = 0 (extremely low risk), level 2 CAC is 1-10 (low risk), level 3 CAC is 11-100 (moderate risk), level 4 CAC is 101-400 (high risk), and level 5 CAC > 400 (extremely high risk for coronary artery disease).

The percentage of Glycated hemoglobin (HbA1c) was classified into four intervals: class interval 1: HbA1c ≤ 5.4%, class interval 2: 5.4% < HbA1c <5.7%, class interval 3:5.7% ≤ HbA1c < 5.9%, and class interval 4: 5.9% ≤ HbA1c ≤ 6.4%

Framingham Risk Score (FRS) was classified to three categories: category 1: FRS ≤ 10% (low risk of CVD), category 2: 10% < FRS ≤ 19% (Intermediate risk for CVD), and category 3: FRS ≥ 20% (High risk for CVD)

Statistics used were *t* test, Chi-square, Cramer's V, and the Logistic Regression Model.

The adjustment of confounding factors between groups was used by adjusting the Odd Ratio.

The difference of a 10-year mean age between the two groups in the study was adjusted by the weighted factor of FRS in each group.

Results

There were 1,639 eligible cases, reviewed on PACS, divided into two groups: (1) the prediabetes group, with 756 cases and (2) the non-diabetes group, with 883 cases. The mean age of the prediabetes group, 54.84 ± 6.87 years, was older than the non-diabetes group, 44.82 ± 7.83 years. The BMI of the prediabetes group, with the average of 27.9 kg/m^2, was significantly higher than that of the non-diabetic group with the average of 21.6 kg/m^2, (P-value = 0.036). The total cholesterol and LDL of the prediabetes group, 199.50 ± 36.7mg/dL and 142 ± 14.8 mg/dL, were significantly higher than those of the non-diabetic group, 158.40 ± 34.9mg/dL and 98 ± 12.8mg/dL, P-value = 0.012 and 0.023, respectively, as seen in Table 1.

Most of the prediabetes participants (456 cases, 60.31%) had an intermediate cardiovascular risk score (Framingham Risk Score: FRS). While most of the non-diabetes participants (665 cases, 75.31%) had low risk of FRS., with statistical difference (Chi-square, P < 0.05), seen in Table 2.

Most of the CACS range in the prediabetes group was 11-100 (272 cases, 35.9%). Most of the CACS in the non-diabetes group was zero (743 cases, 84.1%).

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ISSN 2672-9393

Overall, the highest range of CACS among the participants was zero (926 cases from 1,639cases, 56.49%), and then the CACS 11-100 (326 cases, 19.89%), seen in Table 3, Figure 1.

There was a significant relationship between the diabetic status (prediabetes and non-diabetes) and the presence of coronary artery calcification, with adjusted Odds Ratio of 2.38 [95% CI (1.98– 14.46)]. That means in cases of prediabetes, there was 2.38 times more to present with coronary artery calcification.

The intermediate cardiovascular risk (FRS) was associated with positive coronary artery calcification at 2.36 times to the low cardiovascular risk [Multivariate adjusted OR = 2.36 (95% CI (1.06 – 5.46)]. The high cardiovascular risk (FRS) was associated with positive coronary artery calcification at 8.64 times to the low cardiovascular risk [Multivariate adjusted OR = 8.64 (95% CI (2.65 – 18.58)], seen in Table 4.

Table 1. *Baseline characteristics of the study participants.*

Demographic Characteristics	Prediabetes (n = 756)	Non-diabetes (n = 883)	P-value
Age, mean (SD)	54.84 ± 6.87	44.82 ± 7.83	0.003*
Male (%) / Female (%)	416 (55%) / 340 (45%)	399 (46%) / 484 (54%)	0.47
HbA1c, mean (range)	6.2 (5.7 – 6.4%)	5.1 (4.8 - 5.6%)	< 0.001*
Fasting Blood Sugar (mg/dL), mean (range)	112 (100 – 124)	91 (86 - 99)	< .0001*
History of smoking, n (%)	98 (13%)	101 (12%)	0.45
Total Cholesterol (mg/dL), mean (SD)	199.50 (36.7)	158.40 (34.9)	0.012*
HDL (mg/dL), mean (SD)	48.3 (13.6)	51.4 (10.2)	0.15
LDL (mg/dL), mean (SD)	142 (14.8)	98 (12.8)	0.023*
Triglyceride (mg/dL), mean (SD)	144 (28.8)	136 (26.4)	0.14
Systolic Blood Pressure	128 (8.6)	118 (6.8)	0.51
(mmHg), mean (SD)	128 (8.6)	118 (6.8)	0.51
BMI (Kg/m^2), median (IQR)	27.9 (7.3)	21.6 (5.2)	0.036*
Uric acid (mg/dL), mean (SD)	5.28(1.38)	3.82 (1.13)	<0.001*

