Meta-Analysis of the Association between Fibroblast Growth Factor 23 and Mortality and Cardiovascular Events in Hemodialysis Patients

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Keywords

Fibroblast growth factor 23 · Mortality · Cardiovascular events · Hemodialysis · Meta

Abstract

Introduction: This study was conducted to ensure the correlation between fibroblast growth factor 23 (FGF23) and death and cardiovascular events in hemodialysis patients. **Methods:** We conducted a literature search of PubMed database to April 2018 for relevant articles that reported the association between FGF23 and risk of all-cause mortality and cardiovascular disease (CVD) events. The meta-analysis was performed using the Revman 5.3 software. **Results:** A total of 7 articles were included, and all reported mortality in hemodialysis patients, and 3 reported cardiovascular events in hemodialysis patients. Since the current reagent can detect C-terminal FGF23 (cFGF23) and intact-FGF23 (iFGF23), we discuss the association between cFGF23 and iFGF23 and

death and cardiovascular events in hemodialysis patients. The correlation between serum iFGF23 levels and death in hemodialysis patients: high levels of iFGF23 vs. low levels of iFGF23: RR 1.14, 95% CI (1.01–1.30), $p = 0.04$ ($I^2 = 0\%$, $p = 0.38$). The correlation between serum C-terminal levels and death in hemodialysis patients: high levels of cFGF23 versus low levels of cFGF23: RR 1.39, 95% CI (1.21–1.59), $p < 0.001$ ($I^2 = 2\%$, $p = 0.38$). The correlation of serum iFGF23 levels with cardiovascular events: high levels of iFGF23 versus low levels of iFGF23: RR 1.21, 95% CI (1.13–1.30), $p < 0.001$ ($I^2 = 0\%$, $p = 0.49$). A paper has reported the association between cFGF23 and CVD events, so we did not conduct meta-analysis. **Conclusions:** Elevated serum FGF23 levels are positively associated with all-cause mortality and cardiovascular events in hemodialysis patients, with a 14 or 39% increase in all-cause mortality and a 21% increased risk of cardiovascular events.

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Introduction

The fibroblast growth factor 23 (FGF23) protein comprises 251 amino acids, which is a full-length form of a 32-kDa protein [1]. FGF23 is a member of the FGF family, which contains the N-terminal portion of the processing site [2] and the C-terminal part interacts with α -Klotho [3], and mainly synthesized and secreted by osteocyte and osteoblast. Subtilisin-like proprotein convertases cleave the intact FGF23 (iFGF23) protein between Arg179 and Ser180 to generate non-active N- and C-terminal fragments [4], so there are 3 forms in the blood: N-terminal FGF23, C-terminal FGF23 (cFGF23) and full-length iFGF23. But only iFGF23 is believed to be able to bound the FGFR1c/ α -Klotho complex and activate downstream signaling pathways [5, 6].

It is well established that FGF23 is an important phosphate and vitamin D regulator and is essential for mineral and bone metabolism [7]. Under the synergistic effect of α -Klotho, the combination of FGF23 with FGFR and heparin is the basic structure of FGF23 functioning. FGF23 has many physiological effects: (1) FGF23 binding to the FGFR-klotho complex located in the distal renal tubule downregulate the Na/Pi cotransporter at the proximal tubule, which could reduce urinary phosphate reabsorption, increase urinary excretion, and the final result is a decrease in blood phosphate [8]; (2) FGF23 can directly inhibit 1α -hydroxylase and stimulate 24-hydroxylase, which reduces the synthesis of $1,25(\text{OH})_2\text{D}_3$ and accelerates the inactivation of $1,25(\text{OH})_2\text{D}_3$, leading to a decrease in $1,25(\text{OH})_2\text{D}_3$ levels [9]; (3) FGF23 can directly inhibit the secretion of parathyroid hormone (PTH) and directly increase the PTH by decreasing phosphate and vitamin D, but the PTH is reducing in total [10]; (4) FGF23 also restrains bone mineralization [11]. These 4 major physiological effects determine the close interaction between FGF23 and phosphorus, PTH, vitamin D, and calcium, as well as affect each other.

The past few years have seen a rapidly growing interest in testing the hypothesis that increased FGF23 level is an independent risk factor of mortality and cardiovascular disease (CVD) for hemodialysis patients [12]. At variance with healthy people, the FGF23 metabolism in chronic kidney disease (CKD) patients shows some features [13]: (1) The level of serum FGF23 in patients with CKD was significantly higher than that in the normal population; (2) FGF23 levels rises slowly as GFR declines in early CKD but progressively in CKD4–5 stages. When the patients reach the dialysis stage, FGF23 levels may be 1,000-fold higher than that in healthy individuals; (3) whether reaching the dialysis stage

or not, FGF23 rises earlier than phosphate, vitamin D, and PTH. Moreover, a study found that diurnal variation of different forms FGF23 showed discrepancy [14]: iFGF23 emerged high in the morning and low in night, and was opposite to the rhythm of phosphate and PTH. The circadian rhythm of cFGF23 was relatively insignificant.

