Relationship between fibroblast growth factor and arrhythmogenesis in normotensive patients with polycystic kidney disease

Kemal Karaagac¹, Abdulmecit Yildiz², Osman Can Yontar¹, Erhan Tenekecioglu¹, Fahriye Vatansever¹, Mehmet Demir¹

¹Department of Cardiology, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey  
²Department of Nephrology, Uludag University Medical School, Bursa, Turkey

ABSTRACT

Objectives. Autosomal dominant polycystic kidney disease (ADPKD) is the most common life-threatening genetic disease. Recent prospective studies showed a powerful and dose dependent association between increasing FGF-23 levels and greater risk of mortality among chronic kidney disease patients. In this study, our aim is to evaluate electrocardiogram derived arrhythmogenesis markers such as Tp-e, Tp-e/QT and Tp-e/QTc ratio ADPKD. Methods. Data of 31 patients with ADPKD and age-sex matched 26 healthy were gained for study. Electrocardiogram and echocardiogram measurements, various serum markers were compared between groups. Results. FGF-23 was significantly higher, and eGFR was significantly lower in the ADPKD patients. Myocardial thickness was also higher in ADPKD group. Corrected QT dispersion, Tp-e, Tp-e/QT and Tp-e/QTc were also compared between groups. All indicators were significantly worse in ADPKD group. In the correlation analyzes, FGF-23 was significantly correlated with Tp-e, Tp-e/QT and Tp-e/QTc (r=0.388, p=0.003; r=0.472, p<0.0001; r=0.442, p=0.001, respectively). Conclusions. In this occasion, we suggest that FGF-23, which probably accumulates ventricular electrical remodeling, may be helpful for risk stratification in patients with ADPKD when used with other indicators. Myocardial cell de-arrangement and electrical remodelling due to fibrosis are suggested mechanisms for this effect.

Keywords: Polycystic kidney disease; fibroblast growth factor; arrhythmogenesis; Tp-e interval; Tp-e/QT ratio

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common life-threatening genetic disease [1]. Cardiovascular disease is the leading cause of morbidity and mortality in patients with ADPKD, with over 80% of deaths attributable to coronary artery disease [2,3]. Left ventricular hypertrophy (LVH) is common in these patients, even in the absence of hypertension [4,5]. LVH is also
associated with poor renal outcomes in these patients [6]. Although some studies indicate that increased stimulation of the renin-angiotensin system (RAS) may be responsible from increased LVH in ADPKD, other studies did not support this suggestion [7]. Fibroblast growth factor 23 (FGF-23) is secreted by osteoblasts and osteocytes and increases in response to increase in serum phosphorus and calcitriol levels in patients with chronic renal failure (CRF). Markedly elevated circulating FGF-23 levels are also found in patients with ADPKD when compared with other causes of chronic kidney disease independent of renal function and hormones that regulate phosphate metabolism [8]. It was clearly shown in different stages of CRF that there was a correlation between FGF-23 levels and LVH [9].

For a long time, noninvasive indices of sudden cardiac death derived from surface electrocardiogram (ECG) have been utilized in patients who are at risk of sudden death. These indices mainly depend on the QT interval [10,11]. Prolongation of QT interval, dispersion of QT interval; which is calculated by extracting minimum measured QT interval from maximum measured QT interval, were widely utilized in many studies and were shown to be related with increased sudden death risk in HD patients [12-14].

Recent studies indicate that prolongation of the T wave peak to T wave and interval (Tp-e) on the 12-lead ECG is a marker of ventricular arrhythmogenesis [15-17]. Prolongation of this interval represents a period of potential vulnerability to re-entrant ventricular arrhythmias. Prolonged Tp-e has been associated with increased risk of mortality in the congenital and acquired long QT syndromes, hypertrophic cardiomyopathy and also in patients undergoing primary PCI for myocardial infarction [18-20].

In this study, our aim is to evaluate electrocardiogram derived arrhythmogenesis markers such as Tp-e, Tp-e/QT and Tp-e/QTc ratio, QT interval and QT dispersion in normotensive polycystic kidney disease patients and put forward if there is a relationship between ventricular depolarization heterogeneity and serum FGF-23 levels, which plays role in left ventricular hypertrophy.

Methods

Patients

Data of thirty one patients (male and female) with diagnosis of ADPKD were collected. Data of age-sex matched 26 healthy subjects with similar demographics (13 male and 13 female) were gained for control group. The study was approved by the Institutional Ethics Committee, and written consent was obtained from all patients.

