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NEPHROLOGY - ORIGINAL PAPER

Association of serum calcitonin with coronary artery disease in individuals with and without chronic kidney disease

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Abstract
Background Cardiovascular disease is the leading cause of death in patients with chronic kidney disease (CKD). Recent data implicate disordered bone and mineral metabolism, including changes in serum levels of calcium, phosphate, parathyroid hormone (PTH), vitamin D, fibroblast growth factor-23 (FGF-23), and fetuin A, as novel risk factors for arterial calcification. The potential role of calcitonin, another hormonal regulator of mineral and bone metabolism, has not been studied in detail.
Materials and methods We investigated the link between serum calcitonin and the total burden of coronary artery disease (CAD) using the validated Gensini score, in a cross-sectional study of 88 patients with estimated GFR (eGFR) between 46 and 87 ml/min/1.73 m^2 who underwent coronary angiography.

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We evaluated the associations between serum calcitonin, minerals (calcium, phosphate), calcium × phosphate product, and other factors that regulate mineral metabolism (intact PTH, 25-OH-vitamin D, FGF-23, and fetuin A) and the severity of CAD.

Results The mean serum calcitonin was 11.5 ± 7.8 pg/ml. In univariate analysis, the Gensini CAD severity score correlated significantly with male gender, eGFR, and serum levels of 25-OH-vitamin D, iPTH, FGF-23, fetuin A, and calcitonin ($R = 0.474$, $P = 0.001$ for the latter). In multivariate analysis adjusted for calcium, phosphate, 25-OH-vitamin D, iPTH, FGF 23, fetuin A, and calcitonin, only calcitonin ($\beta = 0.20$; $P = 0.03$), FGF-23, fetuin A, and 25-OH-vitamin D emerged as independent predictors of Gensini score**.** In the second step, we adjusted for the presence of traditional risk factors, proteinuria, and GFR. After these adjustments, the FGF-23 and fetuin A remained statistically significant predictors of the Gensini score, while calcitonin did not.

Conclusions Our study suggests that, in addition to other well-known components of mineral metabolism, increased calcitonin levels are associated with greater severity of CAD. However, this relation was not independent of traditional and nontraditional cardiovascular risk factors. Longitudinal studies in larger populations including patients with more advanced CKD are needed.

Keywords Calcitonin · Coronary artery disease · Mineral · Bone

Introduction

Cardiovascular (CV) complications are the leading cause of death in patients with chronic kidney disease (CKD), and vascular calcifications (VCs) play a major role in the development of these complications [1, 2].

The pathogenesis of VCs is not well understood, but existing studies suggest that traditional risk factors, such as hypertension, advanced age, smoking, diabetes, and dyslipidemia, cannot fully explain the high prevalence of this disorder, and that other "atypical," CKD-related pathogenetic factors are possibly involved. High serum P and Ca × P product, parathormone (PTH), fibroblast growth factor 23 (FGF23), leptin, oxidative stress, and inflammation, as well as both high and low vitamin D levels and low fetuin A levels, have all been linked with VCs and CV mortality in patients with CKD [3, 4].

In a recently published report, we confirmed FGF23 and fetuin A as independent predictors for coronary artery disease (CAD) in 177 patients with eGFR 30–90 ml/min/1.73 m^2 [5]. Long time considered as a passive process resulting from increased serum phosphate (P) and calcium–phosphate product (Ca × P), VCs have recently been demonstrated to be the result of an active osteogenic process, involving regulators of normal bone formation and bone structural proteins [4].

Calcitonin is secreted by the parafollicular cells of the thyroid gland, which lowers blood calcium and phosphate mainly by inhibiting osteoclastic activity in the bone. Furthermore, at high concentrations, calcitonin also increases urinary excretion of calcium and phosphorus, probably by acting on the proximal tubules [6]. We speculated that calcitonin might also have a role in the pathogenesis of CAD and VC. We performed the current study to assess the role of calcitonin among other possible risk factors for CAD, examined by coronary angiography, in a population with eGFR between 30 and 90 ml/min per 1.73 m^2.

