Fibroblast growth factor 21 (FGF21) is a sensitive marker of osteoporosis in haemodialysis patients: a cross-sectional observational study

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Abstract

Introduction: Osteoporosis is one of the important bone abnormalities in chronic kidney disease-mineral and bone disorder (CKD-MBD) and still lacks a sensitive biomarker to diagnose. Fibroblast growth factor 21 (FGF21) can stimulate bone loss in patients with diabetes and increase in CKD patients. In this study, we investigated whether FGF21 could serve as a biomarker to predict osteoporosis in a haemodialysis cohort.

Methods: We recorded demographic information, biochemical data, and serum FGF21 and FGF23 levels and measured the CT attenuation values of 339 haemodialysis patients from two large medical centres. We assessed the correlation of CT attenuation values with serum FGF21 and FGF23 levels and tested whether they were independent factors for osteoporosis. ROC curves were constructed to compare the prognostic value of FGF21 and FGF23 for osteoporosis.

Results: Based on the CT attenuation value, serum FGF21 levels were higher in our osteoporosis group (median 640.86 pg/ml vs. 245.46 pg/ml, *P < 0.01). Meanwhile, FGF21 (r = -0.136, P < 0.05) and FGF23 (r = -0.151, P < 0.05) were both negatively associated with osteoporosis. Moreover, FGF21 (β = -0.067, P < 0.05) was an independent factor for osteoporosis. Furthermore, FGF21 combined with age yielded a marked specificity (90.5 %) and sensitivity (61.8 %) in predicting osteoporosis of haemodialysis patients with less residual renal function.

Conclusions: FGF21 has a positive relationship with the incidence of osteoporosis in patients on haemodialysis. FGF21 combined with age is a good predictive biomarker for osteoporosis in patients on haemodialysis, especially those with less residual renal function.

Keywords: Osteoporosis, Fibroblast growth factor 21, CT attenuation values, Haemodialysis, CKD-MBD
Introduction

Chronic kidney disease-mineral and bone disorder (CKD-MBD), a systemic disorder of mineral and bone metabolism [1], has a high prevalence and morbidity in patients with CKD [2], especially in patients with end-stage renal disease (ESRD) [3]. CKD-MBD is composed of three main aspects: renal bone disease, vascular or other soft-tissue calcification, and biochemical abnormalities such as calcium, phosphate, parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23) [4]. Osteoporosis characterized by low bone mineral density and reduced mechanical strength [5] is the most clinically relevant feature of renal bone disease. As reported, individuals with early stages of CKD may have a higher prevalence of osteoporosis and fracture risk compared to non-CKD and 20% mortality from hip fractures within the first year [6-8]. Many factors, such as secondary hyperparathyroidism, vitamin D deficiency, increased FGF23, and metabolic acidosis, are involved in the pathophysiology of subsequent osteoporosis in patients with CKD [9].

The FGF19 subfamily, composed of FGF19, FGF21, and FGF23, is involved in diverse metabolic regulation of interorgan endocrine signalling axes [10]. FGF23 is a 32-kDa glycoprotein secreted by osteocytes and functions in calcium and phosphorus metabolism disorders [11], bone loss [12], vascular calcification [13] and other CKD-MBD events in patients with ESRD. In previous studies, some scholars proposed that FGF23 could predict bone loss in patients with ESRD through its strong correlation with bone mineral density (BMD) in lumbar spine sites and femoral neck sites [14, 15]. However, Wohlfahrt P and Isakova T et al. drew contradictory conclusions that FGF23 had no correlations with BMD and bone mass corrected for other factors such as height, eGFR and PTH levels [16, 17]. Therefore, the role of FGF23 in the changes in BMD in patients with CKD is still controversial. FGF21, another member of the FGF19 subfamily, is a powerful regulator of glucose and lipid metabolism and is mainly expressed in the liver [18, 19]. FGF21 is excreted primarily by the kidney, and its level increases markedly in patients with impaired renal function [20]. In animal models, genetic FGF21 overexpression decreases bone mass, and systemic FGF21 treatment leads to severe bone loss [21]. Meanwhile, FGF21 can accelerate bone loss by potentiating the effects of peroxisome proliferator-activated receptor γ [21]. Moreover, higher FGF21 levels synthesized in the liver can induce insulin-like growth factor binding protein 1 (IGFBP1) to stimulate osteoclast differentiation and bone resorption [18]. However, the association of FGF21 with bone loss in CKD has rarely been explored in previous studies.

