Changes in Serum Fibroblast Growth Factor 23 in Patients With Acute Myocardial Infarction

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Background: Fibroblast growth factor 23 (FGF23) induces cardiac remodeling. We investigated the changes in serum FGF23 levels in patients diagnosed with acute myocardial infarction (AMI).

Methods and Results: A total of 44 patients diagnosed with AMI were included in the current study. All patients underwent emergency percutaneous coronary intervention (PCI). The median of peak creatine kinase (CK) and CKMB values was 1,816 U/L and 159 U/L, respectively. Serum levels of FGF23, calcium, and inorganic phosphate (iP) were measured before PCI, and on days 1, 3, 5, 7 after PCI. Serum FGF23 levels showed a slight, but significant decrease on days 1 and 3 after PCI, and a 1.5- and 2.0-fold increase on days 5 and 7, respectively, after PCI. As compared with propensity score-matched patients without AMI, serum FGF23 was significantly lower among the current cohort of AMI patients. In 22 subjects who underwent a follow-up echocardiographic examination at 6 months after the onset of AMI, the log-transformed relative increase in FGF23 on day 7 significantly and negatively correlated with changes between LVEF on admission and that at 6 months afterward.

Conclusions: After a slight decrease on days 1 and 3 after admission, serum FGF23 increased significantly on days 5 and 7. The underlying mechanism and potential clinical importance of these observations require further investigation.

Key Words: Biomarkers; Fibroblast growth factor 23 (FGF23); Myocardial infarction
For each study patient, information on clinical history, such as hypertension, diabetes, and smoking status was obtained from the clinical record. All participants underwent emergency percutaneous coronary intervention (PCI). Patients who were in cardiogenic shock on admission or were undergoing chronic hemodialysis were excluded.

**Laboratory Analysis**

Blood samples were collected in the morning after an overnight fast. Aliquots of serum and plasma were immediately obtained and stored at −80°C until analysis. Serum levels of intact FGF23 were measured using a two-step FGF23 enzyme immunoassay kit (Kainos Laboratories, Tokyo, Japan) according to the manufacturer’s instructions. By this method, the FGF23 value was expressed as “pg/dL”, unlike “RU/mL” that has been used for the C-terminal FGF23 values in some previous reports.

Calcium, iP, and C-reactive protein (CRP) levels were measured by routine laboratory methods. When serum albumin was ≤4 mg/dL, serum calcium levels were corrected by the formula [calcium+(4−serum albumin)], and designated as corrected calcium (cCa).

FGF23 levels were measured at the time of admission in a serum sample obtained before PCI was performed, designated FGF23*0d*. Serum FGF23 was periodically measured thereafter, and levels on days 1–2, 3–4, 5–6, and 7–8 after admission were designated FGF23*1d*, FGF23*3d*, FGF23*5d*, and FGF23*7d*, respectively. FGF23 values at each time point relative to the FGF23 level on admission, namely, FGF23*1d*/FGF23*0d*, FGF23*3d*/FGF23*0d*, FGF23*5d*/FGF23*0d*, and FGF23*7d*/FGF23*0d*, were designated relative FGF23*1d*, relative FGF23*3d*, relative FGF23*5d*, and relative FGF23*7d*, respectively. cCa and iP measured at each time point divided by the corresponding value on admission were also termed relative cCa and relative iP, respectively.

**Study Population**

Patients who were diagnosed with AMI between April 2015 and March 2017 and gave informed consent for use of their clinical data and biomarker measurement were enrolled in the study. AMI was defined as the presence of chest pain for more than 30 min associated with persistent ST-segment elevation >1 mm in at least 2 peripheral ECG leads, or >2 mm in at least 2 precordial leads with an increased MB fraction of creatinine kinase (CKMB) or positive cardiac troponin T test (TROP T* assay, Roche, Basel, Switzerland). For each study patient, information on clinical history, such as hypertension, diabetes, and smoking status was obtained from the clinical record. All participants underwent emergency percutaneous coronary intervention (PCI). Patients who were in cardiogenic shock on admission or were undergoing chronic hemodialysis were excluded.

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The estimated glomerular filtration rate (eGFR) was calculated by the following Modification of Diet in Renal Disease equation for Japanese subjects: eGFR (mL/min/1.73 m^2) = 194 × (serum creatinine) ^(-1.094 × (age)^0.287 × (0.739 when female). 18 eGFR measured on admission and 6 months after the onset of AMI was designated eGFR_0d and eGFR_6m, respectively.

Echocardiography
Echocardiographic examinations were performed with a Vivid 7 Dimension instrument equipped with a multifrequency transducer (GE Healthcare, Vingmed, Norway). The LV ejection fraction (LVEF) was calculated in the apical 4-chamber view using the modified Simpson’s method. LVEF measured at the time of admission and 6 months after admission was designated LVEF_0d and LVEF_6m, respectively.

