



## An implication of Klotho-related molecules in different smoking-related health outcomes between men and women



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### ARTICLE INFO

#### Keywords:

Smoking  
 $\alpha$ -Klotho  
 Fibroblast growth factor-21  
 Sex differences  
 Inflammation  
 Metabolic disorders

### ABSTRACT

**Background:** Men and women react differently to some disease states, and women are reported to be more sensitive than men to the toxic effects of smoking. We examined the serum concentration of Klotho-related molecules,  $\alpha$ -Klotho ( $\alpha$ Kl) and fibroblast growth factor (FGF)-21, and the influence of smoking on these molecules in both sexes.

**Methods:** Subjects included 90 men and 140 women in good health who underwent a health examination.

**Results:** Among male subjects, serum concentrations of FGF-21, soluble  $\alpha$ Kl, and inflammation-related cytokine interleukin (IL)-6 were significantly higher in smokers than in never-smokers. In females, serum concentrations of FGF-21 and IL-6 were significantly higher in smokers than in never-smokers; however,  $\alpha$ Kl concentrations were slightly lower in smokers than in never-smokers. Serum concentrations of  $\alpha$ Kl were correlated with smoking status and IL-6 only in male subjects, suggesting an anti-inflammatory effect of  $\alpha$ Kl only in men. Serum concentrations of FGF-21 were correlated with the concentrations of total cholesterol, triglycerides, and HbA1c, which are important factors of metabolic disorders in females, suggesting that metabolic disorders in female smokers may be more serious than that in male smokers.

**Conclusions:** Klotho-related molecules showed a differential association and response to smoking between men and women.

### 1. Introduction

Since there are biological and physiological differences between men and women, some symptoms, reactions to illness, and pathogenesis of disease are different in men and women. Recently, it has been focused to consider the effects of sex differences on health outcomes. Smoking is the leading preventable cause of mortality and morbidity in modern society. It is well known that smoking is a pivotal risk factor for various diseases, such as cardiovascular disease, cancer, and pulmonary disease [1,2]. Although smoking rates are declining, the smoking rate among females is increasing in some populations [3]. As female smokers have a higher risk of lung cancer than male smokers, women are more sensitive than men to some of the toxic effects of smoking [4,5]. Female smokers have been reported to have a higher relative risk of cardiovascular disease than male smokers; however, the molecular mechanisms of sex differences in relation to cardiovascular risk factors have not been elucidated [6,7]. We reported that visceral fat

accumulation was evident, especially in female smokers [8].

We previously reported an association between smoking and Klotho-related molecules  $\alpha$ -Klotho ( $\alpha$ Kl) and fibroblast growth factor (FGF)-21 in male subjects [9].  $\alpha$ Kl is known as an anti-aging gene, and  $\alpha$ Kl gene-deficient mice show aging phenotypes such as skin atrophy, osteoporosis, atherosclerosis, and pulmonary emphysema [10,11]. A soluble form of  $\alpha$ Kl exists in serum and it is reported to decrease with aging. Serum  $\alpha$ Kl concentrations are also reported to change in some disease states [12–14]. FGF-21 is secreted from the liver and interacts with  $\alpha$ -Klotho, a homolog of  $\alpha$ Kl. FGF-21 plays a role in glucose and lipid homeostasis [15]. Serum FGF-21 concentration are shown to increase in subjects with metabolic syndrome, non-alcoholic fatty liver, hyperlipidemia, hypertension, and atherosclerosis [16,17].

We demonstrated that smoking simultaneously increased these 2 Klotho-related molecules in male subjects [9], however, the study included only male subjects and sex differences were not assessed. Since these Klotho-related molecules are relevant to various diseases,

**Abbreviations:** WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure;  $\gamma$ -GTP,  $\gamma$ -glutamyl transaminase; TC, total cholesterol; TG, triglycerides; FGF-21, fibroblast growth factor-21;  $\alpha$ Kl, soluble alpha-Klotho; IL-6, interleukin-6

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<https://doi.org/10.1016/j.cca.2017.11.007>

Received 27 September 2017; Received in revised form 23 October 2017; Accepted 8 November 2017

Available online 10 November 2017

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examining and analyzing sex differences of these molecules may help explain differences in health outcomes between men and women. In the present study, we measured the concentrations of Klotho-related molecules  $\alpha$ Kl and FGF-21 in both sexes. In addition, to consider the influence of smoking, we compared the concentrations of these molecules between smokers and never-smokers of both sexes.

## 2. Methods

### 2.1. Study subjects

The subjects were individuals who underwent a health examination in the Osaka University Health and Counseling Center. Subjects were apparently healthy Japanese; 90 male and age-matched 140 female, 40–64 y, did not take any chronic or frequent medicine from at least 1 y before visiting the health examinations, and did not suffer acute illness within two weeks. This information was obtained via questionnaires and also reconfirmed in expert interview by trained nurses. To evaluate the precise influence by smoking habit, age and body mass index (BMI) were matched among smokers (45 male and 70 female): only current smokers were selected as smokers, and never-smokers (45 male and 70 female) in both sexes. This study was carried out in accordance with the Declaration of Helsinki and the ethics guidelines for clinical research from the Ministry of Health, Labour and Welfare and the Ministry of Education, Culture, Sports, Science and Technology. All experimental protocols in this study were approved by the Ethics Committee of Health and Counseling Center, Osaka University and written informed consent was obtained from all subjects prior to participation in the study.

