ความสัมพันธ์ระหว่างโรคปริทันต์อักเสบเรื้อรังกับเอสเอสทีทูในซีรัมซึ่งเป็นสารบ่งชี้ทางชีวภาพของโรคหัวใจในประชากรไทย

Association between Chronic Periodontitis and Serum sST2, Cardiac Biomarker, in a Thai Population

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บทคัดย่อ

โรคปริทันต์อักเสบเรื้อรังคือโรคที่มีการอักเสบของเนื้อเยื่อรองรับฟันซึ่งไซโทไคน์ที่เกี่ยวกับการอักเสบจากรอยโรคปริทันต์สามารถหลุดเข้าสู่กระแสเลือดและทำให้เกิดการอักเสบทั่วร่างกายได้ สำหรับเอสเอสทีทูเป็นสารบ่งชี้ทางชีวภาพของโรคหัวใจถูกหลั่งเพื่อตอบสนองต่อการอักเสบ ดังนั้นวัตถุประสงค์ของการศึกษานี้เพื่อศึกษาว่าโรคปริทันต์อักเสบเรื้อรังมีความสัมพันธ์กับการเพิ่มระดับเอสเอสทีทูในซีรัมของประชากรไทยหรือไม่ โดยมีผู้เข้าร่วมการศึกษา 1,872คน อายุเฉลี่ย59.4±4.6 ปี ซึ่ง209 คนได้รับการวินิจฉัยว่าไม่เป็นหรือเป็นโรคปริทันต์อักเสบระดับน้อย ในขณะที่อีก984 และ 679 คน ได้รับการวินิจฉัยว่าเป็นโรคปริทันต์อักเสบระดับปานกลางและระดับรุนแรงตามลำดับ ค่ามัธยฐานของเอสเอสทีทูมีค่า 18.1นาโนกรัม/มิลลิลิตร โดยในเพศชายมีค่าสูงกว่าเพศหญิง (18.8 เทียบกับ15.7 นาโนกรัม/มิลลิลิตร) การวิเคราะห์การถดถอยเชิงเส้นแสดงให้เห็นว่าระดับเอสเอสทีทูมีความสัมพันธ์กับแอสปาร์เทต อะมีโนทรานสเฟอเรส แกมมากลูตามิลย์ทรานสเฟอเรส แอลบูมินเบาหวาน ไตรกลีเซอไรด์ และเพศ โดยเอสเอสทีทูในเพศชายมีความสัมพันธ์กับแอสปาร์เทต อะมีโนทรานสเฟอเรส แกมมากลูตามิลย์ทรานสเฟอเรสเบาหวาน และ ไตรกลีเซอไรด์ เอสเอสทีทูในเพศหญิงมีความสัมพันธ์กับแอสปาร์เทต อะมีโนทรานสเฟอเรส แอลบูมิน และโรคปริทันต์อักเสบเรื้อรังระดับปานกลางและระดับรุนแรง ผลการศึกษานี้แสดงให้เห็นว่าเอสเอสทีทูมีความสัมพันธ์กับโรคปริทันต์อักเสบเรื้อรังเฉพาะในเพศหญิง

คำสำคัญ: *โรคปริทันต์อักเสบโรคหัวใจและหลอดเลือดเอสเอสทีทูในซีรัม*

Abstract

Chronic periodontitis is an inflammatory disease of tooth supporting tissues. Inflammatory cytokines produced from periodontitis lesions could leak into circulation and cause systemic inflammation. sST2 is a cardiac biomarker that is secreted in response to systemic inflammation. Therefore, this study aimed to examine whether chronic periodontitis is associated with an increased level of serum sST2 in a Thai population. The study subjects comprised of 1,872 individuals with mean age of 59.4±4.6 years. Of these, 209 individuals were diagnosed with no/ mild chronic periodontitis, while 984 and 679 individuals were diagnosed with moderate and severe chronic periodontitis, respectively. The median sST2 concentration was 18.1 ng/ml. The concentration was higher in male than in female (18.8 VS15.7 ng/ml). Linear regression analysis demonstrated that sST2 levels were associated with aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), albumin, diabetes, triglyceride and sex. The concentration of sST2 in male was associated with AST, GGT, albumin, diabetes and triglyceride. The sST2 in female subjects was associated with AST, albumin, and moderate and severe chronic periodontitis. The findings of the present study indicated that sST2 was associated with chronic periodontitis in female subjects only.