Materials and methods

Patients

The study included 88 patients randomly selected from our study population of 177 eligible patients, after screening 339 patients, previously included in our study [5], with mild chronic kidney disease (eGFR < 90 ml/min per 1.73 m^2), who underwent coronary angiography in the Department of Cardiology at Fatih University Hospital from December 2008 to May 2009. The indications for coronary angiography procedures were based on symptoms, risk factors, and results of appropriate noninvasive tests (positive dobutamine stress echocardiography and echocardiography abnormalities confirmed by exercise stress test)—as per guidelines. Estimated glomerular

filtration rates (eGFR) were determined by Cockcroft-Gault equation just before the angiography procedure. All patients with an eGFR between 30 and 90 ml/min per 1.73 m^2 were deemed eligible. Exclusion criteria were (1) history of coronary artery bypass graft surgery; (2) presence of nephrotic syndrome; (3) presence of primary hyperparathyroidism; (4) use of calcium supplements or vitamin D treatment; and (5) patients with severe congestive heart failure (New York Heart Association class III–IV). Eighty-eight patients were randomly selected from the population of our previous study [5]. The study protocol was approved by the local Hospital Ethics Committee, and all patients signed an informed consent.

Data collection and laboratory measurements

Demographic data (age, gender, comorbidities, current drug therapy, smoking status, body weight, and height) were collected before the angiographic procedure from the individual charts in the hospital's electronic database. On the morning of the procedure, after a 12-h fasting period, blood samples were collected, stored, and analyzed in a single laboratory. Serum levels of creatinine, total cholesterol, HDL- and LDL-cholesterol, and triglycerides were determined using standard techniques. The urinary protein-to-creatinine ratios were determined from samples collected on the morning of the scheduled coronary angiography.

Blood pressure was measured at the non-dominant arm in the morning of the procedure after 5 min of rest. Hypertension was defined for the study purpose according to the 2007 guidelines of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) task force for the management of arterial hypertension [7].

Intact parathyroid hormone (iPTH, normal range: 10–69 pg/ml) was determined by the chemiluminescence method (Immulyte 2000; DPC, Los Angeles, CA, USA).

Serum FGF-23 (C-terminal fragment) levels were measured using an ELISA kit, according to the manufacturer's protocol (Immutopics Inc., San Clemente, CA, USA).The sensitivity of the 2nd generation human FGF-23 (C-Term) ELISA as determined by the 95% confidence limit was calculated: the mean intra-assay precision and coefficient variation were 33.7 (RU/ml) and 2.4%, respectively.

Serum fetuin A levels (μg/ml) were measured using a Human Fetuin-A ELISA kit (BioVendor Laboratory Medicine Inc., Brno, Czech Republic) in an ELISA plate reader (Biotek ELx808). Inter and intra-assay coefficients of variation were 4.1 and 5.2%, respectively.

Serum calcitonin

Serum calcitonin (CT) was measured by ELISA (DRG International Inc., Mountainside, NJ, USA), using rabbit antiserum against two sites of the biologically intact 32-amino acid chain of CT. In the 88 subjects, serum concentration of CT ranged from 0.09 to 42.6 ng/ml (mean = 11 ng/ml). The precision (intra-assay variation) of the DRG® CT test was calculated from 20 replicate determinations on each of the three samples with intra-assay CV of 5.7%.

Coronary angiography imaging procedure and Gensini score calculation

All patients underwent standard coronary angiography assessment performed by a single cardiologist using standard techniques. Two experienced physicians blinded to the study analyzed angiograms with a validated quantitative coronary angiographic system (Philips Allura Xper FD10). The extent of CAD was determined using the Gensini score, which is a measure of the extent of myocardial ischemia and is computed by assigning a severity score to each coronary segment, according to the degree of luminal narrowing and its geographic importance [8]. Reduction in the diameter of the lumen, the roentgenographic appearance of concentric lesions, and eccentric plaques were evaluated (the corresponding Gensini scores for the reductions of 25, 50, 75, 90, 99%, and complete occlusion were 1, 2, 4, 8, 16, and 32, respectively). For each principal vascular segment, a multiplier was assigned according to the functional significance of the myocardial area supplied by this segment: left main coronary artery × 5; proximal segment of the left anterior descending coronary artery (LAD) × 2.5; proximal segment of the circumflex artery × 2.5; midsegment of the LAD × 1.5; right coronary artery distal segment of the LAD, posterolateral artery, and obtuse marginal artery × 1; and others × 0.5.