Statistical Analysis
Baseline characteristics were assessed by standard descriptive statistics. Data are expressed as either mean±standard deviation for normally distributed data or median and interquartile range (IQR) for non-normally distributed and categorical data. Spearman rank correlation test for non-normally distributed data and Pearson’s test for normally distributed data were used to assess the correlation between 2 variables. For the comparison of paired non-normally distributed variables, Wilcoxon signed-rank test following the examination of difference in the overall groups by Friedman test was used, and P values were then adjusted using the Holm method. 19 Propensity matching was performed on baseline characteristics to balance sex, age, iP, and eGFR between AMI patients and non-AMI cardiac patients, using a 1:1 nearest neighbor approach without replacement. Data analysis was performed by SPSS statistics version 22.0 (IBM, Armonk, NY, USA).

Results
Study Patients
In total, 44 patients diagnosed with AMI were enrolled in the current study, and 30 patients (68%) had an eGFR of ≥60 mL/min/1.73 m^2. The patients baseline characteristics and culprit coronary lesions are described in Table 1. All patients underwent immediate PCI; a drug-eluting stent was implanted in 42 patients and plain balloon angioplasty was performed in 2 patients. No patients underwent emergency coronary artery bypass surgery. The mean amount of contrast medium was 189.1±52.5 mL and the average fluoroscopy time was 26.3±12.7 min.

Parameters Associated With FGF23_0d
The FGF23 level measured immediately before the PCI procedure was significantly correlated with eGFR (r=−0.49, P=0.001), but not with age, systolic blood pressure, uric acid, iP, cCa, or LVEF. The serum FGF23 level immediately after PCI was available for 42 patients (median, 31.8 pg/mL; IQR, 21.5–39.9 pg/mL), and was significantly correlated with FGF23_0d (r=0.67, P<0.001). Among the 44 study patients, 20 were diagnosed with diabetes. Serum FGF23_0d did not significantly differ between patients without diabetes (median 30.1 pg/mL; IQR 23.0–52.8 pg/mL) and those with diabetes (median 31.9 pg/mL; IQR 18.6–55.3 pg/mL, P=0.850, by Mann-Whitney U test). FGF23_0d was not significantly correlated with either peak CK (r=0.003, P=0.985) or peak CKMB (r=−0.018, P=0.907; Spearman’s correlation test).

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lower FGF23_0d had higher relative FGF23_7d values, and thus a greater increase in FGF23 at 7 days after PCI (Figure 3). This negative association between FGF23_0d and relative FGF23_7d was significant by Spearman’s correlation test (Table 2). The trend in the relative FGF23 value was examined for subgroups of patients with an initial value above or below the median (31 pg/mL), which showed that the increase in serum FGF23 on day 7 was more prominent among patients with FGF23_0d <31 pg/mL and that the increase on day 7 was not significant among those with FGF23_0d >31 pg/mL (Figure 2A).

Neither the peak CK value nor the peak CKMB value significantly correlated with FGF23_0d or relative FGF23_7d. On the other hand, it was found that time-to-reperfusion was significantly negatively correlated with FGF23_0d and positively with relative FGF23_7d, although it was not significantly correlated with FGF23_7d (Figure 4), indicating that patients with early reperfusion, which increases myocardial salvage, were more likely to have a relatively higher FGF23 value on admission. Time-to-reperfusion was not significantly correlated with either peak CK or peak CKMB (data not shown).

### Table 2. Correlation With Log(Relative FGF23_7d)

<table>
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<th>P value</th>
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<td>Peak CKMB</td>
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</table>

*ccA, corrected calcium; CK, creatine kinase; CKMB, creatine kinase MB fraction; eGFR, estimated glomerular filtration rate; FGF, fibroblast growth factor; iP, inorganic phosphate.*

**Chronological Changes in Serum Levels of FGF23, iP, cCa, and eGFR**

FGF23 showed an initial decrease on days 1 and 3, followed by an increase on days 5 and 7 after PCI, and the differences between the FGF23_0d and FGF23 levels at all other time points (FGF23_1d, FGF23_3d, FGF23_5d, FGF23_7d) was statistically significant (Figure 1). In contrast to the observed dynamic changes in FGF23 levels, changes in relative iP, relative cCa, and relative eGFR were less marked (Figure 2). Although the changes in iP resembled those of FGF23, the relative iP values on days 1, 3, 5, 7 after PCI did not differ significantly from the relative iP_0d. Relative cCa_3d was significantly lower and higher than the relative cCa_0d. None of the relative eGFR values on days 1, 3, 5, and 7 after PCI significantly differed from the relative eGFR_0d.

