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ORIGINAL ARTICLE

Increased levels of circulating fibroblast growth factor 21 in children with Kawasaki disease

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Abstract

The purpose of this study was to examine the serum levels of fibroblast growth factor 21 (FGF21) in children with acute Kawasaki disease (KD) and to investigate its relationship with coronary artery lesions (CALs). Blood samples from 58 children with KD before intravenous immunoglobulin treatment and from 28 healthy children as control group were collected. Serum FGF21 levels in all participants were measured using enzyme-linked immunosorbent assay, and clinical parameters were tested in all KD patients. Serum FGF21 levels were significantly increased in acute KD patients as compared to the control group. Serum levels of FGF21 were substantially higher in the group of KD patients with CALs (KD-CALs) than in KD patients without CALs (KD-NCALs). Positive relationships between serum levels of FGF21 and percentage of leukomonocytes (*L* %), C-reactive protein, activated partial thromboplastin time and D-dimer were observed in KD patients. Furthermore, serum FGF21 levels were negatively correlated with red blood cell counts, hemoglobin (Hb), percentage of neutrophils (*N* %) and albumin. Serum level of FGF21 is associated with inflammation and coagulation. The paradoxical increase in serum FGF21 in acute KD patients may indicate a protective compensatory response.

Keywords Kawasaki disease (KD) · Fibroblast growth factor 21 (FGF21) · Coronary arterial lesions (CALs) · Clinical parameters · Blood coagulation

Introduction

Kawasaki disease (KD) is a kind of self-limiting immune vasculitis that mainly occurs in children under the age of 5 years old and has become the most common cause of acquired heart disease in children. KD primarily affects small and medium-sized blood vessels, particularly the coronary arteries [1]. If not promptly treated, coronary artery lesions (CALs) or coronary artery aneurysms (CAA) could develop in 20–30% children with KD, which could eventually evolve into thrombosis and myocardial infarction [2]. Although the exact pathogenesis of KD is still unclear, a series of evidence has shown that development of KD is induced by genetic and infectious factors, especially the regulation of inflammatory factors by the innate immune system [3, 4]. Previous study has demonstrated that the formation of CALs is mainly related to injuries of the coronary endothelial cells, which could be attributed to inflammatory factors and oxidative stress [5, 6]. Adhesion molecule is a class of molecules that mediate cell–cell and cell–matrix interactions. It has been reported that adhesion molecule can regulate leukocyte migration, angiogenesis, and adhesion between leukocytes and vascular endothelial cells in coronary artery aneurysms associated with Kawasaki disease [7, 8].

White adipose tissue, as an endocrine organ, can produce various kinds of adipokines, which play important roles in metabolic diseases via regulation of fat metabolism.

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Furthermore, adipokines have been associated with immunity and inflammatory response [9]. In recent years, it has been reported that most adipokines are involved in cardiovascular diseases, in addition to metabolic diseases. Specifically, adipokines have been associated with multiple heart diseases, such as coronary atherosclerosis, ischemic heart disease, acute myocardial infarction [10–12]. The fibroblast growth factor 21 (FGF21) is a member of the FGF19 subfamily within the endocrine FGF family [13]. Unlike other subfamily members of FGFs that function via autocrine and paracrine signaling, FGF21 could perform physiological functions in an endocrine fashion, such as regulating glucose and lipid metabolism, suppressing inflammation and protecting myocardium [14, 15]. Furthermore, FGF21 mRNA expression has been found in liver, heart and kidneys. As a novel adipokine, it has been reported that FGF21 can protect coronary endothelial cells from injuries via anti-inflammatory and anti-oxidative mechanisms in coronary atherosclerosis [16, 17]. In addition, Lin et al. have confirmed that FGF21 regulates adiponectin levels in adipocytes by regulating adiponectin gene transcription and protein secretion [18]. Moreover, adiponectin has been shown to exhibit anti-inflammatory protective effects in KD [19]. However, the role of FGF21 on regulating adiponectin production during the pathogenesis of KD remains unclear, and the potential association between KD and FGF21 still needs to be explored. Therefore, we examined the serum levels of FGF21 during acute phase of KD to further determine the association between FGF21 and KD.

