Inverse Association of Serum Fibroblast Growth Factor 19 and Atherogenic Index of Plasma in Type 2 Diabetic Patients

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SUBJECT AREAS

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Abstract

Background

We aimed to explore the relationship between serum fibroblast growth factor 19 (FGF19) and the atherogenic index of plasma (AIP) in type 2 diabetic patients.

Methods

Serum FGF19 levels and lipid profiles were measured in 200 patients with type 2 diabetes (T2D). The levels of serum FGF19 were measured by ELISA. Lipid profiles were measured by enzymatic analysis. AIP and NAFLD fibrosis scores were calculated.

Results

T2D patients showed a significant decreasing trend of FGF19 concentrations depending on the tertiles of AIP ($p$ for trend < 0.05). Simultaneously, the AIP level was closely related to the serum FGF19 level ($p < 0.05$). Furthermore, after adjusting for age, sex, duration, BMI, hypertension, and diabetic treatment, the correlation was still significant ($p < 0.01$), and it remained significant even after further adjusting for non-alcoholic fatty liver disease (NAFLD) and NAFLD fibrosis score (NFS) ($p < 0.01$). However, when stratified by BMI, AIP was positively correlated with FGF19 in normal-weight and overweight T2D patients but not in obese T2D subjects. After adjusting for sex, age, BMI, duration, hypertension, HbA1c, 2hPG, HOMA-IR, AIP, antidiabetic treatments, NAFLD and NFS via multiple stepwise linear regression, AIP was an independent factor affecting serum FGF19 concentrations ($SE = 0.238, \beta = -0.290, p < 0.01$).

Conclusions

Serum FGF19 levels might be a good predictor for atherosclerosis and cardiovascular disease in T2D patients, especially among non-obese patients; serum FGF19 levels were significantly inversely associated with AIP.
Background

Cardiovascular disease (CAD) is a complication with high morbidity and mortality in patients with type 2 diabetes (T2D) [1]. Serum lipid deposition, leucocyte infiltration, and intimal thickening are three main steps in the development of atherosclerosis [2]. Dyslipidemia has been considered a mediator and marker of CAD.

A growing body of evidence shows that non-traditional lipid indexes, including the atherogenic index of plasma (AIP), atherosclerosis coefficient (AC), lipoprotein combined index (LCI), non-high-density lipoprotein cholesterol (non-HDL-c), total cholesterol/high-density lipoprotein cholesterol (TC/HDL-c), and low-density lipoprotein cholesterol/high-density lipoprotein cholesterol (LDL-c/HDL-c), are thought to predict the risk of atherosclerosis and CAD; this is especially true for AIP [3-5]. As a new comprehensive lipid index, AIP is calculated as the log-transformed plasma TG value divided by the HDL-c value [6]. The AIP level in T2D subjects was significantly higher compared with that in healthy controls and may be related to the distribution of body fat and visceral fat area (VFA) [7]. However, few studies have revealed the relationship between AIP and serum fibroblast growth factor 19 (FGF19).

FGF19, an endocrine hormone, is a member of the fibroblast growth factor (FGF) family. FGF19 is mainly produced in the intestinal epithelium and is expressed and functions in target tissues via FGF receptors (FGFR1, 2, 3, and 4) and β-Klotho [8,9]. The main function of FGF19 is to regulate the synthesis of bile acid (BA) by acting on cholesterol 7α-hydroxylase (CYP7A1) [8,9]. As shown in our previous study, FGF19 participates in maintaining the balance of glucose and may protect against the dysfunction of β-cells [10]. The serum FGF19 levels in CAD subjects are lower than those in subjects without CAD and are correlated with the presence and severity of CAD [11]. In T2D patients with metabolic syndrome (MetS), FGF19 levels are negatively associated with the AIP [12]. No
study has shown the correlation of serum FGF19 and the AIP in T2D patients, especially among nonobese subjects.

We performed the current study to investigate the relationship between serum FGF19 concentrations and AIP values in patients with type 2 diabetes and found that FGF19 may also be an indicator of the presence of atherosclerosis and CAD.