The diagnosis of ADPKD was reached by the ultrasonographic criteria described by Ravine et al [21]. All of the patients had family history of ADPKD. Estimated glomerular filtration rate (eGFR) was determined using the 4-variable Modification of Diet in Renal Disease (MDRD) equation. The most commonly used formula is the "4-variable MDRD," which estimates GFR using four variables: serum creatinine, age, race, and gender [22]. All patients had an eGFR >60 mL/min/1.73 m².

Patients with diabetes mellitus, renal failure (eGFR <60 mL/min/1.73 m²), hepatic failure, major cardiac diseases (heart failure, coronary artery disease, arrhythmia, cardiac valvular disease), were excluded from the study. During the baseline examination, fasted weight and height were measured by one examiner using the ambulatory standard measurement devices as the patient was standing.

Body mass index (BMI) was calculated using the formula "weight (kg)/height (m²)". Clinical blood pressure measurements were performed using a mercury sphygmomanometer following 10 minutes rest in the sitting position. Three consecutive readings were obtained using 2-minutes interval settings and the mean of these readings were considered as clinical BP. Patients with systolic BP of >140 mmHg and/or diastolic BP of >80 mmHg or who were already receiving treatment for hypertension were considered to be hypertensive and excluded from the study.

Blood analyses

Fasting glucose, creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride levels were measured by routine techniques. The level of PTH was measured by chemiluminescence method.
on an IMMULITE 2000® analyzer (Diagnostic Products Corporation, Los Angeles, USA). Plasma FGF-23 concentrations were measured with the human FGF-23(C-Term) ELISA kit (Immutopics Inc., San Clemente, CA, USA) according to the manufacturer’s instructions.

Measurement of Tp-e, QT and QRS Intervals from the 12-Lead ECG

All ECGs were scanned. The Tp-e interval was defined as the interval from the peak of T wave to the end of T wave. Measurements of Tp-e interval were performed from precordial leads as it was described [23]. T wave peak to end interval, QT and RR intervals were measured by an engineer with a computer program. By using a ruler, vernier caliper or any other manual measuring tool; getting measurements off from ECG papers could be either inaccurate or slow. Therefore ECG papers were scanned and this made gathering measurements possible in digital environment. These measurements are done by a program which is generated with MATLAB (MathWorks, Natick, Massachusetts, U.S.A.) codes that written by an engineer. These codes are based on image manipulation principles. Image manipulation method could be divided into three subdivisions image processing, image analysis and image understanding. Image analysis is the technique that should be used to gather measurement data from ECG. Running the written code imports the image file first and then, by choice, allows user to pick points that need to be picked to get measurements or generates a matrix that consists of a dedicated numeric value of each pixel's color. Creating a matrix gives user the flexibility of using functions which predefined by program. Inspite of this, hand picking is easier and has a simple interface especially for beginner level users. Algorithms are developed and used to get excellent measurements in order to tolerate differences such are tilting during scanning process, different scanning resolutions and using different ECG.

The QT interval was defined as extending from the beginning of the QRS complex to where T waves descend onto the isoelectric baseline. When a U wave interrupted the T wave before returning to baseline, the QT interval was measured to the nadir of the curve between the T and U waves. The QTc interval was calculated using the Bazett formula: QTc (ms)=QT measured/ RR (sec). All measurements (Tp-e and other surface ECG related ones) were mean value of three calculations. All measurements were double checked by a blinded engineer.

Echocardiography

Whole echocardiographic approach, all measurements and definitions were done according to related clinical guideline [24]. Each echocardiogram was evaluated by 2 experienced cardiologists. Echocardiograms that were difficult to evaluate due to technical defects, and the cases in which the cardiologists could not agree, were excluded from the study.

Statistical analysis

Statistical analysis was performed using SPSS 13.0 for Windows. Normal distribution of the data was checked using the Kolmogorov-Smirnov test. Continuous variables are presented as means ± standard deviations whereas categorical variables are presented as percentages. The differences between the groups for categorical varieties were compared by the Chi-square test. According to the distribution, the differences between the groups for numeric parameters were compared by Student’s t-test or the Mann-Whitney U test. The correlations among the study variables were examined by Pearson or Spearman correlation tests according to normality of distribution. The significance level was assumed as \( p < 0.05 \).

