Clinical Research in Cardiology (2019) 108:341–343
https://doi.org/10.1007/s00392-018-1347-7

LETTER TO THE EDITORS

# Plasma FGF23 does not rise during physical exercise as a physiological model of sympathetic activation

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Received: 8 June 2018 / Accepted: 31 July 2018 / Published online: 8 August 2018


Sirs:

After the failure of conventional pharmacological strategies for cardiovascular prevention in chronic kidney disease (CKD) [1, 2], the phosphaturic hormone FGF23 emerged as a promising therapeutic target for novel cardioprotective interventions in CKD [3, 4]. Elevated FGF23 has been found associated with cardiovascular disease both in experimental studies and in non-interventional human cohort studies [5]. Nevertheless, our understanding of the physiological regulation of FGF23 is incomplete, and its deciphering appears mandatory.

The rise of FGF23 which inevitably occurs during CKD progression cannot be fully explained by canonical pathways within the chronic kidney disease—mineral and bone disorders (CKD-MBD) spectrum [5]. Instead, non-canonical factors may contribute to high plasma FGF23 in CKD patients. Recently, murine data suggested increased sympathetic activity to induce FGF23 synthesis [6].

However, the physiological relevance of such a rise of FGF23 caused by increased sympathetic activity remains unclear. Therefore, we aimed to test the impact of acute physical exercise as a physiological stress model upon FGF23 and phosphate regulation.

15 healthy young men who regularly exercised at moderate intensity [7] were included in a prospective, monocentric cross-over study. Detailed inclusion and exclusion criteria are given in the supplementary. The study was approved by the local ethic committee and conducted in concordance with the Declaration of Helsinki.

In all participants, we determined the individual anaerobic threshold (IAT) by the method of Stegmann et al. [8] using a standardized incremental stepwise ergometry on a bicycle ergometer (Excalibur Supersport, Groningen, Netherlands) starting with 50 W and an increase of 50 W every 3 min until exhaustion. Based on the IAT, two exercise intensities were defined and heart rates for these two intensities were given to guarantee a constant load for each exercise test:

1. Submaximal exercise (SME) at 90% of IAT for 60 min.
2. High-intensity exercise (HIE) at 110% of IAT until physical exhaustion (no longer than 60 min).

The two tests were separated by 7 days and performed at the same time of the day.

Participants were asked to be abstinent from vigorous physical activity (e. g. playing football, running, swimming) 2 days before and 1 day after each bicycle exercise. Furthermore, they were instructed to limit their dietary phosphate intake to a daily maximum of 1200 mg. To achieve this phosphate restriction, they were educated by a dietitian about the phosphate amount of different diets and were handed a list which specified the phosphate content of different foods. Moreover, they were instructed to avoid foods with high phosphate content and to keep a nutritional diary.

24-h urine was collected 1 day before SME and before HIE. Blood samples and spot urines were collected before the bicycle exercise (time point (TP) 0) and 5 min (TP 1), 90 min (TP 2) and 24 h (TP 3) after SME and after HIE, respectively.

Phosphate, calcium and creatinine were measured from plasma and urine samples; cystatin C, 1.25-dihydroxycholecalciferol and parathormone were measured from serum

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00392-018-1347-7) contains supplementary material, which is available to authorized users.

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**Table 1** Indicated are plasma levels of calcium, phosphate and creatinine, as well as excretion fraction of phosphate (FePi) and of calcium (FeCa) at the four time points (TP0–TP3) at submaximal exercise (SME) and at high-intensity exercise (HIE)

| | SMETP0 | SMETP1 | SMETP2 | SMETP3 | *p* | HIETP0 | HIETP1 | HIETP2 | HIETP3 | *p* |
|---|---|---|---|---|---|---|---|---|---|---|
| Calcium (mmol/l) | 2.35 ± 0.08 | 2.39 ± 0.04 | 2.38 ± 0.06 | 2.35 ± 0.05 | 0.356 | 2.34 ± 0.10 | 2.38 ± 0.10 | 2.33 ± 0.11 | 2.32 ± 0.07 | **0.008** |
| Phosphate (mg/dl) | 3.72 ± 0.60 | 4.27 ± 0.80 | 3.75 ± 0.65 | 3.66 ± 0.57 | **< 0.001** | 3.37 ± 0.58 | 4.03 ± 0.74 | 3.47 ± 0.75 | 3.44 ± 0.58 | **< 0.001** |
| Creatinine (mg/dl) | 0.96 ± 0.17 | 1.02 ± 0.16 | 0.96 ± 0.13 | 0.96 ± 0.07 | 0.125 | 0.95 ± 0.14 | 1.11 ± 0.14 | 0.98 ± 0.13 | 0.97 ± 0.19 | **0.006** |
| FePi (%) | 11 ± 5 | 14 ± 4 | 15 ± 4 | 13 ± 5 | **0.007** | 11 ± 4 | 13 ± 4 | 14 ± 5 | 13 ± 6 | 0.346 |
| FeCa (%) | 0.78 ± 0.47 | 0.37 ± 0.25 | 0.51 ± 0.36 | 0.82 ± 0.37 | **< 0.001** | 0.82 ± 0.35 | 0.38 ± 0.24 | 0.36 ± 0.25 | 1.16 ± 0.49 | **< 0.001** |

Significant values are in bold

**Table 2** Intact FGF23 (iFGF23) and c-terminal FGF23 (cFGF23) levels at the four time points (TP0 to TP3) at submaximal exercise (SME) and at high-intensity exercise (HIE)

| | Time point 0 (before exercise) | Time point 1 (5 min after exercise) | Time point 2 (90 min after exercise) | Time point 3 (24 h after exercise) | *p* value |
|---|---|---|---|---|---|
| Submaximal exercise (SME) | | | | | |
| iFGF23 [pg/ml] | 39 [34–50] | 40 [35–47] | 42 [30–49] | 43 [39–55] | 0.135 |
| cFGF23 [RU/ml] | 79 [64–92] | 79 [62–103] | 74 [64–90] | 75 [57–95] | 0.184 |
| High-intensity exercise (HIE) | | | | | |
| iFGF23 [pg/ml] | 34 [29–42] | 41 [31–48] | 39 [33–50] | 39 [32–56] | 0.582 |
| cFGF23 [RU/ml] | 71 [48–94] | 71 [55–97] | 75 [63–134] | 64 [46–84] | 0.763 |

samples according to the standardized methods of the Saarland University central laboratory.