Methods

Study design and population

We recruited 294 subjects who visited and were followed up in the Endocrinology Department at Affiliated Hospital 2 of Nantong University and First People’s Hospital of Nantong City. Sixty subjects did not undergo OGTT (75 g of glucose) examination, 13 participants had incomplete lipid profile data, and 21 patients were taking statins. As a result, 200 T2D subjects were enrolled in the study for the final analysis. The inclusion criteria for T2D patients were age from 20 to 75 years and a diagnosis of T2D [13]. The inclusion criteria for controls were age from 20 to 50 years and having a fasting plasma glucose (FPG) level < 6.1 mmol/L and a 2-h plasma glucose (2hPG) level < 7.8 mmol/L [13]. Subjects who had type 1 diabetes, hyperthyroidism or hypothyroidism, severe hepatic disease, chronic renal insufficiency, cancer, acute diabetic complications, current treatment with systemic corticosteroids and treatment with lipid-lowering drugs were also excluded. All participants provided informed consent, and the study protocol was approved by the Ethics Committee of Affiliated Hospital 2 of Nantong University and First People’s Hospital of Nantong City.

Anthropometric measures and calculation

All participants finished a questionnaire collecting demographic and anthropometric data under the supervision of experienced investigators after fasting for 8 hours. Hypertension was tested at least 3 times and was defined as a systolic arterial blood pressure ≥ 140
mmHg and/or diastolic blood pressure ≥ 90 mmHg after at least 0.5 h of rest. Hepatic steatosis on ultrasound was used to establish the diagnosis of NAFLD. Overweight and obesity were defined as BMI ≥ 24 kg/m² and BMI ≥ 28 kg/m², respectively, according to the criteria of the China Obesity Task Force [14]. The calculation of the homeostatic model assessment for insulin resistance (HOMA-IR), BMI, AIP and NAFLD fibrosis score (NFS) were as follows: HOMA-IR = FPG*FINS/22.5; BMI = the weight/the height squared; AIP = log (TG/HDL-c); NFS = -1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m²) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio– 0.013 × platelet (x10⁹/l)– 0.66 × albumin (g/dl)[15].

**Serum biochemical indicators**

Peripheral blood samples were collected after >12 hours of fasting. TG was measured using colorimetry, TC was measured with the cholesterol oxidase method, LDL-c was determined with the selective melt method and HDL-c was measured using the modified enzyme method. All levels were determined by an automated biochemical instrument (Model 7600, Hitachi). Ionic exchange HPLC (IE-HPLC) in the D-10 haemoglobin analysis system (Bio-Rad) was used to determine the HbA1c level. Insulin levels, fasting blood glucose concentrations and 2-h blood glucose concentrations were measured by laboratory procedures [16,17]. All blood samples were stored at -80°C. Serum FGF19 levels were measured by sandwich ELISA (FGF19 Quantikine® DF1900; R&D Systems, Minneapolis, MN, USA). The intra- and inter-assay coefficients of variation were 4.3% and 5.6%, respectively.

**Statistical analysis**

SPSS 25.0 (Inc., Chicago, IL) statistical software was used. Normally distributed data are expressed as the mean ± SD. The Kruskal-Wallis test was performed to assess the
variables’ distributions. Skewed data were analysed after log transformation. The differences between groups were analysed by one-way analysis of variance (ANOVA). The categorical variables were analysed by the Chi$^2$ test. Univariate analysis was performed to analyse plasma FGF19 levels depending on AIP tertiles. Spearman’s bivariate correlation analysis was used to analyse the risk factors correlated with FGF19 and AIP. Univariate analysis was conducted to detect the difference in serum FGF19 levels based on the tertiles of AIP. Multiple stepwise linear regression analysis was used to explore the relevant risk factors related to FGF19. A $p$ value < 0.05 was defined as significant.