Keywords: *Periodontitis, Cardiovascular disease, serum sST2*

1. Introduction

Chronic periodontitis is an inflammatory disease caused by subgingival plaque microorganisms and progresses due to host immuno-inflammatory response, resulting in periodontal destruction and chronic inflammation. Evidence from epidemiological studies suggests that periodontitis may be associated with an increased risk of atherosclerotic cardiovascular disease (Dietrich et al., 2013). Pro-inflammatory cytokines locally produced from periodontitis lesions such as IL-1α, IL-1β and TNF-α could leak into blood stream, resulting in systemic inflammation(Li et al., 2000), and thus may have an indirect effect on atherosclerosis (Libby, 2006). The studies had been trying to link both diseases by observing inflammatory biomarkers(D'Aiuto et al., 2004, Paraskevas et al., 2008). One of the most studied biomarkers is C-reactive protein (CRP). The serum levels of CRP were increased in subjects with periodontitis whencompared to healthy subjects and were associated withthe riskof cardiovascular disease (CVD) (D'Aiuto et al., 2004). ST2 is a member of the toll-like/interleukine-1 receptor (IL-1R) superfamily. Ithas two main isoforms; transmembrane ST2 (ST2L) and soluble ST2 (sST2) (Ciccone et al., 2013). ST2L binding with IL-33 results in cardioprotection by reducing fibrosis, cardiac hypertrophy and myocyte apoptosis (Sanada et al., 2007). However, sST2 acts as a decoy receptor, preventing those beneficial effects of IL-33 to the heart.

As a result, the serum levels of sST2 have been used as a negative prognosis biomarker of CVD (Mueller et al., 2008). A study in a Thai population showed that sST2 was a good prognostic marker to

predict mortality from heart disease and its ability was superior to CRP (Chanyavanich et al., 2014). An in vitro study showed that cardiac myocytes and alveolar epithelial cells incubated with IL-1α, IL-1β, TNF-α and supernatants derived from LPS-stimulated peripheral blood mononuclear had an increased sST2 secretion (Mildner et al. , 2010) . Because these cytokines are commonly found in subjects with chronic periodontitis, it is reasonable to hypothesize that serum sST2 levels may be elevated in subjects with chronic periodontitis. Nevertheless, linking of periodontitis and serum sST2 levels in community-based studies has not been done before. Therefore, the objective of this research is to examine the association between periodontal disease severity and serum sST2 levels in a Thai population.

2. Objectives

To evaluate the association between periodontal status and levels of serum sST2 in a Thai population.

3. Materials and Methodology

This cross-sectional study was conducted among the EGAT (Electricity Generating Authority of Thailand) employees in year 2002. The study was approved by the Ethics Review Committee of the Faculty of Medicine at Ramathibodi Hospital, Mahidol University and Faculty of Dentistry at Chulalongkorn University, Bangkok, Thailand. All subjects signed an inform consent prior to the study.

3.1 Study Design

Medical data were received from Ramathibodi Hospital. Medical examinations consisting of blood and urine analyses, EKG, chest x-rays and anthropometric measurements. Blood samples were stored at -80°C in year 2002 and were thawed for measurement of sST2 in year 2013. The sST2 levels were measured in citrated plasma using a highly sensitive ELISA (Pressage®ST2 assay, Critical Diagnostics, San Diego, CA, USA) which the detection limit was 2 ng/mL (Dieplinger et al., 2009). Sociodemographic characteristics were obtainedby a questionnaire.

