Coronary artery calcification is associated with alcohol intake but not oxidative stress or inflammation

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Abstract

Coronary artery calcification (CAC) is a component of the development of atherosclerosis. Coronary computed tomography scanning (CCT) can detect calcification and may be useful in individuals considered asymptomatic. Oxidative stress and inflammation are linked through common pathways and both are thought to be involved in the pathogenesis of atherosclerosis. To investigate if CAC was associated with increased oxidative stress (plasma F_2-isoprostanes) and inflammation (high sensitivity C-reactive protein [hs-CRP]), we invited 102 self-selected individuals (mean age 52±7 years) who were undergoing CCT to take part in a study. Height, weight and clinic blood pressure was measured, a blood sample taken and a health and lifestyle questionnaire completed.

CAC was found to be positively correlated with age ($p<0.01$) and alcohol intake ($p<0.001$). There was a trend for higher CAC in men compared to women ($p=0.08$). CAC was higher in ex- and current smokers versus non-smokers (115±45 *vs.* 28±12 Agatston score, $p=0.05$), and lower in non-drinkers versus drinkers (18±17 *vs.* 90±29 Agatston score, $p=0.03$). There were no univariate correlations between CAC and plasma F_2-isoprostanes ($p=0.25$) or HS-CRP ($p=0.36$). In multivariate analysis, age, male gender and alcohol intake remained independent predictors of CAC. We concluded that CAC was not associated with inflammation or oxidative stress, but was related to lifestyle factors including; age, gender and alcohol consumption.

Key words: coronary artery calcification, oxidative stress, inflammation, alcohol.

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Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality[1] and the process of coronary artery calcification (CAC) contributes to the development of atherosclerosis.[2] Coronary computed tomography scanning (CCT) is a sensitive technique for detecting CAC. It may be used for screening high-risk asymptomatic people and for the diagnosis of obstructive CAD. CCT quantitates the extent of calcium detected as a 'mass' or 'score'. Scores correlate with angiographically significant disease and are regarded as a marker of atherosclerotic plaque burden.[2]

Oxidative damage to low-density lipoproteins is thought to be involved in the pathogenesis of atherosclerosis.[3] Atherosclerosis has also been described as an inflammatory disease process.[4] Soft tissue calcification has been observed in areas of chronic inflammation and atherosclerotic calcification may be a process where oxidised lipids are involved in the inflammatory process.[5]

Since the involvement of oxidative stress in early lesion development is still uncertain, the objective of the study was to investigate the relationship between CAC and oxidative stress (plasma F_2-isoprostanes) and inflammation (high-sensitivity C-reactive protein [hs-CRP]).

Methods

Participants

Patients attending Western Australia Cardiology Services to undergo a coronary CT scan were invited into the study. Individuals completed a health and lifestyle questionnaire detailing medication use, physical activity and alcohol intake; they had their height, weight and clinic blood pressure (BP) measured; and they provided a non-fasting blood sample. The study was

Table 1. Patient characteristics

	Total	Men	Women	p value
Number	102	73	29	
Age (years)	52.8±0.7	52.5±0.9	53.6±1.4	0.520
BMI (kg/m^2)	27.05±0.5	28.1±0.6	25.9±0.7	0.034
Systolic BP (mmHg)	129±1.4	130±1.7	126±2.5	0.125
Diastolic BP (mmHg)	80.5±0.8	81.8±0.9	77.2±1.4	0.006
Cholesterol (mmol/L)	5.83±0.12	5.87±0.14	5.75±0.2	0.654
Triglycerides (mmol/L)	2.21±0.15	2.32±0.16	1.94±0.31	0.239
HDL (mmol/L)	1.34±0.07	1.26±0.10	1.55±0.08	0.071
Glucose (mmol/L)	5.5±0.2	5.6±0.2	5.5±0.2	0.491
Alcohol intake (g/wk)	143±18	181±24	46±10	<0.0001
History of hypertension*	36%	41%	25%	0.153
- on 1 drug	10%	11%	7%	
- on 2 drugs	6%	6%	7%	
History of dyslipidaemia*	50%	53%	43%	0.373
- on statins	17%	19%	14%	
- on fibrates	1%		3%	
Type on 2 diabetes	4%	3%	7%	0.317
HRT	12/29		41%	
Gout	4%	4%	4%	0.203
Aspirin	11%	11%	11%	0.955
Antioxidants/vitamins	37%	31%	54%	0.032
Current/ex-/non-smokers	14/43/43%	17/53/30%	4/18/78%	<0.0001
Non-drinkers/drinkers	18/82%	12/88%	32/68%	0.025
Agatston score				<0.0001
0	45%	32%	79%	
< 100	36%	45%	14%	
> 100	15%	18%	7%	