Results

**Basic characteristics**

The characteristics of the participants are shown in Table 1. The mean AIP for the whole group was 0.23±0.25, and the tertiles were Q1 (< 0.10), Q2 (0.10-0.36), and Q3 (> 0.36). BMI, FPG, and TG increased significantly from Q1 to Q2 to Q3 (all $p$ for trend < 0.05). HDL-c had a significant decreasing trend across the three groups ($p$ for trend < 0.01). According to the examination results, there was no significant correlation between TC and LDL-c. Additionally, depending on the tertiles of AIP, prominent differences were found for serum FGF19 levels ($p$ for trend < 0.01). Moreover, from Q1 to Q2 to Q3, the number of T2D patients with NAFLD increased significantly ($p$ for trend < 0.05), but no significant difference was found in the NFS among the three groups, and the mean NFS for all participants was -23.71±2.65, which indicates that for most T2D patients with NAFLD, the negative predictive value for fibrosis was 93% [15].

**Relationship between serum FGF19 level and atherogenic index of plasma**

The Spearman’s bivariate correlation analysis was conducted to detect the relationships between FGF19 levels and lipid indicators for the whole group. As shown in Fig 1, the
serum FGF19 level was significantly negatively related to TG and AIP ($r = -0.285, p < 0.01$; $r = -0.303, p < 0.01$, separately) but not to TC ($r = -0.082, p < 0.251$), HDL-c ($r = 0.131, p < 0.065$), or LDL-c ($r = -0.105, p < 0.138$). Interestingly, the association of AIP and FGF19 concentrations still existed after adjusting for age, sex, duration, BMI, hypertension, and diabetic treatment ($r = -0.272, p < 0.01$; Fig 1) and even after further adjusting for NAFLD and NFS ($r = -0.265, p < 0.01$; Fig 1). Most T2D patients have relatively higher body fat percentages and weight, so we detected the correlation of FGF19 levels and AIP among normal-weight, overweight and obese T2D patients. Finally, the AIP value was negatively correlated with FGF19 levels only among nonobese T2D patients ($r = -0.330, p < 0.01$; $r = 0.288, p < 0.01$, separately; Fig 2).

**Multiple stepwise linear regression analysis**

Via multiple linear regression analysis, we further analysed the risk factors for the serum FGF19 levels in patients with diabetes. We used the FGF19 level as the dependent variable and sex, age, BMI, duration, hypertension, HbA1c, 2hPG, HOMA-IR, AIP, antidiabetic treatments, NAFLD, and NFS as independent variables and found that AIP ($SE = 0.238, \beta = -0.290, p < 0.01$, Table 2) was an independent factor influencing FGF19 levels.

Furthermore, to detect the difference in serum FGF19 levels based on the AIP tertiles, univariate analysis was conducted, and as shown in Table 3, FGF19 levels were significantly negatively related to AIP tertiles after adjusting for age, sex, duration, BMI, SBP, DBP, diabetic treatment (lifestyle intervention alone, insulin injection, insulin secretagogues and insulin sensitizers), hypertension, NAFLD, and NFS ($p < 0.01$).

**Discussion**

We conducted a cross-sectional study of 200 T2D patients to analyse the relationship between serum FGF19 levels and the AIP. In patients with T2D, across the tertiles of AIP, the serum FGF19 concentrations and HDL-c levels decreased significantly and BMI, NAFLD,
FPG and TG levels increased. Spearman’s bivariate correlation analyses showed that serum FGF19 levels were significantly negatively related to TG and AIP levels in T2D patients, even after adjusting for age, sex, duration, BMI, hypertension, and diabetic treatment and again after further adjusting for NAFLD and NFS. However, a negative relationship between AIP values and FGF19 levels was detected only among nonobese T2D patients. Finally, multiple linear regression analysis showed that AIP was an important risk factor for FGF19 levels. Moreover, serum FGF19 levels decreased significantly across increasing tertiles of AIP.