Periodontal examinations were carried out by four experienced periodontists and three post-graduate students from the Department of Periodontology, Faculty of Dentistry, Chulalongkorn University as described in prior study (Torrungruang et al. , 2005) . One maxillary quadrant and one contralateral mandibular quadrant were randomly selected. All teeth in these quadrants were examined except third molars and retained roots. The examinations included the number of missing teeth, probing depth (PD) and gingival recession. PD and gingival recession were measured using a manual probe (PCP-UNC 15, Hu-Friedy Manufacturing Co., Chicago, IL, USA) on six sitesper tooth. Clinical attachment level (CAL) was calculated as the sum of PD and gingival recession.

3.2 Statistical methods

Subjects were categorized into 3 groups according to the CDC/AAP case definition (Page and

Eke, 2007). Group 1 was no/mild chronic periodontitis (< 2 interproximal sites with CAL □ 4 mm and <2 interproximal sites with PD □ 5 mm). Group 2 was moderate chronic periodontitis (□ 2 interproximal sites with CAL □ 4 mm (not on the same tooth), or □ 2 interproximal sites with PD □ 5 mm (not on the same tooth)) . Group 3 was severe chronic periodontitis (□ 2 interproximal sites with CAL □ 6 mm (not on the same tooth) and □ 1 interproximal site with PD □ 5 mm)

SPSS version 17. 0 software (SPSS Inc, Chicago, USA) was used to analyze the data. The sST2 data were not normally distributed, therefore they were presented as median and interquartile ranges (IQR). To compare the medians between three groups, Kruskal-Wallis test and Mann-Whitney U test were used for analysis. The analysis of differences in median between two groups was performed using Mann-Whitney U test. The association of the sST2 with the independent variables was assessed by univariate and multivariate linear regression analysis. For multivariate model, the forward method was used by adding the most significant variable until no more variable was eligible to add. The following independent variables were entered into the forward linear regression models: age, sex, education, income, BMI, aspartate aminotransferase (AST) , gamma-glutamyl transferase (GGT) , albumin, HDL, LDL, triglycerides, cholesterol, diabetes, blood pressure, smoking, drinking, plaque index and chronic periodontitis. Statistical differences with P-value < 0.05 were considered significant.

4. Results

From 2,360 subjects who participated in this study, 2,276 subjects received both medical and dental examinations. We excluded 271 subjects who did not have data on periodontal measurements, 6 subjects who required antibiotic prophylaxis, 54 edentulous subjects, 211 subjects who had fewer than six teeth present in the selected two quadrants (Torrungruang et al., 2005). We also excluded 133 subjects who did not have data on sST2. Total number of subject included in this study was 1,872. The mean age of subjects was 59. 4±4. 6 years and 75. 6% were male. 11. 2% of subjects were diagnosed with no/ mild chronic periodontitis, 52. 5% with moderate chronic periodontitis and 36. 3% with severe chronic periodontitis.

The overall median of sST2 concentration was 18. 1(14. 3-22. 5) ng/ ml. The concentration was 18.8 (14.9-23.3) ng/ml in male and 15.7 (12.9-19.8) ng/ ml in female, in which the difference was statistically significant (P < 0. 001) (Table 1) . Moreover, the sST2 level was higher in subjects with diabetes than in those without disease (P < 0.001). In pairwise analysis, differences in sST2 levels were observed between subjects with severe chronic periodontitis and those with no/ mild chronic periodontitis (P = 0.002). Moreover, the sST2 levels were higher in former smokers when compared to non-smokers (P<0. 001) and were higher in current drinkers when compared to non/occasional drinkers (P <0.001).

Table 1 Serum sST2 levels in relation to clinical parameters.