** P-value < 0.05*

Table 2. *Percentage of cardiovascular risk by Framingham Risk Score (FRS) in prediabetes and non-diabetes.*

Framingham Risk Score (FRS)	Pre-diabetes n (%)	Non-diabetes n (%)	Total	P-value
Low Risk (< 10%)	278 (36.77%)	665 (75.31%)	**943**	0.036*
Intermediate Risk (10-19%)	456 (60.31%)	211(23.59%)	**667**	0.016*
High Risk (≥20%)	22 (2.91%)	7 (0.79%)	**29**	0.057
Total	**756**	**883**	**1,639**	

** P-value < 0.05*

Table 3. *Percentage of CACS in prediabetes and non-diabetes.*

CACS	Pre-diabetes Cases (n, %)	Non-diabetes Cases (n, %)	P-value
CACS = 0	183 (24.2%)	743 (84.1%)	**0.016***
CACS 1 -10	174 (23.0%)	84 (9.5%)	**0.367**
CACS 11-100	272 (35.9%)	54 (6.1%)	**0.013***
CACS 101-400	118 (15.6%)	2 (0.2%)	**0.002***
CACS > 400	9 (1.2%)	0	**< 0.001***
Total	**756**	**883**	**1,639**

** P-value < 0.05*

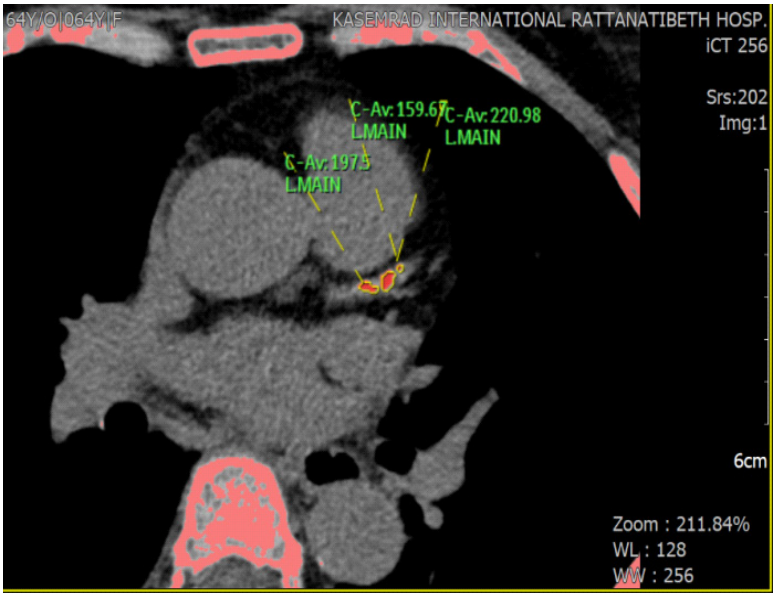

Figure 1. *CT coronary artery calcium score (CACS) in a 64-year-old female, HbA1c 6.3% with moderate cardiovascular risk (FRS = 13%), CACS = 202.3.*

Table 4. *Logistic regression model of positive coronary artery calcification score (CACS > 0) of participants divided by Framingham Risk Score (FRS)*.*

Participants with Framingham Risk Score (FRS)	No. of participants with positive CACS > 0	Multivariate OR (95% CI)
Prediabetes		
• Low Risk (< 10%)	216	1.00 (reference)
• Intermediate Risk (10-19%)	339	2.36 (1.06 – 5.46)
• High Risk (≥20%)	18	8.64 (2.65 – 18.58)
Non-diabetes		
• Low Risk (< 10%)	16	1.00 (reference)
• Intermediate Risk (10-19%)	121	7.86 (3.08-18.18)
• High Risk (≥20%)	3	3.70 (1.59- 8.65)
P for trend		**< 0.001**

**Logistic regression model was used to estimate OR and 95% CI*
Model: adjustment for BMI, LDL, triglyceride, and uric acid.