Patients and methods

Patients

Participants consisting of 58 KD patients (37 males and 21 females, 2.81 ± 1.76 years old) and 28 healthy children (16 males and 12 females, 3.18 ± 1.95 years old) were enrolled from the Children's Hospital of Chongqing Medical University in Chongqing, P.R. China. Children with immune diseases, metabolic diseases, inflammatory diseases, hematological diseases, severe liver and kidney diseases and other heart diseases were excluded from this study. All KD patients had no previous history of KD and did not receive IVIG treatment and anticoagulation therapy prior to collection of blood samples. Participants were divided into the KD groups and the health control (HC) groups. Diagnosis of KD is strictly based on the 5th revised edition of the diagnostic guidelines of the Japanese Kawasaki Disease Research Committee [20]. In addition, according to the presence of coronary artery lesions (CALs), the 58 KD patients were further divided into two groups: KD with CALs (KD-CALs, $n = 30$) and KD without CALs (KD-NCALs, $n = 28$). CAL is determined by the Z value from the results of echocardiography parameters measured 1 day before IVIG treatment and the surface area of lesion. Patients with Z value < 2 are included in the KD-NCALs group, while those with Z value > 2 are included in the KD-CALs group [21]. This study was approved by the Ethics Committee of Children's Hospital and Chongqing Medical University. Informed consent was obtained from the guardians of all participants.

Sample collection and processing

Blood samples were collected from all KD patients 1 day before IVIG treatment. After routine blood tests, the blood samples were immediately centrifuged at 3000 rpm for 10 min to obtain the serum samples, which were stored at − 80 °C until analysis. Serum samples from healthy children were obtained by following the same procedure.

Measurement of serum FGF21 concentrations and clinical parameters

Serum concentrations of FGF21 in all participants were measured using the enzyme-linked immunosorbent assay (ELISA) kits (RayBiotech, Atlanta) according to the manufacturer's instructions. All samples were analyzed in duplicate. The intra- and inter-assay coefficients of variation for the levels of FGF21 were < 10% and < 12%, respectively. Various clinical parameters of the samples were also measured, including white blood cell counts (WBC), red blood cell counts (RBC), hemoglobin (Hb), platelet counts (PLT), percentage of neutrophils (N %), percentage of leukomonocytes (L %), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin and creatine kinase-MB (CK-MB), as well as blood coagulation parameters such as prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), thrombin time (TT) and D-dimer (DD).

Statistical analysis

According to Kolmogorov–Smirnov test, the data conformed to a normal Gaussian distribution. All data were shown as mean ± standard deviation (SD) or number and percent (n, %). Chi-square test was used for comparing frequencies between groups. Differences between groups were assessed using the unpaired 2-tailed t test. One-way ANOVA unpaired two-tailed t test was used for comparison between different groups. Spearman rank correlation was used for analyzing association between serum FGF21 levels and laboratory parameters. All statistical analyses were evaluated by SPSS 21.0 software for Windows (SPSS, Inc., Chicago, IL, USA). P value of < 0.05 was considered to be statistically significant.

Results

Serum FGF21 levels were higher in KD patients than in healthy children

There was no significant difference in age and gender between the KD and HC groups (unpublished data). In this study, the measured serum levels of FGF21 ranged from 21 to 1359 pg/ml. As shown in Fig. 1, serum FGF21 concentration in the KD groups (478.8 pg/ml [21, 1359]) was significantly higher than that in the HC groups (267.8 pg/ml [24, 596]) ($p = 0.0152$).

Serum FGF21 levels and clinical parameters in KD-CALs and KD-NCALs groups

Figure 2 demonstrated that the level of FGF21 was significantly increased in the KD-CALs groups (762.9 pg/ml [335.5, 1359]) compared with the KD-NCALs groups (174.3 pg/ml [20.96, 337.8]) ($p < 0.001$). As shown in Table 1, no statistically significant differences in IVIG, WBC, Hb, *N* %, *L* %, CRP, ESR, PCT, AST and CK-MB were found between the KD-CALs and the KD-NCALs groups ($p > 0.05$). Meanwhile, the levels of RBC and albumin in the KD-CALs groups were significantly lower than those in the KD-NCALs groups ($p < 0.05$).

Correlation between FGF21 levels and clinical parameters in KD patients

No significant correlations between FGF21 levels and IVIG, WBC, PLT, ESR, PCT, ALT, AST, and CK-MB were found ($p > 0.05$). However, serum FGF21 levels were positively correlated with CRP and *L* % levels ($p < 0.05$) and were negatively correlated with RBC, Hb, *N* % and albumin levels ($p < 0.05$) in KD patients (Table 2).

