BMC Oral Health

RESEARCH

Open Access

The elevation of fibroblast growth factor 21 is associated with generalized periodontitis in patients with treated metabolic syndrome

Teerat Sawangpanyangkura[1], Panwadee Bandhaya[1], Pattanin Montreekachon[1], Anongwee Leewananthawet[1], Arintaya Phrommintikul[2], Nipon Chattipakorn[3,4] and Siriporn C. Chattipakorn[3,4,5*]

Abstract

Background: Fibroblast growth factor 21 (FGF21) is closely associated with metabolic syndrome (MetS). An alteration of FGF21 is possibly affected by periodontitis. The present study aimed to investigate the levels of serum FGF21 in MetS patients with generalized periodontitis and its association with periodontal and metabolic parameters.

Methods: One hundred forty-six MetS patients were recruited from the CORE (Cohort Of patients at a high Risk for Cardiovascular Events) Thailand registry. All participants received general data interviewing, periodontal examination and blood collection for measurement of FGF21 levels and biochemistry parameters. Periodontitis was defined according to the new classification and divided into two groups of localized periodontitis and generalized periodontitis.

Results: FGF21 was significantly higher in generalized periodontitis group when compared with localized periodontitis group ($p < 0.05$). The significant correlation was observed between FGF21 and variables including number of remaining teeth, mean clinical attachment loss, hypertriglyceridemia and low high-density lipoprotein cholesterol. The elevation of serum FGF21 was associated with presence of generalized periodontitis after adjusting of covariate factors (OR = 27.12, $p = 0.012$).

Conclusions: The elevation of serum FGF21 might be a potential biomarker for MetS patients who have risk of generalized periodontitis.

Keywords: FGF21, periodontitis, Metabolic syndrome

Background

Fibroblast growth factor 21 (FGF21) is a small molecular weight polypeptide of FGF hormone which is mainly produced in liver [1]. and also expressed in extrahepatic tissues such as adipose tissue and skeletal muscle [2]. FGF21 plays a crucial role in maintaining tissue homeostasis of both glucose and lipid metabolism [3] and responding to various stressful stimuli, such as inflammation [4], oxidative stress and hypoxia [5]. Previous studies showed that the elevation of circulating FGF21 was closely associated with metabolic disorders including obesity, diabetes and metabolic syndrome (MetS) [3, 6].

MetS is defined as a group of metabolic abnormalities including central obesity, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol (HDL-C), hypertension, and an increased fasting plasma glucose level. The studies proposed the significance of MetS as a risk factor of diabetes and cardiovascular disease (CVD)

*Correspondence: siriporn.c@cmu.ac.th; scchattipakorn@gmail.com

[3] Neuroelectrophysiology Unit, Cardiac Electrophysiology Research and Training Center, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand
Full list of author information is available at the end of the article

[7, 8]. An increase of circulating FGF21 in MetS patients was hypothesized as a protective role against to metabolic stress or a compensatory upregulation to FGF21-resistance in tissues induced by obesity [3]. Up to date, multiple findings suggest that FGF21 could be a potential biomarker or promising therapeutic target for MetS [9–12]. In addition, one of the major oral problems which is commonly found in MetS patients is periodontitis [13, 14]. Periodontitis is an inflammatory disease caused by chronic accumulation of dental plaque, leading to the destruction of tooth-supporting tissue and tooth loss [15]. The evidences show that a state of systemic inflammation induced by periodontitis is a major key linking periodontitis to several diseases such as diabetes, CVD and Mets [14, 16, 17]. The several biomarkers linking periodontitis and MetS have been proposed. FGF21 is one of protein molecules that potentially involves the inflammatory and immunity response which is a fundamental process in pathogenesis of MetS and periodontitis. Therefore, FGF21 might be a potential biomarker for linking Mets to periodontitis.

