Cytokine xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Circulating secreted frizzled-related protein 5 and chronic kidney disease in patients with acute ST-segment elevation myocardial infarction

Chao-Ping Wang[a,f,1], Teng-Hung Yu[a,1], Cheng-Ching Wu[a], Wei-Chin Hung[a], Chia-Chang Hsu[b], I-Ting Tsai[d], Wei-Hua Tang[e], Fu-Mei Chung[a], Jer-Yiing Houng[g], Yau-Jiunn Lee[h], Yung-Chuan Lu[c,f,*]

[a] Division of Cardiology, E-Da Hospital, I-Shou University, Kaohsiung 82445, Taiwan
[b] Division of Gastroenterology and Hepatology, E-Da Hospital, I-Shou University, Kaohsiung 82445, Taiwan
[c] Division of Endocrinology and Metabolism, Department of Internal Medicine, E-Da Hospital, I-Shou University, Kaohsiung 82445, Taiwan
[d] Department of Emergency, E-Da Hospital, I-Shou University, Kaohsiung 82445, Taiwan
[e] Division of Cardiology, Department of Internal Medicine, National Yang-Ming University Hospital, Yilan 26058, Taiwan
[f] School of Medicine for International Students, Institute of Biotechnology and Chemical Engineering, I-Shou University, Kaohsiung 82445, Taiwan
[g] Department of Nutrition, Institute of Biotechnology and Chemical Engineering, I-Shou University, Kaohsiung 82445, Taiwan
[h] Lee's Endocrinologic Clinic, Pingtung 90000, Taiwan

ARTICLE INFO

Keywords:
Chronic kidney disease
Glomerular filtration rate
Secreted frizzled-related protein-5
ST-segment elevation myocardial infarction

ABSTRACT

Secreted frizzled-related protein-5 (Sfrp5) known as secreted antagonist binds to Wnt protein. It has been shown to be downregulated by histone acetylation and promoter methylation, and to function as a tumor suppressor gene by inducing apoptosis in renal cell cancer cells. However, its relationship with chronic kidney disease (CKD) has not been well studied. Our objective was to investigate the effect of plasma Sfrp5 levels in subjects with and without CKD. Plasma Sfrp5 levels were determined by enzyme-linked immunosorbent assays in 196 consecutive patients with acute ST-segment elevation myocardial infarction (STEMI). CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min per 1.73 m^2. For the purpose of this study, stage 1 or 2 CKD patients (eGFR ≥ 60 ml/min per 1.73 m^2) were classified as not having CKD. With increasing Sfrp5 tertiles, the patients had higher frequencies of hypertension, stage 4 or 5 CKD, and waist-to-hip ratio, incrementally lower eGFRs and serum hemoglobin levels, and higher levels of blood urine nitrogen (BUN), creatinine, and adiponectin. Multivariate logistic regression analysis showed that an increased plasma Sfrp5 level was independently associated with CKD for all subjects (adjusted odds ratio (OR), 1.08; 95% confidence interval (CI), 1.02–1.14; p = 0.011). Sfrp5 was also significantly positively related to BUN, creatinine, and adiponectin, and significantly negatively related to eGFR and hemoglobin. When the patients were stratified by age, plasma Sfrp5 level was independently related to CKD for patients > 65 years old (adjusted OR, 1.10; 95% CI, 1.00–1.20; p = 0.045), however, the association was not significant for those < 65 years old. In addition, Sfrp5 was significantly positively related to BUN, creatinine, and adiponectin, and significantly negatively related to eGFR and hemoglobin in patients > 65 years old. Our results suggest that Sfrp5 may play a role in the pathogenesis of CKD in acute STEMI patients who are older than 65 years.

1. Introduction

Chronic kidney disease (CKD) has emerged as a major public health burden worldwide. Renal tubulointerstitial fibrosis is the final common pathway of progressive CKD [1,2]. In addition, fibrotic damage is described by increases in myofibroblasts and interstitial fibroblasts [3]. Previous studies have shown that epithelial-to-mesenchymal transition is the crucial process in renal fibrosis, in which tubular epithelial cells are transformed into myofibroblasts and interstitial fibroblasts by the activation of signaling pathways such as Wnt and TGF-β pathways [4–6].