Correlation analysis indicated that no significant correlations were found between serum FGF21 levels and the blood coagulation parameters: PT, TT and FIB ($p > 0.05$). However, serum FGF21 levels were positively correlated with APTT and DD ($p < 0.05$) in KD patients (Table 3).

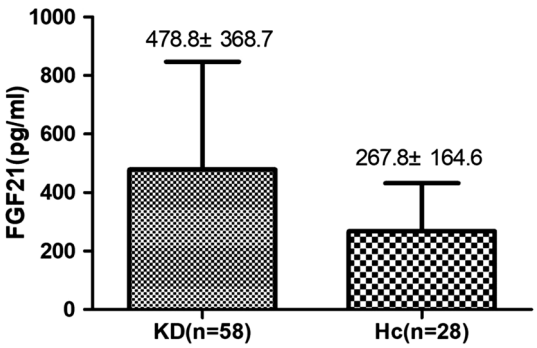

Fig. 1 Comparisons of circulating FGF21 level between the KD and HC group

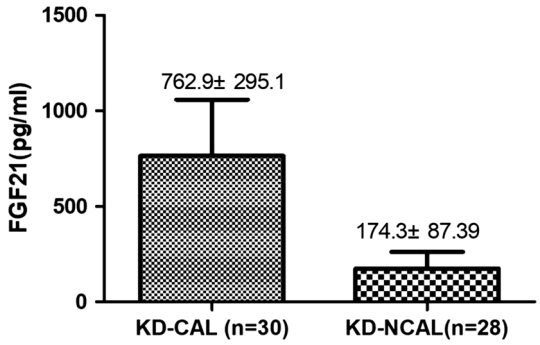

Fig. 2 Comparisons of circulating FGF21 level between the KD-CALs and KD-NCALs group

Discussion

FGF21, a member of the FGF family, plays an important role in the regulation of inflammation and immune system [22, 23]. In this study, we were motivated to examine the expression of FGF21 in KD and investigate the

Table 1 Serum FGF21 level and clinical parameters in KD-CALs and KD-NCALs groups

	KD-CALs	KD-NCALs	*P* value
WBC (10^3/μl)	13.16 ± 5.594	15.36 ± 6.239	0.1568
RBC (10^3/μl)	4.161 ± 0.5437	4.292 ± 0.4937	0.0439*
Time point of IVIG (day)	5.862 ± 1.529	6.296 ± 1.815	0.5343
Hb (g/L)	108 ± 10.17	108.6 ± 22.86	0.1268
Plt (10^3/μl)	405.3 ± 149.4	330.5 ± 99.5	0.0387*
N %	0.6905 ± 0.1011	0.7364 ± 0.1355	0.1053
L %	0.2515 ± 0.0839	0.2065 ± 0.1075	0.0848
CRP (mg/dL)	50.58 ± 31.47	35.12 ± 24.95	0.0705
ESR (mm/h)	52.47 ± 27.12	63.88 ± 25.82	0.1327
PCT	1.370 ± 1.817	1.408 ± 2.287	0.8397
Albumin (g/L)	38.60 ± 3.498	40.49 ± 3.475	0.0226*
ALT (U/L)	48.69 ± 38.42	25.33 ± 29.03	0.0011*
AST (U/L)	34.29 ± 16.61	28.87 ± 13.05	0.1234
CK-MB (U/L)	0.5503 ± 0.5894	0.4196 ± 0.8090	0.0681
FGF21	762.9 ± 295.1	174.3 ± 87.39	< 0.001*

KD Kawasaki disease, *CALs* coronary artery lesions, *WBC* white blood cell counts, *RBC* red blood cell counts, *Hb* hemoglobin, *PLT* platelet counts, *N* % percentage of neutrophils, *L* % percentage of leukomonocytes, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *PCT* procalcitonin, *AST* aspartate aminotansferase, *ALT* alanine aminotransferase, *CK-MB* creatine kinase-MB

