Serum fibroblast growth factor-23 (FGF-23) levels are independently associated with left ventricular mass and myocardial performance index in maintenance haemodialysis patients

Alper Kirkpantur1, Mustafa Balci2, Oguz Alp Gurbuz3, Baris Afsar4, Basol Canbakan1, Ramazan Akdemir5 and Mehmet Deniz Ayli3

1Nephrology, Ministry of Health, Diskapi Training and Research Hospital, Ankara, Turkey, 2Cardiology, Ministry of Health, Diskapi Training and Research Hospital, Ankara, Turkey, 3Infectious Diseases, Ministry of Health, Diskapi Training and Research Hospital, Ankara, Turkey and 4Nephrology, Ministry of Health, Zonguldak Training and Research Hospital, Zonguldak, Turkey

Correspondence and offprint requests to: Alper Kirkpantur; E-mail: alperkirkpantur@yahoo.com

Abstract

Background. Fibroblast growth factor-23 (FGF-23) is a phosphorus-regulating substance. Circulating FGF-23 levels increase markedly in dialysis patients and are independently associated with increased risk of mortality. Given the fact that cardiovascular disease is the leading

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cause of death in dialysis patients, the aim of this study was to test if elevated FGF-23 levels might be associated with left ventricular mass index (LVMI) and left ventricular index of myocardial performance (MPI) in maintenance haemodialysis patients.

Methods. In this cross-sectional study, plasma FGF-23 concentrations were measured using a C-terminal human enzyme-linked immunosorbent assay kit, and echocardiography was performed in 128 maintenance haemodialysis patients (65 women and 63 men, mean age: 55.5 ± 13 years, mean haemodialysis vintage: 52 ± 10 months, all patients are on haemodialysis thrice a week) and 40 control subjects (21 women and 19 men; mean age: 54 ± 11 years) with normal kidney function (eGFR >90 mL/min/1.73 m²).

Results. Serum FGF-23 levels were elevated when compared with age- and gender-matched controls with preserved kidney function [median 958 RU/mL; interquartile range 106–1894 RU/mL] vs (median 27 RU/mL; interquartile range 11–35), P < 0.0001]. Patients with a history of coronary artery disease and aortic valve calcifications had higher levels of log FGF-23 than those without (3.00 ± 0.22 vs 2.82 ± 0.26, P = 0.002; and 3.06 ± 0.19 vs 2.83 ± 0.26, P = 0.0001, respectively). Patients with MPI >0.47 had higher serum FGF-23 levels than those with MPI <0.47 [median 1156 RU/mL; interquartile range 396–1894 RU/mL] vs (median 657 RU/mL; interquartile range 106–1102 RU/mL), P = 0.0001]. Significant correlations were recorded between log FGF-23 levels and LVMI (r = 0.281, P = 0.007) and MPI (r = 0.555, P = 0.0001). Multivariable-adjusted regression analyses revealed that increased log FGF-23 concentrations were independently associated with increased left ventricular mass index (30% increase per 1-SD increase in log FGF-23 concentration, P = 0.002) and increased MPI (28.5% increase per 1-SD increase in log FGF-23 concentration, P = 0.001).

Conclusions. Plasma FGF-23 concentration is independently associated with LVMI and MPI in maintenance haemodialysis patients. Further prospective studies are needed to clarify whether increased serum FGF-23 level is a marker or a potential mechanism for left ventricular involvement in patients with end-stage renal disease.

Keywords: fibroblast growth factor-23; haemodialysis; left ventricular mass index; myocardial performance index

Introduction

Abnormalities of mineral metabolism are a prevalent condition in chronic kidney disease and are important determinants of the bone and vascular system in this patient population. Several studies have shown that hyperphosphataemia, increased serum PTH and low 1,25(OH)2D3 levels are independently associated with increased total and cardiovascular mortality in patients with end-stage renal disease (ESRD) [1–3]. These observations have raised interest in understanding mineral metabolism regulation and its consequences in patients with chronic kidney disease (CKD).

Fibroblast growth factor-23 (FGF-23), a novel hormone secreted by osteocytes and osteoblasts, is an important negative regulator of phosphate and vitamin D metabolism. Initially, FGF-23 was described as the cause of rare hypophosphataemic syndromes characterized by hypophosphataemia, renal phosphate wasting, low serum levels of 1,25(OH)2D3, and osteomalacia or rickets [4,5]. FGF-23 induces renal phosphate wasting by inhibiting the proximal tubular sodium phosphate co-transporter type IIa (NPT2a) and suppressing the renal expression of CYP27B1, resulting in decreased 1,25(OH)2D3 synthesis [6].