Recently, there have been few attempts determining the level of FGF21 in periodontitis patients. One study showed the higher level of FGF21 in gingiva crevicular fluid (GCF) was collected from diabetic patients combined with periodontitis than those without periodontitis [18]. Moreover, after receiving periodontal treatment, the level of FGF21 in GCF was decreased, suggestive the anti-inflammation effect of FGF21 [18]. However, the other studies measuring FGF21 level in serum found that diabetic group demonstrated increased FGF21 following periodontal therapy as a result of improved glycemic control [19, 20]. These controversial outcomes were possibly because of different sources of FGF21 sampling, insufficient sample size to reach the power of a statistical test, various definition of periodontitis cases and no periodontally healthy control group or comparison groups such as localized and generalized periodontitis. Although the studies report contradictory findings, the expression of serum FGF21 in MetS patients might be related to periodontitis-induced inflammation. Up to date, there are no studies investigating the level of circulating FGF21 in patients with MetS and periodontitis. Therefore, the present study aimed to investigate the level of serum FGF21 in MetS patients with or without generalized periodontitis and the association of FGF21 to metabolic and periodontal parameters.

Materials and methods

This cross-sectional study was reviewed and approved by the institutional Human Experimentation Committee of the Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand (Ethical approval number: 49/2016). Written informed consents were obtained from all participants on the date of recruitment. All methods were performed in accordance with the relevant guidelines and regulations. The present study was a sub-study of MetS patients in The Cohort of patients at a high Risk for Cardiovascular Events (CORE) - Thailand registry. The CORE-Thailand registry was an ongoing prospective study involving a cohort of Thai patients with high atherosclerotic risks. Patients with MetS undergoing medical treatment were enrolled from the outpatient clinic at Maharaj Nakorn Chiang Mai Hospital in the period October 2015 to April 2016. The criteria used for MetS diagnosis was according to a joint interim statement took place in 2009 [21]. The flow of participant recruitment was shown in Fig. 1.

Patients willing to receive periodontal examination were included and having the following conditions were excluded from the study: (1) antibiotic prophylaxis needed before periodontal examination; (2) received joint replacement surgery in last 2 years or present history of joint replacement infection; (3) present chronic kidney disease with undergoing hemodialysis; (4) having immunocompromised condition or immunodeficiency; (5) having bleeding disorders or receiving anticoagulants exception for aspirin with concentration under 325 mg/day.

Data collection and sampling

Patient medical history collection, physical examination, fasting blood sampling and periodontal examination were performed on the date of enrollment. Blood samples of all participants were assessed for the calculation of the fasting blood sugar (FBS), HDL-C, LDL-C (low-density lipoprotein cholesterol), triglyceride, insulin and FGF21 levels. Serum FGF21 levels were determined using a human FGF21 enzyme-linked immunosorbent assay (ELISA) kit (R&D systems Inc., Minneapolis, MN, USA).

Periodontal examination

The data including number of remaining teeth without third molars, plaque index (PI), gingival index (GI), probing pocket depth (PPD) and clinical attachment loss (CAL) were recorded. PI and GI indices were determined as described in a previous study [22]. For PPD and CAL, the full mouth examination was evaluated in six sites per tooth with a periodontal probe (PCPUNC 15, Hu-friedy, Chicago, IL, USA). Three calibration experts in periodontics performed a full mouth periodontal examination. Inter-examiner calibration was performed through the intraclass correlation coefficient with higher than 0.8 of the values for PPD and CAL were proven.

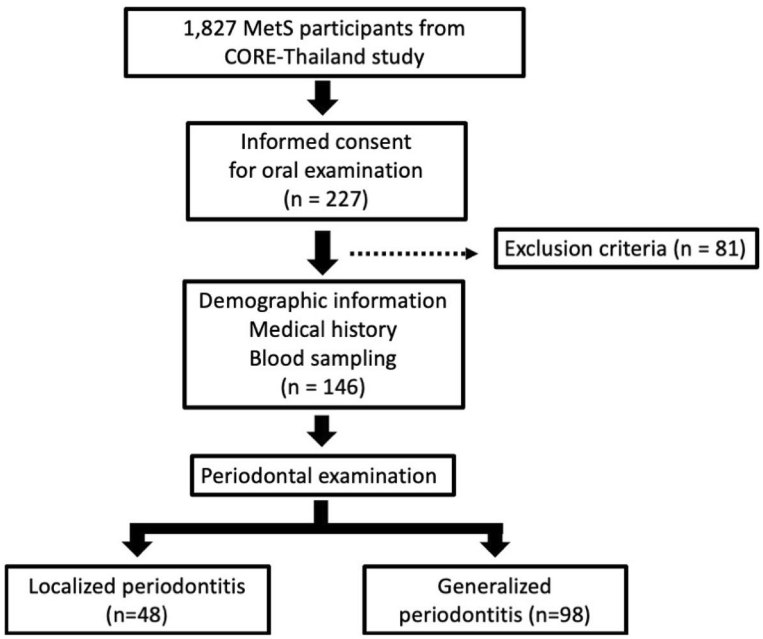

Fig. 1 Schematic illustrating the flow of participant enrollment in the present study

