Altered serum level of cartilage oligomeric matrix protein and its association with coronary calcification in patients with coronary heart disease

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Abstract

Background  Cartilage oligomeric matrix protein (COMP) is mainly found in the skeletal system and vascular smooth muscle cells. Recent researches showed that it had a protective function on blood vessels and could also inhibit vascular calcification. We investigated the serum COMPs in coronary heart disease (CHD) patients, and the relationship between serum COMP and the calcification of coronary artery.

Methods  A total of 233 consecutive chest pain patients who first underwent coronary angiography followed by multi-slice computed tomography (MSCT) within six months were recruited and divided into two groups according to the coronary angiography luminal diameter narrowing percentages: CHD group (diameter narrowing ≥ 50%, n = 194) and control group (diameter narrowing < 50%, n = 39). The Gensini score, Syntax score and coronary artery calcium score (CACs) were calculated. The serum COMP level was determined using ELISA.

Results  The levels of COMP were significantly higher in the CHD group than in the control group 155.7 (124.5–194.5) ng/mL vs. 128.4 (113.0–159.9) ng/mL, P = 0.019. There were no correlation between COMP, Gensini score, Syntax score, severity of coronary stenosis and the number of coronary artery with stenosis > 50%. The serum COMP was correlated with age (r = 0.294, P < 0.001), fasting glucose (r = 0.163, P = 0.015), HbA1c (r = 0.194, P = 0.015) and CACs (r = 0.137, P = 0.037). Stepwise linear regression analysis showed that COMP level and age were independent predictors of CACs in the CHD patients (β = 0.402, t = 2.612, P = 0.015; β = 0.472, t = 3.077, P = 0.005). Performance of COMP for predicting CHD was shown as area under curve (AUC): 0.632, 95% CI: 0.549–0.715 and upper tertile CACs was AUC: 0.602, 95% CI: 0.526–0.678 in receiver operating characteristic (ROC) curve analysis.

Conclusion  Calcification of coronary artery was an independent predictor of serum COMPs.

Keywords: Cartilage oligomeric matrix protein; Coronary artery calcification; Coronary heart disease

1 Introduction

The aging population and increasing prevalence of cardiovascular disease risk factors is leading to a growing burden of coronary heart disease (CHD). Artery calcification, as part of the development of atherosclerosis, occurs almost exclusively in atherosclerotic arteries, and is absent in the normal arterial wall.[1] Vascular calcification is directly related to cardiovascular morbidity and mortality.[2] Coronary artery calcification score could be used as a tool for risk assessment among families with premature coronary artery disease.[3] Cartilage oligomeric matrix protein (COMP), a 524 kDa pentameric noncollagenous glycoprotein, is a macromolecular protein found in the musculoskeletal and cardiovascular systems. Serum COMP levels are always used as a biomarker for monitoring and prognosis of osteoarthritis[4] and rheumatoid arthritis.[5] In the cardiovascular system, recent studies have demonstrated that COMP is a novel inhibitor of post injury neointima formation[6] and vascular calcification[7] in rat abdominal aorta and vascular smooth muscle cells (VSMCs). Bone marrow-derived COMP may play a critical role in atherosclerotic calcification and COMP-deficient macrophages exerted atherogenic and osteogenic characteristics in Apo-E deficiency mice.[8] We performed clinical investigation of serum COMP levels in patients with CHD, and assessed the relationship between COMP and the severity of coronary artery calcification.

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2 Methods

2.1 Study population

This study included 233 consecutive chest pain patients who first underwent coronary angiography followed by multi-slice computed tomography (MSCT) within six months between September 2013 and September 2015. All subjects were divided into two groups according to coronary angiography luminal diameter narrowing percentages: CHD group (diameter narrowing ≥ 50%, n = 194) and control group (diameter narrowing < 50%, n = 39).

Exclusion criteria were as follows: previous percutaneous coronary intervention or bypass grafting operation, peripheral artery disease, osteoarthritis, rheumatoid arthritis, tumor, moderate or severe valvular heart disease, congenital heart disease, systemic inflammatory disorders and organ failures.