Several studies have indicated that serum levels of FGF-23 are elevated in haemodialysis (HD) patients [7,8], and recently, elevated FGF-23 concentrations have been independently associated with increased risk of mortality in patients who are beginning HD treatment [9]. Moreover, serum FGF-23 was shown to be independently associated with left ventricular hypertrophy (LVH) in a pre-dialysis CKD [10] and HD study [11]. However, studies examining the relationship between FGF-23 and LVH are not sufficient in the ESRD population. Furthermore, to the best of our knowledge, the relation between FGF-23 and myocardial function has not been studied yet in these patients. Therefore, we conducted a cross-sectional study to test the hypothesis that elevated FGF-23 concentrations are independently associated with left ventricular mass index (LVMI) and myocardial performance index in maintenance HD patients.

Materials and methods

Subjects

Out of 137 adult HD patients, 4 patients refused, and 5 patients were excluded due to known malignancies (n = 1), autoimmune diseases (n = 2) and clinically evident active infections (n = 2). Overall, 128 maintenance HD patients participated (65 women and 63 men, mean age 55.5 ± 13 years, mean HD time: 52 ± 10 months, on HD thrice a week). The patients suffered from ESRD due to diabetic nephropathy (n = 34), hypertensive nephrosclerosis (n = 30), chronic glomerulonephritis (n = 27), chronic pyelonephritis (n = 15) and polycystic disease (n = 10). The renal diagnosis was unknown in 12 patients.

Patients were prescribed treatments including CaCO3 (27%), sevelamer (11%), Ca acetate (41%), alfalcaldiol (62%), warfarin (18%) and erthropoietin (70%). The mean erthropoietin dose was 145 U/kg/week achieving a mean haemoglobin (Hb) serum level of 11.4 g/dL; <10% of patients had serum Hb <10 g/dL.

All patients were receiving conventional 4-h HD with polysulphone dialysers F6HPS and F7HPS (Fresenius AG, Bad Homburg, Germany) thrice a week, with bicarbonate dialysate, and low-molecular-weight heparin for standard anticoagulation. Mean blood flow rate was 300 mL/min during the HD session (range 250–340 mL/min). Dry weight was considered optimal when the patients had no residual symptoms of orthopnoea, dyspnoea and oedema during the interdialytic period. Urea (Kt/V) values were calculated according to the Daugirdas second-generation formula [12].

Blood pressure (BP) of the patients was measured with a conventional mercury manometer prior to each HD session. Hypertension was defined as a systolic BP of 140 mmHg or above, diastolic BP of 90 mmHg or above, and patients on antihypertensive medication [13]. Average values of systolic and diastolic BP obtained in the first 3 weeks of the study were used in statistical analysis. Patients were on antihypertensives: angiotensin-converting enzyme inhibitors (n = 22), angiotensin receptor blockers (n = 14), beta-blockers (n = 30) and calcium channel blockers (n = 28). No patient was on statin therapy.
Forty control subjects (21 women and 19 men; mean age: 54 ± 11 years) with normal kidney function (eGFR >90 mL/min/1.73 m²) were recruited to investigate the relationship between serum FGF-23 levels and LVMI and myocardial performance index in non-chronic kidney disease patients. These subjects were enrolled from inpatient services at the Diskapi Training and Research Hospital, Ankara, Turkey. The subjects were ≥18 years old and had no evidence of cardiac disease such as acute myocardial infarction, known cardiomyopathy, known aortic or mitral valvular disease, pericardial disease, and ejection fraction <40%. All the subjects were clinically stable. These subjects were planned to undergo echocardiograms that were ordered by their primary doctors.

The study was approved by the local ethics committee of Diskapi Training and Research Hospital, and all the patients and controls provided written informed consent before entering the study.