FGF23_0d and relative FGF23_7d values were plotted on scatter plot, which showed that patients with relatively lower FGF23_0d had higher relative FGF23_7d values, and thus a greater increase in FGF23 at 7 days after PCI (Figure 3). This negative association between FGF23_0d and relative FGF23_7d was significant by Spearman’s correlation test (Table 2). The trend in the relative FGF23 value was examined for subgroups of patients with an initial value above or below the median (31 pg/mL), which showed that the increase in serum FGF23 on day 7 was more prominent among patients with FGF23_0d <31 pg/mL and that the increase on day 7 was not significant among those with FGF23_0d >31 pg/mL (Figure 2A).

Neither the peak CK value nor the peak CKMB value significantly correlated with FGF23_0d or relative FGF23_7d. On the other hand, it was found that time-to-reperfusion was significantly negatively correlated with FGF23_0d and positively with relative FGF23_7d, although it was not significantly correlated with FGF23_7d (Figure 4), indicating that patients with early reperfusion, which increases myocardial salvage, were more likely to have a relatively higher FGF23 value on admission. Time-to-reperfusion was not significantly correlated with either peak CK or peak CKMB (data not shown).
Comparison With Propensity Score Matched Non-AMI Cardiac Patients

In the AMI group, the FGF23₀d value was used for FGF23. AMI, acute myocardial infarction. Other abbreviations as in Table 2.

Relative FGF2₃₀d was not significantly correlated with relative iP₀ or relative eGFR₀ (data not shown). When sex, age, peak CK, CRP, uric acid, and FGF2₃₀d were entered as potential independent variables in a stepwise linear regression analysis, FGF2₃₀d and peak CK were factors that were significantly associated with log(relative FGF2₃₀d) with a standardized β of −0.60 (P<0.001) and −0.28 (P=0.021), respectively. When time-to-reperfusion was added in the stepwise model, time-to-reperfusion was not selected as an independent factor that had a relation with log(relative FGF2₃₀d) (data not shown).

Figure 5. Correlation of log(relative FGF2₃₀d) with changes in LVEF and eGFR and the trend in relative FGF23 at 6 months after admission for acute myocardial infarction. (A, B) Log(relative FGF2₃₀d) correlated significantly with the net difference in LVEF over the 6-month period (A) but not with the difference in eGFR (B) over the same period. (C) Data for patients in whom the serum FGF23 value was measured at 6 months after admission (n=32) were analyzed. Patients with FGF23 below the median value (31 pg/mL, n=20) on initial presentation (₀d) had significantly greater relative FGF23 at both day 7 (7d) and 6 months (6m) after admission. However, changes in the FGF23 value were not significant at either time point among those with FGF23 above the median value (n=12) on initial presentation. P values were adjusted using the Holm method after values were obtained Wilcoxon signed-rank test. **P<0.01 vs. the corresponding values at the time of admission. eGFR, estimated glomerular filtration rate; FGF, fibroblast growth factor; LVEF, left ventricular ejection fraction.
were included as potential explanatory variables, FGF23 0d and peak CK were selected as factors that had a significant correlation with the decline in LVEF at 6 months after onset. Among those with FGF23 0d >31 pg/mL (n=12), the log(relative FGF23 7d) did not significantly correlate with the change in eGFR over the 6 months (Figure 5A). Among the 32 selected patients in whom serum FGF23 was available at 6 month after admission, FGF23 0d was significantly greater than FGF23 7d (Figure 5C). When subjects were divided according to the initial value above or below the median (31 pg/mL), those who had FGF23 0d <31 pg/mL (n=20) had an increase in FGF23 at both 7 days and 6 months afterward (Figure 5C). On the other hand, among those with FGF23 0d >31 pg/mL (n=12), serum FGF23 did not significantly change at either both 7 days and 6 months after the admission (Figure 5C).

### Discussion

In the current study, we showed that serum FGF23 levels were significantly increased on days 5 and 7 after emergency PCI for AMI after an initial decrease on days 1 and 3. In contrast, changes in iP and eGFR at these time points were not significant. In a multivariate linear regression analysis in which age, sex, FGF23 0d, peak CK, CRP, and uric acid were included as potential explanatory variables, FGF23 0d and peak CK were selected as factors that had a significant negative association with log(relative FGF23 0d), which was significantly correlated with the decline in LVEF at 6 months after onset.

Epidemiological studies have shown that individuals with increased serum FGF23 levels are more likely to have cardiac hypertrophy and reduced cardiac systolic function, and may be at a higher risk of all-cause death and poor cardiovascular prognosis. In addition, animal studies have suggested that the observed association between serum FGF23 level and cardiac remodeling may be, at least in part, caused by FGFR4-dependent activation of the phospholipase C-γ/calciuemir/NFAT pathway.  