### 2.2. Physical and biochemical parameters

BMI and waist circumference (WC) were measured as anthropometric measurements. WC at the umbilical concentration was measured in the late exhalation phase in standing position. Serum was collected from subjects after overnight fasting and kept at  $\leq -20$  °C until assay. The serum interleukin (IL)-6 concentration was measured with a chemiluminescent enzyme immunoassay (CLEIA) system (Fujirebio Inc.). Serum concentrations of soluble  $\alpha$ Kl and FGF-21 were measured with a sandwich enzyme-linked immunoassay (ELISA) system according to the manufacturer's instructions (Immuno-Biological Labs and R&D Systems Inc.).

### 2.3. Lifestyle assessments

Information on medical history, use of medicines and personal smoking status, and psychological stress were obtained via questionnaires. Each information was reconfirmed in expert interview by trained nurses. Smoking status and psychological stress was semi-quantified as following scale. Smoking status: 0 = never-smoker, 1 = smoker, psychological stress: 1 = almost no stress, 2 = sometimes feel stressed, 3 = often feel stressed, 4 = always feel stressed.

### 2.4. Statistical analysis

All statistical analyses were performed using Stata 14. Student's *t*-test or Mann-Whitney *U* test was used to assess the difference between 2 groups. Kendall's rank correlation coefficient was used to analyze the correlations between each variables. Statistical significance was set at  $P < 0.05$ .

**Table 1**  
Characteristics of the study subjects.

	All	Male	Female	P-value
	(n = 230)	(n = 90)	(n = 140)	
Age (years)	47.3 ± 6.4	47.7 ± 6.6	47.1 ± 6.3	0.5231
BMI (kg/m <sup>2</sup> )	21.8 ± 2.7	23.3 ± 2.6	20.8 ± 2.4***	< 0.0001
WC (cm)	76.4 ± 8.6	82.2 ± 6.9	72.7 ± 7.3***	< 0.0001
SBP (mm Hg)	115 ± 15	122 ± 14	111 ± 14***	< 0.0001
DBP (mm Hg)	73 ± 11	79 ± 10	69 ± 10***	< 0.0001
AST (IU/l)	20 ± 6	22 ± 8	19 ± 3**	0.0001
ALT (IU/l)	19 ± 13	27 ± 17	14 ± 4***	< 0.0001
$\gamma$ GTP (IU/l)	32 ± 26	48 ± 33	21 ± 13***	< 0.0001
TC (mg/dl)	201 ± 30	206 ± 32	198 ± 29*	0.0336
TG (mg/dl)	89 ± 57	110 ± 76	75 ± 35***	< 0.0001
HDL-C (mg/dl)	64 ± 15	59 ± 15	67 ± 13***	< 0.0001
HbA1c (%)	5.3 ± 0.6	5.5 ± 0.8	5.2 ± 0.3**	0.0010
FGF-21 (pg/ml)	164 ± 132	237 ± 168	124 ± 83***	< 0.0001
$\alpha$ Kl (pg/ml)	531 ± 180	509 ± 181	545 ± 177	0.1779
IL-6 (pg/ml)	1.6 ± 0.7	2.0 ± 0.8	1.4 ± 0.5***	< 0.0001

Data are expressed as mean ± SD.

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase;  $\gamma$ GTP,  $\gamma$  guanosine-5'-triphosphate; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; FGF-21, fibroblast growth factor-21;  $\alpha$ Kl, soluble alpha-klotho; IL-6, interleukin-6.

\*  $P < 0.05$ .

\*\*  $P < 0.005$ .

\*\*\*  $P < 0.0001$  versus male.

## 3. Results

### 3.1. Comparison of physical and biochemical parameters in males and females

The characteristics of the study subjects are shown in Table 1. The mean ages of the male and female subjects were  $47.7 \pm 6.6$  and  $47.1 \pm 6.3$  y, respectively. BMI, WC, systolic blood pressure (SBP) diastolic blood pressure (DBP), aspartate aminotransferase (AST), alanine aminotransferase (ALT),  $\gamma$ -guanosine-5'-triphosphate ( $\gamma$ -GTP), total cholesterol (TC), triglycerides (TG), HbA1c, FGF-21, and IL-6 were all significantly higher in males than in females. In contrast, high-density lipoprotein-cholesterol concentrations were significantly higher in females than in males.

Table 2 shows the characteristics of never-smokers versus smokers in both sexes. Among male subjects, serum concentrations of FGF-21,  $\alpha$ Kl, and IL-6 were significantly higher in smokers than in never-smokers. Among female subjects, serum concentrations of FGF-21 and IL-6 were significantly higher in smokers than in never-smokers, as was the case for male subjects. However, unlike in male smokers, increased serum concentrations of  $\alpha$ Kl were not observed in female smokers.

In the study, the mean age in female subjects was close to the average age of menopause: 50 y. Since menopause causes various effects to women, we divided the female subjects into 2 groups at 50 y and examined the characteristics in both groups (see Supplementary Table S1). Among younger group (< 50 y), serum concentrations of FGF-21 were significantly higher in smokers than in never-smokers. Serum concentrations of  $\alpha$ Kl tended to decrease and IL-6 tended to increase in smokers, as was the case for all female subjects, however significant differences were not observed. Among elder group ( $\geq 50$  y), serum concentrations of FGF-21,  $\alpha$ Kl, and IL-6 did not show any significant differences, but same tendency as in younger group and all female subjects was observed.

The details of smoking habit in smokers are summarized in Table 3. As smoking amount was significantly higher in male smokers than in female smokers, we examined the correlations between smoking amount and serum concentrations of FGF-21,  $\alpha$ Kl, and IL-6. However, significant correlations were not shown (see Supplementary Table S2).

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