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Letter to the Editor

LETTER TO THE EDITOR

Effect of roxadustat on intact and C-terminal FGF23 levels in patients undergoing peritoneal dialysis: a *post hoc* analysis of a randomized trial

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Hypoxia-inducible factor–proline hydroxylase inhibitors (HIF-PHIs) are an emerging approach in the treatment of erythropoietin (EPO) deficiency among chronic kidney disease (CKD) patients with anaemia. In recent years, fibroblast growth factor 23 (FGF23) has been shown to interact with renal anaemia [1]. However, evidence on the direct effect that HIF-PHIs exert on the change in FGF23 levels in the context of anaemic patients with CKD is limited. Based on our previous trial of roxadustat treatment in CKD patients with anaemia [2], we examined the effect of roxadustat on the change in levels of FGF23 and the associated mineral parameters in patients undergoing peritoneal dialysis (PD). Paired *t*-tests and Wilcoxon signed-rank tests were used to compare parameter differences between baseline and the end of follow-up. We performed a mixed model analysis of variance adjusting for baseline corresponding values to compare the effects of the different doses of roxadustat on the absolute parameter changes at 12 weeks from baseline.

A total of 100 patients were included. In the entire population, roxadustat significantly increased haemoglobin levels both in the standard-dose group and the low-dose group (107.8 ± 6.8 g/l versus 114.8 ± 10.3 g/l, $P < .001$; 108.1 ± 6.5 g/l versus 113.9 ± 13.0 g/L, $P = .005$) at week 12. Hepcidin levels were decreased after 12 weeks of roxadustat administration, with borderline significance in the entire cohort {140.2 ng/ml [interquartile range (IQR) 85.2–194.4] versus 110.5 ng/ml [IQR 46.1–167.1], $P = .050$} (Table 1). Overall, there were no differences in the changing trend of intact FGF23 (iFGF23), C-terminal FGF23 (cFGF23) and the iFGF23:cFGF23 ratio after adjusting for the baseline corresponding values between the initial dose groups ($P > .05$ for all) (Fig. 1). There were no differences in terms of cFGF23 (5507.4 ± 4868.6 pg/ml versus 5991.6 ± 4215.7 pg/ml, $P = .201$), iFGF23 [7362.9 pg/ml (IQR 3097.3–18 406.9) versus 9088.5 pg/ml (IQR 3729.4–21 218.0), $P = .217$) and the iFGF23:cFGF23 ratio (3.6 ± 5.3 versus 3.6 ± 5.4, $P = .994$) between baseline and week 12 in the entire population (Fig. 1).

We next analysed the effect of roxadustat on the change in serum phosphate, calcium and intact parathyroid hormone (iPTH). As shown in Fig. 2, there were no differences in the changing trend of serum phosphate, calcium and iPTH between baseline and week 12 in the standard-dose group and low-dose group ($P > .05$ for all). Compared with baseline, levels of phosphate, calcium and iPTH remained unchanged at week 12 in the entire population ($P > .05$ for all).

An *in vivo* study suggested that plasma FGF23 levels were elevated after HIF-PHI treatment, but the peak levels of FGF23 were lower when equivalent hematopoietic doses were

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Table 1: Changes in the haemoglobin and iron parameters between baseline and week 12 in the two roxadustat initial-dose groups.

	Total population			Standard-dose group			Low-dose group		
Variable	Baseline	Week 12	*P*-value	Baseline	Week 12	*P*-value	Baseline	Week 12	*P*-value
Haemoglobin (g/l), mean ± SD	108.0 ± 6.6	114.4 ± 11.7	<.001	107.8 ± 6.8	114.8 ± 10.3	<.001	108.1 ± 6.5	113.9 ± 13.0	.005
Serum iron (mmol/l), mean ± SD	15.2 ± 6.5	15.2 ± 5.5	.948	14.5 ± 7.1	15.2 ± 6.0	.541	15.8 ± 5.9	15.2 ± 5.0	.560
Ferritin (ng/ml), median (IQR)	279.1 (147.0–396.4)	238.2 (111.4–360.9)	.028	291.0 (151.7–386.9)	257.6 (133.4–343.8)	.076	273.7 (129.8–405.2)	230.7 (98.8–419.0)	.205
TIBC (mmol/l), mean ± SD	45.7 ± 7.1	51.8 ± 9.2	<.001	45.7 ± 7.5	50.2 ± 8.2	<.001	45.7 ± 6.7	53.3 ± 9.9	<.001
TSAT (%), mean ± SD	34.0 ± 15.1	30.4 ± 12.5	.035	33.0 ± 17.1	31.0 ± 12.9	.460	35.0 ± 13.0	29.8 ± 12.2	.015
Hepcidin (ng/ml), median (IQR)	140.2 (85.2–194.4)	110.5 (46.1–167.1)	.050	140.2 (95.8–202.3)	148.4 (45.7–191.4)	.566	142.0 (64.4–193.2)	93.6 (45.5–165.3)	.024