Reindl et al showed in a recent study that the serum FGF23 level, measured 2 days after AMI onset, was associated with aggravat long-term LV remodeling, as assessed by cardiac magnetic resonance imaging and defined as at least a 20% increase in LV end-diastolic volume between the baseline scan and follow-up scan at 4 months. As in the current study, they did not assess whether an elevated level of FGF23 predicted LV remodeling independent of other cardiac biomarkers or calcium/phosphate-related parameters, presumably because of the small sample size. Pöss et al showed that circulating FGF23 levels were higher among patients with cardiogenic shock than among those with uncomplicated AMI, which suggests that the serum FGF23 level may change according to the patient’s physiological condition; however, patients with cardiogenic shock were not included in our study. Pöss et al also reported that FGF23 levels among patients with uncomplicated AMI did not significantly differ from those in patients with stable coronary artery disease. They measured FGF23 levels in samples collected immediately after admission to the intensive care unit, which was presumably the day of AMI onset. In an animal model of MI and subsequent reperfusion, elevation of the serum FGF23 level was demonstrated at 2- and 4-weeks post-MI, although whether or not it had changed at earlier time points was not reported. These findings collectively raise the possibility that the alteration in the serum FGF23 level may be related to various cardiac injury or hemodynamic alterations.

The mechanisms underlying the upregulation of serum FGF23 levels in AMI patients, if present, are unknown; however, there are some possibilities. As described before, FGF23 is a bone-secreted hormone that has a phosphaturic effect, and the serum FGF23 level may increase under the conditions of renal failure, where serum iP levels tend to increase because of decreased urinary iP excretion. In addition, recent studies suggested that serum FGF23 levels may be elevated in the early phase of renal dysfunction before the serum phosphate starts to elevate. We have also demonstrated that serum FGF23 levels correlate with the serum phosphate level in cardiology patients with preserved renal function. It was reported that phosphate levels in the coronary venous blood draining the ischemic myocardium were increased in an experimental model of coronary ischemia. Although the change in iP during the first 7 days was not found to be significant, the pattern of relative changes resembled that of FGF23. Taking these observations into consideration, the possibility exists that FGF23 may be upregulated in response to increased levels of iP, which may, in turn, facilitate the urinary iP excretion that may make the change in serum iP levels inconspicuous and non-significant. This possibility should be examined in further investigations.

According to the findings from the experimental model of MI, it is possible that FGF23 production may be increased in the injured myocardium, although the mechanism remains unknown. In addition, other possibilities potentially involved in FGF23 upregulation include an increase in circulating inflammatory cytokines and sympathetic activation, which may occur under conditions of acute myocardial ischemia. In a recent study, by examining patients with acute inflammation/sepsis, Dounousi et al demonstrated that, compared with measurements before the resolution, the FGF23 level after the resolution of inflammation was significantly greater (194%), with the average interval of these examinations being 8.6 days. Although the mechanisms by which FGF23 is downregulated by active inflammation remains unclear, examining the link between FGF23 and inflammation is considered to be a growing field. Together with the results from Dounousi et al, it suggests that the serum FGF23 might be downregulated in response to certain pathological conditions, such as active inflammation.

The serum FGF23 levels of the present study patients before the occurrence of AMI were not available. It was found that, before the increase on days 5 and 7, the serum FGF23 level showed a slight but significant decrease on days 1 and 3 after admission; therefore, the possibility exists that FGF23 was not increased on day 5 or 7, but...
rather was decreased at the time of admission and showed a recovery towards the 7-day time point. To investigate this possibility, we compared the FGF23 levels with those of propensity score-matched non-AMI patients. Between the AMI group and non-AMI group, there were no differences in age, sex, eGFR, or iP; however, the serum FGF23 levels on admission were significantly lower in the AMI group (Table 3). Although the non-AMI patients had certain cardiovascular disorders that might have influenced serum FGF23 levels, these findings suggest that serum FGF23 was decreased at the time of admission. This finding should be examined in future investigations.

Serum FGF23 was observed to increase at 7 days after admission, but is there any physiological importance in such regulation? A preliminary assessment to address this question showed that the relative change in FGF23 on day 7 after admission negatively correlated with changes in LVEF at 6 months after the onset (Figure 5A,B). Thus, a greater increase in FGF23 on day 7, irrespective of whether or not it was attributed to a greater decline at the time of admission, might be an indicator of poor recovery of cardiac function, suggesting a possible interaction between FGF23 and various pathologic conditions of the cardiovascular system. This possibility should be investigated in future studies based on a larger study sample.

Study Limitations

First, only a small number of patients were included. Second, the mechanisms responsible for the change in serum FGF23 level after AMI remain unknown. Third, because of the short follow-up period, the clinical relevance of this observation, if any, should be clarified in future studies including a larger study population with a longer follow-up period.

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Disclosures

The authors have declared that no competing interests exist.

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