*p value of < 0.05

Table 2 Correlations between FGF21 levels and clinical parameters in KD patients

	FGF21	
	r	*p*
WBC (10^3/μl)	−0.111	0.4067
RBC (10^3/μl)	−0.5387	<0.001*
Time point of IVIG (day)	−0.0611	0.6575
Hb (g/L)	−0.4188	0.0016*
Plt (10^3/μl)	0.1992	0.1399
N %	−0.4297	0.0018*
L %	0.3981	0.0046*
CRP (mg/dL)	0.3086	0.0232*
ESR (mm/h)	−0.2137	0.1073
PCT	0.01830	0.8926
Albumin (g/L)	−0.3369	0.0097*
ALT (U/L)	0.1497	0.2620
AST (U/L)	0.1969	0.1459
CK-MB (U/L)	−0.0079	0.9546

WBC white blood cell counts, *RBC* red blood cell counts, *Hb* hemoglobin, *PLT* platelet counts, *N* % percentage of neutrophils, *L* % percentage of leukomonocytes, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *PCT* procalcitonin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CK-MB* creatine kinase-MB

*p value of <0.05

Table 3 Correlations between FGF21 levels and the blood coagulation parameters in KD patients

	FGF21	
	r	*p*
PT (s)	0.1271	0.3999
APTT (s)	0.3279	0.0261*
TT (s)	−0.0096	0.9493
FIB (g/L)	−0.1619	0.2881
DD (mg/L)	0.3780	0.0114*

PT prothrombin time, *APTT* activated partial thromboplastin time, *FIB* fibrinogen, *TT* thrombin time, *DD* D-dimer

*p value of <0.05

relationship between serum FGF21 levels and CALs in KD patients. Our results showed that (1) serum FGF21 levels were significantly increased in acute KD patients as compared to healthy control, (2) serum levels of FGF21 were substantially higher in the KD-CALs group than the KD-NCALs group, while serum levels of RBC and albumin were decreased in the KD-CALs group as compared to the KD-NCALs group, (3) the levels of albumin, *N* %, *L* %, RBC, Hb, CRP, APTT and DD were correlated with FGF21 levels in KD patients.

FGF21, a novel adipokine, is expressed in the liver and heart. FGF21 has been demonstrated to exhibit lipid-lowering, anti-inflammatory and antioxidant properties, which explain its critical role in cardiovascular diseases. As reported, FGF21 can protect the heart from ischemic reperfusion injury and myocardial infarction, specifically by protecting coronary endothelial cells from injuries via inhibition of the NF-kB pathway and resistance of oxidative stress in coronary atherosclerosis [24]. A series of studies have reported that FGF21 may be used as a pharmacological target for heart disease. However, the potential role of FGF21 in KD has not been reported so far. This study found that serum FGF21 levels in KD patients were higher than those in healthy controls. This observation is similar to the investigation of FGF21 in coronary atherosclerosis and hypertensive heart disease, which indicates that the up-regulation of FGF21 may be a compensatory mechanism in acute phase of KD. It has been reported that paradoxical increase of FGF21 levels in vivo is suggestive of a compensatory response in coronary atherosclerosis, and the increase of FGF21 has been confirmed to demonstrate therapeutic effects in vitro [25, 26]. The feedback loop of the body regulates the increase in FGF21 to compensate for the impaired FGF21 receptor signal in obesity [27]. The paradoxical increase of FGF21 levels may be a mechanism that is similar to insulin resistance [28]. Furthermore, the levels of FGF21 were even higher in the KD-CALs group than the KD-NCALs group. The formation of CALs is caused by inflammatory factors and oxidative stress in KD patients. FGF21 has been shown to exhibit anti-inflammatory and antioxidant effects in most immune and inflammatory diseases [16, 29]. Our results demonstrated that FGF21 level was negatively correlated with *N* % and CRP in KD patients, indicating that FGF21 might play a protective role during the formation of CALs in acute phase of KD.