Wnt family members are secreted glycoproteins that play important

* Corresponding author at: E-Da Hospital, I-Shou University, No. 1, Yi-Da Rd, Jiau-Shu Village, Yan-Chao Township, Kaohsiung 82445, Taiwan.
E-mail addresses: ed100232@livemail.tw (C.-P. Wang), tenghungy@yahoo.com.tw (T.-H. Yu), maxvic24@gmail.com (C.-C. Wu), hwc.cct@msa.hinet.net (W.-C. Hung), aladarhsu1107@gmail.com (C.-C. Hsu), tsai.iting@gmail.com (I.-T. Tsai), africapaul12@yahoo.com (W.-H. Tang), chungfumei@gmail.com (F.-M. Chung), jyhoung@isu.edu.tw (J.-Y. Houng), lee@leesclinic.org (Y.-J. Lee), gregory.yclu@msa.hinet.net (Y.-C. Lu).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.cyto.2018.04.009
Received 20 July 2017; Received in revised form 5 March 2018; Accepted 7 April 2018

roles in several cellular functions [7,8]. Alterations in Wnt signaling play a crucial role in chronic organ failure [9] either directly through the activation of downstream channel proteins of the Wnt signaling cascade or through the overexpression of Wnt ligands. The key genes in Wnt signaling have been shown to be markedly upregulated in patients with CKD, and to be involved in cell adhesion, differentiation, proliferation, polarization, migration, and invasion [10]. Doxorubicin can induce the activation of Wnt/β-catenin thereby inhibiting the expression of nephrin and subsequent formation of proteinuria [11]. It has also been reported that in patients with stage 4 or 5 CKD, the genetic expression of Wnt signaling in mononuclear blood cells is markedly elevated [12]. Moreover, the Wnt/β-catenin pathway has also been shown to be activated in the process of kidney development and renal fibrosis [13–15].

Secreted frizzled-related protein (Sfrp) is a secreted Wnt antagonist which interacts directly with the Wnt ligand [16–18]. The Sfrp family consists of five members (Sfrp1 to Sfrp5). Among the five Sfrp family members, Sfrp1, Sfrp2, and Sfrp5 are classified as the Sfrp1 subfamily due to similarities in their sequences [18]. The redundancy of the protein function was noted in the single knock-out mice null for Sfrp1, Sfrp2, or Sfrp5, however, double or triple Sfrp knock-out mice have a embryonic lethal phenotype with reduced anterior-posterior patterning [19]. In addition, previous studies shown that one of the function of Sfrp1/2/5 is regulate Wnt/β-catenin and Wnt/PCP pathways [19,20]. Sfrp5, a recently discovered protein secreted by adipocytes, has also been shown to be involved in inflammation and insulin resistance in mouse models of obesity and type 2 diabetes mellitus [21]. A previous, study also showed that Sfrp5 is downregulated by histone acetylation and promoter methylation, and that it can function as a tumor suppressor gene that induces apoptosis in renal cell cancer cells [22]. However, little is known about the function of Sfrp5 in pathological CKD.

The aim of the present study was to clarify the clinical significance of circulating Sfrp5 levels in the context of CKD. We determined circulating Sfrp5 levels in acute ST-segment elevation myocardial infarction (STEMI) patients who did or did not have CKD, and then evaluated the association between those levels and the risk of CKD. In addition, we also evaluated the relationship between plasma Sfrp5 levels and CKD according to the age of the patients.

