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Relationship between calcium-phosphorus product and coronary artery calcification

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Abstract: *Abnormal calcium and phosphorus metabolism is closely related to coronary artery calcification (CAC), but the relationship between calcium-phosphorus product(Ca-P product) and coronary artery calcification in other population is not completely clear. A retrospective analysis was performed on 199 patients who had received coronary computed tomography angiography(CCTA). Univariate and multivariate analyses were performed to evaluate the association between Ca-P product and coronary artery calcification. Compared with the non-calcification group, the Ca-P product was significantly increased in the mild and moderate calcification groups, while there was no significant change in the severe calcification group. After excluding severe calcification, logistics regression analysis after adjusting confounding factors indicated that the Ca-P product was positively correlated with CAC>0 (OR1.121,95%CI(1.035, 1.216),P=0.006). In addition, the total CACS and the prevalence of CAC in the high Ca-P product group were significantly higher than those in the low Ca-P product group. In the non-coronary group, the CAC group had a higher Ca-Pproduct than the non-CAC group. Excluding severe calcification patients,Ca-P product is associated with CAC.*

Keywords: *Ca-P product; Coronary artery calcification; Coronary atherosclerotic heart disease*

1. Introduction

The incidence of atherosclerotic diseases is increasing year by year. Coronary artery calcification (CAC) usually accompanies the development of atherosclerosis, and there is a strong correlation with Coronary atherosclerotic heart disease(CAD)[1-2].

For this reason, some guidelines use CAC as a risk marker to predict future cardiovascular risk[3]. In recent years, most studies have suggestted that CAC is closely related to the occurrence of cardiovascular events, and its predictive value is significantly superior to traditional risk factors[4]. Studies have confirmed that the risk of severe CAD events and all-cause death is significantly increased with the increase of calcification[5].Early quantification of coronary artery calcification can contribute to identify people at high risk of cardiovascular events in a timely manner, thereby reducing the incidence of adverse events.

The natural course of vascular calcification is related to the evolution of atherosclerotic plaques, and complex calcification processes, including active and passive mechanisms, are increasingly being understood. These studies suggest that vascular calcium phosphate deposition, smooth muscle cell transdifferentiation and inflammatory factors may play a role in the development of coronary artery calcification[6-8].

A large number of studies have highlighted the close relationship between high Ca-P product and increased risk of vascular calcification in chronic kidney disease(CKD)[9].Studies have found that coronary artery calcification is more prevalent and severe in patients with CKD, and it was more common in dialysis patients than that in non-dialysis patients. A high Ca-P product predicts a very high coronary calcium score[10-11]. In several observational studies, the Ca-P product was also found to be significantly associated with aortic and mitral valve calcification, as well as with increased all-cause mortality and cardiovascular mortality[12-13]. However, the association between calcium-phosphorus product and coronary calcification in other groups is not fully understood.

ISSN 2618-1584 Vol. 6, Issue 7: 84-89, DOI: 10.25236/FMSR.2024.060710

2. Materials and Methods

2.1 General Information

Data of 199 patients admitted to Lishui People's Hospital from August 2023 to February 2024 due to chest tightness, chest pain and other symptoms were retrospectively analyzed. All patients underwent coronary CTA examination.

Exclusion criteria: patients with previous coronary intervention therapy, acute and chronic infections, severe liver and kidney diseases, and malignant tumors.

2.2 Clinical data

Systematically collect patients age, sex, and clinical characteristics (smoking history, drinking history, hypertension history, and diabetes history) and Laboratory measures (fasting blood glucose(FBG), triglycerides(TG), tatol cholesterol(TC),high density lipoprotein cholesterol(HDL-C),low density lipoprotein cholesterol(LDL-C), calcium, phosphorus, etc.). People who smoked regularly in the past 6 months were considered current smokers, and those who drank more than 3 times per week were considered drinkers. Ca-p product (mg2/dL2) = Ca(mmol/L)×4. 1×P(mmol/L)×3.

Coronary artery calcification score

A coronary CTA examination was performed and the images were being analyzed by three experienced radiologists. They performed the calculations using specific software to obtain an Agastston score for each patient. Patients were also divided into non-calcification (CACS=0), mild calcification (0 < CACS < 100), moderate calcification (100≤CACS < 400), and severe calcification (CACS≥400) based on the coronary artery calcification score (CACS).

2.3 Statistical Analysis

Continuous variables with a normal distribution were expressed as mean ± standard deviation and compared using the independent sample t test and one-way ANOVA.Continuous variables with a non-normal distribution were expressed using the median and quartile, and compared between groups using the Kruskal Wallis test. Categorical variables were shown as examples (%), and Chi-square test was used to analyze differences among groups. Multi-factor analysis was carried out using logistics regression analysis.All statistical analyses were performed using SPSS 26.0 software, with $p<0.05$ indicating statistically significant differences.