In the present study, we evaluated the relationship between FGF21 and FGF23 and osteoporosis in a population-based retrospective HD cohort. First, we compared the serum FGF21 and FGF23 levels in patients on HD with or without osteoporosis on the basis of CT attenuation values. Second, we clarified whether FGF21 and FGF23 were independently associated with CT attenuation values. Ultimately, we explored the predictive values of serum FGF21 and FGF23 on osteoporosis in our HD cohort.

Materials and methods

Study design and subjects

This was a cross-sectional observational study composed of 339 patients on HD from two large haemodialysis centres, Nanjing Zhongda Hospital and the First People’s Hospital of Changzhou, from January 2018 to December 2019 (Fig. 1). The exclusion criteria were as follows: (1) age not within 18 to 90 years old, (2) acute phase of infections, (3) malignancy, (4) parathyroidectomy history, (5) hepatobiliary disease history, (6) other acute illnesses, and (7) decline to participate in this study. All enrolled patients had received regular dialysis (3 ~ 4 times per week) for at least one month. The study protocol was approved by the Ethics Committee of Zhongda Hospital affiliated with Southeast University, and the study was conducted in accordance with the Helsinki Declaration and Chinese law. The details of the study were explained to every patient; a signed informed consent was obtained from all subjects. We confirmed that all methods were carried out in accordance with relevant guidelines and regulations.

Clinical and biochemical data

Blood samples containing haemoglobin (Hb), serum albumin (Alb), uric acid, calcium (Ca), phosphate (Pi), total cholesterol (TC), triglyceride (TG), dicarboxide and intact parathyroid hormone (iPTH) were collected before dialysis and measured via routine laboratory methods. Serum iPTH was measured by Electrochemiluminescence Technology (Cobase411 analyser, Germany, Roche Diagnostics®). This method is an immunological test for the quantitative determination of iPTH. The interassay coefficient of variation for iPTH was lower than 4%. We also recorded the comorbidities (hypertension, diabetes mellitus and cardiocerebrovascular disease [CVD]) and medical usages (calcium supplements, vitamin D, ACEI/ARB and cinacalcet) for every individual by checking their medical records.

Measurement of serum FGF21 and FGF23 in patients on HD

Blood samples were collected under the fasting overnight and before dialysis. They were withdrawn in
vacuum tubes and then centrifuged at 3000 rpm for 10 min. The upper serum was collected and stored at -80 °C immediately for future analyses. Serum FGF21 and FGF23 levels were assessed by enzyme-linked immunosorbent assay (ELISA) kits for human FGF21 (Neobioscience, China) and for human FGF23 (Joyee biotechnics, China), respectively. The interassay and intraassay coefficients of variation were both less than 10 % for FGF21 and FGF23.

**Attenuation assessment on CT scans**

Discovery HD 750 64-slice CT (GE Health care, USA) was used to measure osteoporosis. We identified the L1 vertebra in the axial plane and viewed it in bone tissue

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**Fig. 1** Flow chart of the study process. HD, haemodialysis; FGF21, fibroblast growth factor 21; FGF23, fibroblast growth factor 23

**Fig. 2** Axial image through the vertebral body of L1 on a thoracoabdominal-pelvic CT scan. Placement of the region of interest within the trabecular bone and assessment of the CT attenuation value in Hounsfield units (182.3 HU left and 96.5 HU right in this example)
windows. Then, we placed the largest elliptical ROI on an area of the central part of the vertebral body trabecular bone of L1 to measure the vertebral BMD. In this process, the cortical margins should be excluded to prevent volume averaging, as shown in Fig. 2. All CT scans were performed by a single observer and the same CT machine to ensure consistency of regions. The mean CT attenuation values for each patient were measured in HU. We defined CT attenuation values less than 135 HU as osteoporosis [22].