Biochemical assays
Venous blood samples were drawn after an overnight fast. The blood sample was obtained directly through an arteriovenous fistula or central catheter on a mid-week non-dialysis day. Serum total cholesterol and triglycerides were quantified by commercial colorimetrical assay methods (GPO-PAP and CHOD-PAP; Boehringer-Mannheim, Mannheim, Germany). High-density lipoprotein cholesterol (HDLC) was quantified by the photophotometric acid precipitation method. Low-density lipoprotein cholesterol (LDLC) was calculated by the Friedewald formula (LDLC = CHOL – TG/5 – HDLC), where CHOL is serum total cholesterol and TG is triglycerides. CRP was detected by rate nephelometry (IMAGE). Serum biochemical parameters (creatinine, blood urea nitrogen, glucose, electrolytes, albumin and complete blood count) and intact parathormone levels were studied by means of a computerized autoanalyser (Hitachi 717; Boehringer-Mannheim). We measured serum CRP levels of all patients thrice a year in order to monitor cardiovascular events. Serum albumin levels were routinely measured monthly with other biochemical parameters in the routine follow-up of the patients in our institution. Thus, mean values of serum chemistries (total of 12 values) and CRP levels (total of three values) over 12 months were taken into account in statistical analysis.

Echocardiography
Conventional and Doppler echocardiography with TDI (Vingmed, WI, USA) were performed on a mid-week non-dialysis day. The ejection fraction, end-diastolic diameter of the LV, and the thicknesses of the LV posterior wall and interventricular septum were measured from the long-axis parasternal plane according to the American Society of Echocardiography (ASE) guidelines [14]. The LVMI was calculated with the Devereux formula [15]. Body surface area was calculated with the formula of DuBois and DuBois. In the Framingham Heart Study, the mean values ± two standard deviations for the left ventricular mass indexed by body surface area were 131 and 100 g/m² for men and women, respectively [16,17]. Left ventricular hypertrophy was diagnosed when the LVMI was greater than these values.

On Doppler echocardiography, we calculated the Tei index (myocardial performance index) as the sum of the isovolumetric relaxation and contraction time divided by ejection time [18]. The Tei index has proved to be a reliable method for the evaluation of LV systolic and diastolic function [19]. Clear advantages over older established indexes and prognostic value have been reported in many kinds of heart disease like heart failure [20], idiopathic dilated cardiomyopathy [21], heart transplantation [22], coronary artery disease [23], valvular disease [24] and congenital heart disease [25]. Some preload dependency of the Tei index has been suggested under different conditions, but, however, the extent of changes has been reported to be smaller than 10% [19]. Higher values of the Tei index were reported in patients with heart failure than in controls and were correlated with LV end-diastolic pressures [26]. Receiver operator curve analysis revealed that discriminatory power of the Tei index could be enhanced by selecting arbitrary ‘cut-points’ of ≥0.47 which identified patients with heart failure with a sensitivity of 86% and a specificity of 82% [27].

Fig. 1. Correlations between log FGF-23 and septal thickness ($r = 0.221$, $P = 0.048$; a), posterior wall thickness ($r = 0.452$, $P = 0.0001$, b), and left ventricular end-diastolic diameter ($r = 0.242$, $P = 0.029$, c).
Plasma FGF-23 concentrations were measured using a C-terminal human ELISA (Immunotopics, San Clemente, CA, USA) [4]. Measurements were made in duplicate and averaged. The sensitivity of the second generation Human FGF-23 C-terminal ELISA as determined by the 95% confidence limit on 20 duplicate determinations of the 0 RU/mL Standard is 1.5 RU/mL. The intra-assay and inter-assay variation of plasma FGF-23 measurements were 5% and 5–7.3%, respectively.

Table 1. Characteristics of the haemodialysis population (mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FGF-23 quartile 1&lt;sup&gt;§&lt;/sup&gt; (&lt;454 RU/mL)</th>
<th>FGF-23 quartile 2&lt;sup&gt;§&lt;/sup&gt; (454–1023 RU/mL)</th>
<th>FGF-23 quartile 3&lt;sup&gt;§&lt;/sup&gt; (&gt;1023 RU/mL)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (n, %)</td>
<td>41 (32.1%)</td>
<td>44 (34.3%)</td>
<td>43 (33.6%)</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>19/20</td>
<td>22/23</td>
<td>22/22</td>
<td>0.51</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54 ± 14</td>
<td>55 ± 14</td>
<td>56 ± 13</td>
<td>0.76</td>
</tr>
<tr>
<td>Body mass index (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>24.0 ± 3.2</td>
<td>23.9 ± 2.6</td>
<td>24.2 ± 3.1</td>
<td>0.35</td>
</tr>
<tr>
<td>HD duration (months)</td>
<td>49 ± 7</td>
<td>52 ± 11</td>
<td>51 ± 10</td>
<td>0.37</td>
</tr>
<tr>
<td>Diabetes (n, %)</td>
<td>11 (27%)</td>
<td>13 (29.5%)</td>
<td>10 (23%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Smoking (n, %)</td>
<td>7 (17%)</td>
<td>9 (20%)</td>
<td>9 (21%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>24 (58.5%)</td>
<td>22 (50%)</td>
<td>25 (58%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>138 ± 27</td>
<td>140 ± 22</td>
<td>144 ± 19</td>
<td>0.30</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>77 ± 19</td>
<td>80 ± 17</td>
<td>79 ± 19</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Medications

