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Serum cystatin C levels were correlated with cardiometabolic features and cardiovascular diseases in patients with primary hyperparathyroidism.

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Introduction

Patients with **primary hyperparathyroidism** (PHPT) are at risk of chronic kidney disease (CKD). Kidney is a target of PTH action: a fifth to a half of PHPT patients experienced kidney stones or, less frequently, nephrocalcinosis. Reduction of glomerular filtration rate (GFR, <60 ml/min) has been reported in both symptomatic, affected with kidney stones and osteoporosis, and asymptomatic PHPT patients and is considered a criteria for surgery in patients with asymptomatic PHPT according the clinical guidelines from the Fourth International Workshop.

Cystatin C (Cys-C), a low-molecular weight protein secreted by nearly all cells, freely filtered at renal glomerular level and then metabolized by the proximal tubule, is considered a more reliable tool to assess GFR than serum creatinine as it is not affected by factors like sex, race and muscle mass. Moreover, Cys-C levels have been demonstrated to display stronger associations with adverse outcomes related to impaired kidney function, such as cardiovascular disease, heart failure and all-cause mortality in different populations, than estimated GFR (eGFR) derived from creatinine.

Aim of the study To investigate 1) serum Cys-C levels and its correlation with clinical, biochemical and cardiometabolic parameters, 2) kidney function by the eGFR equation based on both cystatin and creatinine levels (eGFRcr-cys), and 3) association of eGFRcr-cys with the occurrence of cardiovascular events in a series of PHPT patients.

Patients and methods

PHPT patients: **190 consecutive patients with PHPT** (146 females, 44 males, age 59.7±14.2 years) were enrolled in two Italian centers (Fondazione IRCCS Ca' Granda, Milan, and IRCCS Policlinico San Donato, San Donato Milanese) from 2005 through 2010. PHPT was surgically confirmed in 54% of patients. Osteoporosis was diagnosed in 58% and kidney stones in 54% of PHPT patients; moreover, arterial blood hypertension occurred in 51%, overt type 2 diabetes (T2DM) in 12%, obesity in 13%, dyslipidemia in 70% of PHPT patients.

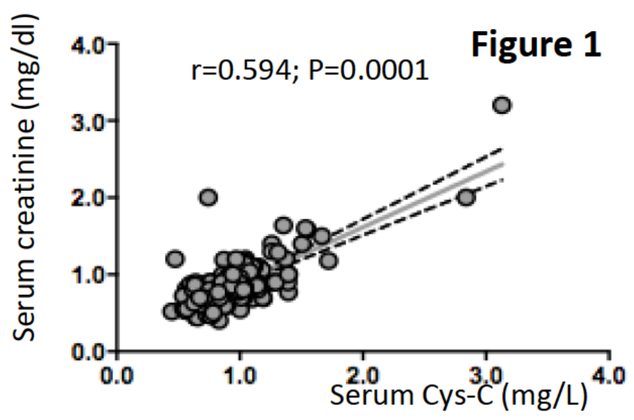
Healthy controls: **135 age- and sex-matched healthy subjects** (88 females, 47 males, age 56.0±17.2 years) were enrolled as controls; hypertension, diabetes, neoplasia and established CKD were criteria of exclusion.

Estimated glomerular filtration rate: The eGFRcr was derived from serum creatinine by the CKD-EPI Creatinine Equation (2009), while the eGFRcr-cys by the CKD-EPI Creatinine-Cystatin C Equation (2012) using the GFR calculators at http://mdrd.com.

Serum creatinine and cystatin C assays: Serum creatinine was analyzed by the Jaffe's alkaline picrate method. Serum Cys-C was measured by means of a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Dade Behring) with a nephelometer (BNII, Dade Behring); the sensitivity and specificity were 94% and 82%, respectively.