3. Results

3.1 Baseline characteristics

Table 1: Baseline characteristics

Variables	CSCS=0 (n=49)	0<CACS<100 (n=44)	100≤CACS<400 (n=56)	CACS≥400 (n=50)	P value
Age(years)	60.94±11.28	64.36±10.56	66.98±8.68b	71.72±8.85c	<0.001
Male,n(%)	33(67.3)	28(63.6)	30(53.6)	29(58.0)	0.495
Smoking,n(%)	15(30.6)	16(36.4)	20(35.7)	17(34.0)	0.934
Alcohol,n(%)	15(30.6)	11(25.0)	14(25.0)	14(28.0)	0.908
Hypertension,n(%)	18(36.7)	23(52.3)	30(53.6)	37(74.0)c	0.003
SBP(mmHg)	138. 10±21.79	138.25±16.40	137.54±21.31	136.34±17.60	0.962
DBP(mmHg)	83.86±12.20	83.34±13.69	80.54±12.58	79.54±10.98	0.235
Diabetes,n(%)	4(8.20)	13(29.5)a	19(33.9)b	18(36.0)c	0.006
CAD,n(%)	2(4. 1)	12(27.3)a	43(76.8)b	49(98)c	<0.001
TG(mmol/L)	1.52(0.89-2.31)	1.26(1.02-2.34)	1.83(1.06-2.66)	1.47(1.05-2.04)	0.209
TC(mmol/L)	4.58±0.97	4.79±0.94	4.69±1.24	4.46±1. 11	0.408
HDL-C(mmol/L)	1.32±0.33	1.34±0.34	1.33±0.32	1.28±0.28	0.832
LDL-C(mmol/L)	2.32(1.77-2.86)	2.42(1.89-3)	2.38(1.63-2.77)	2. 15(1.49-2.76)	0.297
Ca-P product(mg2/dL2)	26.27±4.61	28.81±5.77a	29.86±5.88b	27.29±5.21	0.004
FBG(mmol/L)	4.81(4.38-5.54)	5.24(4.71-6.52)a	5.45(3.59-5.36)b	5.26(4.74-6. 17)	0.029

[a],0<CACS<100 vs CSCS=0,[b], 100≤CACS<400 vs CSCS=0,[c],CACS≥400 vs CSCS=0

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The study population included 199 patients, including 120 males (60.3%) and 79 females (39.7%), who were divided into four groups according to CACS.The characteristics of the patients in the four groups are shown in Table 1. The results suggested that the moderate and severe calcification groups were older than the non-calcification group. Compared with the non-calcification group, the calcification group had more diabete and CAD patients, and higher fasting blood glucose levels. Ca and P product were higher in the mild and moderate calcification groups compared to the non-calcification group, while there was no significant change in the severe calcification group (Table 1).

3.2 Relationship between Ca-P product tertiles and CAC

Patients with CACS<400 were divided into three groups, according to the tertiles product of Ca and P, with significant differences in CACS among the three groups. Compared with tripartite group 1 (T1), the total CACS in tripartite group 3 was significantly higher, and the calcification score in the left anterior descending branch was also significantly higher. In addition, the likelihood of calcification increased with the increase of the Ca-P product (Table 2).

Table 2: Relationship between Ca-P product tertiles and CAC

variables	Tertile 1(n=50)	Tertile 2(n=50)	Tertile 3(n=50)	P value
Tototl CACS	3.54(0, 132.83)	6. 15(0, 156.44)	119.98(25.50,228.03	0.002
LAD scores	2. 11(0, 110. 17)	0(0,62.21)	59.27(1.04, 140.56)	0.005
LCX scores	0(0, 1.59)	00,0. 17)	0(0, 16.48)	0.542
RCA scores	0(0, 1.79)	0(0,8.38)	0(0, 15.93)	0.566
Presence of CAC, n(%)	26(52)	32(64)	43(86)	0.001

3.3 Association between CAC and risk factors

For patients with CACS<400,they were divided into a non-CAC group (CACS=0) and a CAC group (CACS>0).Logistic regression analysis suggested that age, diabetes history, fasting glucose, and calcium-phosphorus product were statistically significant. After adjusting for confounders,the Ca-P product was still correlated with coronary artery calcification, which was consistent with the above results (Table 3).

Table 3: Association between CAC and risk factors

variables	OR(95%CI)	P value	adjusted OR(95%CI)	P value
Age(years)	1.049(1.013-1.087)	0.007	1.062(1.020, 1.206)	0.004
Diabetes,n(%)	5.217(1.728, 15.756)	0.003	3.531(1.096, 11.370)	0.035
Ca-P product(mg2/dL2)	1. 115(1.042, 1. 192)	0.002	1. 121(1.035, 1.216)	0.006
FBG(mmol/L)	1.340(1.046, 1.717)	0.021		

3.4 Baseline characteristics of CAD and non-CAD

After excluding severe calcification, patients were divided into CAD group and non-CAD group , of which 58 cases were CAD group and 92 cases were non-CAD group. Compared with the non-CAD group, the CAD group was older, had more patients complicated with hypertension and diabetes, had higher CACS, including the scores of all coronary branches,and the likelihood of calcification was also increasing.But there was no statistically significant difference in the Ca-P product(Table4).