- ACEI/ARB<sup>†</sup> 22 (54%) 24 (55%) 22 (51%) 0.36
- Beta-blockers 14 (24%) 11 (25%) 11 (26%) 0.84
- CCB<sup>‡</sup> 16 (39%) 17 (39%) 16 (37%) 0.56
- CaCO<sub>3</sub> 11 (27%) 12 (27%) 12 (28%) 0.92
- Ca acetate 19 (46%) 23 (52%) 21 (49%) 0.68
- Sevelamer–HCl 4 (10%) 6 (13%) 4 (10%) 0.82
- Alfacalcidol 24 (59%) 27 (61%) 28 (65%) 0.54
- Haemoglobin (g/dL) 10.9 ± 1.1 11.2 ± 0.9 11.3 ± 0.8 0.77
- Calcium (mg/dL) 9.1 ± 0.4 9.0 ± 0.6 9.1 ± 0.7 0.78
- Phosphorus (mg/dL) 4.3 ± 1.0 4.9 ± 0.9 5.2 ± 0.6 0.002
- Intact parathormone level (pg/mL) 121 (76–144) 345 (230–412) 566 (458–992) 0.01
- Serum creatinine (mg/dL) 10.5 ± 2.8 10.6 ± 2.4 10 ± 2.0 0.69
- Total cholesterol (mg/dL) 148 ± 49 154 ± 41 149 ± 42 0.71
- Triglycerides (mg/dL) 143 ± 55 151 ± 29 143 ± 40 0.46
- LDL-C (mg/dL)<sup>**</sup> 89 ± 24 87 ± 27 88 ± 20 0.62
- HDL-C (mg/dL)<sup>**</sup> 40 ± 15 42 ± 19 40 ± 13 0.87
- C-reactive protein (mg/dL) 1.8 ± 1.3 1.8 ± 1.6 1.6 ± 1.9 0.95
- Kt/V 1.35 ± 0.33 1.32 ± 0.27 1.34 ± 0.30 0.69

<sup>§</sup>The lower quartile of FGF-23, FGF-23 Q1, is the number that cuts off lowest 25% of data (equals to the 25th percentile); FGF-23 Q2 cuts data set in half (also known as the median quartile that equals to the 50th percentile); and the upper quartile, FGF-23 Q3, is the number that cuts off highest 25% of data, or lowest 75% (equals to the 75th percentile) of FGF-23.

Table 2. Echocardiographic parameters by tertile of serum FGF-23 and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls with preserved renal function</th>
<th>FGF-23 quartile 1&lt;sup&gt;§&lt;/sup&gt; (&lt;454 RU/mL)</th>
<th>FGF-23 quartile 2&lt;sup&gt;§&lt;/sup&gt; (454–1023 RU/mL)</th>
<th>FGF-23 quartile 3&lt;sup&gt;§&lt;/sup&gt; (&gt;1023 RU/mL)</th>
<th>P-value&lt;sup&gt;†&lt;/sup&gt; (trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal thickness (cm)</td>
<td>0.90 ± 0.12&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.34 ± 0.21&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.45 ± 0.18&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.59 ± 0.19&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.004</td>
</tr>
<tr>
<td>Posterior wall thickness (cm)</td>
<td>0.88 ± 0.10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.11 ± 0.22&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.23 ± 0.17&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.36 ± 0.18&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.009</td>
</tr>
<tr>
<td>LV EDDD (cm)</td>
<td>4.00 ± 0.62&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.17 ± 0.69&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.49 ± 0.72&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.81 ± 0.75&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.010</td>
</tr>
<tr>
<td>LV ESDD (cm)</td>
<td>3.05 ± 0.77</td>
<td>3.27 ± 0.99</td>
<td>3.35 ± 0.84</td>
<td>3.57 ± 0.72</td>
<td>0.230</td>
</tr>
<tr>
<td>EF (%)</td>
<td>68 ± 7.4</td>
<td>60.9 ± 9.17</td>
<td>62 ± 11</td>
<td>62 ± 10.1</td>
<td>0.960</td>
</tr>
<tr>
<td>FS</td>
<td>31 ± 4.8</td>
<td>30.6 ± 6.7</td>
<td>31.4 ± 6.3</td>
<td>32.1 ± 6.1</td>
<td>0.680</td>
</tr>
<tr>
<td>LVMI (g/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>49 ± 13&lt;sup&gt;a&lt;/sup&gt;</td>
<td>94 ± 15&lt;sup&gt;a&lt;/sup&gt;</td>
<td>103 ± 14&lt;sup&gt;a&lt;/sup&gt;</td>
<td>111 ± 18&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.040</td>
</tr>
<tr>
<td>LVH (%)</td>
<td>4 (10%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>19 (46%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>31 (70%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>41 (95%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.002</td>
</tr>
<tr>
<td>MPI</td>
<td>0.21 ± 0.05&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.30 ± 0.09&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.40 ± 0.10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.53 ± 0.14&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.008</td>
</tr>
</tbody>
</table>

LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; EF, ejection fraction; FS, fractional shortening; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; MPI, myocardial performance index.

<sup>a</sup>The lower quartile of FGF-23, FGF-23 Q1, is the number that cuts off lowest 25% of data (equals to the 25th percentile); FGF-23 Q2 cuts data set in half (also known as the median quartile that equals to the 50th percentile); and the upper quartile, FGF-23 Q3, is the number that cuts off highest 25% of data, or lowest 75% (equals to the 75th percentile) of FGF-23.

**LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

<sup>†</sup>P-value for linear trend includes only haemodialysis patients.

Plasma FGF-23 levels

Plasma FGF-23 concentrations were measured using a C-terminal human ELISA (Immunotopics, San Clemente, CA, USA) [4]. Measurements were made in duplicate and averaged. The sensitivity of the second generation Human FGF-23 C-terminal ELISA as determined by the 95% confidence limit on 20 duplicate determinations of the 0 RU/mL Standard is 1.5 RU/mL. The intra-assay and inter-assay variation of plasma FGF-23 measurements were 5% and 5–7.3%, respectively.
Statistical analysis was performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA). Whether the distributions of continuous variables were normal or not was determined by using the Shapiro–Wilk test. Data were shown as mean, standard deviation, median and interquartile range. To test for associations between serum FGF-23 levels and echocardiographic parameters, we examined serum FGF-23 levels in quartiles according to the distribution of values in HD patients. The non-normally distributed variable FGF-23 was also log-transformed to achieve a normal distribution and used in subsequent statistical analysis. Degrees of associations between continuous variables were calculated by Spearman’s analysis of non-symmetrically distributed data.

A cut-off of 0.47 was chosen for the Tei index, because it is the value which has been previously shown to identify patients with heart failure with a sensitivity of 86% and a specificity of 82% according to a recent receiver operator curve analysis [27].

Linear regression was used to examine the association between LVMI, MPI and baseline demographic, clinical, and laboratory variables. Multivariable models were used to examine the relationship between FGF-23 levels, LVMI and myocardial performance index, adjusting for covariates that were significantly (P < 0.05) associated with LVMI and myocardial performance index in univariate analyses. Adjustments for treatment with phosphorus binders and vitamin D were also performed because these medications may influence serum FGF-23 levels [28]. Three models were used (Table 3) for myocardial performance index: Model 1, crude model; Model 2, adjusting for ‘presence of coronary artery disease’; and Model 3, adjusting for both ‘presence of coronary artery disease’ and ‘serum phosphate levels’. Two-tailed P-value <0.05 was considered statistically significant.

Results

Serum FGF-23 levels

Serum FGF-23 levels were elevated when compared with age- and gender-matched healthy controls [(median 958 RU/mL; interquartile range 106–1894 RU/mL) vs (median 27 RU/mL; interquartile range 11–35), P < 0.0001]. Mean log FGF-23 was 2.9 ± 0.29. Log FGF-23 levels were not significantly different in patients with a history of type 2 diabetes mellitus (2.9 ± 0.29 vs 2.9 ± 0.26, P = 0.96) and smoking (2.93 ± 0.25 vs 2.89 ± 0.26, P = 0.60) compared with those without. However, patients with a history of coronary artery disease and aortic valve calcifications had higher levels of log FGF-23 than those without (3.00 ± 0.22 vs 2.82 ± 0.26, P = 0.002; and 3.06 ± 0.19 vs 2.83 ± 0.26, P = 0.0001). Significant correlations were observed between serum FGF-23 levels and serum phosphate (r = 0.469, P < 0.0001; Figure 1a) and intact PTH levels (r = 0.374, P = 0.001; Figure 1b).