Definition of periodontitis

Periodontitis is diagnosed as presence of detectable interdental CAL at two non-adjacent teeth and full-mouth BOP percentage ≥ 10%, according to new classification of periodontal disease. Moreover, the severity of disease was categorized into 4 stages with two levels of distribution including localized (< 30%) and generalized (≥30%) of affected teeth [23].

Statistical analysis

Normality of data was analyzed by Kolmogorov-Smirnov test. Bivariate analysis was performed by unpaired T-test and Mann-Whitney U test for continuous variables. The comparison of nominal data between groups was performed by Chi-square test. The post hoc power based on FGF21 level was 0.96 with the effect size of 0.66. The Spearman rank was used to test correlation between continuous parameters. The association between the presence of generalized periodontitis and the serum FGF21 level was examined using multiple logistic regression analysis. The confounding factors that might affect periodontitis and FGF21 including age, gender, smoking, alcohol consumption, diabetic status, presence of component FBS, TG, HDL were adjusted. The analysis was conducted by SPSS version 17 (IBM Corp., Armonk, NY, USA).

Results

146 MetS participants were recruited in the present study. Most subjects (87%) were classified as stage III periodontitis while no patients with clinical periodontal health was observed in the present study. According to the given distribution, to compare the collected data we reassembled participants into two groups as localized periodontitis and generalized periodontitis as shown in Table 1. The result demonstrated that all general demographic and metabolic variables were not significantly different, exception for slightly higher frequency of alcohol consumption in generalized periodontitis group. MetS patients with generalized periodontitis demonstrated significantly greater proportion of severe CAD events than those with localized periodontitis (39% vs. 10%, $p < 0.05$) (Table 1).

For the validation of serum FGF21 level, patients with generalized periodontitis presented the significantly higher level of FGF21 level when compared to localized periodontitis group (Table 1). The correlation between FGF21 and periodontal parameters including number of teeth, mean CAL and %tooth with CAL ≥ 5 mm were significant (Table 2). Furthermore, both groups showed the correlation between FGF21 level and hyperglycemia, hypertriglyceridemia and lowered HDL which were metabolic components that were significantly correlated to FGF21 level (Table 3).

Table 1 Demographic data, metabolic syndrome and periodontal parameters of two groups according to periodontal status