Mean ± SEM, Independent samples *t*-test

Key: BMI = body mass index; BP = blood pressure; HDL = high-density lipoproteins; HRT = hormone replacement therapy; *hypertension and dyslipidaemia were defined as previous diagnosis by clinician or use of antihy pertension or lipid-lowering therapy, respectively

Figure 1. Coronary artery calcium and smoking. Pearson Chi-square 17.8, p<0.001

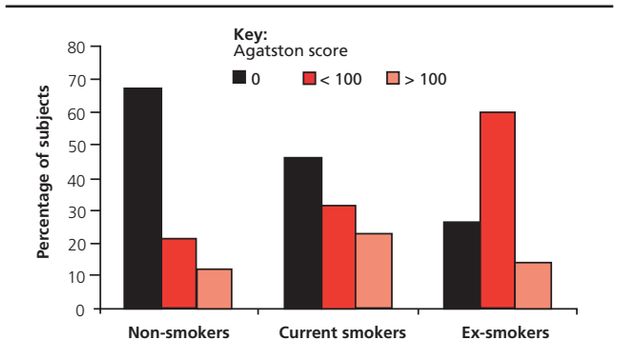
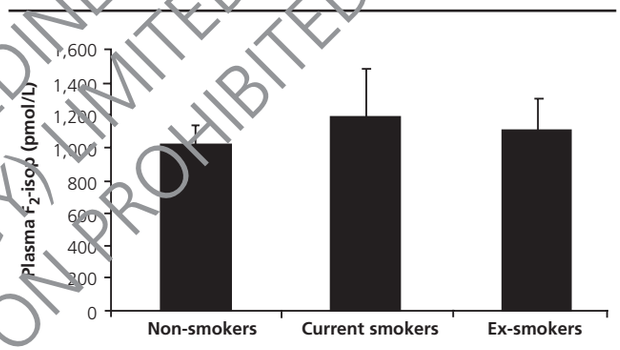


Figure 2. Plasma F_2-isoprostanes and smoking. ANOVA, p=0.378



approved by the Fremantle Hospital and Health Services Human Research Ethics Committee. A written informed consent was obtained before inclusion in the study.

Coronary computed tomography scanning

Coronary computed tomography scanning (CCT) studies were performed on a Toshiba AQUILION CT Scanner. Helical studies were performed from the root of the aorta to the cardiac apex at 3 mm slices and 0.3 seconds per slice, utilising 3–4 breath holds. CAC was grouped in pre-selected categories; 0 Agatston score, 1–100 Agatston score and > 100 Agatston score, as previously described.[6]

Biochemistry

Plasma F_2-isoprostane concentrations were analysed using gas-chromatography mass spectrometry.[7] Serum hs-CRP was analysed via particle-enhanced immunonephelometry. Lipids and glucose were measured using an automated analyser.

Statistical analysis

Statistical analysis was carried out using the Statistical Package for Social Sciences. Non-normally distributed data was log-transformed prior to analysis and results presented as mean ± SEM or geometric mean (95% confidence intervals). Independent samples *t*-tests were used to determine gender differences. Pearson Chi-squared and ANOVA with Bonferroni post-hoc comparisons were used to determine relationships between CAC and oxidative stress, inflammation, smoking and alcohol intake. Logistical regression was used to determine predictors of CAC.

Results

Seventy-three men and 29 women took part in the study. Men had significantly higher body mass index (BMI), diastolic BP and alcohol intake, and were more likely to be smokers, ex-smokers and drinkers. Women were higher consumers of antioxidant or vitamin supplements (table 1). Over 50% of the whole group had detectable calcification, although this was significantly more pronounced in men (table 1).