Statistical analyses
Statistical analyses were performed using SPSS 18.0 software. The data are given as the mean ± SD for normally distributed variables and as the median and interquartile range for non-normally distributed variables. Univariate analyses were performed to compare the differences between two groups. Meanwhile, we used bivariate correlation analyses to assess the correlation of CT attenuation with serum FGF21 and other clinical parameters. We employed stepwise multivariate linear regression analyses to evaluate the independent association of variables with L1 attenuation. ROC curves were constructed to calculate the AUC and compared the prognostic value of every independently associated factor or group of factors to osteoporosis. All analyses were two-tailed, and a P value < 0.05 was considered to be statistically significant.

Results
General characteristics of subjects
In this cross-sectional study, of the 962 patients on HD screened, a total of 339 patients were eligible (193 men, 56.5%) with a mean (SD) age of 56.79 (15.60) years (Table 1). In the process of data collection, 89 patients lack blood data and 124 patients lack CT scans, we excluded 213 patients for the accuracy of our study. The dialysis duration was 4.33 ± 4.91 years, and the body mass index was 22.99 ± 4.01 kg/m². According to the threshold of osteoporosis (CT attenuation values ≤ 135 HU) proposed by Pickhardt et al. [22], 98 (28.9%) patients were enrolled in the osteoporosis group, and 241 (71.1%) were enrolled in the non-osteoporosis group. The basic characteristics of all patients divided into these two groups are presented in Table 1. In the osteoporosis group, patients on HD had a mean age of 66.45 ± 13.28 years and a median serum FGF21 level of 640.86 pg/ml (interquartile range 1.72, 3176.14). In the non-osteoporosis group, patients had a mean age of 52.86 ± 14.77 years and a median serum FGF21 level of 245.46 pg/ml (interquartile range 0.95, 1764.29). As shown in Table 1, there were significant differences in age, diastolic blood pressure (DBP), and vitamin D usage rate between these two groups (all P < 0.05). Serum FGF21 levels were significantly higher in the osteoporosis group (P < 0.001), while serum FGF23 levels were not significantly different between these two groups. Additionally, the percentage of patients who suffered diabetes and cardiocerebrovascular disease (CVD) in the osteoporosis group was higher than that in the non-osteoporosis group (P < 0.001). The baseline characteristics based on the FGF21 median were shown in Table 2. Compared to low serum FGF21 group, hemoglobin, albumin and dicarbonate levels were all significantly lower in high serum FGF21 level group (P < 0.05). Meanwhile, the proportion of patients with hypertension (OR = 1.065, P < 0.001) and DM (OR = 1.362, P < 0.05) and comorbidity of hypertension (β = -0.575, P < 0.05) were independently associated with serum FGF21 levels in patients on HD, as shown in Table 3. In addition, CT attenuation values were negatively correlated with DBP (r = -27.01, P = 0.028), while the CT attenuation values positively correlated with serum FGF21 level (r = 0.420, P < 0.001) (Supplemental Table 1).

Multivariate linear regression analyses for independently associated factors of CT attenuation values and serum FGF21 levels
Those parameters that were different between the osteoporosis and non-osteoporosis groups and well-known risk factors, such as dialysis duration, SBP, Hb, Alb, TG, Ca, Pi, iPTH and FGF23, were all included in multivariate linear regression analyses. As shown in Table 4, only FGF21 (β = -0.067, P < 0.05), age (β = -1.362, P < 0.05) and DM (β = -27.013, P < 0.05) were independently and negatively associated with CT attenuation in patients on HD. Meanwhile, albumin (β = -0.062, P < 0.001), dicarbonate (β = -0.079, P < 0.001), calcium (β = 0.796, P < 0.05), CT attenuation (β = -0.519, P < 0.05) and comorbidity of hypertension (β = -0.575, P < 0.05) were independently associated with serum FGF21 levels in patients on HD, as shown in Table 5. In multivariate logistic regression analysis, CT attenuation is positively associated with age (OR = 1.065, P < 0.001) and FGF21 levels (OR = 1.002, P < 0.001) (Supplemental Table 2).
In this study, receiver operating characteristic (ROC) curves were constructed to assess distinguished values of independently associated factors in predicting osteoporosis (Table 6). The area under the curve (AUC) of FGF21 in predicting osteoporosis was 0.71 (95% CI, 0.64 to 0.78, $P < 0.001$), with good sensitivity (80.2%) but low specificity (41.1%). Notably, the AUC of FGF21 combined with age in predicting osteoporosis increased significantly to 0.829 (95% CI, 0.78 to 0.88, $P < 0.001$) with optimal sensitivity (91.4%) and higher specificity (47.9%). In the two