2.2 Coronary angiography and Gensini score, Syntax score

Selective coronary angiography was performed through femoral or radial artery approach. The severity of coronary stenosis was determined according to the Gensini score based on the degree of luminal narrowing and its geographical distribution.[9] The complexity of the lesions was recorded as Syntax score based on the coronary dominance using the Syntax score calculator, Version 2.11 (available at: http://www.syntax-score.com). The vessels with a diameter of ≥ 1.5 mm and the lesions with ≥ 50% stenosis were scored. Scoring was performed for each patient according to the following parameters: coronary dominance; number of lesions; segments involved per lesion; the presence of total occlusion, trifurcation, bifurcation, aorto-steal lesion, severe tortuosity, calcification, thrombus, diffuse/small vessel disease; and lesion length > 20 mm. Both coronary angiography and scoring were performed by two experienced interventional cardiologists blinded to the COMP level.

2.3 MSCT and coronary artery calcification score

All MSCT examinations were performed using a 64-row scanner (General Electric, South San Francisco, California) with a protocol for prospective triggering (SnapShot Pulse, GE Healthcare). Scanning parameters for the unenhanced calcium scoring scan were: 100 kV tube voltage, tube current was adjusted according to the body mass index (BMI), 0.28 s rotation time, and 2.5 mm slice thickness. Coronary artery calcification score (CACs) measurements were individually performed by two experienced readers blinded to the patient information using the CaScoring software and then the average was used as the score. CACs was defined as a plaque of at least three contiguous pixels (area of 1.02 mm²) with a density >130 Hounsfield units. The lesion score was calculated by multiplying the lesion area by a density factor derived from the maximal Hounsfield unit within this area, as described by Agatston, et al.[10]

2.4 Biochemical analysis

Serum glucose, creatinine, uric acid, total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol, triglycerides, and glycosylated hemoglobin were measured using standard laboratory techniques. Serum COMP levels were determined by sandwich ELISA with a commercially available kit (Rabbit COMP ELISA kit, Elab science Biotechnology Co., Wuhan, China) according to the manufacturer’s instructions.

2.5 Statistical analysis

Continuous variables were presented as mean ± SD, discrete data was described as median with 25%–75% range, and categorical data was summarized as frequency with percentage. The Kolmogorov-Smirnov test was used to test for normal or abnormal distribution of continuous variables. Student’s t-test and one-way ANOVA was used for comparing normal distribution data. Mann-Whitney U test was used for abnormal distribution data. Proportions were compared by the chi-square test. Pearson’s correlation coefficient was used for parametric correlation and the Spearman test was used for nonparametric correlation. Multiple linear regression analysis was used to identify factors that were independently associated with COMP level. SPSS 21.0 (SPSS Inc, Chicago, IL) was used for all analyses. P < 0.05 (2-tailed) was considered to be statistically significant.

The study protocol was approved by the Ethics Committee of Peking University Health Science Center and written informed consent was obtained from all participants.

3 Results

3.1 Clinical characteristics of participants

Baseline clinical characteristics and biochemical measurements are presented in Table 1. The mean age of the patients was 64.6 ± 10.5 years and 143 patients (61.4%) were male. Significant differences in gender, prevalence of hypertension, creatinine and high HDL-C existed between the CHD group and control group. The prevalence of hypertension and female percentage were higher in the control group. The CHD patients had higher levels of creatinine and lower HDL-C.
Table 1. Clinical and biochemical characteristics of the patients.