SD: standard deviation; TIBC: total iron binding capacity; TSAT: transferring saturation.

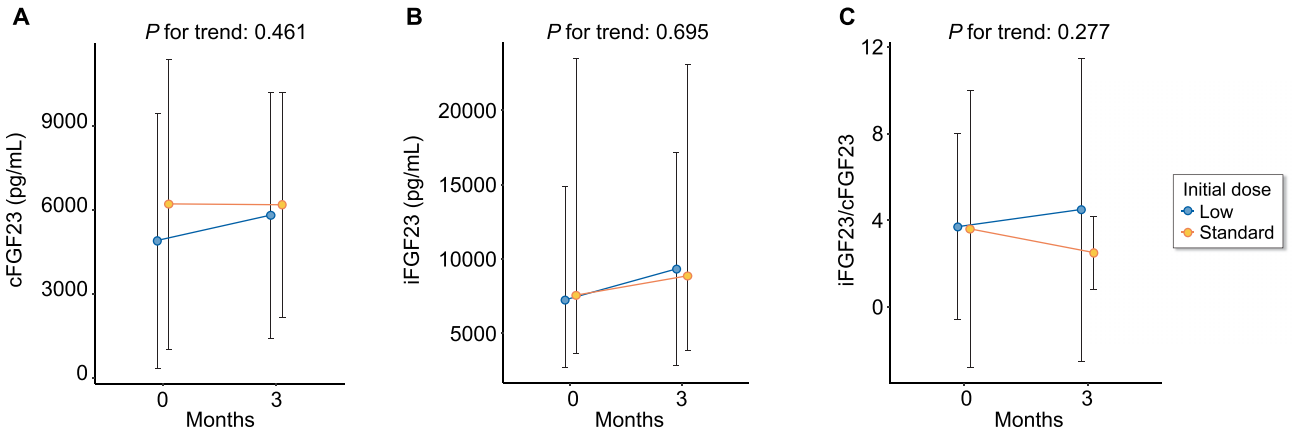

Figure 1: Comparison of cFGF23, iFGF23 and cFGF23:iFGF23 levels between the standard-dose group and the low-dose group. Data are presented as mean ± standard deviation for cFGF23 and iFGF23:cFGF23 and median (IQR) for iFGF23.

applied compared with recombinant human EPO [3]. In patients with CKD, anaemia, iron deficiency and inflammation were all marked factors associated with higher FGF23 levels [4, 5]. Alleviating these risk factors would counteract the original HIF-PHIs' induction of FGF23. For example, circulating iFGF23 was significantly attenuated (>60%) in the HIF-PHI-treated anaemic CKD mice [6]. In addition, exogenous hepcidin injection can stimulate FGF23 production, preferentially increasing circulating concentrations of cFGF23 [4].

Our study demonstrated that roxadustat decreased iron-regulatory hormone hepcidin levels with borderline significance, indicating an improvement in the functional iron deficiency status. Given that the half-life of roxadustat is only ≈10 hours, we cannot fully exclude the short-term fluctuation of the target parameters influenced by drug metabolism. Also, the sample size of this study was relatively small and the follow-up period was 12 weeks, which precluded our ability to find more modest effects on FGF23 levels that may have been observed through a longer period. Independent studies with larger sample sizes are needed to validate the findings between the FGF23 change and HIF-PHI administration.

In conclusion, this post hoc analysis of a previous randomized study showed that 12 weeks of oral roxadustat therapy did not affect plasma iFGF23, cFGF23 and mineral parameters in anaemic patients on peritoneal dialysis.