Variable	%	sST2levels (Median(IQR))	P	
1. Sex: Male	75.6	18.8 (14.9-23.3)	<0.001†	
: Female	24.4	15.7 (12.9-19.8)		
2. Diabetes: Yes	16.0	19.6 (15.6-24.7)	<0.001†	
: No	84.0	17.8 (14.2-22.0)		
3. Periodontitis			0.01¶	
: No/mild	11.2	17.0 (13.2-21.3)		
: Moderate	52.5	18.1 (14.3-22.6)		*
: Severe	36.3	18.5 (14.7-23.0)		
4. Smoking			0.002¶	
: Non-smoker	47.8	17.3 (14.0-21.6)		
: Former smoker	37.6	19.1 (15.0-23.4)		*
: Current smoker	14.6	18.1 (14.6-23.2)		
5. Alcohol			<0.001¶	
: Never/occasional	55.2	17.5 (13.2-21.7)		
: Quit	17.2	17.3 (14.3-21.5)		*
: Current	27.6	19.0 (14.8-23.7)		

¶The data was analyzed by Kruskal-Wallis H test. † The data was analyzed by Mann-Whitney U test. * Significant difference between groups at P < 0.005, analyzed using Mann-Whitney U test.

Univariate linear regression analysis showed that sST2 levels were associated with sex, GGT, AST, albumin, triglyceride, LDL, diabetes, smoking, drinking and plaque index (P < 0. 05) (Table 2). However, the association between sST2 levels and severe chronic periodontitis was marginally significant (P = 0.05). According to multivariate linear regression model, AST, GGT, albumin, diabetes, triglyceride and sex were significantly associated with sST2 levels (P < 0.05).

Table 2 Linear regression models estimating the association between sST2 and independentvariables.

VAR	Univariable*			Multivariable†		
	β	SE	P	β	SE	P
Sex	-3.14	0.48	<0.01	-2.19	0.48	<0.01
GGT	0.04	0.00	<0.01	0.02	0.00	<0.01
AST	0.14	0.01	<0.01	0.10	0.01	<0.01
Alb	-0.42	0.06	<0.01	-0.31	0.07	<0.01
DM	3.10	0.56	<0.01	2.26	0.59	<0.01
TG	0.01	0.002	<0.01	0.00	0.00	<0.01
LDL	-0.01	0.01	<0.01	-	-	-
Smk	0.99	0.02	0.001	-	-	-
Alc	0.69	0.17	<0.01	-	-	-
PI	0.02	0.01	<0.01	-	-	-
CP1	-0.04	0.42	0.91	-	-	-
CP2	0.83	0.43	0.05	-	-	-

Abbreviations: VAR = variable, β= regression coefficient, SE = standard error, GGT = gamma-glutamyl transferase, AST = aspartate aminotransferase, Alb = albumin, DM = diabetes, TG = triglyceride, LDL = low density lipoprotein, Smk = smoking, Alc = alcohol, PI = plaque index, CP1 = moderate chronic periodontitis, CP2 = severe chronic periodontitis. * Linear regression analysis of each variable individually. † Multivariate linear regression analysis, building by forward method.

Because sST2 levels were much higher in male than in female, multivariatelinear regression modelswere built separately for male and female. The result showed that factors influencing sST2 levels differed between sexes. In male, sST2 was associated with AST, GGT, albumin, diabetes and triglyceride (Table 3). In female, the concentration of sST2 was

associated with AST, albumin, and moderate and severe chronic periodontitis.

Table 3 Multivariate linear regression models estimating the association between sST2 and independent variables, categorized by sex[†].

VAR	Male			Female		
	β	SE	P	β	SE	P
GGT	0.028	0.004	<0.01	-	-	-
AST	0.119	0.017	<0.01	0.071	0.022	<0.01
Alb	-0.328	0.089	<0.01	-0.21	0.085	0.01
DM	2.443	0.721	<0.01	-	-	-
TG	-0.008	0.004	0.02	-	-	-
CP1	-	-	-	1.575	0.663	0.01
CP2	-	-	-	2.022	0.829	0.01

Abbreviations: VAR = variable, β= regression coefficient,SE = standard error, GGT = gamma-glutamyl transferase, AST = aspartate aminotransferase, Alb = albumin,DM = diabetes, TG = triglyceride, CP1 = moderate chronic periodontitis, CP2 = severe chronic periodontitis. [†] Multivariate linear regression analysis, building by forward method.