| Table 1 | Comparison of clinical characteristics and laboratory data between the osteoporosis and non-osteoporosis groups in patients on HD |
|---------|----------------------------------------------------------------------------------------------------------------------------------|
| Number  | All HD patients | Osteoporosis | Non-Osteoporosis | $P$ value     |
| General data | | | | |
| Age(years) | 56.79 ± 15.60 | 66.45 ± 13.28 | 52.86 ± 14.77 | $< 0.001^{**}$ |
| Sex(male %) | 193(56.93 %) | 60(61.22 %) | 133(55.19 %) | 0.309 |
| Dialysis vintage(years) | 4.33 ± 4.91 | 4.63 ± 4.87 | 4.21 ± 4.94 | 0.469 |
| Body mass index(BMI) | 22.99 ± 4.01 | 22.93 ± 4.03 | 23.01 ± 4.01 | 0.868 |
| Systolic BP(mmHg) | 145.78 ± 24.40 | 145.94 ± 24.37 | 145.72 ± 24.46 | 0.940 |
| Diastolic BP(mmHg) | 82.32 ± 14.60 | 78.51 ± 14.55 | 83.87 ± 14.36 | 0.002** |
| Blood data | | | | |
| Hemoglobin(g/L) | 97.57 ± 20.14 | 98.47 ± 20.94 | 97.20 ± 19.84 | 0.601 |
| Albumin(g/L) | 35.89 ± 6.13 | 35.36 ± 6.41 | 36.11 ± 6.02 | 0.309 |
| Uric acid(mmol/L) | 378.64 ± 125.83 | 368.83 ± 120.70 | 382.63 ± 127.89 | 0.361 |
| Triglycerides(mmol/L) | 1.81 ± 1.37 | 1.75 ± 1.45 | 1.84 ± 1.33 | 0.438 |
| Total cholesterol(mmol/L) | 4.13 ± 1.12 | 4.06 ± 1.00 | 4.16 ± 1.17 | 0.605 |
| Dicarbonate(mmol/L) | 22.65 ± 3.76 | 22.63 ± 3.87 | 22.66 ± 3.72 | 0.943 |
| Calcium(mmol/L) | 2.26 ± 0.24 | 2.28 ± 0.25 | 2.26 ± 0.24 | 0.548 |
| Phosphate(mmol/L) | 1.70(0.19,4.16) | 1.69(0.28,4.16) | 1.76(0.19,3.35) | 0.305 |
| Parathormon(pg/ml) | 374.07 ± 418.87 | 347.02 ± 385.80 | 385.07 ± 431.87 | 0.449 |
| FGF21 quartiles (pg/ml) | 386.67 | 930.23 | 288.80 | $< 0.001^{**}$ |
| FGF23 quartiles (pg/ml) | 9309.83 ± 10410.89 | 9529.83 ± 9485.39 | 9220.37 ± 10782.06 | 0.804 |
| Comorbidity | | | | |
| Diabetes(%) | 112(33.04 %) | 45(45.92 %) | 67(27.80 %) | 0.001** |
| Hypertension(%) | 298(87.91 %) | 87(88.78 %) | 211(87.55 %) | 0.754 |
| CVD(%) | 94(27.73 %) | 48(48.98 %) | 46(19.09 %) | $< 0.001^{**}$ |
| Medicine usage | | | | |
| Vitamin D(%) | 151(44.54 %) | 31(31.63 %) | 120(49.79 %) | 0.002** |
| Calcium supplements(%) | 86(25.37 %) | 22(22.45 %) | 64(26.56 %) | 0.431 |
| Cinacalcet(%) | 52(15.34 %) | 11(11.22 %) | 41(17.01 %) | 0.180 |
| ACEI/ARB(%) | 94(27.73 %) | 28(28.57 %) | 66(27.39 %) | 0.825 |
| FRAX(306)* | Major Osteoporosis | 3(0.914) | 4(0.103) | 2.55(0.914) | $< 0.001^{**}$ |
| Hip fracture | 0.8(0.010) | 1.95(0.10) | 0.5(0.10) | $< 0.001^{**}$ |

The values are shown as the mean ± SD, median (interquartile range) or numbers (%), *$P<0.05$, **$P<0.01$.