| Parameters                  | All patients (n = 233) | Control group (n = 39) | CHD group (n = 194) | P  |
|-----------------------------|------------------------|------------------------|---------------------|----|
| Clinical characteristics    |                        |                        |                     |    |
| Male                        | 143 (61.4%)            | 16 (41%)               | 127 (65.5%)         | 0.004 |
| Age, yrs                    | 64.6 ± 10.5            | 64.4 ± 11.1            | 64.7 ± 10.4         | 0.883 |
| Current Smoking             | 64 (27.5%)             | 9 (23%)                | 55 (28.9%)          | 0.283 |
| Hypertension                | 168 (72.1%)            | 30 (76.9%)             | 138 (71.1%)         | 0.012 |
| Hyperlipidemia              | 110 (47.2%)            | 20 (51.3%)             | 90 (46.4%)          | 0.404 |
| Diabetes mellitus           | 58 (24.9%)             | 6 (15.4%)              | 52 (26.8%)          | 0.061 |
| Biochemical characteristics |                        |                        |                     |    |
| Creatinine, µmol/L          | 84.0 ± 17.5            | 75.8 ± 13.5            | 85.7 ± 17.7         | 0.003 |
| Uric acid, µmol/L           | 353.7 ± 96.6           | 313.9 ± 115.3          | 361.4 ± 90.9        | 0.201 |
| TC, mmol/L                  | 4.36 ± 1.07            | 4.44 ± 0.90            | 4.47 ± 0.99         | 0.775 |
| HDL-C, mmol/L               | 1.05 ± 0.35            | 1.25 ± 0.48            | 1.01 ± 0.29         | 0.006 |
| LDL-C, mmol/L               | 2.52 ± 0.81            | 2.52 ± 0.89            | 2.52 ± 0.79         | 0.969 |
| Glucose, mmol/L             | 5.54 ± 1.03            | 5.52 ± 0.94            | 5.63 ± 1.65         | 0.807 |
| HbA1C, %                    | 6.35 ± 1.04            | 6.07 ± 0.29            | 6.37 ± 1.08         | 0.631 |
| COMP, ng/mL                 | 150.3 (120.4–191.2)    | 128.4 (113.0–159.9)    | 155.7 (124.5–194.5) | 0.019 |

Data are presented as n (%), mean ± SD or median (1/4 quartile ranges–3/4 quartile ranges). CAD group had higher male percentage, serum creatinine and COMP; *lower hypertension disease prevalence and HDL-C level. There was no significant difference in other parameters. CAD: coronary artery disease; COMP: cartilage oligomeric matrix protein; HbA1C: Glycosylated hemoglobin; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TC: Total cholesterol.

3.2 COMP, Gensini score, Syntax score and CACs

The levels of COMP were significantly higher in the CHD group than the control group [155.7 (124.5–194.5) vs. 124.5 (113.0–159.9) ng/mL, P = 0.019] (Table 1). The CHD group was further divided according to the number of diseased coronary arteries and the range of Gensini score, Syntax score and CACs. Serum COMP level had no correlation with the number of diseased coronary arteries (P = 0.130) (Figure 1A), severity of coronary stenosis determined by Gensini score (P = 0.446) (Figure 1B) or the complexity by Syntax score (P = 0.256) (Figure 1C). The serum level of COMP was significantly elevated in the upper tertile (P = 0.033) (Figure 1D).

3.3 Correlation between COMP levels and other parameters

The serum COMP was correlated with age (r = 0.294, P < 0.001) (Figure 2A), fasting glucose (r = 0.163, P = 0.015) (Figure 2B), HbA1c (r = 0.194, P = 0.015) (Figure 2C), and CACs (r = 0.137, P = 0.037) (Figure 2D). There was no correlation between COMP and gender, hypertension, dyslipidemia, cholesterol and creatinine levels, Gensini score and Syntax score. Stepwise linear regression analyses showed that after adjustment for age, cigarette smoking, fasting glucose and HbA1c, CACs was the independent predictor in the final model for COMP level (β = 0.270, t = 2.134, P = 0.037).
Figure 2. The correlation between COMP and the clinical indicators. (A): the indicators associated with COMP, including age \((r = 0.294, P < 0.001)\); (B): fasting glucose \((r = 0.163, P = 0.015)\); (C): HbA1c \((r = 0.194, P = 0.015)\); and (D): CACs \((r = 0.137, P = 0.037)\).

CACs: coronary artery calcification score; COMP: cartilage oligomeric matrix protein.

3.4 ROC curve of COMP for predicting CHD and upper tertile CACs

Receiver operating characteristic (ROC) analysis was used to determine a cut-off COMP value for CHD (Figure 3A) and upper tertile CACs (Figure 3A). COMP > 144.68 ng/mL had 70.2% sensitivity and 58.8% specificity to predict CHD [area under curve (AUC): 0.632, \(P = 0.009\), 95% CI: 0.549–0.715]. COMP > 158.9 ng/mL had 55.8% sensitivity and 59.6% specificity to predict upper tertile CACs (AUC: 0.602, \(P = 0.039\), 95% CI: 0.526–0.678) (Figure 3B).

