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Original article

Hypocalcemia is related to left ventricular diastolic dysfunction in patients with chronic kidney disease

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ABSTRACT

Background: Left ventricular (LV) diastolic dysfunction in patients with chronic kidney disease (CKD) is of a complex nature and is the predominant cause of congestive heart failure in this group of patients. This work aimed to evaluate the potential effect of disturbances in calcium-phosphorus (Ca-P) metabolism in patients with CKD on LV diastolic function as assessed by echocardiography.
Materials and methods: The study group consisted of 81 ambulatory patients with CKD, stages 2–5, with preserved LV systolic function–LV ejection fraction >50% and with sinus rhythm. Standard echocardiography was performed in all patients with tissue Doppler echocardiography for the evaluation of the systolic velocity and both diastolic velocities of LV (EmLV and AmLV). The following laboratory parameters were measured: serum creatinine concentration, estimated glomerular filtration rate, and the levels of urea, P, Ca, parathormone, platelet count, hemoglobin level, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. Patients were divided into two groups according to the results of EmLV: group with LV diastolic dysfunction (EmLV < 8 cm/s) DF (+) and group with normal LV diastolic function DF (−), when EmLV was ≥8 cm/s.
Results: Patients in DF (+) group, as compared to DF (−) patients, manifested a lower serum Ca level and an elevated NT-proBNP level [9.03 ± 0.76 mg/dL vs 9.44 ± 0.78 mg/dL, $p = 0.02$, and 257.9 (32.6–12,633) pg/ml vs 149 (11.7–966) pg/ml, $p = 0.035$, respectively]. The area under the receiver operating characteristics (ROC) curve of Ca for diastolic dysfunction was 0.627, 95% CI (0.511–0.734), $p = 0.04$, whereas ROC derived Ca value of ≤9.82 mg/dL was characterized by a sensitivity of 91.8% and specificity of 38.1% for diagnosing LV diastolic dysfunction. The only independent variable predicting LV diastolic dysfunction as measured by a multivariate logistic regression analysis was Ca level ≤ 9.82 mg/dL with odds ratio = 8.81 (95% CI 1.49–51.82), $p = 0.014$.
Conclusions: Hypocalcemia is an independent predictive factor for LV diastolic dysfunction in patients with CKD.

Introduction

Left ventricular (LV) diastolic dysfunction in patients with chronic kidney disease (CKD) is of a complex nature and is the predominant cause of congestive heart failure in this group of patients. The most frequent cause, substantially described in literature, is LV hypertrophy, and is mainly associated with arterial hypertension and anemia. Additionally, the development of LV diastolic dysfunction can result from disturbances in calcium-phosphorus (Ca-P) metabolism. In patients with CKD, significant relationships have been already reported between altered Ca-P metabolism and blood cell morphology and myocardial function and arterial bed function, including coronary vessels. In CKD patients, depending on the stage of the disease, the biochemical disturbances are dominated by a decreased level of serum Ca, especially its ionized fraction (Ca^{2+}) in plasma, lower level of the biologically active form of vitamin D, i.e. calcitriol, elevated serum P, and parathormone (PTH) levels. Clinical consequences of these abnormalities include renal osteodystrophy and extraskeletal calcifications, mainly in the cardiovascular system. The latter significantly affect the progressively developing dysfunction of the cardiovascular system in CKD patients, most likely associated with damage to the small vessels, including coronary vessels, as a result of Ca-P deposits and accelerated atherosclerosis [1,2]. It has been proven that

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hyperphosphatemia (above 5.0 mg/dL), high values of the Ca-P product (Ca x P – above 55 mg^2/dL^2), as well as high levels of PTH are correlated with higher prevalence of CKD and mortality rates in this population of patients [2,3]. Hyperphosphatemia is currently considered as the key biochemical disturbance in uremia, leading to progressive vascular calcifications. The term "calcification" is used in the literature, whereas in fact the essence of this process involves the synthesis of calcium phosphates (hydroxyapatites), and consequently the value of Ca x P index is particularly important here.

The direct effect of hypocalcemia on the cardiovascular system in the complicated metabolic circumstances occurring in CKD remains unresearched. Neither data in the literature, nor wide-ranging research has been found proving a direct correlation between a lower serum Ca level in CKD patients and cardiac function.

Reports, published recently, concerning the relation between diet Ca intake, its supplementation, and cardiovascular risk and mortality are not unanimous. Some studies indicate that Ca supplementation is associated with a higher cardiovascular risk, whereas others contradict this thesis [4–6]. In our study, we hypothesized that disturbances in Ca-P metabolism, and hypocalcemia in particular, can contribute to LV diastolic dysfunction.