THE ASEAN JOURNAL OF RADIOLOGY
ISSN 2672-9393

Discussion

The significant results of the 5-year retrospective case study which analyzed the correlation between prediabetes, HbA1c 5.7 to 6.4%, cardiovascular risks determined by Framingham Risk Score (FRS) and coronary artery calcium score (CACS) represent performance and potential usage of CACS. CACS can explore coronary atherosclerosis in prediabetes with an intermediate risk of FRS. The combination of CACS and FRS is complementary to evaluate the potential risk of CVD. The benefits of results can be used for decision making of the statin therapy and lifestyle modification, according to the ACC/AHA primary prevention guidelines (2019). There are four issues during decision making, as follows:

1. The Power of CACS Testing

On March 5, 2022, there was a recent Asia Pacific symposium of SCCT (Society of Cardiovascular Computed Tomography) in Hong Kong [3]. The meeting reveals the power of coronary artery calcium (CAC) scanning in the situation of screening Atherosclerotic Cardiovascular Disease (ASCVD) and planning prevention, according to the ACC/AHA guideline on management of blood cholesterol (2018) [4]. The most important recent observation studies have been the findings that a CACS of zero indicates a low ASCVD risk for the subsequent 10 years.

Many studies found a significant positive association between CAC and inflammation of blood vessels, an inflammatory pathway of cytokines, C-reactive protein, aging, degenerative process, diabetes, prediabetes, metabolic syndrome, dyslipidemia, non-communicable diseases (NCDs), dyslipidemia, and a family history of premature coronary heart disease. In our study, the findings and results were consistent with well-known worldwide studies [5,6,7] as shown in the symposium. The CACS is the power of screening ASCVD in patients with low to intermediate CVD risks (by Framingham Risk Score) to prevent further morbidity of ASCVD.

2. Is Uric Acid a CVD Risk Factor?

Uric acid (UA) is a new challenging ASCVD risk factor in the present. The recent scientific studies [8-11] show association between uric acid and cardiovascular disease via the fructose (pentose) phosphate pathway. Consuming fructose-sweetened and beverages increases visceral fat, decreases insulin sensitivity, and promotes diabetes. An excessive level of fructose will increase the serum uric acid via the fructose (pentose) phosphate pathway. Uric acid (UA) is the final product of purine metabolism. It is a well-known risk factor for gout. Moreover, a high level of serum UA is also a biomarker for cardiovascular disease (CVD) morbidity and mortality [6].

3. Radiation Dose of CAC Scanning

The radiation dose exposure in CAC scanning is less than 1 mSV with care dose protocol for patients' safety as ALARA principle (As Low as Reasonably Achievable), named "i-care" software in Philips 256-slice CT scanner of our study, CARE (Combined Applications to Reduce Exposure) and SAFIRE (Sinogram Affirmed Iterative Reconstruction) in Siemen's scanner, and SURE-Exposure technology in Cannon scanner.

4. Benefit of Combination CACS and FRS for Evaluation ASCVD

FRS represents a prediction of CVD, while CACS represents evidence of coronary atherosclerosis. The combination of CACS and FRS evaluate ASCVD complements each other. According to the ACC/AHA primary prevention guidelines (2019), the statin therapy was recommended in two groups: (1) CACS 1-99 especially after the age of 55, and (2) CACS ≥ 100 and /or ≥ 75th percentile. This is an obvious benefit of CACS in the clinical practice guideline for decision making regarding the statin therapy.

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ISSN 2672-9393

Conclusion and suggestion

Subclinical prediabetes with an intermediate risk of FRS and the presence of coronary artery calcification (atherosclerosis) should be treated with a statin therapy and lifestyle modification according to the AHA guideline (2019). CACS screening in these patients benefit their lives in the long run. The role of preventive medicine and health promotion depend on the combination of CACS and FRS for screening. In fact, FRS represents a prediction of ASCVD, while CACS represents evidence of coronary atherosclerosis. The combination of CACS and FRS to evaluate ASCVD complements each other.

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