Evidence from previous studies has shown that FGF19 participates in the synthesis of BA, the balance of glucose metabolism, and the reduction of weight in mice [18-21]. In accordance with our data, J. Zhang et al. showed that serum FGF19 levels were significantly lower in normal glucose tolerance (NGT) subjects than in isolated-impaired glucose tolerance (I-IGT) subjects and isolated-impaired fasting glucose (I-IFG) participants [22] via glucose effectiveness (GE) and hepatic glucose production (HGP). In our study, the FGF19 levels of the T2D group decreased significantly from Q1 to Q2 to Q3. Our previous study showed that the decrease in FGF19 in T2D patients correlated with endogenous beta cell function, as assessed by the insulin secretion-sensitivity index-2 (ISSI-2). In T2D patients with MetS, serum FGF19 levels are significantly lower than they are in other T2D patients. Moreover, FGF19 levels were significantly negatively related to AIP and TG in T2D patients with MetS [12]. Most T2D patients had higher body fat percentages and weight, and we found that FGF19 levels were negatively correlated with AIP tertiles among nonobese T2D patients. However, P. Song et al. found that T2D patients had abnormal body fat levels and higher AIP values. AIP was also positively correlated with the visceral fat area [7]. FGF19 may regulate the lipid balance at the beginning of obesity and may be a protective factor. The reason for this discrepancy may be related to
diabetic treatments. FGF19 levels were also lower in patients with postbariatric hypoglycemia and may be related to GLP-1 secretion [23].

AIP is a main marker for the presence of atherosclerosis and CAD [24,25]. The patients with diabetic neuropathy and MetS had significantly higher AIP levels than their counterparts. Increased AIP levels were correlated with the risk of hypertension and were associated with insulin resistance (HOMA-IR) [26]. Insulin resistance and dyslipidemia promote the development of NAFLD. In our study, the level of AIP was closely correlated with serum FGF19 levels in T2D patients. The correlation still existed after adjusting for age, sex, duration, BMI, hypertension, diabetic treatment and even after further adjusting for NAFLD and NFS. In postmenopausal women with CAD, the values of non-HDL-c, TC/HDL-c, LDL-c/HDL-c, AC, AIP, and LCI were all higher than in the control group. After multivariate logistic regression analysis, AIP was shown to be independently related to CAD, which indicated that AIP was a significant marker for the incidence of CAD [27]. In agreement with our study, P. Song et al. revealed that the AIP was obviously higher in T2D participants than in non-T2D participants. Meanwhile, the AIP level was higher in patients with a VFA ≥ 100 cm² than in patients with a VFA < 100 cm². The AIP was positively related to VAF in patients with T2D [7]. In a cohort study of diabetic foot patients with and without osteomyelitis, diabetic foot patients with osteomyelitis had higher AIP values than those without. AIP could be a marker for the diagnosis of diabetic foot osteomyelitis [28]. In elderly women with hypertension, the AIP level was higher and was positively related to the risk of all-cause mortality after an analysis of ten years of follow-up [29]. Wei Ni et al. showed that in Chinese people, the AIP level was different between coronary heart disease (CHD) patients with multivessel lesions and healthy controls. Simultaneously, AIP was independently correlated with CHD in males but not in females [30]. Similarly, Gaojun Cai et al found that in the Han Chinese population, AIP was a predictor for the incidence of
CAD [31]. In a study of 315 Chinese patients with suspected or established CAD, the serum FGF19 level was an independent predictor of the Gensini score, which represents the presence and severity of CAD [11]. As shown in our research, the serum FGF19 level decreased with increasing tertiles of AIP and was independently associated with the AIP value in patients with T2D. Therefore, serum FGF19 levels may be a predictor of atherosclerosis and CAD in patients with T2D. However, more research should be conducted to analyse the relationship between FGF19 levels and arterial lesions.