Both intact and c-terminal FGF23 (iFGF23; cFGF23) were measured from plasma samples by second generation ELISA (Immunotopics, San Clemente, USA).

Statistical analyses were performed by SPSS 20. Continuous data are presented as mean ± standard deviation or as median [interquartile range (IQR)], and compared using *t* test or ANOVA, as appropriated. Comparison over time was performed by Friedman-test and Wilcoxon-rank-test. Two-sided $p$ values < 0.05 were considered significant.

Baseline characteristics are summarized in the supplementary [9, 10].

During the exercise plasma phosphate rose significantly both in SME ($p < 0.001$) (average maximal heart rate 146 ± 12 bpm, lactate 1.66 ± 0.67 mmol/l) and in HIE ($p < 0.001$) (average maximal heart rate 165 ± 11 bpm; lactate 4.95 ± 2.84 mmol/l). Plasma calcium increased in HIE significantly ($p = 0.008$) but not in SME ($p = 0.356$). Fraction excretion of phosphate increased ($p = 0.007$; $p = 0.346$), whereas fraction excretion of calcium decreased significantly during exercise in SME ($p < 0.001$) as well as in HIE ($p < 0.001$) (Table 1).

No increase in iFGF23 or cFGF23 occurred in either SME or HIE (Table 2).

FGF23 measurements from all individual participants are depicted in Fig. 1.

Our findings challenge the hypothesis from animal studies [6] that sympathetic activation induces an increase of plasma FGF23. While we did not directly measure plasma catecholamines in our study, there is plain evidence from earlier studies that our stress models must have induced substantial sympathetic activation [11, 12]. Our findings stand in seeming contrast to results of Lombardi et al., who reported increasing iFGF23 in nine participants of the 2011 Giro d'Italia. However, in that study [13] confounders such as high-altitude exposure or time point of venipunctures may have interfered.

Therefore, we question the clinical relevance of sympathetic activation as a causal factor for high FGF23 in various diseases, e. g. in CKD-MBD. Instead, other potentially more important regulating factors should be identified in future studies, before FGF23 may become the goal for novel treatment strategies for CKD patients with cardiovascular disease.

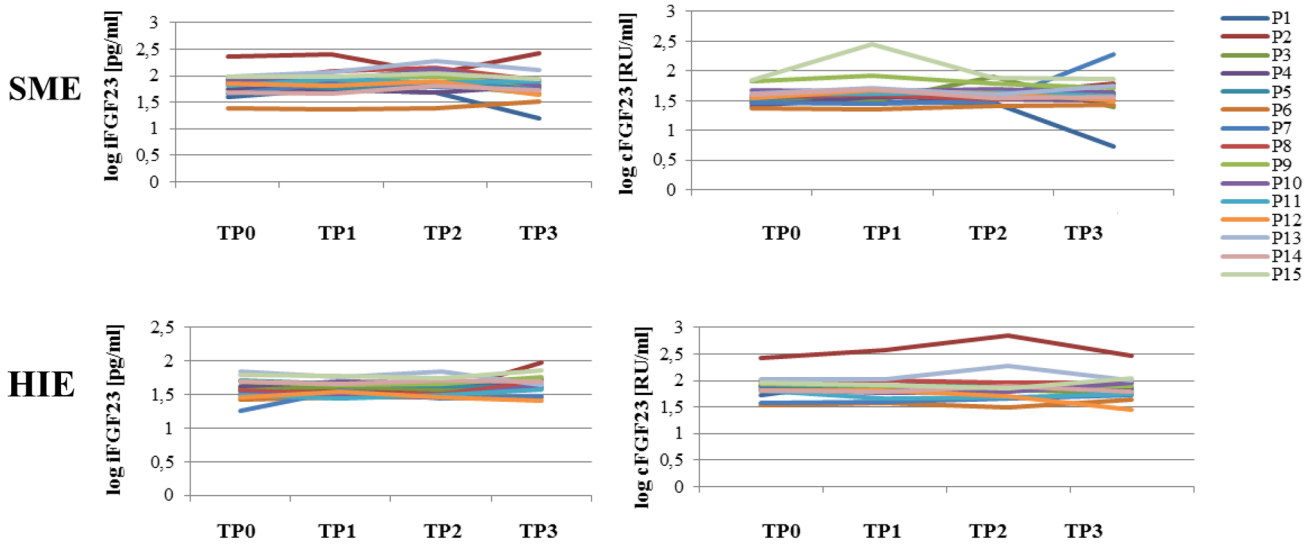


**Fig. 1** Indicated are plasma levels of log-transformed intact FGF23 (logiFGF23) and log-transformed c-terminal FGF23 (logcFGF23) at the four time points (TP) of all 15 participants of the Fit@HOMe study in submaximal exercise (SME) and in high-intensity exercise (HIE)

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