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Mineral metabolism and inflammation: factors related to left ventricular hypertrophy in patients with diabetic nephropathy

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ABSTRACT

Left ventricular hypertrophy (LVH) is an important risk factor for cardiovascular disease in patients with diabetic nephropathy (DN) and is an independent predictor of mortality in patients with chronic kidney disease (CKD). The aim of this study was to evaluate the association of LVH with mineral metabolism and inflammation in a population of patients with DN. In an observational study were included 119 type 2 diabetic patients with CKD stages 3 and 4. The population was divided into two groups, according to the presence of LVH: group 1 (G-1) with LVH (left ventricular mass index (LVMI) > 125 g/m^2 in male patients and LVMI > 110 g/m^2 in female patients) and group 2 (G-2) without LVH (LVMI ≤ 125 g/m^2 in male patients and LVMI ≤ 110 g/m^2 in female patients). The patient characteristics of each group were compared regarding several biological and laboratory parameters. Patients with LVH displayed lower values of estimated glomerular filtration rate (eGFR) (p = 0.0001) and albumin (p = 0.046), and higher levels of phosphorus (p = 0.0001), intact parathyroid hormone (iPTH) (p = 0.0001), insulin resistance (HOMA-IR) (p = 0.0001) and interleukin-6 (IL-6) (p = 0.0001), compared with patients without LVH. In a logistic regression model, phosphorus (odd ratio (OR) = 1.825 (1.075-4.414), p = 0.038), iPTH (OR = 1.991 (1.098-3.000), p = 0.004) and IL-6 (OR = 3.538 (1.863-6.719), p = 0.0001) were independently related to LVH. In a multiple linear regression model, phosphorus (r = 0.602, p = 0.038), iPTH (r = 1.009, p = 0.044) and IL-6 (r = 1.264, p = 0.0001) were positively related to LVMI. Phosphorus, PTH and IL-6 were related to LVH in our diabetic population with CKD stages 3 and 4.

Key-Words: Chronic kidney disease; diabetic nephropathy; interleukin-6; left ventricular hypertrophy; parathormone; phosphorus.

INTRODUCTION

Diabetic nephropathy (DN) is the most common cause of end-stage renal disease (ESRD)[1] and its mortality is mainly due to cardiovascular disease (CVD) [2]. Compared with general population, a large proportion of patients with chronic kidney disease (CKD) die from CVD[3]. Left ventricular hypertrophy (LVH) is an independent risk factor for CVD[4,5].

Previous reports have demonstrated that non-traditional risk factors, such as parathyroid hormone (PTH)

and phosphorus are involved in the pathogenesis of a number of cardiovascular (CV) abnormalities in CKD patients, including LVH[6,7].

Recently, the impact of inflammation on LVH in CKD patients have gained attention in nephrology[8]. The aim of our study was to evaluate the association of LVH with mineral metabolism and inflammation in a population of type 2 diabetic patients with nephropathy.

MATERIALS AND METHODS

Study population

In a cross-sectional study were included 119 type 2 diabetic patients, recruited between December 2007 and May 2013 with diagnosis of CKD in a stable clinical condition attending our outpatient clinic. The classification of diabetes was based on the guidelines from the American Diabetes Association[9]. The CKD stages were defined by the estimated glomerular filtration rate (eGFR) calculated with the modification of diet in renal disease (MDRD) formula at the time of assessment[10]. Exclusion criteria were previous CVD – defined as a history of one or more of the following: non-fatal myocardial infarction, angina pectoris (stable or unstable), stroke or transient ischaemic attacks, peripheral vascular disease or congestive heart failure; uncontrolled hypertension (BP ≥ 140/90mmHg), urine albumin-to-creatinine ratio (UACR) > 500, eGFR ≤ 15mL/min or > 80mL/min, type 1 diabetes, non-diabetic renal disease, neoplastic or infectious diseases. The study was approved by the local Ethnics Committee, and written informed consent was obtained from each participant. The study was conducted according to the principles of the Declaration of Helsinki.

Follow-up

Follow-up of patients was conducted 2-3 times a year during in-person visits on nephrology consultation. Patients with more severe conditions returned approximately every 3 months, while the other patients returned approximately every 6 months. No patient was "lost to follow-up".

Blood measurements

Several laboratory parameters were determined using a standard methodology in routine blood samples drawn after an overnight fast. The serum levels of calcium and phosphorus were measured using the ARCHITECT c Systems and the AEROSET System (Abbott Diagnostics Division, Abbott Laboratories Abbott Park, IL, USA). Interleukin-6 (IL-6) levels were measured using a sandwich enzyme-linked immunoassay (ELISA) kit (eBioscience, San Diego, California, USA). Haemoglobin (Hb) and intact PTH (iPTH) levels were measured using spectrophotometry technique and electrochemiluminescent immunoassay (ECLIA), respectively. The iPTH concentrations were measured on an Immulite 2000 Intact PTH assay (Cat. # L2KPP2, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA).