The demographic and clinical characteristics of the study patients according to the FGF-23 quartiles are depicted in Table 1. Patients in the highest quartile had higher serum levels of intact PTH, phosphate and Ca × P product.

Serum FGF-23 levels and left ventricular echocardiographic findings

Mean septal and posterior wall thicknesses, end-diastolic left ventricular diameter, LVMI, and MPI increased with increasing tertiles of FGF-23 (Table 2). Compared with controls with preserved renal function, HD patients had significantly higher mean MPI, LVMI, septal and posterior wall thicknesses, end-diastolic diameters, and percentage of LVH (Table 2).

Patients with MPI >0.47 had higher serum FGF-23 levels than those with MPI <0.47 [(median 1156 RU/mL; interquartile range 396–1894 RU/mL) vs (median 657 RU/mL; interquartile range 106–1102 RU/mL), P = 0.0001]. Moreover, log FGF-23 concentrations were significantly correlated with septal thickness (r = 0.221, P = 0.048, Figure 1a), posterior wall thickness (r = 0.452, P = 0.0001, Figure 1b), left ventricular end-diastolic diameter (r = 0.242, P = 0.029, Figure 1c), LVMI (r = 0.281, P = 0.007, Figure 2a) and myocardial performance index (Tei index, r = 0.555, P = 0.0001, Figure 2b).

Univariate analysis showed that BMI (8% increase per 1-kg/m² increase in BMI; P < 0.0001), hypertension (19% increase when compared with those without; P = 0.007), serum phosphate levels (11% increase per 1-mg/dL in-
increase in serum level; \( P = 0.01 \)), increased log FGF-23 concentrations (34% increase per 1-SD increase in log FGF-23; \( P = 0.001 \)), and diabetes mellitus (10% increase when compared with those without; \( P = 0.03 \)) were significantly associated with L VMI. In the multivariable model, BMI (5.2% increase per 1-kg/m\(^2\) increase in BMI; \( P = 0.001 \)) and log FGF-23 (30% increase per 1-SD increase in log FGF-23 concentration, \( P = 0.002 \)) were the only parameters that remained significantly associated with L VMI. The results did not differ significantly when further adjusted for vitamin D and phosphate binder use (data not shown).

In univariate analysis, presence of coronary artery disease (17% increase when compared with those without; \( P = 0.003 \)), serum phosphate levels (6% increase per 1-mg/dL increase in serum level; \( P = 0.01 \)) and log FGF-23 (38% increase per 1-SD increase in log FGF-23; \( P = 0.001 \)) concentrations were significantly associated with myocardial performance index. Log FGF-23 concentrations were significantly associated with increased myocardial performance index, independently of serum phosphate and presence of coronary artery disease (Table 3). The results were statistically significant in crude and adjusted models (Table 3). Similar results were obtained in multi-category models (Table 3).

**Discussion**

In the present study, plasma FGF-23 level was shown to be associated with increased L VMI and increased MPI, independently of established known risk factors. The significant and positive association of plasma level with L VMI and MPI raises the possibility of a specific pathophysiologic effect of FGF-23 on left ventricular mass and function, distinct from its effects on serum calcium, phosphorus and intact parathormone.

FGF-23 has emerged as a novel important negative regulator of circulating phosphate and 1,25(OH)\(_2\)D3 levels [29]. FGF-23 levels are progressively elevated in patients with chronic kidney disease and when the patients reach end-stage renal disease. FGF-23 levels are often 100–1000 times higher than the normal range [9]. Despite the fact that elevated FGF-23 levels in progressive chronic kidney disease seem to be appropriate to compensate hyperphosphataemia, chronically elevated FGF-23 might have actions on organs other than the kidney and the parathyroid gland.