5. Discussion

To our knowledge, this is a first community-based study of the association between chronic periodontitis and sST2. The results showed that sST2 concentrations were associated with AST, GGT, albumin, diabetes, triglyceride and sex. The subgroup analysis by sex demonstrated that sST2 levels were associated with AST, GGT, albumin, diabetes and triglyceride in male, but were associated with AST, albumin and chronic periodontitis in female.

Our study found that sST2 concentrations were higher in men than in women. This finding is in agreement with previous studies (Chanyavanich et al., 2014, Coglianese et al., 2012). Several studies have found that sST2 concentrations are varied among individuals and its levels are influenced by age, sex and race (Chanyavanich et al., 2014, Coglianese et al., 2012). A possible explanation of this observation is a genetic factor which may account for approximately 40% of the variation in sST2 levels (Ho et al., 2013). Moreover, the researchers hypothesized that the difference in sST2 levels between sexes may be due to differences in sex hormone. However, a recent study reported that there was no association between the levels of androgen and estrogen and sST2 levels in both genders (Dieplinger et al., 2011). Therefore, biological explanation for the variation of sST2 between sexes is still inconclusive.

We also found that sST2 levels were associated with AST, GGT, albumin, diabetes and triglyceride in our study population. The GGT and AST are well-known liver enzymes that are used to evaluate liver function. They are also found in cell membrane of many tissues such askidney, intestine and heart. Both GGT and AST have been used to predict the risk of mortality and cardiovascular events (Mason et al., 2010, Shen et al., 2015). Moreover, GGT might involve in atheroma formation (Emdin et al., 2005). In addition, a recent study in China found that sST2 levels in heart failure patients were associated with abnormal liver function and low levels of albumin (Zhang et al., 2014). Triglyceride and diabetes are traditional risk factors of CVD and have been used to predict the CVD risk (Khot et al., 2003). Moreover, the association between sST2 and diabetes

has been shown in several studies (Chanyavanich et al., 2014, Coglianese et al., 2012). The association of sST2 with diabetes, triglyceride and enzymes that used to evaluate CVD risk suggests that sST2 levels may be used as an indicator of cardiometabolic syndrome in this population.

In this study, the association between sST2 and chronic periodontitis was found only in female subjects. However, the mechanism linking between sST2 and chronic periodontitis is not clear. An in vitro study showed sST2 mRNA was elevated in periodontal tissues from chronic periodontitis subjects when compared with tissues from healthy periodontium(Malcolm et al., 2015). Moreover, sST2 mRNA expression was upregulated in a cultured gingival cell line after stimulated with *Porphyromonasgingivalis*. In addition, in healthy subjects who were administrated with LPS, serum inflammatory cytokines, including IL-6 and TNF-α were elevated in 4 hours, followed by a massive augmentation of sST2 secretion in 24 hours(Mildner et al., 2010). Therefore, it is possible that periodontal pathogens or cytokines released from tissues with chronic periodontitis may lead to an elevated level of serum sST2.If confirmed in other studies, serum sST2 could be another biological mechanism linking chronic periodontitis to the risk of CVD, particularly in women.

One of the limitations of this study was that the study participants were not randomly selected, thereby may not be representative of the Thai population. However, the EGAT enterprise was composed of the individuals with a wide range of socio-demographic backgrounds (Vathesatogkit et al., 2012). Therefore, these study subjects represented a diverse group of the Thai population. Moreover, periodontal examination in this study was half-mouth examinations that may produce biases for severity and extent of disease estimates. However, a recent systematic review showed that the half mouth analysis based on six-sites examination had a high sensitivity for prevalence estimates and a low bias for severity and extent of disease estimates(Tran et al., 2013).

6. Conclusion

The result of this study showed that sST2 levels were associated with sex, AST, GGT, albumin, diabetes and triglyceride. Moreover, the association between sST2 and chronic periodontitis was shown only in female subjects. However, the mechanism linking between sST2 and chronic periodontitis was still unknown. Therefore, the association between sST2 and chronic periodontitis requires further investigation in both clinical and community-based studies for a better understanding of their association.

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