The degree of insulin resistance (IR) was estimated using homeostatic model assessment (HOMA)-IR described by Matthews *et al.* [11].

Serum creatinine was measured by enzymatic method, using the ARCHITECT device (Abbott Diagnostics Division, Abbott Laboratories Abbott Park, IL, USA). Glomerular filtration rate was estimated using a formula derived by MDRD study group[10].

Echocardiography

Transthoracic echocardiography was performed using General Electrical Medical Systems echograph, model Vivid 7 with a probe (GE Healthcare, Wisconsin, USA). Left ventricular mass index (LVMI) was calculated by applying the regression equation from the Penn convention[12].

Definitions

Left ventricular hypertrophy was defined as LVMI > 125 g/m^2 in male patients and LVMI > 110 g/m^2 in female patients[13]. Subjects were classified into two groups accordingly to the presence of LVH: group 1 (G-1) with LVH and group 2 (G-2) without LVH.

Statistical analyses

Analyses were performed by using descriptive statistics, and for comparisons between groups the student's *t*-test and the chi-squared test were used. The factors associated to LVH and their odds ratio (OR) were calculated using multivariate logistic regression. We also used a multiple linear regression model to evaluate the factors that influenced the LVMI. A *p*-value of < 0.05 was considered significant. Statistical analysis was performed with SPSS 17.0 for Windows.

RESULTS

The clinical characteristics of the population (N = 119) are provided in Table I. The mean age was 62.8 ± 12.43 years, 52.7% were male and 47.3% were female patients. Fifty-five patients had LVH.

Table II displays a comparison of patients' characteristics between G-1 (patients with LVH) and G-2 (patients without LVH). Patients with LVH were older, had lower values of eGFR (p = 0.0001) and albumin (p = 0.046), and higher levels of phosphorus (p = 0.0001), iPTH (p = 0.0001), HOMA-IR (p = 0.0001) and IL-6 (p = 0.0001), compared with patients without LVH.

In a logistic regression model, LVH was used as the dependent variable. Gender, age, body mass index (BMI), systolic blood pressure (SBP), eGFR, albumin, Hb, phosphorus, iPTH, UACR, HOMA-IR and IL-6 (Table III) were considered independent variables. In this model, phosphorus (odds ratio (OR) = 1.825 (1.075-4.414), p = 0.038), iPTH (OR = 1.991 (1.098-3.000), p = 0.004) and IL-6 (OR = 3.538 (1.863-6.719), p = 0.0001) were independently related to LVH.

To evaluate possible causes of increased LVMI, a multiple linear regression model adjusted for age, eGFR, phosphorus, iPTH, UACR, HOMA-IR and IL-6 (Table IV)

Table I

Baseline patients' characteristics (n = 119)

Characteristics	Values
Age (years)	62.8 ± 12.4
BMI (kg/m2)	26.6 ± 5.0
Creatinine (mg/dL)	1.8 ± 0.9
eGFR (mL/min/1.73 m2)	44.9 ± 25.2
Hb (g/dL)	12.7 ± 1.8
Calcium (mg/dL)	9.5 ± 0.8
Phosphorus (mg/dL)	4.3 ± 1.2
iPTH (pg/mL)	132.4 ± 110.1
LVMI (g/m2)	108.3 ± 23.6
UACR (µg/mg)	245.2 ± 131.5
HOMA-IR	2.0 ± 1.7
IL-6 (pg/mL)	5.0 ± 3.2

BMI (body mass index); eGFR (estimated glomerular filtration rate); Hb (haemoglobin); iPTH (parathyroid hormone); LVMI (left ventricular mass index); UACR (urine albumin-to-creatinine ratio); HOMA-IR (homeostatic model assessment of insulin resistance); IL-6 (interleukin-6).