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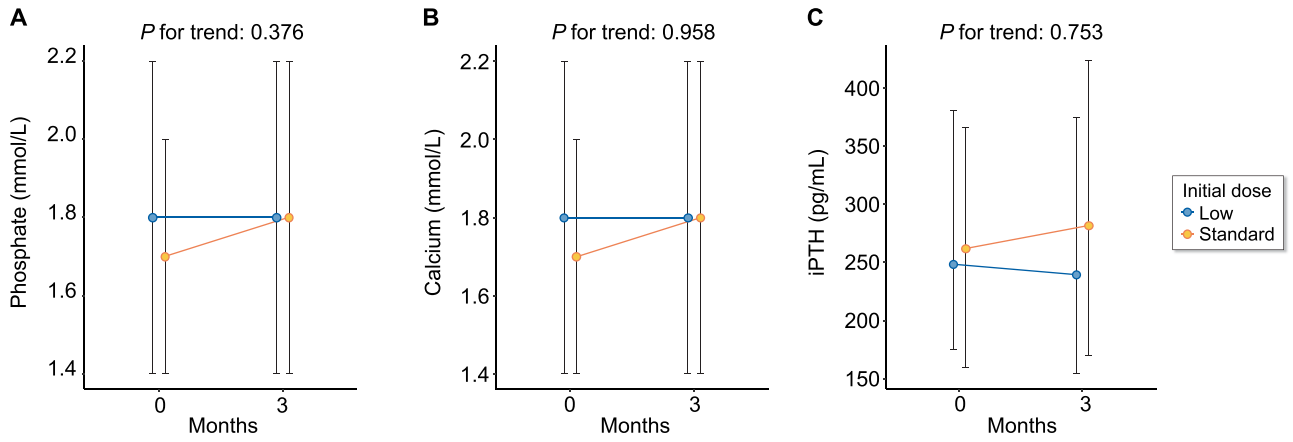

Figure 2: Comparison of serum phosphate, calcium and iPTH levels between the standard-dose group and the low-dose group. Data are presented as mean ± standard deviation for phosphate and calcium and median (IQR) for iPTH.

AUTHORS' CONTRIBUTIONS

All authors were responsible for the study concept and design. Z.W., X.X., D.S., B.Y., Y.X., T.M., Z.Y., G.F. and J.Z. were responsible for data acquisition. Z.W., X.X. and J.D. were responsible for statistical analysis. Z.W., X.X., T.M., Z.Y. and J.D. were responsible for manuscript drafting or revision. J.D. was responsible for supervision or mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. The results presented in this article have not been published previously in whole or in part.

REFERENCES

1. Edmonston D, Wolf M. FGF23 at the crossroads of phosphate, iron economy and erythropoiesis. *Nat Rev Nephrol* 2020;**16**:7–19. https://doi.org/10.1038/s41581-019-0189-5
2. Yang Z, Ma T, Xu X *et al.* Randomized study on the efficacy of standard versus low roxadustat dose for anemia in patients on peritoneal dialysis. *Kidney Int Rep* 2022;**7**:455–64. https://doi.org/10.1016/j.ekir.2021.12.025
3. Flamme I, Ellinghaus P, Urrego D *et al.* FGF23 expression in rodents is directly induced via erythropoietin after inhibition of hypoxia inducible factor proline hydroxylase. *PLoS One* 2017;**12**:e0186979. https://doi.org/10.1371/journal.pone.0186979
4. Noonan ML, Clinkenbeard EL, Ni P *et al.* Erythropoietin and a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHDi) lowers FGF23 in a model of chronic kidney disease (CKD). *Physiol Rep* 2020;**8**:e14434. https://doi.org/10.14814/phy2.14434
5. David V, Martin A, Isakova T *et al.* Inflammation and functional iron deficiency regulate fibroblast growth factor 23 production. *Kidney Int* 2016;**89**:135–46. https://doi.org/10.1038/ki.2015.290
6. Noonan ML, Ni P, Agoro R *et al.* The HIF-PHI BAY 85-3934 (Molidustat) improves anemia and is associated with reduced levels of circulating FGF23 in a CKD mouse model. *J Bone Miner Res* 2021;**36**:1117–30. https://doi.org/10.1002/jbmr.4272