Variable	Localized periodontitis ($n = 48$)	Generalized periodontitis ($n = 98$)	*p*-value
Age (years)	62.25 ± 7.8	63.60 ± 7.9	0.33
Gender			0.1
Male	18 (37.5)	51 (52.0)	
Female	30 (62.5)	47 (48.0)	
Alcohol consumption			**0.049**
Never	**38 (79.2)**	**65 (66.3)**	
Occasionally	**7 (14.6)**	**31 (31.6)**	
Frequently	**3 (6.3)**	**2 (2.0)**	
Smoking			0.22
Never	34 (70.8)	55 (56.1)	
Former	12 (25.0)	35 (35.7)	
Current	2 (4.2)	8 (8.2)	
Diabetes mellitus type 2			0.1
No	11 (22.9)	12 (12.2)	
Yes	37 (77.1)	86 (87.8)	
Metabolic parameters			
BMI (kg/m^2)	28.31 ± 6.34	27.99 ± 6.93	0.66[a]
Waist circumference (cm)	96.01 ± 13.88	96.24 ± 12.59	0.75[a]
FBS (mg/dL)	110.79 ± 57.79	102.19 ± 49.68	0.92[a]
HbA1C	6.88 ± 1.10	7.0 ± 1.37	0.81 [a]
LDL-C (mg/dL)	86.21 ± 46.08	83.59 ± 44.58	0.73 [a]
HDL-C (mg/dL)	46.53 ± 22.39	40.99 ± 22.69	0.10 [a]
Triglyceride (mg/dL)	112.09 ± 53.79	129.49 ± 63.99	0.09 [a]
Systolic blood pressure (mmHg)	136.28 ± 16.52	138.16 ± 18.41	0.56
Diastolic blood pressure (mmHg)	75.98 ± 10.04	74.67 ± 9.81	0.46
MetS components: n (%)			
FBS ≥ 110 mg/dL	22 (45.83)	57 (58.16)	0.20
SBP ≥ 130 or DBP ≥ 85 mmHg	43 (89.6)	87 (88.8)	0.88
Triglycerides ≥ 150 mg/dL	10 (20.83)	24 (24.5)	0.67
Low HDL	31 (64.6)	72 (73.5)	0.27
High WC	41 (85.4)	78 (79.6)	0.39
Periodontal status (± SD)			
Number of teeth	**24.48 ± 3.6**	**19.51 ± 6.94**	**< 0.001**[a]
Mean PPD (mm.)	**2.44 ± 0.27**	**2.91 ± 0.61**	**< 0.001**[a]
Mean CAL (mm.)	**2.91 ± 0.36**	**4.34 ± 1.28**	**< 0.001**[a]
GI	**1.26 ± 0.28**	**1.50 ± 0.43**	**0.001**[a]
PI	**1.28 ± 0.30**	**1.68 ± 0.54**	**< 0.001**[a]
%Tooth with PPD ≥ 5 mm	**4.40 ± 6.90**	**25.08 ± 26.07**	**< 0.001**[a]
%Tooth with interdental CAL ≥ 5 mm	**14.10 ± 13.67**	**61.71 ± 26.70**	**< 0.001**[a]
History of severe CAD: n (%)			
No	**38 (79.2)**	**59 (60.2)**	**0.02**
Yes	**10 (20.8)**	**39 (39.8)**	
FGF21 level (ng/dl)	**231.79 ± 160.47**	**432.03 ± 398.25**	**0.001**[a]

Data were presented as mean ± SD or n (%). Bold values present significant difference ($P < 0.05$). Categorical data using Chi-square.

[a] = mean comparison using Mann-witney U-test (Unpaired T-test for the other variables)

Finally, the multivariate model demonstrated the positive association between FGF21 and generalized periodontitis with an odds ratio of 27.12 (95% CI: 5.24–140.35), independently on age, smoking, alcohol consumption, and metabolic disturbance, as shown in Table 4.

Table 2 Correlation between FGF21 level and periodontal parameters

	Group		% PI	% GI	Number of teeth	Mean PPD	Mean CAL	% tooth with PPD ≥ 5	% tooth with interdental CAL ≥ 5
FGF21 level (ng/dl)	**All**	r	0.06	0.13	**−0.21**	0.05	**0.24**	0.08	**0.27**
		P	0.50	0.12	**0.01**	0.54	**0.003**	0.35	**0.001**
	Localized periodontitis	r	0.06	−0.11	0.02	−0.004	0.039	−0.113	0.02
		P	0.70	0.47	0.88	0.98	0.79	0.45	0.91
	Generalized periodontitis	r	−0.04	0.15	−0.17	−0.08	0.14	−0.01	0.15
		P	0.72	0.15	0.10	0.43	0.17	0.91	0.14

All correlation analyzed by Spearman rank test. Bold values present significant difference ($P < 0.05$)

Table 3 Correlation between FGF21 level and metabolic components

	Group		FBS	BP	TG	HDL	WC
FGF21 level (ng/dl)	**All**	r	**0.18**	0.11	**0.29**	**0.18**	0.05
		P	**0.03**	0.20	**< 0.001**	**0.03**	0.56
	Localized periodontitis	r	0.16	0.12	**0.38**	−0.01	0.18
		P	0.28	0.43	**0.01**	0.94	0.21
	Generalized periodontitis	r	0.17	0.13	**0.27**	**0.24**	0.016
		P	0.11	0.21	**0.01**	**0.02**	0.88