*306 of 339 patients agreed to complete the FRAX questionnaire.

HD haemodialysis; BP blood pressure; FGF21 fibroblast growth factor 21; FGF23 fibroblast growth factor 23; CVD cardiocerebrovascular disease; ACEI angiotensin-converting enzyme; ARB angiotensin receptor II antagonist; FRAX fracture risk assessment tool

### Prediction by FGF21 and FGF23 of osteoporosis in patients on HD

In this study, receiver operating characteristic (ROC) curves were constructed to assess distinguished values of independently associated factors in predicting osteoporosis (Table 6). The area under the curve (AUC) of FGF21 in predicting osteoporosis was 0.71 (95% CI, 0.64 to 0.78, $P < 0.001$), with good sensitivity (80.2%) but low specificity (41.1%). Notably, the AUC of FGF21 combined with age in predicting osteoporosis increased significantly to 0.829 (95% CI, 0.78 to 0.88, $P < 0.001$) with optimal sensitivity (91.4%) and higher specificity (47.9%). In the two
subgroups based on 24-hour urine volume in HD patients, the area under the curve (AUC) of FGF21 in predicting osteoporosis were 0.657 (95% CI, 0.558 to 0.755, \(P = 0.001\)) and 0.691 (95% CI, 0.606 to 0.775, \(P = 0.001\)) respectively (Table 6). FGF21 has a good specificity (86.7% vs. 92.1%) but low sensitivity (44.2% vs. 41.8%) in two subgroups. In HD patients with 24-hour urine volume \(>100\)ml, the AUC of FGF21 combined with age in predicting osteoporosis was 0.837 (95% CI, 0.778 to 0.896, \(P < 0.001\)) with better sensitivity (70.1%) and specificity (81.4%). In HD patients with 24-hour urine volume \(\leq 100\)ml, the AUC of FGF21 combined with age in predicting osteoporosis was 0.833 (95% CI, 0.772 to 0.894, \(P < 0.001\)) with good sensitivity (61.8%) and specificity (90.5%).

### Table 2
Comparison of clinical characteristics and laboratory data between the low serum FGF21 level group and high serum FGF21 level group in patients on HD