Statistical analyses

All data are presented as mean ± standard deviation (SD), unless stated otherwise. Continuous variables were checked for the normal distribution assumption using the Kolmogorov–Smirnov statistics, and those that did not satisfy the criteria were log-transformed to attain normality. The study group was divided in two subgroups based on the median Gensini score. Significant differences between groups were assessed using the Student's *t* test. Chi-square test was used to test differences in frequencies. All potential (physiologically meaningful) determinants of the Gensini score were investigated in a univariate screening procedure, using the Pearson's coefficient of correlation test. The nonparametric Spearman rho coefficient of correlation was used to assess correlations between variables without normal distribution. Significant determinants identified from this analysis were studied in a stepwise multiple regression model using the F statistic. All variables associated with these parameters with a level of significance <0.1 were included in the multivariable model. Variables were forced in the model using a stepwise procedure. A $P < 0.05$ for the final model was considered as statistically significant. Data were analyzed using the SSPS 15.0 for Windows software (SPSS® Inc. Chicago IL).

Results

The mean values for parameters of mineral metabolism in the entire study population were serum calcium concentration, 9.3 ± 0.52 mg/dl, serum phosphate concentration, 3.37 ± 0.6 mg/dl, iPTH, 61.2 ± 36.6 pg/ml, and 25-OH-vitamin D, 22.4 ± 8.4 ng/ml. The mean serum values for calcitonin, FGF23, and fetuin A in the entire study population were 11.5 ± 7.8 pg/ml, 22.9 ± 11.2 RU/ml, and 474.3 ± 153.2 μg/ml, respectively.

The demographic, clinical, and biochemical characteristics of the study population as categorized according to the median Gensini score are presented in Table 1. Compared to patients below the median, patients with a Gensini score above the median had a higher serum calcitonin ($P = 0.004$), higher FGF 23 ($P = 0.001$), higher PTH ($P = 0.018$), and lower GFR ($P = 0.018$), serum vitamin D ($P = 0.001$), and fetuin A levels ($P = 0.001$). There were no differences in age, gender, hypertension, smoking, LDL- and HDL-cholesterol, and urine protein/creatinine ratio (Table 1).

Univariate and multivariate analyses for the Gensini score

The Gensini score values correlated significantly in univariate analyses with gender ($R = -0.38$, $P = 0.001$), calcitonin level ($R = 0.47$, $P = 0.001$), FGF 23 ($R = 0.64$, $P = 0.001$), fetuin A ($R = -0.29$, $P = 0.006$), 25-OH-vitamin D ($R = -0.41$, $P = 0.001$), eGFR ($R = -0.32$, $P = 0.002$), iPTH ($R = 0.26$, $P = 0.015$), but not with hypertension, diabetes mellitus, alkaline phosphatase, and serum lipids.

The calcitonin values correlated significantly in univariate analyses with eGFR ($R = -0.34$, $P = 0.001$), FGF 23 ($R = 0.36$, $P = 0.001$), fetuin A ($R = -0.28$, $P = 0.008$), 25-OH-vitamin D ($R = -0.22$, $P = 0.03$), PTH ($R = 0.18$, $P = 0.05$) but not with alkaline phosphatase ($R = 0.18$, $P = 0.07$). In the unadjusted analysis, serum calcitonin level and the severity of CAD were positively correlated (Fig. 1; Table 2). Furthermore, in the unadjusted analysis, serum calcitonin level and eGFR were negatively correlated (Fig. 2).