2. Material and methods

2.1 Study participants

We prospectively enrolled 214 consecutive patients with acute STEMI who were admitted to the Cardiovascular Ward of E-Da Hospital between June 2015 and June 2016. The estimated glomerular filtration rates (eGFRs) were calculated by the CKD-EPI two-concentration race equation [23], and the status of CKD was confirmed by follow-up eGFR measurements 3 months after hospital discharge. We used the modified National Kidney Foundation classification of CKD [24]. In the present study, an eGFR < 60 ml/min per 1.73 m^2 was defined as CKD, and patients with stage 1 or 2 CKD (eGFR ≥ 60 ml/min per 1.73 m^2) were classified as not having CKD [25]. The patients with a history of concomitant inflammatory diseases (including liver disease, malignancy, sepsis, infection, and collagen disease), surgery or steroid use within 1 month prior to admission on the basis of interviews, biochemistry laboratory, physical examinations data and urinalysis were excluded from the study. In addition, patients who were unable or unwilling to give informed consent wee also excluded. After excluding 18 patients, a total of 196 patients with acute STEMI were included in this study. Diabetic patients were defined as those who were currently being treated for diabetes, those with a fasting plasma glucose level equal or greater than 126 mg/dl on 3 separate days, or casual glucose level ≥ 200 mg/dl. Hypertension was defined as resting systolic blood pressure of ≥ 140 mmHg, diastolic blood pressure of ≥ 90 mmHg or both, and those with a history of hypertension and the use of anti-hypertensive drugs. Hyperlipidemia was defined as a total cholesterol level of > 200 mg/dl, and/or a low-density lipoprotein cholesterol (LDL-C) level of > 130 mg/dl, and/or a high-density lipoprotein cholesterol (HDL-C) level of < 40 mg/dl, and/or a triglycerides level of > 180 mg/dl, or those undergoing treatment for lipid disorders. The study protocol was approved by the Human Research Ethics Committee of our hospital. All patients provide written informed consent before enrollment.

In the present study, all of the study patients were of Han Chinese origin and lived in the same region. All patients underwent complete routine biochemical analyses of blood and urine and physical examinations. Anthropometric parameters included the waist-to-hip ratio and body mass index (BMI). Waist and hip circumferences were measured at the end of a normal respiration and each measurement is repeated twice. The measurements are taken as the nearest 0.1 cm at the narrowest point between the lower border of the ribs and the right iliac crest, and hip circumferences were measured at the widest point. Seated blood pressure was also measured by a trained nurse with a digital automatic blood pressure monitor (Omron model HEM-907, Omron, Japan) after the patients had rested for 5 min. Plasma biochemical parameters were measured after overnight fasting. Plasma total cholesterol, LDL-C, HDL-C, triglycerides, creatinine, glucose, and uric acid were measured with standard commercial methods as described in our previous reports [26,27]. The patients who had smoked within one year of the examination were defined as current smokers, and those who had stopped smoking for more than one year before the examination were defined as nonsmokers.

2.2 Plasma adiponectin, hs-CRP, and Sfrp5 measurements

All patients of blood samples were drawn after overnight fasting, and all the plasma samples were kept at -80 °C for subsequent assay. The concentrations of plasma Sfrp5 were measured by using a commercial enzyme-linked immunosorbent assay (ELISA) kit (NovaTec Immundiagnostica GmbH, Dietzenbach, Germany and Wuhan ElAab Science Co., Ltd, China). The analytical sensitivity was 0.64 ng/mL for Sfrp5. The ELISA was performed according to the instructions of the manufacturer. On the basis of the manufacturer, the Sfrp5 ELISA had excellent specificity for the detection of human Sfrp5, and no significant interference with analogues or cross-reactivity was observed. The molecular weight of high plasma adiponectin concentrations was measured by commercial solid phase ELISA kit (B-Bridge International, Sunnyvale, CA), with the dilution curve in parallel to the standard curve. The intra- and inter-assay coefficients of variation of the assay were 3.2–7.3% (n = 3) and 3.1–6.2% (n = 4), respectively. In addition, plasma high sensitivity C-reactive protein (hs-CRP) was determined using a Beckman Coulter IMMAGE Immunochemistry System (Brea, CA). Samples were measured in duplicate in a single experiment and the detection limit of this hs-CRP assay system was 0.2 mg/L.

2.3 Statistical analysis

Data normality was analyzed using the Kolmogorov-Smirnov test. Continuous normally distributed variables are described as mean ± standard deviation. Non-normally distributed variables are described as median (interquartile range). Statistical differences in variables were compared using a one-way ANOVA for variables of normal distribution followed by the Tukey pairwise comparison. Categorical variables are presented as frequencies and percentages, and inter-group comparisons were tested using the chi-square test. Logarithmically transformed values of plasma Sfrp5, hs-CRP, adiponectin, and triglyceride were used in the statistical analysis since their distributions were skewed. Associations between the presence of CKD and clinical/biochemical parameters including sex, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, total cholesterol, triglyceride,