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Extended Abstract
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Cardiology-2020: High Serum Level of Secreted Frizzled-Related Protein 5 (sfrp5) is Associated with Future Cardiovascular Events - Yi Zhang - Shanghai Tenth People's Hospital, China

Yi Zhang
Shanghai Tenth People's Hospital, China

Introduction:

Coronary artery disease (CAD), as a metabolic and inflammatory disease, carried a high incidence of hospital readmission and a high mortality risk, making it one of the deadliest diseases in the world. Novel indicators as a prediction of these outcomes of CAD patients in an early stage is essential.

Adipose tissue secrets multiple adipokines, modulating the systemic inflammatory responses that contribute to inflammatory disorders such as metabolic syndrome, atherosclerosis and coronary artery disease. Secreted frizzled-related protein 5 (SFRP5), as an emerging adipokine, played an important role in the glucose metabolism and diabetes mellitus. Recently, SFRP5 has been identified as a novel adipokine with the anti-inflammatory function. In the cardiovascular setting, studies about SFRP5 is indeed limited. Previous studies have shown that the SFRP5/Wnt5a regulatory system influenced the angiotensin II (AngII)-induced cardiomyocyte hypertrophy through the AT1 receptor/Rho/ROCK1/JNK signaling pathway, downregulating

BNP and TNF-a at the same time. It could also diminish the cardiac inflammation to play a protective role. Notably, a crosssectional study demonstrated for the first time that in the subjects with CAD (stenosis over 50%), the serum SFRP5 levels were significantly lower than those in the non-CAD (stenosis<50%) subjects, low SFRP5 levels may contribute to CAD. However, in recent studies, the role of SFRP5 in the prediction of future cardiovascular events were not under the notice, making it uncertain.

The aim of this 4-year follow-up study was to investigate whether SFRP5 is associated with future cardiovascular events in both CAG(+) and CAG(-) subgroups, in terms of a composite primary endpoint of combined occurrence of major adverse cardiovascular events (MACE).

Methods

Participants

All patients were prospectively recruited in a cardiac catheterization laboratory at the cardiology department of Shanghai Tenth People's Hospital (China). The study population was Shanghai residents undergoing coronary angiography to evaluate suspected or established CAD for clinical indications (most frequently chest pain, dyspnea on exertion), by physician's decision. Participating CAG(+)patients had a coronary stenosis >50% at catheterization while CAG(-) group had a coronary stenosis <50%.

Biochemical measurements

Serum was isolated from blood samples collected after overnight fasting, and stored at -80â??. Serum liver and renal function as well as the metabolic parameters like lipid profile were measured with standard laboratory techniques on colorimetric enzymatic assay systems (Roche MODULAR P-800, Switzerland). Levels of serum SFRP5 was measured with enzyme-linked immune-sorbent assays (ELISAs) (Human ELISA kit, Wuhan USCN Science Co, Ltd, China). ELISA's detection range was 1.56-100 ng/mL. Intra-assay and inter-assay CVs were 10% and 12% for SFRP5.

Angiography

Patients were conducted with a coronary angiography through a radial artery with standard judkins technique. We defined CAG(+) as the presence of luminal diameter stenosis ≥ 50% in the left anterior descending artery (LAD), right coronary artery (RCA), left circumflex coronary artery (LCX) and their main branches. Over 50% luminal narrowing of the left main trunk stenosis was considered as two-vessel disease. We categorized the severity of coronary atherosclerosis by the number of coronary vessels with significant stenosis as 0, 1, 2, or ≥ 3 vessels,

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respectively. The imaging procedures were conducted by 2 professional interventional cardiologists, masked to the cohort data.