Recently, increased FGF-23 concentrations have been reported to be independently associated with mortality among patients who are beginning HD treatment [9] and also among patients treated with long HD sessions [30]. The results of the present study revealed that markedly elevated FGF-23 levels were associated with L VMI and MPI. LVH is an important cardiovascular risk factor for mortality in patients with CKD [31,32], and these findings may add evidence to explain the link between elevated FGF-23 levels and mortality in ESRD population. In agreement with the current study, similar results were obtained in pre-dialysis chronic kidney disease patients [10] as well as in a Taiwanese HD study [11]. Importantly, FGF-23 exhibited the strongest association with concentric left ventricular hypertrophy, the most malignant form of left ventricular hypertrophy [10]. Moreover, the results of current study stated that FGF-23 also showed significant association with the Tei index, the myocardial performance index.

The Tei index has been introduced by Chuwa Tei as an index of myocardial performance, considering systolic and diastolic function in combination [33]. Numerous studies have shown its clinical utility as a sensitive method for evaluation of left ventricular function in several cardiac conditions [21,27,34,35], and the Tei index correlates closely with invasive measurements of left ventricular systolic and diastolic function [36]. In the present work, haemodialysis patients with MPI >0.47 had higher FGF-23 levels than patients with lower MPI levels, suggesting a decrease in myocardial performance with higher FGF-23 levels. The results should be cautiously interpreted due to the preload dependency of the Tei index in renal and non-renal patients [37–39]. Recent reports demonstrated that haemodialysis treatment led to an increase in the Tei index [37,40]. To the best of our knowledge, this is the first study demonstrating such a novel, functional and negative asso-
hyperphosphataemia is associated with reduction in L VMI [49,50]. Moreover, Ayus et al. has recently published their study suggesting that correction of hyperphosphataemia to be associated with increased L VMI and hypertrophy [49]. However, as Klotho is either expressed in the cardiac myocytes nor in coronary vasculature, it seems unlikely that FGF-23 affects cardiovascular tissues in an endocrine fashion [29].

Secondly, supraphysiological concentrations of FGF-23, observed in many dialysis patients, may induce unspecific, Klotho-independent, FGF receptor signalling [29]. FGF receptors, FGFR1 and FGFR4, are markedly expressed in cardiac myocytes, tunica media of coronary arteries and veins [41]. Activation of these FGF receptors with FGFs may yield to myocardial hypertrophy and fibrosis. It has been shown that FGF-2 may increase both fibroblast and myofibroblast proliferation and lead to increased scar formation or a stiffer myocardium in the presence of cardiac injury in vivo [42–44]. Moreover, addition of FGF-2 to cultured neonatal cardiac myocytes has resulted in fetal contractile protein gene expression, characteristic of pressure overload-induced cardiac hypertrophy in vivo [45]. Furthermore, addition of FGF-2 and human pericardial fluid (rich in FGF-2 levels) was shown to induce adult cardiomyocyte in vitro [46]. Finally, mice deficient in FGF-2 developed significantly less ventricular hypertrophy than wild-type mice in a model of pressure-overload hypertrophy induced by aortic coarctation [47].

Based on the above-mentioned data, we might speculate that chronically and remarkably elevated FGF-23 levels in dialysis patients may induce hypertrophic and fibrotic response in the myocardium of uraemic patients by binding to FGF receptors. However, this hypothesis remains to be proven and, unfortunately, does not work in the kidney, as Klotho-null mice were not able to correct elevated serum phosphate and 1,25(OH)2D3 levels despite markedly elevated levels of FGF-23 [48]. Moreover, patients with X-linked hypophosphataemic rickets and tumour-induced osteomalacia who have high circulating FGF-23 but not chronic renal disease do not experience an increased cardiovascular risk [29]. On the other hand, in elderly patients, serum FGF-23 was found to be positively associated with LVMI and increased risk of having left ventricular hypertrophy [49], and most importantly, the associations were remarkably much stronger when restricted to subjects with decreased eGFR [49]. Evidence from pre-dialysis CKD patients [10] and dialysis patients [11] in addition to the present work were also in agreement.

Serum phosphate levels were associated with LVMI and MPI, but were independently associated only with MPI in multivariate analysis. Previous studies have shown hyperphosphataemia to be associated with increased LVMI and LVH in uraemic patients [50,51]. Moreover, Ayus et al. has recently published their study suggesting that correction of hyperphosphataemia is associated with reduction in LVMI [52]. Based on the current work, it appears that log FGF-23 might be superior to serum phosphate levels to suggest a link between left ventricular geometry, function and phosphate metabolism in haemodialysis patients. However, according to our findings, serum phosphate levels influence MPI independently, suggesting that poor mineral metabolism might affect left ventricular function. In agreement with this, Hayashi et al. demonstrated that elevated serum phosphorus and calcium–phosphorus product are associated with decreased isovolumetric contraction velocity and peak systolic velocities [53].