Although many studies focused on the connection FGF23 and CVD and death, but these studies are still controversial: FGF23 was associated with death in hemodialysis patients, but there was no correlation with CVD. Therefore, this literature analyzes the correlation between FGF23 and death and cardiovascular events in hemodialysis patients. In consideration of the assay to measure FGF23 and the discrepancy of circadian rhythm of cFGF23 and iFGF23, we conducted a subgroup analysis.

Methods

Data Source and Search Strategy

We performed a literature search on PubMed without time or language restriction up to April 2018 to identify studies focused on the association between FGF23 and risk of all-cause mortality and CVD events. We did the search following medical subject headings and keywords, such as FGF23 (All Fields); death, or mortality or all-cause mortality (All Fields); CVD events or CVDs (All Fields); hemodialysis or dialysis (All Fields). To avoid leaving out the relevant study, the literature search was performed by 2 authors (S.G. and S.Z.).

Study Selection and Data Extraction

We included any prospective cohort study that met the following criteria: (1) All patients in study should undergo maintenance hemodialysis for more than 3 months before enrolling in study; (2) The exposure was plasma or serum FGF23 concentrations; (3) All-cause mortality, cardiovascular mortality, and CVD events should be included in the study outcomes. HR and its 95% CI in the study should be reported or calculated; (4) All study follow-up should be ≥ 6 months.

Titles and abstracts were screened independently by 2 authors (S.G. and S.Z.); they discarded studies that were not pertinent to the topic. Case reports, reviews, editorials, letters, and fundamental research were excluded. The same 2 reviewers independently evaluated the remaining full-text articles on the basis of pre-stated inclusion criteria. A third reviewer (J.X.) solved the disagreements on study judgments. Data extraction and analysis were performed by 2 reviewers (S.G. and S.Z.) and independently verified by another (S.G.).

Data Analysis

Literature quality was evaluated on the Newcastle-Ottawa scale by 2 reviewers (S.G. and S.Z.) independently. To calculate summary estimates and 95% CI of the risk for FGF23, we pooled both RRs and HRs by using either fixed-effects models or, in the presence of heterogeneity, random-effects models. The presence of heterogeneity across studies was evaluated by using the Q statistic

Fig. 1. Study selection flow.

Table 1. Characteristics of 7 prospective cohort studies of FGF23 and all-cause mortality and cardiovascular events

Source	Number of patients	Female, %	Age, years	Duration, months	FGF23 measurement	Outcomes	NOS
Jean, 2009 [15]	219	43.0	66.6±14	23.2	C-terminal	All-cause mortality	7
Hsu, 2009 [16]	124	40.7	59.3±13.0	24	C-terminal	All-cause mortality	6
Olauson, 2010 [17]	229	34.9	55 (33–68)	23	Intact	All-cause mortality	7
Sugimoto, 2013 [18]	92	37.0	60.3±11.8	53.2	Intact	All-cause mortality, CVD events	8
Nowak, 2014 [19]	234	36.0	68±14	30.8	C-terminal	All-cause mortality	8
Scialla, 2015 [20]	446	45.0	57.9±14.8	40.8	C-terminal	All-cause mortality, CVD events	9
Chonchol, 2015 [21]	670	55.0	57±14	50.9	Intact	All-cause mortality, CVD events	9

with a conservative p value of 0.10. Potential publication bias was evaluated by Begg and Egger tests at the $p < 0.10$ level of significance. Meta-analyses were performed using Revman 5.3 and publication bias Comprehensive Meta-Analysis V2 if data on the same outcome were provided by more than 2 studies. A p value < 0.05 was considered statistically significant.

Results

Search Results

Two hundred and forty eight potentially relevant references were initially retrieved. By screening titles and abstracts, a total of 213 citations were excluded; the peo-

ple were not hemodialysis patients and the articles were reviews, case reports, or experimental studies. Among the 35 studies selected for full-text examination, 28 studies were excluded because of the following reasons: study design and outcomes were not pertinent to the criteria ($n = 21$); reviews and meta-analyses were excluded ($n = 7$). A total of 7 articles were, therefore, reviewed in detail. Figure 1 summarizes the study flow of this review.

Study Characteristics

The main characteristics of studies in the meta-analysis are presented in Table 1. Of the 7 studies included here, 7 studies reported all-cause mortality and 3 studies

Fig. 2. The total and subgroup hazard ratio (HR) for the association between FGF23 and all-cause mortality.