Several possible mechanisms may explain the link between decreased FGF19 levels and atherosclerosis in T2D patients. FGF19 regulates gluco-lipid homeostasis and nutrient metabolism via the FGFR4-β-Klotho complex. In rodent studies, FXR-/- mice showed a pro-atherogenetic lipoprotein profile and defects in the formation of any detectable plaques on a high-fat (HF) diet. FXR agonists protect against the formation of aortic plaques in murine models that have a pro-atherogenetic lipoprotein profile and accelerated atherosclerosis [32]. In hepatic FXR-knockout and FXR-knockdown mice, the reconstitution of FXR expression upregulated the transport of cholesterol. Consistent with its role of phosphorylating FXR, the nonreceptor tyrosine kinase Src regulated the formation of cholesterol and ameliorated arterial lesions. Therefore, the phosphorylation of hepatic FXR induced Src via FGF15/19 and then played a role in the balance of cholesterol homeostasis, preventing the formation of atherosclerosis [33]. Moreover, Mei Zhou, R. et al. revealed that NGM282, an FGF19 analogue, regulated cholesterol in mice by activating MEK1 and reduced atherosclerosis in Apoe-/- mice with dyslipidemia. Furthermore, the HDL-c levels of healthy volunteers improved after the administration of NGM282 for a week [34]. Our research revealed that FGF19 levels were closely related to AIP in the T2D group even after adjusting for age, sex, duration, BMI, SBP, DBP, diabetic treatment (lifestyle intervention alone, insulin injection, insulin secretagogues and insulin
sensitizers), hypertension, NAFLD, and NFS. Meanwhile, the mechanism of the relationship underlying the relationship between FGF19 and atherosclerosis in T2D patients, especially in nonobese T2D patients, remains unclear, and more clinical and basic studies are needed to explore this relationship.

This study had several limitations that should be addressed. This study had a cross-sectional design based on a small sample size and could not explain any causal connection between the decreased serum FGF19 level and increased risk of atherosclerosis and CAD as assessed by AIP. Our research was a single-centre study conducted among Chinese participants, and the generalizability of our data needs to be assessed. The influence of diabetic and hypertensive treatment on the formation of atherosclerosis is unknown, and the influence of medication history on AIP has not been determined. However, FGF19 levels differed significantly based on the tertiles of AIP and were closely related to AIP even after adjusting for age, sex, duration, BMI, SBP, DBP, diabetic treatment, hypertension, NAFLD, and NFS. Therefore, larger, prospective follow-up studies need to be conducted to better investigate the correlation between FGF19 levels and the risk of CAD in T2D patients.

In our study, we revealed that serum FGF19 levels decreased significantly in the T2D group as the tertiles of the AIP increased. The AIP was closely associated with the FGF19 level. A correlation existed among nonobese T2D patients. The AIP was independently associated with the concentration of FGF19 after multiple stepwise regression analysis. Serum FGF19 levels might be a useful predictor of the risk of atherosclerosis and CAD in T2D patients.

Conclusions

In T2D patients, serum FGF19 levels decreased significantly as the AIP tertiles increased and were independently associated with the AIP value. The FGF19 level might be a useful
predictor of atherosclerosis and CAD, especially among nonobese patients, as the levels were significantly inversely associated with the AIP values.

**Abbreviations**

CAD: cardiovascular disease; T2D: type 2 diabetes; BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, 2hPG: 2-hour postprandial blood glucose, HbA1c: glycosylated haemoglobin A1c, HOMA-IR: homeostatic model assessment for insulin resistance; TC: total cholesterol, TG: triglyceride, HDL-c: high-density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol, FGF19: fibroblast growth factor 19, AC: atherosclerosis coefficient, AIP: atherogenic index of plasma, LCI: lipoprotein combined index, ISSI-2: insulin secretion-sensitivity index-2, OGTT: oral glucose tolerance test, NGT: normal glucose tolerance; I-IGT: isolated-impaired glucose tolerance; I-IFG: isolated-impaired fasting glucose; GE: glucose effectiveness, HGP: hepatic glucose production; VFA: visceral fat area; MetS: metabolic syndrome; CHD: coronary disease; HF: high-fat; NAFLD: non-alcoholic fatty liver disease; NFS: NAFLD fibrosis score.

**Declarations**

**Authors’ contributions**

WL, MT and TX participated in the design of the study, data collection, analysis of the data, and drafting of the manuscript. JS and XW conceived of the study, participated in its design and revised the manuscript. MT and TX participated in the analysis of the data and revised the manuscript. FX, DZ, QZ, JC and HW participated in data collection. All authors read and approved the final manuscript.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The current data are available to all interested researchers upon reasonable request.