|                          | Low FGF21 group (FGF21 \(\leq 184.50\)pg/ml) | High FGF21 group (FGF21 >184.50pg/ml) | \(P\) value |
|--------------------------|---------------------------------------------|--------------------------------------|-------------|
| **Number**               | 170                                         | 169                                  |             |
| **General data**         |                                              |                                      |             |
| Age (years)              | 55.82 ± 15.60                               | 57.76 ± 15.59                        | 0.253       |
| Sex (male %)             | 100 (58.82%)                                | 93 (55.03%)                          | 0.481       |
| Dialysis vintage (years) | 4.17 ± 4.45                                 | 4.49 ± 5.35                          | 0.540       |
| Body mass index (BMI)    | 22.93 ± 3.93                                | 23.05 ± 4.09                         | 0.794       |
| Systolic BP (mmHg)       | 145.75 ± 24.91                              | 145.82 ± 23.95                       | 0.979       |
| Diastolic BP (mmHg)      | 82.39 ± 13.95                               | 82.25 ± 15.27                        | 0.933       |
| **Blood data**           |                                              |                                      |             |
| Hemoglobin (g/L)         | 99.92 ± 19.80                               | 95.21 ± 20.07                        | 0.031*      |
| Albumin (g/L)            | 36.80 ± 6.39                                | 34.98 ± 5.74                         | 0.006**     |
| Uric acid (mmol/L)       | 379.78 ± 134.65                             | 377.50 ± 116.68                      | 0.868       |
| Triglycerides (mmol/L)   | 1.75 ± 1.39                                 | 1.88 ± 1.35                          | 0.412       |
| Total cholesterol (mmol/L)| 4.19 ± 1.11                                | 4.08 ± 1.13                          | 0.346       |
| Dicarbonate (mmol/L)     | 23.06 ± 3.74                                | 22.24 ± 3.74                         | 0.044*      |
| Calcium (mmol/L)         | 2.27 ± 0.24                                 | 2.26 ± 0.24                          | 0.639       |
| Phosphate (mmol/L)       | 1.73 ± 0.56                                 | 1.75 ± 0.61                          | 0.744       |
| Parathormon (pg/ml)      | 369.08 ± 452.80                             | 379.08 ± 383.00                      | 0.826       |
| **CT**                  |                                              |                                      |             |
| L1 attenuation (HU)      | 168.90 (137.75, 197.00)                     | 159.10 (118.15, 212.00)              | 0.363       |
| **Comorbidity**          |                                              |                                      |             |
| Diabetes (%)             | 60 (35.29%)                                 | 50 (29.59%)                          | 0.262       |
| Hypertension (%)         | 155 (91.18%)                                | 141 (83.43%)                         | 0.032*      |
| CVD (%)                  | 43 (25.29%)                                 | 34 (20.12%)                          | 0.255       |
| **Medicine usage**       |                                              |                                      |             |
| Vitamin D (%)            | 76 (44.71%)                                 | 75 (44.38%)                          | 0.952       |
| Calcium supplements (%)  | 41 (24.12%)                                 | 45 (26.63%)                          | 0.595       |
| Cinacalcet (%)           | 31 (18.24%)                                 | 21 (12.43%)                          | 0.138       |
| ACEI/ARB (%)             | 52 (30.59%)                                 | 42 (24.85%)                          | 0.238       |
| **FRAX(306)**            |                                              |                                      |             |
| Major Osteoporosis       | 3.78 ± 2.56                                 | 3.64 ± 2.70                          | 0.637       |
| Hip fracture             | 1.61 ± 1.85                                 | 1.57 ± 2.04                          | 0.881       |

The values are shown as the mean ± SD, median (interquartile range) or numbers (%). *\(P<0.05\), **\(P<0.01\).

*306 of 339 patients agreed to complete the FRAX questionnaire.

HD haemodialysis; BP blood pressure; FGF21 fibroblast growth factor 21; HU hounsfield unit; CVD cardiocerebrovascular disease; ACEI angiotensin-converting enzyme; ARB angiotensin receptor II antagonist; FRAX fracture risk assessment tool
Discussion
In the present study, we showed that serum FGF21 levels were significantly higher in the osteoporosis group of patients on HD. FGF21 rather than FGF23 is independently and negatively associated with CT attenuation values in patients on HD. Furthermore, FGF21 combined with age showed good specificity (90.5 %) and sensitivity (61.8 %) for the prediction of osteoporosis in patients on HD with less residual renal function.

Many previous researches have showed the values of L1 trabecular attenuation at routine CT can identify the risk of osteoporosis in general population and the most optimized threshold was 135 HU [22, 23]. In our study, we found that the mean age of the osteoporosis group was higher and that CT attenuation values declined with ageing in bivariate correlation analyses, which is in line with the characteristic of osteoporosis that the bone mass reaches its highest level in adolescence and then is subsequently lost with ageing [24]. In addition, we found that the percentage of vitamin D supplements was higher in the non-osteoporosis group, which may be due to the protective function of vitamin D on improving osteoporosis by affecting the number of osteoblasts, osteoclasts and osteocytes in bone [25].

FGF23 is a recently identified hormone that is produced in bone by osteocytes and osteoblasts [26]. In previous studies, FGF23 suppressed bone mineralization by inhibiting cell differentiation, number, activity and bone turnover [27–29]. In animal models, the role of FGF23 in regulating phosphate metabolism can be one causative factor of abnormal bone mineralization [30, 31]. Our result that the FGF23 level was negatively associated with CT attenuation values was potent evidence for its role in bone loss as well. However, our results indicated that FGF23 was not an independent risk factor for osteoporosis (Table 3), and it had no value in predicting osteoporosis in this study (data not shown), even though Mirza Ma and Lane Ne et al. demonstrated that serum FGF23 levels were related independently to fracture risk in elderly men with decreased estimated glomerular filtration (eGFR) [32, 33]. These discrepancies may be due to the different methods used to measure bone mineral density, as dual-energy X-ray absorptiometry (DXA) was mostly used in previous studies.