Correlation analysis showed that serum FGF21 levels were positively correlated with CRP and *L* % levels, while negatively correlated with *N* % levels in KD patients. Previous studies have reported that the formation of KD is closely related to respiratory illness and viral infections [30, 31]. We found a correlation between FGF21 and *N* %, *L* % in KD patients. There is no evidence that infection by pathogens causes a change in the level of FGF21. Recent evidence demonstrated that FGF21 not only regulates inflammatory reaction, but also promotes immune modulation in cardiovascular diseases. As an anti-inflammatory factor, FGF21 not only inhibits the nuclear importing of activated NF-κB (p65) to down-regulate inflammatory factors, such as IL-1, IL-6, and TNF-α, but also up-regulates IL-10 production to improve LPS-Induced inflammation [32]. As an immune-related factor, FGF21 regulates a variety of immune factors, such as TH17, CD4 + T cell, and CD8 + T cell. Lydia et al. [4, 33] have reported that FGF21 participates in innate immune regulation in obesity. Inflammatory and immune factors have been proven to be closely related to

the development of KD. Vieira et al. [34] have explored targeting the cardiac lymphatic system to constrain the innate immune response, which could prevent the long-term escalation of innate immunity to a chronic inflammatory state. In our study, our results indicate that FGF21 may be involved in KD via regulation of the immune system to increase lymphocytes and inhibit neutrophil levels. It has been reported that CRP increases in KD, and high CRP level suggests a high likelihood of large CAA in KD [35, 36]. Elevated CRP levels represent inflammation in the body, and high levels of FGF21 reflect the severity of inflammation in coronary atherosclerosis, chronic kidney disease and rheumatoid arthritis [37, 38]. Our study showed that FGF21 levels were positively correlated with CRP, which was consistent with the results found by Lin et al. [38] in chronic kidney disease. This observation further indicates that FGF21 may play an anti-inflammatory role during the acute phase of KD.

Furthermore, the albumin level in the KD-CALs group was lower than that in the KD-NCALs group. Meanwhile, serum FGF21 levels were negatively correlated with albumin levels in KD patients. This observation could be attributed to the increased permeability of inflammatory vessel walls, endothelial cell damage and albumin leakage in KD with CALs. Previous studies have shown that FGF21 protects coronary endothelial cells by inhibiting the downregulation of NO production via the PI3 K/AKT pathway and by reducing the aggregation of cell adhesion molecules in coronary atherosclerosis [39, 40]. Given the severity of vasculitis in KD, the damage of coronary endothelial cells becomes more serious. Our body protects against endothelial cell damage by regulating the increase in FGF21, thereby attributing to a negative correlation between FGF21 and albumin. These results also indicate that FGF21 may play the role of an antioxidant and prevent coronary artery from injury during the acute phase of KD.

Existing studies have demonstrated that systemic oxidative stress associated with premature erythrocyte aging is closely related to the complications of KD [41]. In this study, we also found that serum FGF21 levels were negatively correlated with RBC and Hb levels in KD patients, indicating that changes in RBC and Hb may be related to the antioxidant activity of FGF21 in KD. Previous studies have reported that thrombosis occurs when coronary endothelial cells are severely damaged and lead to hypercoagulation in KD. Although little evidence has supported the relationship between FGF21 and coagulation parameters in thrombosis, FGF21 has been found to protect vascular endothelial cells from injury and regulate hypoproteinemia, hyperlipidemia and cell adhesion molecules that could lead to increased blood viscosity. In addition, high FGF21 levels are associated with higher risk of cardiovascular events and stroke [40, 42, 43]. In our study, we found that DD was increased in the KD-CALs group compared with the KD-NCALs group ($p = 0.0352$ unpublished data). In addition, serum FGF21 levels were positively correlated with APTT and DD levels in KD patients. These results suggest that FGF21 may be involved in one of the coagulation processes, even though the exact mechanism of this action requires further investigation.

There are several limitations to this study. We did not collect serum samples from KD patients after they were treated with IVIG for comparison purposes. In addition, the sample size was relatively small.

In conclusion, this in vivo study indicates, for the first time, that serum FGF21 levels were significantly elevated in KD patients, especially in KD patients with CALs. Moreover, serum levels of FGF21 were associated with levels of *L* %, *N* %, CRP and albumin in KD patients. These observations indicate that high level of FGF21 may be a compensatory mechanism that plays a protective role in the antioxidant/anti-inflammatory response during acute phase of KD. Furthermore, FGF21 may be involved in one of the coagulation processes in acute phase of KD, although the relationship between FGF21 and coronary artery thrombosis requires additional exploration. Finally, future studies are needed to elucidate the role of FGF21 in vasculitis and the development of CALs in KD.

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Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

Ethical approval This present study was approved by the Ethics Committee of Children's Hospital, Chongqing Medical University.

Informed consent Informed consent was obtained from guardians of all participants.

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