All correlation analyzed by Spearman rank test. Bold values present significant difference ($P < 0.05$). **Abbreviation:***FBS* Fasting blood sugar ≥ 100 mg/dl or treated, *BP* Systolic or diastolic blood pressure ≥ 130/85 mmHg or treated, *TG* Triglyceride ≥ 150 mg/ dl or treated, *HDL* High density lipoprotein cholesterol < 40 mg/dl in men and < 50 mg/dl in women, *WC* Waist circumference ≥ 90 cm in men and ≥ 80 cm in women

Table 4 Multiple logistic regression showing the association between FGF21 level and generalized periodontitis

				FGF21 level[a]			
Analysis outcome	***B***	**SE**	**Wald**	**Crude odds ratio (95% C.I.)**	***P*-value**	**Adjusted odds ratio[¶](95% C.I.)**	***P*-value**
Localized periodontitis (control)				1.00		1.00	
Generalized periodontitis	3.30	0.84	15.48	**9.71 (2.71–34.91)**	**< 0.001**	**27.12 (5.24–140.35)**	**0.012**

[¶] Model mutually adjusted for age, gender, smoking, alcohol consumption, diabetic status, presence of component FBS, TG, HDL. [a] = Log transformed; *B* = regression coefficient; SE = standard error; Wald = Wald test

Discussion

This is the first study reporting the alterations of serum FGF21 levels in MetS patients with periodontitis. The major findings showed that MetS patients with generalized periodontitis demonstrated a significantly higher level of serum FGF21 than those with localized periodontitis. Moreover, the correlation between FGF21 level and periodontal parameters including Number of remaining teeth and CAL was observed. The level of serum FGF21 was also associated with the presence of generalized periodontitis after adjusting of confounding factors.

FGF21 is a hormone primarily produced by the liver which plays a potential role in regulation of metabolic processes, especially in improving glucose level, insulin activity and lipid metabolism [3]. Previously, the animal and human studies have consistently proposed this protein as a therapeutic biomarker for MetS [10–12, 20, 24, 25]. The finding of this study presented that metabolic parameters correlated with FGF21 level were hypertriglyceridemia and low HDL-C, which was in line with the previous reports [26–28]. In mice model, the study showed that FGF21 is able to lower plasma triglycerides via regulating CD36 which results in stimulating TG uptake into adipose tissue [29]. Likewise, obesity and diabetic patients who received human recombinant FGF21 for 4weeks demonstrated improved level of HDL-C [24]. Therefore, it was possibly implied that individuals who had periodontitis might comprise a higher chance of dyslipidemia development, which subsequently increased an expression of FGF21 level as a protective role.

In addition to metabolic parameters, the main outcome of the current study demonstrated a higher level of serum FGF21 in generalized periodontitis group, when compared to group with localized periodontitis. It was in concordance with the previous report conducted in Cairo [18]. The findings suggested that the elevation of FGF21 in GCF might act as a protective mechanism to oppose periodontal inflammation in diabetic patients with periodontitis. This was confirmed by the reduction of FGF21 level following periodontal treatment. The anti-inflammation effect of FGF21 was also evident by Li and colleagues in mice model [30], in which the expression of FGF21 was responsible for LPS-induced inflammation through inhibiting IL-1β expression in NF-κB pathway and enhancing elevation of IL-10.

Furthermore, our findings presented that periodontal parameters including CAL and number of remaining teeth were significantly correlated with FGF21 level. It was obvious that CAL represents the past destruction of periodontal tissues which is one of the main clinical features for periodontitis related to tooth loss. Although there have been no studies focusing on FGF21 and periodontal parameters before, the association between these parameters and MetS have been widely established [31–34]. The evidence showed that CAL was significantly associated with increased C-reactive protein, a major biomarker representing the state of systemic inflammation which mainly contributed to metabolic disturbance [35]. It was thus possible that the elevation of serum FGF21 level might be a result of its anti-inflammation effect responsive to systemic inflammation induced by generalized periodontitis. Additionally, the latest meta-analysis highlighted that MetS patients were more likely to has lesser number of remaining teeth, suggestive the negative effect on functional dentition and fiber intake. A worsen chewing function might lead patients to unavoidably take more high cholesterol foods and finally develop metabolic disorder [34]. In this context, increased serum FGF21 might be an indirect consequence of a compensatory up-regulation against a presence of dyslipidemia components as shown as the correlation analysis in this study.