***Serum cystatin C levels in PHPT patients*:** Circulating Cys-C concentrations ranged 0.45-3.13 mg/L in PHPT patients and 0.52-2.98 mg/L in age- and sex-matched controls, with no difference between males and females. Serum Cys-C correlated with serum creatinine in PHPT patients (r=0.594, P=0.0001; **Figure 1**) and in controls (r=0.209, P=0.01). In PHPT patients, Cys-C levels positively correlated with age (r=0.542, p=0.0001) and BMI (r=0.270, P=0.0002).

Figure 1



Serum cystatin C levels in PHPT patients compared with controls: Median Cys-C level was significantly higher in PHPT patients than in controls (0.93±0.02 *vs* 0.78±0.01 mg/L, P=0.001; **Figure 2**), even considering normo-tensive and normoglicemic PHPT patients (0.82±0.19 mg/L, P=0.03).

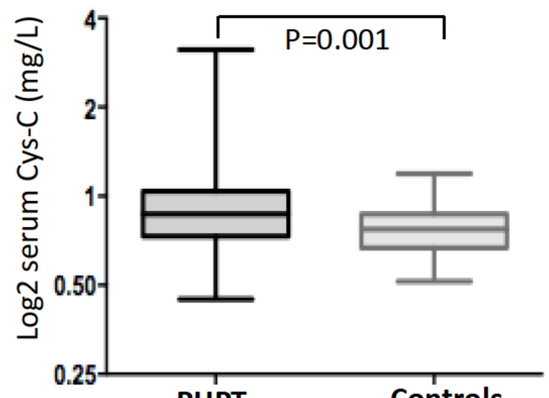
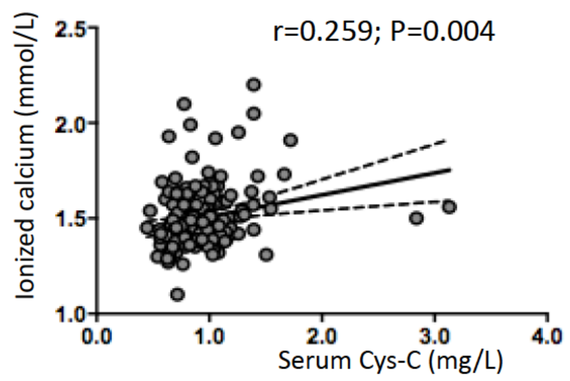


Figure 2

25.8% of PHPT patients had Cys-C levels higher than the 95th percentile value in controls (1.03 mg/L). Among PHPT patients with eGFRcr >60 ml/min/1.73m^2 (n=169), 18.4% had Cys-C levels >1.03 mg/L, consistent with a condition of "**preclinical kidney disease**". Arterial blood hypertension was more frequent (80% *vs* 41%, P=0.01) and HOMA-IR was higher (4.5 *vs* 2.1, P=0.008) in PHPT patients with preclinical kidney disease compared with patients with conserved kidney function.

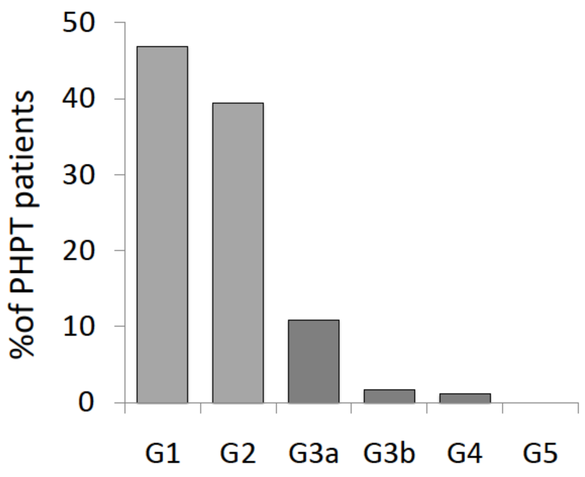
Serum cystatin C levels correlated with PHPT parameters:

Figure 3



Cys-C levels positively correlated with serum total and ionized calcium (r=0.151, P=0.024and r=0.259, P=0.004, respecti-vely) (**Figure 3**), serum PTH (r=0.176, P=0.01), and negatively with urine calcium and phosphate excretions (r=-0.349, P=0.0001 and r=-0.208, P=0.009, respectively).