Results

The baseline clinical and laboratory characteristics of the patients and controls are summarized in Table 1. There was no statistically significant difference between the two groups with respect to age, gender, systolic blood pressure, diastolic blood pressure, weight, height and body mass index. The biochemical characteristics of the patients did not differ in creatinine, serum phosphate, calcium, uric acid, 25- OH vitamin D, PTH and lipid levels except
**Table 1.** Comparison of biochemical and echocardiographic variables of ADPKD patients and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>ADPKD group (n=31)</th>
<th>Control group (n=20)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.30±11.10</td>
<td>35.54±6.40</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>10/21</td>
<td>13/13</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>126±13</td>
<td>123±11.40</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>73±12.10</td>
<td>70±8</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.20±4.40</td>
<td>26.50±4.10</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (%) (n)</td>
<td>40 (9)</td>
<td>50 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>85.60±9.90</td>
<td>84.30±6.80</td>
<td>NS</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>28.50±8.90</td>
<td>26.10±7.60</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.70±0.16</td>
<td>0.60±0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.53±0.40</td>
<td>9.45±0.20</td>
<td>NS</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>3.44±0.47</td>
<td>3.25±0.42</td>
<td>NS</td>
</tr>
<tr>
<td>eGFR (mL/dk)</td>
<td>104±16.70</td>
<td>116±12.80</td>
<td>0.03</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>58.30±33</td>
<td>76±42.50</td>
<td>NS</td>
</tr>
<tr>
<td>FGF-23 (RU/ml)</td>
<td>536.70±506</td>
<td>42.70±23.10</td>
<td>0.0001</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>191±33</td>
<td>188±28.60</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>52±12.80</td>
<td>48±13.20</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>115±26.70</td>
<td>118±23</td>
<td>NS</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>125±90.90</td>
<td>117±96.20</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>47.80±3.20</td>
<td>45.60±5.4</td>
<td>NS</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>28.30±5.60</td>
<td>26.5±6.20</td>
<td>NS</td>
</tr>
<tr>
<td>IVSD (mm)</td>
<td>1.06±0.10</td>
<td>0.95±0.13</td>
<td>0.01</td>
</tr>
<tr>
<td>LVPW (mm)</td>
<td>1.02±0.09</td>
<td>0.90±0.001</td>
<td>0.01</td>
</tr>
</tbody>
</table>

ADPKD=autosomal dominant polycystic kidney disease, BMI=body mass index, PTH=parathyroid hormone, TG=triglycerides, TC=total cholesterol, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, eGFR=estimated glomerular filtration rate, FGF-23=fibroblast growth factor 23, LVEDD=left ventricular end diastolic diameter, LVESD=left ventricular end systolic diameter, IVSD=interventricular septum diameter, LVPD=left ventricular posterior wall diameter, EF=ejection fraction. Data are presented as means±SD, NS=nonsignificant

**Table 2.** Comparison of electrocardiographical features of ADPKD patients and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>ADPKD group (n=31)</th>
<th>Control group (n=20)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc dispersion (ms)</td>
<td>36.60±12.70</td>
<td>19.50±8.30</td>
<td>0.001</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>418±24.60</td>
<td>427±44</td>
<td>NS</td>
</tr>
<tr>
<td>Tp-e interval (ms)</td>
<td>87.10±12.50</td>
<td>74±8.50</td>
<td>0.001</td>
</tr>
<tr>
<td>Tp-e/QT ratio</td>
<td>0.24±0.03</td>
<td>0.20±0.02</td>
<td>0.001</td>
</tr>
<tr>
<td>Tp-e/QTc ratio</td>
<td>0.20±0.02</td>
<td>0.17±0.02</td>
<td>0.001</td>
</tr>
</tbody>
</table>

ADPKD=autosomal dominant polycystic kidney disease, QTc=corrected QT, QTd=QT dispersion, Tp-e=T wave peak to T wave end interval. Data are presented as means±SD. NS=non-significant
for FGF-23 were significantly higher and eGFR was significantly lower in the ADPKD patients. Electrocardiogram derived risk indicators corrected QT dispersion (cQTd), Tp-e, Tp-e/QT and Tp-e/QTc were also compared between groups. All indicators were significantly worse in ADPKD group (Table 2).

In the correlation analyzes; FGF23 was significantly correlated with Tp-e (Figure 1) and Tp-e/QTc (Figure 2) \( r=0.388 \ p=0.003; \ r=0.442 \ p=0.001 \) respectively).  