Requests for access to data should be made to the principal investigators of the study, Wang-shu Liu (e-mail: 569572444@qq.com) and Xue-qin Wang (e-mail: wangxueqin108@163.com).

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study was approved by the institutional review board of Affiliated Hospital 2 of Nantong University and First People’s Hospital of Nantong City, and written informed consent was obtained from all participants.

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References

1. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006; 3:e442
2. Crowther MA. Pathogenesis of atherosclerosis. Hematology Am Soc Hematol Educ Program 2005:436-441

3. Chang Y, Li Y, Guo X, Dai D, Sun Y. The Association of Ideal Cardiovascular Health and Atherogenic Index of Plasma in Rural Population: A Cross-Sectional Study from Northeast China. Int J Environ Res Public Health 2016; 13

4. Zhan Y, Xu T, Tan X. Two parameters reflect lipid-driven inflammatory state in acute coronary syndrome: atherogenic index of plasma, neutrophil-lymphocyte ratio. BMC Cardiovasc Disord 2016; 16:96

5. Niroumand S, Khajedaluee M, Khadem-Rezaiyan M, Abrishami M, Juya M, et al. Atherogenic Index of Plasma (AIP): A marker of cardiovascular disease. Med J Islam Repub Iran 2015; 29:240

6. Dobiasova M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER(HDL)). Clin Biochem 2001; 34:583-588

7. Song P, Xu L, Xu J, Zhang HQ, Yu CX, et al. Atherogenic Index of Plasma is Associated with Body Fat Level in Type 2 Diabetes Mellitus Patients. Curr Vasc Pharmacol 2018; 16:589-595

8. Kliewer SA, Mangelsdorf DJ. Bile Acids as Hormones: The FXR-FGF15/19 Pathway. Dig Dis 2015; 33:327-331

9. Degirolamo C, Sabba C, Moschetta A. Therapeutic potential of the endocrine fibroblast growth factors FGF19, FGF21 and FGF23. Nat Rev Drug Discov 2016; 15:51-69

10. Tang MJ, Su JB, Xu TL, Wang XQ, Zhang DM, et al. Serum fibroblast growth factor 19 and endogenous islet beta cell function in type 2 diabetic patients. Diabetol Metab Syndr 2019; 11:79
11. Hao Y, Zhou J, Zhou M, Ma X, Lu Z, et al. Serum levels of fibroblast growth factor 19 are inversely associated with coronary artery disease in Chinese individuals. PLoS One 2013; 8:e72345

12. Barutcuoglu B, Basol G, Cakir Y, Cetinkalp S, Parildar Z, et al. Fibroblast growth factor-19 levels in type 2 diabetic patients with metabolic syndrome. Ann Clin Lab Sci 2011; 41:390-396

13. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998; 15:539-553

14. <PredictiveValuesofBodyMasIndex.pdf>.

15. <show.pdf>.

16. Fang Q, Li H, Song Q, Yang W, Hou X, et al. Serum fibroblast growth factor 19 levels are decreased in Chinese subjects with impaired fasting glucose and inversely associated with fasting plasma glucose levels. Diabetes Care 2013; 36:2810-2814

17. Ovadia C, Perdones-Montero A, Spagou K, Smith A, Sarafian MH, et al. Enhanced Microbial Bile Acid Deconjugation and Impaired Ileal Uptake in Pregnancy Repress Intestinal Regulation of Bile Acid Synthesis. Hepatology 2019; 70:276-293

18. Zhou M, Learned RM, Rossi SJ, DePaoli AM, Tian H, et al. Engineered FGF19 eliminates bile acid toxicity and lipotoxicity leading to resolution of steatohepatitis and fibrosis in mice. Hepatol Commun 2017; 1:1024-1042

19. Tomlinson E, Fu L, John L, Hultgren B, Huang X, et al. Transgenic mice expressing human fibroblast growth factor-19 display increased metabolic rate and decreased adiposity. Endocrinology 2002; 143:1741-1747