Conversely, the other two studies validating serum FGF21 in diabetic patients with periodontitis presented the contradictory results [19, 20]. They found that serum FGF21 level was increased after periodontal treatment and negatively correlated with improved HbA1c. These was presumed that alteration of serum FGF21 was mainly attributed to glycemic controls which was beneficially affected by reduction of periodontal inflammation. Nevertheless, these studies had small sample size and no periodontal control group to compare.

Finally, the multiple logistic regression analysis confirmed the association between FGF21 and presence of generalized periodontitis (OR = 27.12) even after adjusting confounding variables including age, gender, smoking, alcohol consumption, diabetic status, presence of components FBS, TG, HDL. Therefore, it was possible that the altered expression of serum FGF21 might be also modified by the systemic inflammation induced by generalized periodontitis apart from metabolic abnormalities. However, a true linking mechanism explaining this phenomenon is still not fully understood.

There were some limitations in the current study. First, the outcomes from this cross-sectional study could not be explained in causal-effect direction between FGF21 and periodontitis in MetS patients. Longitudinal study or clinical controlled trials investigating FGF21 before and after periodontal treatment might clarify the role of periodontitis to FGF21. Secondly, MetS components or medications might affect the level of FGF21. The future study with healthy control group would clarify these confounders. Thirdly, the older population can affect both periodontal status and serum FGF21 level so a different age group is still needed to be investigated. Lastly, the biomarkers such as TNF-α and IL-1β, which are targeted by FGF21 and involved in periodontitis development, were not determined in the present study. Therefore, the further studies about relationship between FGF21 and periodontitis is still needed to be clarified.

Conclusions

The elevation of serum FGF21 might be a potential biomarker for MetS patients who have risk of generalized periodontitis. Several parameters including CAL, number of teeth, and dyslipidemia demonstrated a correlation to serum FGF21 level. Although the present study was not able to fully answer the relationship between FGF21 and periodontitis, the data elucidates the significant effect of periodontal disease on systemic health, especially MetS. Periodontal examination and therapy should be included as a part of treatment for MetS patients.

Abbreviations

FGF21: Fibroblast growth factor 21; MetS: Metabolic syndrome; HDL-C: High-density lipoprotein cholesterol; FBS: Fasting blood sugar; CVD: Cardiovascular disease; GCF: Gingiva crevicular fluid; ELISA: Enzyme-linked immunosorbent assay; LDL-C: Low-density lipoprotein cholesterol; PI: Plaque index; GI: Gingival index; PPD: Probing pocket depth; CAL: Clinical attachment loss; CAD: Coronary artery disease; IL: Interleukin.

Acknowledgements

This work was supported by a Senior Research Scholar Grant from the National Research Council of Thailand (SCC.), the NSTDA Research Chair Grant from the National Science and Technology Development Agency Thailand (NC), the Chiang Mai University Centre of Excellence Award (NC), and the Research Fund for Faculties of the Faculty of Dentistry, Chiang Mai University (PB).

Authors' contributions

Conceptualization, T.S., P.B., P.M., A.L. and S.C.; Methodology, T.S., P.B., P.M., A.L. and S.C.; Formal analysis, T.S. and S.C.; Investigation, T.S., P.B., P.M. and A.L.; Resources, P.B.,

A.P., N.C. and S.C.; Data Curation, T.S., P.B., A.P., N.C. and S.C.; Writing - Original Draft Preparation, T.S. and S.C.; Writing - Review & Editing, T.S., P.B., and S.C.; Visualization, T.S., A.P. and S.C.; Supervision and Project administration, P.B. and S.C.

Funding
This work was supported by a Senior Research Scholar Grant from the National Research Council of Thailand (SCC.), the NSTDA Research Chair Grant from the National Science and Technology Development Agency Thailand (NC), the Chiang Mai University Centre of Excellence Award (NC), and the Research Fund for Faculties of the Faculty of Dentistry, Chiang Mai University (PB).