All the parameters that correlated significantly with the Gensini score, as well as other possible risk factors for CAD, were introduced in the standard multivariate regression analysis, in a two-step procedure, using the enter method. In the first step, we wanted to see the independent influence of the mineral metabolism parameters, calcitonin, FGF-23, and fetuin A on the Gensini score. In this first step, calcitonin ($\beta = 0.20$; $P = 0.03$), FGF-23 ($\beta = 0.47$, $P = 0.001$), fetuin A ($\beta = -0.28$, $P = 0.027$), and 25-OH-vitamin D ($\beta = -0.23$; $P = 0.03$) were the only statistically significant independent factors that correlated with the Gensini score (Table 2).

In the second step, we adjusted for the presence of traditional risk factors (gender, hypertension, smoking, diabetes, and lipid profile), proteinuria, and GFR. After these adjustments, the FGF-23 ($\beta = 0.43$, $P = 0.001$), and fetuin A ($\beta = -0.17$, $P = 0.023$), remained statistically significant predictors of the Gensini score (Table 2). Although the point estimate for calcitonin changed minimally in this model, it did not retain statistical significance ($\beta = 0.18$, $P = 0.09$).

Table 1 Demographic and laboratory data of the patients with mild-to-moderate CKD, categorized according to the median Gensini score (=18)

	Entire group ($n = 88$)	Gensini score < 18 ($n = 44$)	Gensini score ≥ 18 ($n = 44$)	*P* value
Age (years)	61.2 ± 6.1	61.7 ± 6.3	60.6 ± 6.0	0.38
Gender (male, *n*, %)	55; 62.5%	25; 56.8%	30; 68%	0.56
Hypertension (*n*; %)	58; 66.7%	25; 58.1%	33; 75%	0.09
Diabetes mellitus (*n*; %)	20; 22.7%	6;13.6%	14; 31.8%	0.04
Smoking (*n*; %)	44; 50%	20; 45.5%	24; 54.5%	0.39
eGFR (ml/min/1.73 m^2)	72.0 ± 8.6	74.3 ± 7.0	69.6 ± 9.5	0.029
Urinary Pr/Cr ratio (mg/g)	0.13 ± 0.06	0.12 ± 0.06	0.16 ± 0.08	0.08
Total cholesterol (mg/dl)	196.7 ± 46.1	199.5 ± 39.7	194.1 ± 53.6	0.29
LDL cholesterol (mg/dl)	121.4 ± 37.8	124.3 ± 30.6	118.4 ± 44.5	0.31
HDL cholesterol (mg/dl)	43.2 ± 11.7	44.6 ± 12.0	41.9 ± 11.5	0.25
Triglycerides (mg/dl)	168.4 ± 120.7	148.7 ± 72.5	187.2 ± 151.9	0.51
Calcium (mg/dl)	9.3 ± 0.52	9.1 ± 0.44	9.8 ± 0.54	0.31
Phosphate (mg/dl)	3.37 ± 0.6	3.4 ± 0.6	3.6 ± 0.7	0.74
CaxP product (mg^2/dl^2)	31.2 ± 5.9	31.3 ± 6	31.6 ± 7.1	0.79
Alkaline phosphatase (U/l)	83 ± 21.8	87.3 ± 26.4	96 ± 47.1	0.79
Calcitonin (pg/ml)	11.5 ± 7.8	9.1 ± 6.9	14.0 ± 7.9	0.004
iPTH (pg/ml)	61.2 ± 36.6	52.2 ± 25.6	70.2 ± 43.4	0.018
25-OH-vitamin D (ng/ml)	22.3 ± 8.4	25.1 ± 9.6	19.4 ± 5.7	0.001
FGF 23 (rμ/ml)	22.9 ± 11.2	17.1 ± 5.3	28.7 ± 12.5	0.001
Fetuin A (μg/ml)	474.3 ± 153.2	524.8 ± 153.5	423.9 ± 136.9	0.002
ACE inhibitor (*n*; %)	24; 27.3%	8; 18.2%	16; 36.4%	0.057
ARB (*n*; %)	21; 24.1%	10; 23.3%	11; 25%	0.85
Statins (*n*; %)	24; 27.6%	7; 16.3%	17; 38.6%	0.02

eGFR glomerular filtration rate, *Urinary Pr/Cr ratio* urinary protein/creatinine ratio, *iPTH* intact parathyroid hormone, *LDL cholesterol* low-density lipoprotein cholesterol, *HDL cholesterol* high-density lipoprotein cholesterol, *FGF 23* fibroblast growth factor 23, *ACE* angiotensin conversion enzyme, *ARB* angiotensin receptor blockers

