Iron status and the Pi/FGF-23-axis in HFrEF in relation to renal function

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Background: Recent studies linked dysregulated phosphate metabolism, fibroblast growth factor-23 (FGF-23) and iron deficiency (ID) with worse clinical outcome and mortality in heart failure with reduced ejection fraction (HFrEF). These factors are intertwined as FGF-23 regulates inorganic phosphate (Pi) through increased renal phosphate secretion and is stimulated by elevated Pi levels and ID. This interplay has recently gained attention as intravenous iron supplementation has hypophosphataemia as a side effect. The relationship between ID and the Pi/FGF-23-axis, particularly concerning renal function, has not been investigated in detail.

Purpose: We aimed to evaluate the relationship between iron status, Pi and FGF-23 in relation to renal function in HFrEF.

Methods: Stable HFrEF patients were enrolled at our outpatient clinic between 2018 and 2023 in a prospective registry. Baseline characteristics, medications and laboratory values were documented. For this study patients with complete phosphate, intact FGF-23 and iron status were analyzed (n=429). Patients were divided into three groups based on their renal function determined by estimated glomerular filtration rate (GFR): GFR > 60, GFR 60-30, GFR < 30.

Results: The median age was 65 (IQR 52-74), 310 (72%) patients were male, median NT-proBNP was 1657 pg/ml (IQR 512-4116) and median GFR was 57 ml/min/BSA (IQR 37-74). Of the 429 patients, 180 (42%) suffered from ID.

Pi levels did not vary based on NYHA stage and showed only a weak correlation with NT-proBNP (r = 0.13, p = 0.008). In contrast, FGF-23 increased with NYHA stage (NYHA I vs NYHA II vs NYHA III/IV: 69.9 (IQR 50-90.2) vs 82.4 (IQR 58.9-115.8) vs 104.2 (IQR 77-199.5), p<0.0001) and correlated positively with NT-proBNP (r = 0.43, p<0.0001) (Figure 1 a, b). Patients with a GFR < 30ml/min/BSA had significantly higher concentrations of Pi and FGF-23 compared to GFR 30-60 ml/min/BSA or > 60ml/min/BSA [Pi: 1.36 mmol/l (IQR 1.15-1.61) vs 1.145 mmol/l (IQR 0.96-1.27) vs 1.1 mmol/l (IQR 0.98-1.25), p<0.0001; FGF-23: 253.1 pg/ml (141.1-936.2) vs 94.3 pg/ml (IQR 75.43-121.5) vs 71.7 pg/ml (IQR 53.18-89.33), p<0.0001]) (Figure 1 c, d). While there was no difference regarding mortality according to Pi levels, patients in the highest FGF-23 tertile had excess mortality (p=ns and p=0.0002, log rank test) (Figure 1 e).

Interestingly, Pi and FGF-23 levels did not differ between patients without and with ID (p=ns for both, Figure 2 a). No correlation could be shown between transferrin saturation and Pi or FGF-23 (p=ns, Figure 2 b).

Conclusion: The regulation of Pi and FGF-23 is dependent on renal function. Patients with a GFR < 30ml/min/BSA exhibited the highest levels of both FGF-23 and Pi. The phosphaturic effect of FGF-23 seems to rely on renal function, as elevated FGF-23 cannot sufficiently decrease Pi in patients with a GFR < 30ml/min/BSA. No correlation between iron status and FGF23/Pi could be identified for HFrEF.
Figure 1. Pi and FGF-23 in heart failure. Comparison of Pi and FGF-23 in different NYHA stages and association with NTproBNP (a, b). Comparison and distribution of Pi and FGF-23 in different GFR groups (c, d). Kaplan-Meier curves for all-cause mortality according to tertiles of Pi and FGF-23 (e). ANOVA Kruskal-Wallis test with Dunn’s multiple comparisons test was used to compare differences between groups. Correlation coefficients were computed by Spearman’s rank correlation. Log Rank test was calculated for Kaplan-Meier curves. Correlation coefficients, p-values or levels of significance are indicated within the respective figure. *p < 0.05, ****p < 0.0001.
Figure 2

Figure 2. Association of FGF-23 and Pi with ID in heart failure. Pi and FGF-23 levels in patients with and without ID (a). Association of transferrin saturation with Pi and FGF-23 (b). The Mann-Whitney U-test was used for comparisons for not normally distributed data. Correlation coefficients were computed by Spearman's rank correlation. P-values are indicated within the respective figure. Ns = not significant.