Table II

Comparison between G-1 and G-2 according to patients' characteristics

	G-1 n = 55	G-2 n = 64	p-Value
Age (years)	66.7 ± 11.9	59.4 ± 12.0	0.001
Gender (female/male)	26/29	28/36	Ns
BMI (kg/m2)	27.1 ± 5.5	26.2 ± 4.4	Ns
SBP (mmHg)	131.4 ± 18.5	127.7 ± 16.8	Ns
DBP (mmHg)	77.2 ± 11.0	77.6 ± 11.0	Ns
eGFR (mL/min/1.73 m2)	34.0 ± 19.4	54.3 ± 25.9	0.0001
Albumin (mg/dL)	4.1 ± 0.6	4.3 ± 0.4	0.046
Cholesterol (mg/dL)	196.0 ± 41.9	194.7 ± 42.1	Ns
Hb (g/dL)	12.4 ± 1.9	13.0 ± 1.7	Ns
HbA1c (%)	7.4 ± 1.5	7.9 ± 1.8	Ns
Calcium (mg/dL)	9.5 ± 0.7	9.5 ± 0.9	Ns
Phosphorus (mg/dL)	4.8 ± 1.1	3.8 ± 1.02	0.0001
iPTH (pg/mL)	181.2 ± 104.5	90.5 ± 97.3	0.0001
UACR (ug/mg)	266.0 ± 109.4	227.3 ± 146.8	Ns
HOMA-IR	3.3 ± 1.4	0.8 ± 1.0	0.0001
IL-6 (pg/mL)	7.7 ± 2.5	2.8 ± 1.3	0.0001

LVH (left ventricular hypertrophy); G-1 (patients with LVH); G-2 (patients without LVH); BMI (body mass index); SBP (systolic blood pressure); DBP (diastolic blood pressure); eGFR (estimated glomerular filtration rate); Hb (haemoglobin); HbA1c (haemoglobin A1c); iPTH (parathyroid hormone); UACR (urine albumin-to-creatinine ratio); HOMA-IR (insulin resistance); IL-6 (interleukin-6); Ns (non-significant).

Table III

Logistic regression analysis – Factors associated to LVH

Variable	Adjusted OR (95% CI)	p-Value
Gender	0.364 (0.064-2.076)	0.255
Age	0.968 (0.890-1.053)	0.455
BMI	1.185 (0.969-1.448)	0.098
SBP	0.992 (0.944-1.043)	0.757
eGFR	0.975 (0.930-1.021)	0.279
Albumin	0.979 (0.137-7.012)	0.983
Hb	1.273 (0.770-2.106)	0.347
Phosphorus	1.825 (1.075 -4.414)	0.038
iPTH	1.991 (1.098-3.000)	0.044
UACR	0.999 (0.993-1.006)	0.865
HOMA-IR	1.525 (0.746-3.114)	0.247
IL-6	3.538 (1.863-6.719)	0.0001

LVH (left ventricular hypertrophy) BMI (body mass index); SBP (systolic blood pressure); eGFR (estimated glomerular filtration rate); Hb (haemoglobin); iPTH (intact parathyroid hormone); UACR (urine albumin-to-creatinine ratio); HOMA-IR (insulin resistance); IL-6 (interleukin-6).

Table IV

Multiple linear regression analysis – Factors associated to increased LVMI

Variable	Coefficient	SE	p-Value
Age	0.010	0.120	0.930
eGFR	- 0.037	0.067	0.578
Phosphorus	1.473	1.502	0.029
iPTH	0.023	0.018	0.009
UACR	0.028	0.010	0.066
HOMA-IR	2.816	1.351	0.079
IL-6	4.560	0.724	0.0001

eGFR (estimated glomerular filtration rate), phosphorus, iPTH (intact parathyroid hormone), UACR (urine albumin-to-creatinine ratio), HOMA-IR (insulin resistance), IL-6 (interleukin-6)

were used. In this model, phosphorus (r = 0.602, p = 0.038), iPTH (r = 1.009, p = 0.044) and IL-6 (r = 1.264, p = 0.0001) were positively related to LVMI.

DISCUSSION

Patients with CKD have a high prevalence of LVH, ranging from 36% to 74% in different studies and its prevalence increases as renal function declines[14-16]. Hypertension, hypervolaemia, and anaemia have been identified as major determinants of LVH in a population with CKD[17]. Other factors, such as inappropriate activation of the renin-angiotensin-aldosterone system, oxidative stress and inflammation, may also play a role in left ventricular growth in ESRD[18-20].

In this study, we found that iPTH, phosphorus and IL-6 were independently associated with LVH in type 2 diabetic patients with CKD stages 3 and 4. These findings suggest that disturbances of mineral metabolism and inflammation are linked to LVH in patients with DN.