Materials and methods

The study group consisted of 81 ambulatory patients with CKD, stages 2–5, with preserved LV systolic function defined by LV ejection fraction (LVEF) > 50% and lack of regional wall motion abnormalities, and with sinus rhythm. Exclusion criteria comprised: non-sinus rhythm, LV systolic dysfunction, previous myocardial infarction, cardiomyopathy, severe valvular heart disease, and pericardial fluid above 10 mm at diastole. Diagnostic criteria for CKD were consistent with the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) standards [7]. Body mass index (BMI) was also calculated for each patient.

Echocardiography

Standard echocardiography was performed for all patients using a GE 6S (GE, Fairfield, CT, USA) device with 2.5–3.5 MHz transducer. In order to increase the credibility of the obtained echocardiographic results, the physician who performed the examination did not know the biochemical parameters of the patients. The examinations were conducted when the patients had been stabilized. Particular attention was placed on retaining optimal hydration.

Using the M-MODE in the parasternal long-axis view the following parameters were assessed: LV end-diastolic dimension (LVEDD), right ventricular end-diastolic dimension (RVEDD), left atrial diastolic dimension (LAD), interventricular septal diastolic diameter (IVSd), and LV posterior wall dimension at diastole (LVPWd). Additionally, LV fractional shortening (LVFS) was assessed. In the four chamber view, LV ejection fraction (LVEF) was calculated with the modified Simpson's rule [8]. LV mass (LVM) was calculated with the formula recommended by the American Society of Echocardiography modified by Devereux [9]. The obtained results of LVM were indexed by the body surface area of the patient and presented as LVM index (LVMI).

In order to assess transmitral flow, pulsed wave Doppler echocardiography was performed in a four chamber view. The Doppler gate was placed at the level of the mitral annulus and a two-phase flow profile was obtained, including: early (E) and late (A) transmitral velocities, deceleration time (DT) of the E wave; E/A ratio was also calculated [8].

Tissue Doppler echocardiography

In pulsed wave tissue Doppler echocardiography, diastolic and systolic velocities were measured by placing the Doppler gate on the lateral mitral annulus at the posterior leaflet of the mitral valve. The following parameters were measured: peak mitral annular systolic velocity (SmLV), peak early diastolic velocity (EmLV), and peak late diastolic velocity (AmLV) of the lateral part of the examined annulus [10]. All parameters were calculated as the mean of measurements taken in 3 consecutive cardiac cycles. LV diastolic dysfunction was defined as EmLV < 8 cm/s [11].

Biochemical tests

On the day of the echocardiographic examination, the following laboratory parameters were recorded for all patients: serum creatinine concentration, estimated glomerular filtration rate (eGFR) evaluated by the modified MDRD formula, as well as the serum levels of urea, P, Ca, PTH, platelets (PLT), and hemoglobin (Hb). Additionally, N-terminal proB-type natriuretic peptide (NT-proBNP) levels were calculated by immunoassay with the Stratus® CS Acute Care™ (Siemens, Munich, Germany).

Patients were divided into two groups depending on the results of EmLV: DF (+) group with LV diastolic dysfunction (EmLV < 8 cm/s) and DF (−) group with normal LV diastolic function, when EmLV ≥ 8 cm/s [11].

Statistical analysis

Values of parameters with a normal distribution are presented as a mean ± standard deviation, whereas values with non-normal distributions are expressed as median and range. In order to compare both groups, Student's *t*-test and the Mann–Whitney test were used, depending on the parameter distribution. χ^2 test was used to compare qualitative variables in contingency tables.

The correlation between the statistically significant parameters for both groups and the parameter indicating LV diastolic dysfunction (EmLV < 8 cm/s) is also presented.

Receiver operating characteristic (ROC) analysis curves served to determine the optimal cutoff points for identifying patients with LV diastolic dysfunction.

In order to determine the diagnostic value of the evaluated parameters, univariate and multivariate logistic regression was employed. To assess the diagnostic value, odds ratio for particular laboratory and echocardiographic parameters was calculated. In the analysis the parameters were treated either continuously or dichotomously using their values as determined in the ROC analysis.

All patients consented in writing for inclusion in the research. The study protocol was approved by the Bioethics Committee (no. 555/2011).

Results

The study group consisted of 81 ambulatory patients with CKD. CKD etiology in the study group included: hypertensive and ischemic nephropathy in 40 patients, glomerulonephritis in 5 patients, interstitial nephritis in 8 patients, diabetic nephropathy in 3 patients, polycystic kidney disease in 6 patients, autoimmune disease in 1 patient, whereas unknown etiology was present in 18 cases. Fifteen patients had stage 2 CKD (eGFR 89–60 ml/min), 41 patients had stage 3 CKD (eGFR 59–30 ml/min), 18 patients – stage 4 CKD (eGFR 29–15 ml/min), and 7 patients – stage 5 CKD (eGFR < 15 ml/min).

The DF (+) group – with LV diastolic dysfunction (EmLV < 8 cm/s) consisted of 39 patients; 42 patients were included in the group