Calcification was significantly higher in current or ex-smokers (figure 1). Plasma F_2-isoprostane concentrations tended to be

Figure 3. Coronary artery calcium and alcohol intake. Pearson Chi-square 17.5, p=0.008

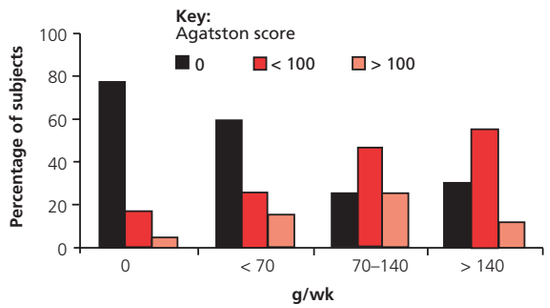
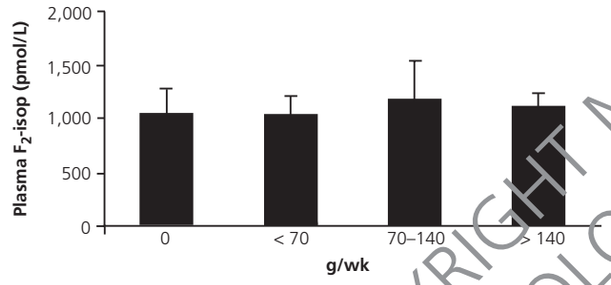


Figure 4. Plasma F_2-isoprostanes and alcohol intake. ANOVA, p=0.785



higher in current or ex-smokers (figure 2). Individuals who consumed one or more standard alcoholic drinks per day (> 70 g/week) had more CAC (figure 3), but there was no difference for plasma F_2-isoprostanes (figure 4). Plasma F_2-isoprostane concentrations were not different between tertiles of CAC (1,101 [992, 1,212] *vs.* 1,041 [863, 1,528] *vs.* 1,022 [829, 1,248] pmol/L for an Agatston score of 0, 1–100 or > 100, respectively, p=0.779). The hs-CRP was not significantly different between tertiles of CAC (1.78 [1.27, 2.48] *vs.* 1.78 [1.27, 2.49] *vs.* 1.56 [1.22, 2.70] mg/L for an Agatston score of 0, 1–100, > 100, respectively, p=0.908).

Independent predictors of CAC were age (B=0.098, p=0.014), male gender (B=2.139, p=0.003) and alcohol intake (B=2.428, p=0.021). Neither hs-CRP nor plasma F-isoprostanes predicted CAC.

Discussion

This study has shown positive associations of CAC with age, male gender and alcohol intake, and greater CAC prevalence in smokers. There was no association between CAC and oxidative stress or inflammation.

Our data support a recent study which observed a direct association between high alcohol intake and coronary calcification in young, healthy asymptomatic individuals.[8] Our present study included middle-aged individuals with existing cardiovascular disease. Taken together, these results may highlight an association between increasing alcohol intake and CAC in individuals of all ages and disease states. Although men consumed more alcohol than women, our association remained significant after adjustment for age and gender.

Low plasma ascorbic acid[9] and increased plasma F_2-isoprostanes[10] are associated with CAC. However, we saw no association between plasma F_2-isoprostanes and CAC. Previous studies included young, healthy individuals[9,10] while our study included older participants; several had pre-existing cardiovascular risk factors. Furthermore, over 50% of our subjects had detectable CAC, suggesting the present population had a greater prevalence and possibly more advanced atherosclerosis. It may be that oxidative stress predicts the development of CAC at an early stage but the relationship is lost in an older population with existing cardiovascular disease risk factors.

Another significant difference is that lipid peroxidation was previously assessed by measurement of free plasma F_2-isoprostanes[10] while we examined total plasma isoprostanes (sum of free and phospholipid-bound isoprostanes). Free plasma isoprostane levels may be a result of increased phospholipase A_2 (PLA_2) activity, which hydrolyses phospholipids. Thus, the previous association[10] may actually reflect an association between PLA_2 and CAC. A positive association between lipoprotein-associated phospholipase A_2 and risk of heart disease has been described.[11]

Additional factors contributing to these differences may include large heterogeneity within the population, use of a self-selected population, self-reported medical history and relatively small group sizes, particularly in relation to women. However, this heterogeneity is reflective of the general population.

The positive associations we observed between CAC and age and male gender are not unexpected. We also observed higher prevalence of CAC in current or ex-smokers and drinkers. Although smoking[12,13] and alcohol intake[14,15] are important sources of oxidative stress, this does not appear to explain the link with CAC. We did not show any association between CAC and inflammation, which is supported by a previous study.[16]

In conclusion, the present study has shown that CAC score is not related to oxidative stress or inflammation in this population. Age, male gender and alcohol intake were positively associated with CAC, consistent with the involvement of lifestyle factors in CVD.

Key messages

- Coronary artery calcification was not related to oxidative stress or inflammation in this self-selected population
- Lifestyle factors such as age, male gender and alcohol consumption were independent predictors of coronary artery calcification

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Conflict of interest

This study was supported by a Fremantle Hospital Medical Research Foundation Grant, Australia.

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