Begg and Mazumdar rank correlation		Egger's regression intercept	
Kendall's S statistic (P-Q)	-1.00000	Intercept	-0.28598
		Standard error	1.08714
Kendall's tau without continuity correction		95% lower limit (2-tailed)	-3.08056
		95% upper limit (2-tailed)	2.50859
Tau	-0.04762	t value	0.26306
z value for tau	0.15019	df	5.00000
p value (1-tailed)	0.44031	p value (1-tailed)	0.40150
p value (2-tailed)	0.88062	p value (2-tailed)	0.80300

Fig. 3. The result of evaluated publication bias (Begg and Egger tests).

reported CVD events. Four studies tested C-terminal fragments FGF23, and 3 studies measured iFGF23. A total of 2,014 hemodialysis patients were included. Among them, 45.3% were female, and the mean age was 62.3 years. The median follow-up was 35.1 months. Seven studies are all of good quality, with the lowest 6 'stars' in Newcastle-Ottawa scale. Detailed information is shown in Table 1.

Overall, elevated FGF23 was associated with increased all-cause mortality in fixed-effect model (HR 1.25, 95% CI 1.14–1.37, $p < 0.001$). Substantial heterogeneity was observed ($I^2 = 33\%$, $p = 0.17$; Fig. 2). Subgroup analysis was performed based on FGF23 assays. High iFGF23 was

associated with increased all-cause mortality in the fixed-effect model (HR 1.14, 95% CI 1.01–1.30, $p = 0.04$), with low heterogeneity ($I^2 = 0\%$, $p = 0.38$; Fig. 2). In accordance with iFGF23, cFGF23 increasing is connection with all-cause mortality rising in the fixed-effect model (HR 1.39; 95% CI 1.21–1.59, $p < 0.001$), and its heterogeneity is low ($I^2 = 2\%$, $p = 0.38$). The Begg and Egger tests also showed no evidence of publication bias among studies of FGF23 and all-cause mortality (Begg, $p = 0.440$; Egger, $p = 0.402$; Fig. 3).

As shown in Fig. 4, elevated FGF23 was associated with increased CVD events in the fixed-effect model (HR 1.22, 95% CI 1.14–1.31, $p < 0.001$). The Q statistics shows a low

Fig. 4. The total and subgroup hazard ratio (HR) for the association between FGF23 and CVD events.

heterogeneity with $I^2 = 2\%$ ($p = 0.38$). Because a study using the cFGF23 assay reported the CVD events, we checked the association between iFGF23 and CVD events alone. iFGF23 increasing is connection with CVD events rising in the fixed-effect model with HR 1.21 (95% CI 1.13–1.30, $p < 0.001$), and its heterogeneity is $I^2 = 0\%$ ($p = 0.49$; Fig. 4).

Discussion

The current meta-analysis found that elevated FGF23 was associated with a higher risk of 25% for all-cause mortality and 22% for CVD events in maintenance hemodialysis patients. Subgroup analyses showed that which-ever form of FGF23 elevating were associated with the all-cause mortality and CVD events, indicating FGF23 predicts poor outcome in these individuals. The mechanism of elevated FGF23 levels leading to the increasing risk of mortality and CVD events remained to be not well established. According to the current evidence, hyperphosphatemia is an independent risk of death and CVD events in CKD and ESRD patients [22]. FGF23 is the strongest phosphate regulator and FGF23 inhibits the re-absorption of urinary phosphorus and synthesis of vitamin D by α -klotho expressing in proximal renal tubule [23]. In addition, FGF23 has direct cardiac and vascular poisonous [24, 25], independent on α -klotho. Several

clinical researches have confirmed that FGF23 had an association with left ventricular mass, ejection fraction, left ventricular end-diastolic dimension, and vascular calcification [26, 27]. These factors are associated with an adverse outcome in health individuals and hemodialysis patients.

But recent studies put forward a doubt on the association between FGF23 and mortality [28, 29]. Marthi et al. [29] confirmed the association between FGF23 and mortality by meta-analysis. But Marcais et al. [23] provided that evaluating the FGF23 without Klotho data may over highlight the detrimental effect. They proposed this assumption based on the findings FGF23 and Klotho were both cardiovascular morbidity and mortality and independent from each other [30]. Moreover, patients with high Klotho and FGF23 did not present increased morbidity and mortality [30]. Although animal model supported the Marcais's hypothesis [31], but FGF23 unexpressing in cardiomyocytes and the cardiac toxicity of FGF23 dependent on the FGFR4 [32, 33] may explain the effect of FGF23 and Klotho on cardiovascular morbidity and mortality independent from each other.

In accordance with Marthi et al. [29], our data support the conclusion that elevated FGF23 increases the risk of all-cause mortality and CVD. In a word, FGF23 is a potential risk prediction factor and may be help for clinical practice.

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Ethics Statement

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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Authors Contribution

Research idea and study design: S.G., J.X., and S.Z.; data acquisition: S.G. and S.Z.; data analysis/interpretation: S.G. and S.Z.; statistical analysis: S.G. and S.Z.; manuscript writing: S.G., J.X. and S.Z.

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