Statistical Analysis

Baseline demographic and clinical characteristics are presented as mean ± SD, median (interquartile range), or frequency counts, and the differences between the two groups were evaluated with t-test or the Mann-Whitney test, as appropriate. Kolmogorov-Smirnov test were preferred to determine whether the data were normally distributed. The assessment of relations of SFRP5 with other biomedical indicators were evaluated using the multivariate regression. Games Howell test was performed to compare the SFRP5 levels in subgroups of different number of lesion vessels. Adjusted efficacy (hazard ratio) was estimated using the Cox regression model controlling for the confounders including age, gender, DM, hypertension history, CAD, smoking habits, and usage of statin. Kaplan-Meier curves were performed to show the MACE-free survival. In our analysis, we took the median value of the serum SFRP5 to distinguish high/low levels, and participants were divided into elder (over 65 years old) and younger (≤65 years old) subgroups separately. Statistical analysis was performed using SPSS 19.0 for Windows (SPSS Inc., Chicago, IL). A two-sided significant level of 5% was considered as statistical significance.

Results:

Characteristics of study participants at baseline

The characteristics of a total of 168 subjects including CAG(+) and CAG(-) participants. No significant differences were found between CAG(+) and CAG(-) subjects with respect to age, BMI, systolic blood pressure, blood urine nitrogen, triglyceride (TG), hypertension or diabetes and antihypertensive medications including ACEI/ARB, CCB. Serum hs-CRP levels in CAG(-) subjects were significantly lower than in CAG(+) subjects (5.15 ± 3.26 and 11.56 ± 5.89 ng/mL, respectively; p<0.001). And creatinine (76.6 ± 23.1 vs. 84.8 ± 26.1 umol/L, p=0.02) and uric acid levels (328.9 ± 112.4 vs. 366.0 ± 97.1 umol/L, p=0.04) were also greater in the CAG(+) group. For this entire cohort, the CAG(+) participants had a better lipid profile including a lower total cholesterol (4.8 ± 1.0 vs. 4.3 ± 1.1 mmol/L, p=0.009) and a lower LDL-c (2.8 ± 0.8 vs. 2.4 ± 0.9 mmol/L, p=0.02) than the CAG(-) group , presumably as a result of the statin usage (4(5) vs. 19(23), p<0.001). Of note, as shown in , there was no significant difference of SFRP5 between CAG(+) and CAG(-) group (p=0.63

Discussion

In the literature, there were limited data available on the prognostic significance of SFRP5 in the field of cardiovascular disease, but SFRP5 was always considered as a potential CV biomarker. Our study is the first one evaluating the association between circulating SFRP5 levels and future MACE. We demonstrated that increased SFRP5 levels was significantly associated with the occurrence of MACE, especially in patients over 65 years old.

The mean age of the 168 patients (93 males, 55%) was 65 ± 11 years. 108 patients (64%) had a history of hypertension, 40 (24%) had diabetes mellitus and 33 (20%) were current smokers. We found no significant differences in the distribution of gender and age between high/low SFRP5 groups, which is consistent with the previous studies. Of note, pro-BNP, LDL-c, cTNT and hs- CRP were unaffected by low or high SFRP5 levels. Whether SFRP5 is associated with DM remains controversial. In our study, we found that DM rate in patients with low SFRP5 was significantly higher than those with high SFRP5.

In our study, there is no significant difference of SFRP5 levels between CAG(+) and CAG(-) groups. There is even no significant difference of SFRP5 levels between the groups of different lesion vessel numbers. However, a previous cross-sectional study revealed that, for a group of 185 participants who were from Kagawa Prefectural Central Hospital, serum SFRP5 levels were significantly associated with CAD (stenosis over 50%). And for the younger group (<65 years old), SFRP5 serves as a strong CAD indicator. There were several reasons to explain this difference. First of all, for both of these two studies, the limited sample size has impact on the results at baseline. On the other hand, it has been widely accepted that there are always differences between ethnics in many aspects such as pharmacokinetics. And for the biological marker, the existence of such differences

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between the ethnics can also be accepted. Finally, though SFRP5 has been considered as a metabolism-associated adipokine in many other aspects such as inflammation, oxidative stress and role of biomarker, the role of SFRP5 in human cardiovascular physiology remains unknown.

Conclusion:

We demonstrated for the first time that high serum concentration of SFRP5 is associated with the future cardiovascular events, independent from other conventional risk factors. Furthermore, the impact of high SFRP5 seems to be greater in elderly. Measurement of circulating SFRP5 levels may be used to evaluate the risk of future cardiovascular event.

ysizshcn@gmail.com

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