Figure 3. The diagnostic ability of COMP in CHD and upper tertile of CACs. CACs: coronary artery calcification score; CHD: coronary heart disease; COMP: cartilage oligomeric matrix protein.
4 Discussion

Serum COMP level was used as a biomarker for monitoring and prognosis of osteoarthritis and rheumatoid arthritis. To the best of our knowledge, the level of COMP in CHD patients has not yet been reported. This is the first study to show that higher level of serum COMP is associated with CHD and coronary calcification. The level of serum COMP [150.3 (48.81–1290.4) ng/mL] was elevated in the CHD group and ROC curve showed that COMP > 144.68 ng/mL predicted CHD with 70.2% sensitivity and 58.8% specificity. The serum COMP level was significantly elevated in upper tertile group of CACs, COMP > 158.9 ng/mL had 55.8% sensitivity and 59.6% specificity to predict severe coronary calcification. Additionally, CAC was the independent predictor of COMP in CHD patients.

4.1 Relationship between COMP and CHD

COMP is now recognized as a normal component of vascular extracellular matrix (ECM) in humans and has been implicated in attachment and hapatosis of vascular smooth muscle cells (VSMCs). Media-to-intima migration of VSMCs is pivotal to intimal thickening in atherosclerosis, restenosis after coronary angioplasty, and late failure of vein grafting. Normally VSMCs are quiescent, and surrounded by and embedded in an ECM scaffold that acts as a barrier to their migration. ECM degradation and remodeling require the activation of extracellular proteases, which in turn facilitate VSMC migration. Adams-7 facilitated VSMC migration and neointima formation through degeneration of vascular COMP, and COMP over-expression could replenish this migration. The degeneration of a normal ECM protein COMP was found within injured rat arteries and the size of degraded fragments of COMP within injured vessels greatly assembled from arthritic cartilage. COMP is involved in the assembly of collagen fibrils and has been identified as a matrix component in human atherosclerotic and restenotic plaques, as well as in plaques from different murine atherosclerotic models. In addition to our in vivo and in vitro results, which indicated that COMP plays important roles during atherosclerosis, the circulation COMP in CHD patients increased as well, possibly due to an increase in COMP degradation fragment.

4.2 Relationship between COMP and vascular calcification, especially coronary calcification: previous studies

Our study showed that the serum level of COMP was unrelated to the number or degree of luminal narrowing and lesion’s geographical distribution or complexity, but related to the severity of coronary calcification. Bond, et al. found that ApoE- and ApoE/COMP-knockout mice favored the extent of cartilaginous metaplasia and thicker collagen fibrils as compared to ApoE-knockout mice. Du, et al. found that when exposed to high calcium, COMP knockdown greatly exacerbated calcium deposition by 50% in VSMCs in vitro, and COMP overexpression may inhibit both high Pi- or CaCl2-induced vascular calcification in aortic-ring organ culture model in vivo. COMP deficiency has a significant impact on coronary calcification. The extent of coronary artery calcium strongly correlates with the rate of future cardiac events. Clinical experience has shown that severe calcification assessed by intravascular imaging limits stent expansion, which can be associated with adverse events including restenosis and stent thrombosis. Intravascular ultrasound (IVUS) or optical coherence tomography (OCT) are the current gold standards for coronary calcium detection. CACs may help to evaluate risk factors for atherosclerotic plaque burden as well as the actual risk. Our previous study had demonstrated that coronary artery calcification was an independent predictor for cardiovascular events and indicated complexity of complications in the CHD population who had received percutaneous coronary intervention procedure. But IVUS, OCT and CACs are expensive and have to be operated under ray. In our study, COMP was elevated in the upper tertile group of CACs, so it could be a screening biomarker in CHD patients with severe calcification.

4.3 Conclusions

This is the first study to demonstrate that CHD patients had higher circulating levels of COMP than controls. Serum COMP levels positively correlated with CACs and could be used as a screening biomarker in coronary calcification.

4.4 Limitations

This study was limited by a small sample size that constituted a unique cohort, which may restrict the generalizability of our results. Further prospective studies are required to determine the effects that elevated COMP levels have on clinical outcomes in patients with CHD and coronary calcification.

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