Availability of data and materials
The datasets generated and/or analysed during the current study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Written informed consents were obtained from all participants. This cross-sectional study was reviewed and approved by the institutional Human Experimentation Committee of the Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand (Ethical approval number: 49/2016). All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Department of Restorative Dentistry and Periodontology, Faculty of Dentistry, Chiang Mai University, Chiang Mai 50200, Thailand. [2]Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. [3]Neuroelectrophysiology Unit, Cardiac Electrophysiology Research and Training Center, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand. [4]Center of Excellence in Cardiac Electrophysiology Research, Chiang Mai University, Chiang Mai 50200, Thailand. [5]Department of Oral Biology and Diagnostic Sciences, Faculty of Dentistry, Chiang Mai University, Chiang Mai 50200, Thailand.

Received: 17 July 2022 Accepted: 25 October 2022
Published online: 06 December 2022

References

1. Badman MK, Pissios P, Kennedy AR, Koukos G, Flier JS, Maratos-Flier E. Hepatic fibroblast growth factor 21 is regulated by PPARalpha and is a key mediator of hepatic lipid metabolism in ketotic states. Cell Metab. 2007;5(6):426–37.
2. Patel R, Bookout AL, Magomedova L, Owen BM, Consiglio GP, Shimizu M, et al. Glucocorticoids regulate the metabolic hormone FGF21 in a feed-forward loop. Mol Endocrinol. 2015;29(2):213–23.
3. Zhang X, Yeung DC, Karpisek M, Stejskal D, Zhou ZG, Liu F, et al. Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. Diabetes. 2008;57(5):1246–53.
4. Yu Y, He J, Li S, Song L, Guo X, Yao W, et al. Fibroblast growth factor 21 (FGF21) inhibits macrophage-mediated inflammation by activating Nrf2 and suppressing the NF-κB signaling pathway. Int Immunopharmacol. 2016;38:144–52.
5. Salminen A, Kaarniranta K, Kauppinen A. Integrated stress response stimulates FGF21 expression: systemic enhancer of longevity. Cell Signal. 2017;40:10–21.
6. Sonoda J, Chen MZ, Baruch A. FGF21-receptor agonists: an emerging therapeutic class for obesity-related diseases. Horm Mol Biol Clin Investig. 2017;30(2):20170002.
7. Meigs JB, Wilson PW, Fox CS, Vasan RS, Nathan DM, Sullivan LM, et al. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. J Clin Endocrinol Metab. 2006;91(8):2906–12.
8. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol. 2010;56(14):1113–32.
9. Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation. 2004;110(10):1245–50.
10. Bobbert T, Schwarz F, Fischer-Rosinsky A, Pfeiffer AF, Möhlig M, Mai K, et al. Fibroblast growth factor 21 predicts the metabolic syndrome and type 2 diabetes in Caucasians. Diabetes Care. 2013;36(1):145–9.
11. Choi JR, Kim JY, Park IH, Huh JH, Kim KW, Cha SK, et al. Serum fibroblast growth factor 21 and new-onset metabolic syndrome: KoGES-ARIRANG study. Yonsei Med J. 2018;59(2):287–93.
12. Ong KL, McClelland RL, Allison MA, Kokkinos J, Wu BJ, Barter PJ, et al. Association of elevated circulating fibroblast growth factor 21 levels with prevalent and incident metabolic syndrome: the multi-ethnic study of atherosclerosis. Atherosclerosis. 2019;281:200–6.
13. Lamster IB, Pagan M. Periodontal disease and the metabolic syndrome. Int Dent J. 2017;67(2):67–77.
14. Gobin R, Tian D, Liu Q, Wang J. Periodontal diseases and the risk of metabolic syndrome: an updated systematic review and meta-analysis. Front Endocrinol (Lausanne). 2020;11:336.
15. Page RC, Kornman KS. The pathogenesis of human periodontitis: an introduction. Periodontol. 2000;1997(14):9–11.
16. Preshaw PM, Alba AL, Herrera D, Jepsen S, Konstantinidis A, Makrilakis K, et al. Periodontitis and diabetes: a two-way relationship. Diabetologia. 2012;55(1):21–31.
17. Sanz M, Marco Del Castillo A, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P, et al. Periodontitis and cardiovascular diseases: consensus report. J Clin Periodontol. 2020;47(3):268–88.
18. Amr E, Mostafa R, Shaker O. Possible role of gingival crevicular fluid levels of Chemerin and fibroblast growth factor 21 as biomarkers of periodontal disease in diabetic and non-diabetic patients. A diagnostic accuracy study. Adv. Dent J. 2019;1(2):52–63.
19. Wang S, Liu J, Zhang J, Lin J, Yang S, Yao J, et al. Glycemic control and adipokines after periodontal therapy in patients with type 2 diabetes and chronic periodontitis. Braz Oral Res. 2017;31:e90.
20. Panezai J, Altamash M, Engström PE, Larsson A. Association of glycated proteins with inflammatory proteins and periodontal disease parameters. J Diabetes Res. 2020;2020:6450742.
21. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; National Heart, Lung, and Blood Institute; American Heart Association; world heart federation; international atherosclerosis society; and International Association for the Study of obesity. Circulation. 2009;120(16):1640–5.
22. Löe H. The gingival index, the plaque index and the retention index systems. J Periodontol. 1967;38(6):610–6.
23. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: framework and proposal of a new classification and case definition. J Clin Periodontol. 2018;45(suppl 20):S149–61.
24. Gaich G, Chien JY, Fu H, Glass LC, Deeg MA, Holland WL, et al. The effects of LY2405319, an FGF21 analog, in obese human subjects with type 2 diabetes. Cell Metab. 2013;18(3):333–40.
25. Talukdar S, Zhou Y, Li D, Rossulek M, Dong J, Somayaji V, et al. Long-acting FGF21 molecule, PF-05231023, decreases body weight and improves lipid profile in non-human primates and type 2 diabetic subjects. Cell Metab. 2016;23(3):427–40.
26. Jin QR, Bando Y, Miyawaki K, Shikama Y, Kosugi C, Aki N, et al. Correlation of fibroblast growth factor 21 serum levels with metabolic parameters in Japanese subjects. J Med Investig. 2014;61(1–2):28–34.
27. Gao RY, Hsu BG, Wu DA, Hou JS, Chen MC. Serum fibroblast growth factor 21 levels are positively associated with metabolic syndrome in patients with type 2 diabetes. Int J Endocrinol. 2019;2019:5163245.
28. Tyynismaa H, Raivio T, Hakkarainen A, Ortega-Alonso A, Lundbom N, Kaprio J, et al. Liver fat but not other adiposity measures influence circulating