Discussion

Cardiovascular disease is the leading cause of premature mortality in patients with ADPKD [25]. A wide range of factors that end up with structural myocardial disease are responsible for this adverse outcome. A variety of subclinical organ damage markers such as LVH, increased carotid intima-media thickness, endothelial dysfunction, microalbuminuria, decreased coronary flow velocity reserve and low-grade systemic inflammation, and chronic oxidative stress have been reported in several studies of patients with ADPKD with well-preserved renal function [26, 27]. Functional data supporting a role of FGF-23 in vascular biology is derived from Klotho null mice, which carry no functional FGF-23 activity due to lack of co-receptors [28]. Recent prospective studies showed a powerful and dose dependent association between increasing FGF-23 levels and greater risk of mortality among CKD patient [29, 30]. The reason for increased cardiovascular mortality in CKD may be associated with LVH. Recent experimental studies have clearly demonstrated that FGF-23 can directly induce LVH [31]. The action of FGF-23 in the kidney and the parathyroid gland is different from that in the heart. In renal and parathyroid tissue, FGF-23 acts via the classical pathway, by stimulating FGF receptor and Klotho, the obligatory co-receptor, to inhibit both renal phosphorous reabsorption and 1,25-OH vitamin D synthesis through ras/mitogen-activated protein (MAP)-kinase pathway. In contrast, at the level of cardiomyocytes, FGF-23 acts through the phospholipase C gamma/calcineurin pathway, independent of Klotho. A recent trial in ADPKD patients at different stages of CKD showed markedly elevated levels of FGF-23 compared with other CKD etiologies. Because of the absence of Klotho in cardiomyocytes, increased FGF-23 levels may explain increased rates of LVH in normotensive ADPKD patients with normal renal functions. In our study, ADPKD subjects had higher levels of FGF-23 but normal calcium and phosphate levels when compared to controls.

Marked fibrosis or de-arrangement of uniformity of ventricular myocardium may lead to heterogeneous scattering of electrical wavelet through cardiomyocytes. In fact it is the most frequent cause of ventricular arrhythmogenic substrate development which leads to sudden cardiac death.
death in heart failure [32]. There is a high variety of comorbidities in renal disease patient population. Burden of multiple factors that increase myocardial fibrosis preceding repolarization heterogeneity, electrolyte imbalance that causes myocardium cell depolarization defects, neuro-humoral instability with increased automaticity end up with a substrate for sudden cardiac death [33, 34]. Prolongation of QT interval and increased QT dispersion in renal disease are subjects of interest for a long time. Previously published articles mainly point out similar findings these indices of sudden death on the surface ECG are significantly higher in patients with CKD [12, 35]. Because of increased risk of cardiac mortality in this large patient group, risk stratification becomes more and more important to save lives. Newly introduced surface ECG indices may contribute in risk prediction. T wave peak to end interval is a measure of transmural dispersion of repolarization in the left ventricle and accepted as a surrogate for increased ventricular arrhythmogenesis risk. Tp-e/QT and Tp-e/QTc are relatively new markers which also indicate repolarization defects. Published studies clearly suggest the applicability of Tp-e/QT ratio as a potentially important index of arrhythmogenesis, both under the conditions of short, normal and long QT interval, as well as in congenital and acquired channelopathies. In various high-risk populations, such as, patients with long QT syndrome [36], inducible ventricular tachycardia [37, 18], repaired tetralogy of Fallot [38] or Brugada syndrome [39]. T wave peak to end interval had been found to be more prolonged than control patients. In our study, we exhibited that there was a strong positive correlation between serum FGF-23 levels and ECG derived arrhythmia indicators, Tp-e, Tp-e/QT and Tp-e/QTcd but not QT and QTd. Prolonged QT and increased QTd are established indicators of SCD, however these relatively newer indicators are more specific and sensitive [25] and do not get affected from heart rate [40]. Our study corresponds with previous studies that show significant relationship between FGF-23 and cardiac mortality, yet, this is the first study which evaluates FGF-23 by using surface ECG parameters including Tp-e and Tp-e/QT. Also, this is the first study that introduces Tp-e and derived indicators in polycystic renal disease.

The limitations of our study are retrospective method, absence of a hypertensive control group and the small sample size. In this occasion, we suggest that FGF-23, which probably accumulates ventricular electrical remodeling, may be helpful for risk stratification in patients with ADPKD when used with other indicators.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

References