Despite the negative association between 1,25(OH)2D3 and FGF-23 in patients with chronic kidney disease, adjustments for 1,25(OH)2D and phosphorus binders did not affect the level of the association between FGF-23 and LVMI. This may originate not only from the cross-sectional design of the study but also from a possible independent relationship between FGF-23 and LVMI, as suggested by the present work. However, this needs to be confirmed by further studies.

FGF-23 might be an important adaptive factor preventing early hyperphosphataemia in progressive CKD [54]. Before initiation of renal replacement therapy, serum FGF-23 level may be a valuable biomarker of phosphate load and phosphate exposure that may be analogous to the predictive value of HbA1c in the evaluation of diabetes management [54]. Given the findings regarding FGF-23 to be a strong and independent predictor of mortality, FGF-23 may be a biomarker of the cardiovascular damage potential of phosphate loads, partly independent of the magnitude of serum phosphate levels [54]. Yet, recent evidence and the results of the present work still remain insufficient proof for definitively establishing a causal link between serum FGF-23 level and cardiovascular disease. This kind of proof might only derive from interventional studies in which serum FGF-23 is modified by an appropriate intervention [55].

There are several limitations of this cross-sectional study. Due to the design of the study, we investigated echocardiographic parameters of left ventricular function and geometry in which changes generally occur by time. Then, we tried to find out associations of these with single point in time measurements of plasma FGF-23 levels. Uncertain possible variations in plasma FGF-23 levels may take place. Moreover, the study was performed in one centre in Turkey, revealing limitations in number and race of patients. Furthermore, no causal relationship could be observed; only association data were presented. An important limitation of this study is that serum levels of 25(OH)D3 and 1,25(OH)2D3 were not measured. The inverse relationship between 1,25(OH)2D3 and FGF-23 is well known [6], and low vitamin D status (tissue or circulating levels, therefore high FGF-23 state) is associated with left ventricular hypertrophy and cardiovascular disorders [56,57]. The prescription and supplementation of vitamin D do not indicate the real vitamin D status. The associations between FGF-23 and cardiac parameters would be more significant when adjusted to circulating levels of vitamin(s) D, not to prescription.

Despite these limitations, we were able to detect independent associations between log FGF-23 and LVMI and MPI. However, due to the cross-sectional design, the re-
sults should be interpreted with caution, and causal relationship could not be suggested. Further prospective studies are needed to clarify whether increased serum FGF-23 level is a marker or a potential mechanism for left ventricular involvement in patients with end-stage renal disease.

Conflict of interest statement. None declared.

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Use of handgrip strength in the assessment of the muscle function of chronic kidney disease patients on dialysis: a systematic review

Viviane O. Leal¹, Denise Mafra¹,², Denis Fouque³ and Luiz A. Anjos¹,⁴

¹Medical Science Post Graduate Program, Fluminense Federal University (UFF), Niterói, Brazil, ²Clinical Nutrition Department, Nutrition Faculty, Fluminense Federal University (UFF), Niterói, Brazil, ³Department of Nephrology, Hôpital E. Herriot, Univ. Lyon, Lyon, France and ⁴Social Nutrition Department, Nutrition Faculty, Fluminense Federal University (UFF), Niterói, Brazil

Correspondence and offprint requests to: Viviane de Oliveira Leal; E-mail: vivianoleal@yahoo.com.br

Abstract

Background. Even though handgrip strength (HGS) is considered a simple and reliable method to evaluate muscle function and, indirectly, the nutritional status in clinical settings, there is still no consensus concerning its use in patients with chronic kidney disease (CKD) undergoing dialysis. This study presents a systematic review of the literature on the use of HGS as a parameter for nutritional assessment and a prognostic marker in patients on dialysis.

Methods. The MEDLINE database (1966 to October 2009) was consulted for this systematic review by using the search terms hand strength or muscle strength dynamometer and dialysis. Eighteen articles were identified and included in the analysis.

Results. Similar to the general population, HGS values were associated with age and gender. The analysed studies showed correlation between muscle function estimated by HGS and variables used in the assessment of muscle mass and nutritional status, as well as the prediction of clinical complications.

Conclusions. The analysis indicates that HGS is a useful tool for continuous and systematic assessment of muscle mass related to nutritional status in patients on dialysis.