FGF21 is another member of the FGF19 subfamily that is primarily secreted from the liver under physiological conditions and other sites, including adipose tissue, skeletal muscle, heart and kidney [34]. Multiple studies have shown that high-levels of serum FGF21 have association with the loss of bone mineral density in adults and post-menopausal women with normal renal function [35, 36]. Moreover, its level increased progressively with a decline in renal function, as renal clearance is considered to be

| Variables | Age | Dialysis | SBP | DBP | Hb | Alb | TG | Ca | Pi | iPTH | FGF21 | FGF23 | MO | HF |
|-----------|-----|----------|-----|-----|----|-----|----|----|----|------|-------|-------|----|----|
| r         | -0.440 | -0.120 | 0.030 | 0.274 | -0.019 | -0.027 | 0.017 | -0.022 | 0.089 | 0.105 | -0.136 | -0.151 | -0.383 | -0.411 |
| P value   | < 0.001** | 0.028* | 0.580 | < 0.001** | 0.721 | 0.623 | 0.761 | 0.692 | 0.104 | 0.053 | 0.012* | 0.005** | < 0.001** | < 0.001** |

*P<0.05, **P<0.01

FGF21 fibroblast growth factor 21; FGF23 fibroblast growth factor 23; SBP systolic blood pressure; DBP diastolic blood pressure; Hb haemoglobin; Alb albumin; Ca calcium; Pi phosphate; TG triglyceride; iPTH intact parathyroid hormone; MO major osteoporosis; HF hip fracture

Fig. 3 Correlation of serum FGF21 and albumin and L1 attenuation in osteoporosis group of HD patients. Log (FGF21) was significantly correlated with (a) albumin (r = -0.290, P < 0.05); (b) L1 attenuation (r = -0.238, P < 0.05). FGF21, fibroblast growth factor 21; Alb, albumin
Table 4 Multivariate linear regression analyses for the establishment of factors independently associated with CT attenuation

| Variables             | β(95 % CI) | P value |
|-----------------------|------------|---------|
| Age                   | -1.021(-2.212, -0.512) | <0.001** |
| Dialysis duration     | -0.040     | 0.467   |
| BMI                   | -0.064     | 0.192   |
| SBP                   | -0.042     | 0.547   |
| DBP                   | 0.692(0.256, 1.127) | 0.002** |
| TG                    | -0.098     | 0.079   |
| TC                    | -0.093     | 0.094   |
| Ca                    | 0.005      | 0.923   |
| Pi                    | -0.085     | 0.148   |
| iPTH                  | 0.044      | 0.429   |
| FGF21                 | -0.067(-0.104, -0.030) | 0.019*   |
| FGF23                 | -0.012     | 0.832   |
| CVD                   | -0.084     | 0.147   |
| DM                    | -18.029(-31.217, -4.841) | 0.008*   |
| Ca usage              | -0.041     | 0.480   |
| Vitamin D usage       | 0.044      | 0.451   |

*P<0.05, **P<0.01

FGF21 fibroblast growth factor 21; FGF23 fibroblast growth factor 23; TC total cholesterol; TG triglyceride; Ca calcium; Pi phosphate; iPTH intact parathyroid hormone; CVD cardiocerebrovascular disease; DM diabetes mellitus

Table 5 Multivariate linear regression analyses for the establishment of factors independently associated with FGF21

| Variables             | β(95 % CI) | P value |
|-----------------------|------------|---------|
| Age                   | 0.092      | 0.089   |
| Dialysis duration     | 0.065      | 0.240   |
| BMI                   | 0.013      | 0.799   |
| SBP                   | 0.077      | 0.138   |
| DBP                   | 0.093      | 0.082   |
| TG                    | -0.053     | 0.309   |
| TC                    | 0.055      | 0.296   |
| Ca                    | 0.796(0.111, 1.482) | 0.023*   |
| Pi                    | 0.005      | 0.924   |
| iPTH                  | 0.000      | 0.994   |
| Alb                   | -0.062(-0.088, -0.035) | <0.001** |
| Dicarbonate           | -0.079(-0.121, -0.038) | <0.001** |
| CVD                   | -0.048     | 0.362   |
| DM                    | -0.019     | 0.726   |
| HBP                   | -0.575(-1.020, -0.130) | 0.011*   |
| Ca usage              | 0.039      | 0.460   |
| Vitamin D usage       | -0.005     | 0.922   |