***Evaluation of kidney function using the eGFRcr-cys equation in PHPT patients*:**



G1, eGFR≥90 ml/min/1.73m^2
G2, eGFR 60-90 ml/min/1.73m^2
G3a, eGFR 45-59 ml/min/1.73m^2
G3b, eGFR 30-44 ml/min/1.73m^2
G4, eGFR 15-29 ml/min/1.73m^2
G5, eGFR <15 ml/min/1.73m^2

Therefore, **CKD** (stages G3a, 3b and 4) was diagnosed in **13.7%** of PHPT patients.

PHPT patients with eGFRcr-cys<60 ml/min/1.73m^2 compared with PHPT patients with eGFRcr-cys>60 ml/min/1.73m^2.

The stepwise regression analysis identified **hypertension** and **HOMA-IR** values as independent variables predicting eGFRcr-cys in PHPT patients (β 0.218±0.077, P=0.0001 and 0.126±0.119, P=0.04, respectively), while hypertension alone was associated with eGFRcr (β 0.206±0.09, P=0.0001).

	eGFR<60	eGFR>60	P
n	25	161	
Age (yrs)	70.0±1.9	58.8±1.1	0.0002
Sex (males/ females)(% males)	10/15 (40)	32/129 (20)	**0.047**
BMI (kg/m^2)	27.3±0.9	25.3±0.4	**0.041**
Ionized calcium (mmol/L)	1.59±0.04	1.48±0.01	**0.003**
Serum Calcium (mg/dl)	11.6±0.23	11.0±0.07	**0.005**
Serum Phosphate (mg/dl)	2.5±0.10	2.4±0.04	0.778
Serum PTH (pg/ml)	300.3±46.5	166.0±10.7	**0.0001**
Calcium excretion (mg/kg/24h)	3.4±0.4	4.8±0.2	**0.019**
Phosphate excretion (g/24h)	0.72±0.05	0.75±0.04	0.690
Serum 25OHD (ng/ml)	22.3±4.9	20.3±1.7	0.690
Glucose (mg/dl)	96.2±4.5	90.8±1.3	0.186
Serum insulin (mU/L)	15.6±3.3	9.4±0.7	**0.010**
HOMA-IR	4.1±1.0	2.2±0.2	**0.003**
Total-cholesterol (mg/dl)	203.9±7.6	209.4±3.4	0.564
HDL-cholesterol (mg/dl)	51.7±4.2	60.4±1.4	**0.044**
LDL-cholesterol (mg/dl)	129.3±8.9	127.7±2.9	0.853
Triglycerides (mg/dl)	139.0±12.9	127.7±5.0	0.061
Diabetes (%)	12.0	11.2	0.819
Hypertension (%)	84.0	47.5	**0.001**
Kidney stones (%)	48.0	53.0	0.764
Kidney cysts (%)	65.0	28.1	**0.033**

Serum cystatin C levels were associated with cardiovascular diseases in PHPT patients: 52 CVD diagnosis (coronaropathy, arithmopathy, cerebral vascular diseases) were recorded at time of the evaluation. After adjustment for age and sex, CVD was positively correlated with Cyst-C levels (β 0.305±0.109; P=0.006) and negatively with eGFRcr-cys values (β -0.005±0.002; P=0.011).

Conclusions: evaluation of serum cystatin C in PHPT patients revealed that:

1) it might represent a more sensitive tool than creatinine;
2) preclinical kidney disease occurring in about one sixth of patients, which showed an unfavorable cardiometabolic profil;
3) hypertension and insulin resistance/overt diabetes were the two major clinical conditions associated with reduced eGFRcr-cys in PHPT patients as reported in the general population.

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