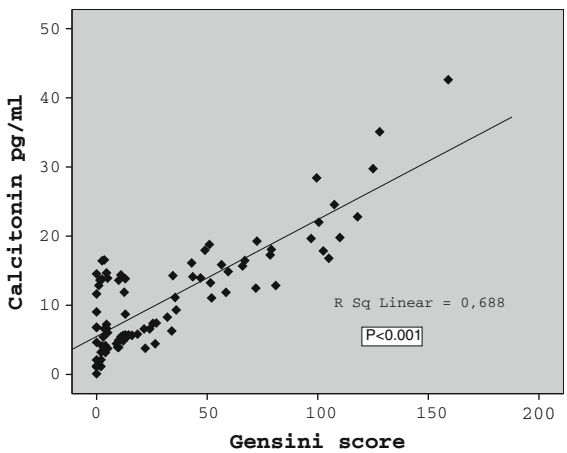

Fig. 1 Correlation between serum calcitonin level and severity of coronary artery disease defined with Gensini score

Discussion

In this population with mild eGFR impairment (30–90 ml/min per 1.73 m^2), we found that the severity of CAD was positively correlated with serum levels of calcitonin and FGF23 and inversely correlated with serum 25-OH-vitamin D and fetuin A in univariate analyses. The association between calcitonin and severity of CAD remained significant when it was adjusted only for the mineral metabolism parameters, FGF 23, and fetuin A. However, after including Framingham risk factors, eGFR, and proteinuria, this association did not reach statistical significance. In multivariate analysis, after adjustment for other possible risk factors, only FGF23 and fetuin A remained significant predictors of the severity of CAD. Although

Table 2 Multiple regression models of Gensini score in patients with mild chronic kidney disease

	Unadjusted (β, P)	Model 1 (β, P)	Model 2 (β, P)
Calcitonin	0.38 (0.004)	0.20 (0.03)	0.18 (0.09)
FGF 23		0.47 (0.001)	0.43 (0.001)
Fetuin A		−0.28 (0.027)	−0.17 (0.023)
Calcium		0.07 (0.48)	0.12 (0.89)
Phosphate		0.08 (0.37)	0.35 (0.59)
iPTH		0.20 (0.06)	0.30 (0.1)
25 (OH)D Vit		−0.23 (0.03)	−0.27 (0.2)
eGFR			−0.12 (0.53)
Proteinuria			0.14 (0.24)
Age			0.16 (0.13)
Gender			−0.31 (0.03)
HT			0.09 (0.39)
DM			0.20 (0.07)
T-cholesterol			0.24 (0.08)
Smoking			0.15 (0.36)

eGFR glomerular filtration rate, *Urinary Pr/Cr ratio* urinary protein/creatinine ratio, *iPTH* intact parathyroid hormone, *t-cholesterol* total cholesterol, *FGF 23* fibroblast growth factor 23, *DM* diabetes mellitus, *HT* hypertension

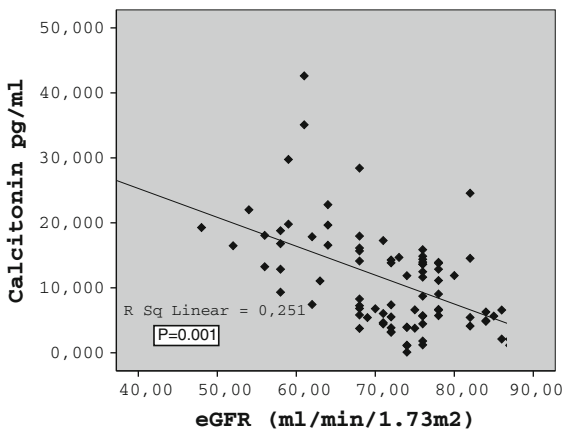

Fig. 2 Correlation between serum calcitonin level and estimated glomerular filtration rate (eGFR)

we did not directly assess coronary calcifications, we hypothesize that the mechanisms underlying the associations we observed probably include modulation of the coronary artery calcification process.