*P<0.05, **P<0.01

FGF21 fibroblast growth factor 21; BMI body mass index; TC total cholesterol; TG triglyceride; Ca calcium; Pi phosphate; iPTH intact parathyroid hormone; Alb albumin; CVD cardiocerebrovascular disease; DM diabetes mellitus; HBP high blood pressure

In this study, our results showed an approximately independent positive correlation between FGF21 and age (P = 0.089), although this relationship had insufficient statistical significance which may due to the relatively small sample size. Previous study has indicated that serum FGF21 level was increased in population with obesity or diabetes [41]. However, FGF21 levels has no difference between HD patients with or without comorbidity of diabetes in our study. The discordance may be attributed to following factors: (1) Eun SH et al. found that serum FGF21 level was only increased to 1.5 times in patients with type 2 diabetes compared with that in healthy individuals [42]. While in our study, serum FGF21 level of HD patients was 3–5 times higher than that in control group and this huge increase may mask the impact of diabetes on FGF21; (2) the independent correlation between diabetes and FGF21 can also be diminished by the high incidence of secondary glucose and lipid metabolic disorders in HD patients.
Currently, DXA and CT are the main techniques to assess bone loss and diagnose osteoporosis in patients on HD in clinical practice, and they still have some disadvantages, such as exposure to radiation and high cost. Besides, the 2009 KDIGO Guideline recommended that BMD testing not be performed routinely in patients with CKD G3a to G5D [1]. In our study, we found that FGF21 had a great value in predicting osteoporosis with a relatively high sensitivity (80.2 %). Moreover, the sensitivity of predicting osteoporosis could rise to 91.4 % when FGF21 was combined with age. However, both of their specificities were below 50 %, which could be ascribed to the different residual renal function (RRF) in their specificities were below 50 %, which could be ascribed to the different residual renal function (RRF) in this research and complicated bone metabolism in CKD.

Variables All HD patients | HD patients with anuria | HD patients without anuria
---|---|---
Age | 0.712 (0.644,0.779) | 0.756 (0.681,0.832) | 0.754 (0.685,0.822)
FGF21 | 0.710 (0.638,0.781) | 0.657 (0.558,0.755) | 0.691 (0.606,0.775)
Age + FGF21 | 0.829 (0.776,0.882) | 0.837 (0.778,0.896) | 0.833 (0.772,0.894)

*P<0.05, **P<0.01
FGF21 fibroblast growth factor 21; HD haemodialysis

The area under the curve (AUC) of separated and grouped independently associated factors of L1 CT attenuation in ROC curve analyses in HD patients

Since serum FGF21 level is strongly dependent on RRF this research and complicated bone metabolism in CKD.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12882-021-02393-z.

Additional file 1.

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Not applicable.

Authors’ contributions
Lili Zhu, Bi-Cheng Liu and Bin Wang contributed to the research idea and study design; Lili Zhu, Min Li, Qianqian Zha, Min Yang, Liqiong Jiang, Mingming Pan, Qin Yin and Meixia Xia contributed to data acquisition; Lili Zhu, Jirong Yu, Liqiong Jiang and Bin Wang contributed to data analysis/interpretation; Lili Zhu and Liqiong Jiang performed statistical analysis; Bi-Cheng Liu and Bin Wang provided supervision and mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work were appropriately investigated and resolved. The author(s) read and approved the final manuscript.

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Availability of data and materials
The datasets analysed during the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee of Zhongda Hospital affiliated with Southeast University. The details of the study were explained to every patient; a signed informed consent was obtained from all subjects. All methods were confirmed to be carried out in accordance with relevant guidelines and regulations.
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