In the past years, there has been compelling evidence that the cardiovascular system is a major target of PTH action, suggesting that its chronic elevation in ESRD patients adversely affects myocardial metabolism and function[21]. A recent study suggests that PTH retains substantial independent predictive value for major CV events and for all-cause mortality[22]. Left ventricular hypertrophy in uraemic patients is not only characterized by an increased myocardial fibre mass but also by myocardial interstitial fibrosis[23] and it has been observed that elevated PTH levels in ESRD cause irreversible interstitial fibrosis with collagen deposition[24]. *In vitro* studies have shown that PTH appears to have chronotropic, inotropic, as well as hypertrophic effects on cardiomyocytes[25]. The mechanisms by which PTH induces LVH have not been completely elucidated. Studies have shown increased cytosolic calcium and/or protein kinase C activation and expression of cardiac proto-oncogene may be enhanced, which in turn may lead to altered expression of several genes involved on cardiac structure and action and ultimately stimulate the translation of contractile and non-contractile cardiac muscle proteins leading to LVH[26]. Other mechanisms have also been reported to explain the association of secondary hyperparathyroidism and LVH: increased IR and pancreatic ß-cell dysfunction, predisposing to the metabolic syndrome and diabetes; activation of renin-angiotensin system, increasing blood pressure and leading to myocardial cells apoptosis and fibrosis; stimulation of systemic and vascular inflammation and calcification, augmenting atherogenesis[27].

Supporting a causal CV role, PTH receptors have been discovered in the heart and vasculature, and surgical parathyroidectomy for primary hyperparathyroidism and renal transplantation for secondary hyperparathyroidism have been reported to reduce this risk of CVD[28-30]. Following parathyroidectomy in animals with chronic renal failure, a reduction of collagen deposition in the myocardium is consistently observed[26]. Interactions between PTH levels and cardiac abnormalities specifically related to LVH and left ventricular diastolic dysfunction were shown in patients with primary hyperparathyroidism as well[6,31,32]. Such abnormalities were independent of plasma calcium levels and hypertension and also regressed following parathyroid mass reduction[6,31-33].

Hyperphosphatemia is a cardiovascular risk factor in patients with chronic kidney disease; Dingra *et al.* demonstrated that serum phosphorus in patients with CKD stages 1 and 2, free of heart failure and ischaemic heart disease, were positively associated with increased LVMI and LVH[34]. Several attempts have been made to determine the pathophysiology of the relationship between phosphorus and myocardial damage. Recent studies reported severe hyperparathyroidism or hyperphosphatemia and elevated levels of fibroblast growth factor-23 (FGF-23) in dialysis patients[35], that were significantly associated with increased LVMI and the probability of developing LVH[36,37]. It is unclear whether FGF-23 is a mere marker, or a potential mechanism of LVH in patients with CKD.

The consequences of inflammation, a non-traditional risk factor, have gained attention in nephrology. Attention has been attracted to IL-6 with regard to myocardial dysfunction as increased levels are strongly prognostic of mortality[38]. Increased production of pro-inflammatory cytokines, as IL-6, from "microinflammation" activation of the sympathetic nervous system in CKD patients, has also been implicated in LVH[39,40]. Experimental studies have shown IL-6 overexpression in diabetic kidneys, which is associated with glomerular basal membrane thickening in type 2 diabetes patients and mesangial expansion in kidney biopsies of diabetic patients[41], and its levels are higher in patients with overt proteinuria compared to microalbuminuria or normoalbuminuria[42].

Meléndez *et al.* found that IL-6 induced significant concentric LVH[43] and this finding is consistent with the previous reports by Hirota[44] *et al.*, who described a pattern of concentric hypertrophy in the hearts of mice overexpressing both IL-6 and the IL-6 receptor. In his study, Meléndez describes that the soluble IL-6 receptor in combination with IL-6 was found to be essential to

producing increased collagen concentration by isolated cardiac fibroblasts and also played a role in mediating a phenotypic conversion to myofibroblasts; these novel observations demonstrate that IL-6 induces a myocardial phenotype almost identical to that of the hypertensive heart, identifying IL-6 as potentially important in this remodelling process. The presence of the IL-6 receptor has been demonstrated previously in adult cardiac fibroblasts, where it was reported to be essential for fibroblast growth[45]. Interestingly, cardiac fibroblasts stimulated with angiotensin II have been shown to secrete members of the IL-6 family, including IL-6 itself, which induced cardiomyocyte hypertrophy via activation of the gp130 receptor[46]. These observations demonstrate that IL-6 induces a myocardial phenotype almost identical to that of the hypertensive heart, identifying IL-6 as potentially important in this remodelling process.

There are several limitations in the current study, such as the relatively small sample size and, consequently, the limited statistical power of the tests applied. Prospective studies with larger sample size and robust statistical analyses are required in order to confirm these associations.

CONCLUSION

In a population of type 2 diabetic patients with CKD stages 3 and 4, phosphorus, PTH and IL-6 were independently related to LVH.

Further studies are warranted to confirm whether a decrease in levels of phosphorus, PTH and IL-6 would reduce the LVH and consequently the CV risk in diabetic type 2 patients with nephropathy.

Disclosure of potential ***conflicts of interest:*** none declared

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