Although there were likely too few patients to prove independence from traditional cardiovascular disease risk factors, this study suggests a novel association between calcitonin and CAD that has not been previously reported neither in the general population nor in CKD patients. This finding seems surprising and even counterintuitive, considering the physiologic effects of calcitonin. Calcitonin is a small peptide hormone (32 amino acids, molecular weight 3,400), secreted by the parafollicular cells of the thyroid gland (also known as "C-cells"), which lowers blood calcium and phosphate mainly by inhibiting osteoclastic activity in the bone. At high concentrations, calcitonin also increases urinary excretion of calcium and phosphorus, probably by acting on the proximal tubules, but this effect is modest, transient, and likely physiologically unimportant [6]. To date, calcitonin has not been shown to have any significant vascular effects in humans. However, it can prevent experimental induction of atherosclerotic calcified plaques, by blocking the calcium influx in the vascular smooth muscle in rabbits [9]. Still, the link between calcitonin and CAD is difficult to explain in the context of current knowledge.

In patients with stage 5 CKD treated by dialysis, serum concentrations of calcitonin were found to exceed the normal range for the general population, in 25–83% of cases, more often in men than in women and more in hemodialysis than in peritoneal dialysis patients [10–13]. The explanation of this hypercalcitoninemia is unclear, since calcitonin concentrations do not change after a hemodialysis session, although they do decrease significantly after renal transplantation [10, 11]. Some authors have found correlations between serum calcitonin and other factors involved in mineral metabolism, such as serum calcium, alkaline phosphatase, and PTH, whereas others did not [11, 13, 14]. To the best of our knowledge, this is the first study that investigated calcitonin levels in patients across a broad range of kidney function, where we report that serum calcitonin increases as eGFR declines. Additionally, we observed that serum calcitonin is directly correlated with serum FGF23 and inversely correlated with serum fetuin A and vitamin D. These latter findings may provide possible clues for the link between calcitonin and VCs, namely a putative modulator effect of calcitonin on these three VC-regulating factors.

It is also noteworthy that traditional risk factors such as advanced age, hypertension, smoking, diabetes, dyslipidemia, proteinuria, and serum calcium and

phosphate levels, did not predict the severity of the Gensini score in this small study population. This illustrates that, indeed, patients with eGFR impairment represent a unique population, in which the high prevalence of CV disease is to a greater extent explained by non-traditional risk factors (such as high calcitonin and FGF23 and low fetuin A and vitamin D levels), rather than by typical risk factors, as seen in the general population.

There are several limitations of our study. First, this is a cross-sectional analysis that precludes inference regarding causality and direct relationships between vascular calcifications and mineral metabolism and calcitonin as a novel risk factor. Second, we used an unselected population and estimated the renal function using the Cockcroft-Gault formula, which is known to be a less precise estimation of renal function, and third, we had no data on the inflammatory status, which is a well-recognized risk factor for atherosclerosis progression. The relative strength of our study is the design: we assessed a population in which the interference of traditional cardiovascular risk factors was minimized and biases in mineral metabolism markers related to treatment with phosphate binders and vitamin D supplements were excluded. Most importantly, besides Ca and P levels, all hormones currently implicated in maintaining Ca–P homeostasis were investigated together with direct assessment of end organ damage.

In conclusion, our present study confirms the associations of FGF23, fetuin A, and vitamin D with CV complications in patients with CKD, as previously shown by us and others [5]. On the other hand, it brings forth calcitonin as a new factor possibly involved in this process. This finding deserves further experimental and clinical exploration, in order to first confirm and then to explain the underlying mechanisms linking serum calcitonin with the risk of CAD.

Conflict of interest None.

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