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Table 4: Baseline characteristics of CAD and non-CAD

Variables	Non-CAD group(n=92)	CAD group(n=58)	P value
Age(years)	62.87±10.76	66.53±9.45	0.035
Male,n(%)	56(60.90)	35(60.30)	0.949
Smoking,n(%)	28(30.40)	23(39.70)	0.246
Alcohol,n(%)	29(31.50)	11(19)	0.09
Hypertension,n(%)	38(41.30)	34(58.60)	0.039
Diabetes,n(%)	15(16.30)	21(36.20)	0.005
TG(mmol/L)	1.52(1.02,2.37)	1.75(1.05,2.63)	0.223
TC(mmol/L)	4.72±1.01	4.63±1.16	0.608
HDL-C(mmol/L)	1.35±0.34	1.28±0.29	0.200
LDL-C(mmol/L)	2.38(1.88,2.87)	2.38(1.61,2.80)	0.417
Ca-P product(mg2/dL2)	27.71±5.44	29.57±5.89	0.051
Tototl CACS	0(0,36,85)	197.36(105.83,320.65)	<0.001
LAD scores	0(0, 11.54)	104.56(52.85, 178.46)	<0.001
LCX scores	0(0,0)	0.98(0,36.46)	<0.001
RCA scores	0(0,0)	5. 15(0,59.64)	<0.001
Presence of CAC, n(%)	45(48.91)	56(97.55)	<0.001

3.5 Relationship between Ca-P product and CAC in non-CAD patients

After excluding severe CAC patients, non-CAD patients were divided into non-CAC group and CAC group according to CACS. There were statistically significant differences in the product of calcium and phosphorus between the two groups (Table5).

Table 5: Relationship between Ca-P product and CAC in non-CAD patients

		Ca-P product	P value
Non-CAD	CAC=0 (n=47)	26,24±4.69	0.007
	CAC>0 (n=45)	29.26±5.78	

4. Discussion

The development of CAC were strongly correlated with traditional atherosclerotic factors, such as age, sex, dyslipidemia, hypertension history, and history of diabetes. Studies have shown that men have higher CACS than women, and that increasing age is positively associated with CAC[14]. In addition, LDL-C plays an important role in the development of atherosclerosis, and some studies have found that levels of LDL-C have a significant effect on coronary artery calcification[15-16]. However, our study suggests that there is no significant difference in LDL-C between the calcified and non-calcified groups, especially those with severe calcification. This may be related to the use of therapeutic drugs.

As traditional risk factors for cardiovascular disease, age and diabetes were significantly associated with CAC in both univariate and multivariate analyses[17]. It is well known that CAC tends to be higher in people with diabetes and is an independent risk factor for the development of CAD. Elevated blood glucose levels can promote oxidative stress and induce the formation of free radicals, reactive oxygen species and advanced glycosylation end products through a variety of pathways, leading to vascular inflammation, insulin resistance and endothelial dysfunction, thereby increasing the risk of atherosclerosis[18-19]. Consistent with previous views, in this study, fasting glucose was positively correlated with coronary artery calcification and was an important risk factor for coronary artery calcification.

The Ca-P product can be calculated by detecting two laboratory indicators, calcium and phosphorus, so the Ca-P product detection is convenient and low cost. This study showed that Ca-P product were higher in the mild and moderate calcification groups compared to the non-CAC group, while there was no significant difference in the severe calcification group. This may be related to the small sample size and the use of therapeutic drugs. After excluding severe calcification, total CACS increased significantly in patients with high Ca-P product. After adjusting for confounders, the Ca-P product was still significantly associated with CAC.

The occurrence of CAC usually precedes CAD, and the development of CAD is often accompanied

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by the occurrence of CAC.It has a certain predictive ability for the occurrence of CAD[20]. In this study, for non-CAD patients, the CAC group had a higher Ca-P product than the non-CAC group. This means that high Ca-P product is significantly associated with coronary artery calcification in non-CAD patients, which contributes to the early detection of CAC and the prevention of CAD.

Despite the efforts made in this study, there are still some limitations. First, some early calcification may be missed due to limitations in the methods used to measure CAC. Second, our study population was relatively small, and the study participants were all from one center, so multi-center studies with larger sample sizes should be considered in the future. Last, calcium and phosphorus, blood lipid and other parameters will change over time, but we only collected data at one point in time.

5. Conclusion

In the non-CDK population, the Ca-P product was significantly associated with mild and moderate CAC. The same was true in patients without coronary heart disease.

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