20. Massafra V, Milona A, Vos HR, Burgering BM, van Mil SW. Quantitative liver proteomics identifies FGF19 targets that couple metabolism and proliferation. PLoS
21. Hansen AMK, Vienberg SG, Lykkegaard K, Zhao X, Tingqing G, et al. Differential receptor selectivity of the FGF15/FGF19 orthologues determines distinct metabolic activities in db/db mice. Biochem J 2018; 475:2985-2996

22. Zhang J, Li H, Bai N, Xu Y, Song Q, et al. Decrease of FGF19 contributes to the increase of fasting glucose in human in an insulin-independent manner. J Endocrinol Invest 2019; 42:1019-1027

23. Mulla CM, Goldfine AB, Dreyfuss JM, Houten S, Pan H, et al. Plasma FGF-19 Levels are Increased in Patients with Post-Bariatric Hypoglycemia. Obes Surg 2019; 29:2092-2099

24. Nwagha UI, Ikekepazu EJ, Ejezie FE, Neboh EE, Maduka IC. Atherogenic index of plasma as useful predictor of cardiovascular risk among postmenopausal women in Enugu, Nigeria. Afr Health Sci 2010; 10:248-252

25. Cai G, Shi G, Xue S, Lu W. The atherogenic index of plasma is a strong and independent predictor for coronary artery disease in the Chinese Han population. Medicine (Baltimore) 2017; 96:e8058

26. Li Z, Huang Q, Sun L, Bao T, Dai Z. Atherogenic Index in Type 2 Diabetes and Its Relationship with Chronic Microvascular Complications. Int J Endocrinol 2018; 2018:1765835

27. Wu TT, Gao Y, Zheng YY, Ma YT, Xie X. Atherogenic index of plasma (AIP): a novel predictive indicator for the coronary artery disease in postmenopausal women. Lipids Health Dis 2018; 17:197

28. Nie X, Gao L, Wang L, Wang J. Atherogenic Index of Plasma: A Potential Biomarker for Clinical Diagnosis of Diabetic Foot Osteomyelitis. Surg Infect (Larchmt) 2019;

29. Bendzala M, Sabaka P, Caprnda M, Komornikova A, Bisahova M, et al. Atherogenic
index of plasma is positively associated with the risk of all-cause death in elderly women: A 10-year follow-up. Wien Klin Wochenschr 2017; 129:793-798

30. Ni W, Zhou Z, Liu T, Wang H, Deng J, et al. Gender-and lesion number-dependent difference in "atherogenic index of plasma" in Chinese people with coronary heart disease. Sci Rep 2017; 7:13207

31. Xie F, Zhou H, Wang Y. Atherogenic index of plasma is a novel and strong predictor associated with fatty liver: a cross-sectional study in the Chinese Han population. Lipids Health Dis 2019; 18:170

32. Mencarelli A, Fiorucci S. FXR an emerging therapeutic target for the treatment of atherosclerosis. J Cell Mol Med 2010; 14:79-92

33. Byun S, Jung H, Chen J, Kim YC, Kim DH, et al. Phosphorylation of hepatic farnesoid X receptor by FGF19 signaling-activated Src maintains cholesterol levels and protects from atherosclerosis. J Biol Chem 2019; 294:8732-8744

34. Zhou M, Learned RM, Rossi SJ, Tian H, DePaoli AM, et al. Therapeutic FGF19 promotes HDL biogenesis and transhepatic cholesterol efflux to prevent atherosclerosis. J Lipid Res 2019; 60:550-565

Figures
Figure 1

The correlation of FGF19 with TG and AIP. b. Unadjusted. c. Adjust for age, gender, duration, BMI, hypertension, diabetic treatment. d. Adjust for age, gender, duration, BMI, hypertension, diabetic treatment, NAFLD, NFS

$a. \quad r = -0.330, p = 0.007$
b. \[ r = -0.288, \ p = 0.008 \]

c. \[ r = -0.277, \ p = 0.051 \]
Figure 2

The correlation of FGF19 and AIP among three groups. a. Normal-weight T2D patients b. Overweight T2D patients c. Obese T2D patients

Supplementary Files

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