FGF21 levels in healthy young adult twins. J Clin Endocrinol Metab. 2011;96(2):E351–5.
29. Schlein C, Talukdar S, Heine M, Fischer AW, Krott LM, Nilsson SK, et al. FGF21 lowers plasma triglycerides by accelerating lipoprotein catabolism in white and brown adipose tissues. Cell Metab. 2016;23(3):441–53.
30. Li JY, Wang N, Khoso MH, Shen CB, Guo MZ, Pang XX, et al. FGF-21 elevated IL-10 production to correct LPS-induced inflammation. Inflammation. 2018;41(3):751–9.
31. Iwasaki M, Sato M, Minagawa K, Manz MC, Yoshihara A, Miyazaki H. Longitudinal relationship between metabolic syndrome and periodontal disease among Japanese adults aged ≥70 years: the Niigata study. J Periodontol. 2015;86(4):491–8.
32. Furuta M, Liu A, Shinagawa T, Takeuchi K, Takeshita T, Shimazaki Y, et al. Tooth loss and metabolic syndrome in middle-aged Japanese adults. J Clin Periodontol. 2016;43(6):482–91.
33. Kaye EK, Chen N, Cabral HJ, Vokonas P, Garcia RI. Metabolic syndrome and periodontal disease progression in men. J Dent Res. 2016;95(7):822–8.
34. Souza ML, Massignan C, Glazer Peres K, Aurélio PM. Association between metabolic syndrome and tooth loss: a systematic review and meta-analysis. J Am Dent Assoc. 2019;150(12):1027–39.e7.
35. Pejcic A, Kesic LJ, Milasin J. C-reactive protein as a systemic marker of inflammation in periodontitis. Eur J Clin Microbiol Infect Dis. 2011;30(3):407–14.

Publisher's Note