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Original Research Article

Osteoprotegerin and osteoprotegerin/TRAIL ratio are associated with cardiovascular dysfunction and mortality among patients with renal failure

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ABSTRACT

Purpose: The high prevalence of cardiovascular morbidity and mortality among patients with chronic kidney disease (CKD) is observed especially in those undergoing dialysis. Osteoprotegerin (OPG) and its ligands, receptor activator of nuclear factor kappa-B ligand (RANKL) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) have been associated with cardiovascular complications. Our aim was to study their role as cardiovascular risk factors in stage 5 CKD patients.

Patients and methods: OPG, RANKL and TRAIL concentrations were measured in 69 hemodialyzed CKD patients and 35 healthy volunteers. In CKD patients, cardiovascular dysfunction was assessed with aortic pulse wave velocity (AoPWV), carotid artery intima-media thickness (CCA-IMT), coronary artery calcium score (CACS) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) serum concentrations. Cardiovascular and overall mortality data were collected during a 7-years follow-up.

Results: OPG plasma concentrations were higher in CKD patients comparing to controls. Total soluble RANKL was lower and OPG/RANKL ratio higher in patients. Soluble TRAIL concentrations did not differ between the groups and OPG/TRAIL ratio was higher in CKD patients. OPG and OPG/TRAIL positively predicted long-term mortality (all-cause and cardiovascular) in CKD patients. OPG positively correlated with AoPWV, CCA-IMT and NT-proBNP whereas OPG/TRAIL with AoPWV and NT-proBNP. Described relationships were independent of classical and non-classical cardiovascular risk factors, with exception of age.

Conclusions: Our study confirmed the role of OPG as a biomarker of cardiovascular dysfunction and a predictor of mortality in stage 5 CKD. OPG/TRAIL ratio can be proposed as a predictor of cardiovascular dysfunction and mortality.

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1. Introduction

Cardiovascular complications are the main cause of mortality among chronic kidney disease (CKD) patients treated with dialysis, with the rate about 10–20-times higher comparing to general age- and sex-matched population [1]. Accelerated atherosclerosis in these patients is accompanied by Mönckeberg calcification of vascular *media* [2]. In addition to classical cardiovascular risk factors, atherosclerosis and vascular calcification are accelerated by chronic inflammation, malnutrition (malnutrition-inflammation-atherosclerosis syndrome), bone and mineral metabolism disorders (both with low and high bone turnover), elevated serum homocystein and oxidative stress. These abnormalities are well recognized in stage 3–5 CKD patients [3,4].

Osteoprotegerin (OPG) is a secretory glycoprotein belonging to tumor necrosis factor receptor superfamily. It is involved in bone metabolism regulation as well as vascular calcification, inflammation and apoptosis (reviewed in [5,6]). In bones, OPG is secreted by

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osteoblasts and acts as a soluble decoy receptor for receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL), leading to reduced osteoclastogenesis. OPG/RANKL/RANK triad is also involved in cellular and humoral immune responses, including T cell proliferation and B cell maturation [6]. Besides RANKL, OPG has been shown to bind specifically the tumor necrosis factor related apoptosis inducing ligand (TRAIL) and neutralize its pro-apoptotic functions [7]. Both OPG ligands are present in blood in a soluble form (sRANKL, sTRAIL).

Despite numerous studies, the role of OPG in atherosclerosis and vascular calcification is not clear. In rodents, OPG seems to be protective against vascular calcification and, less consistently, atherosclerosis [8,9]. In humans, however, high OPG concentrations are repeatedly associated with cardiovascular pathology. In general population, high serum OPG have been shown to predict the incidence and severity of cardiovascular disease [10–13] and related mortality [10,11]. In patients with CKD, OPG concentrations are higher comparing to general population [14], negatively correlate with GFR [15] and have been associated with adverse cardiovascular outcomes [16–18].

Also, several epidemiological studies connect OPG ligands with cardiovascular diseases. In general population, serum RANKL concentrations have been shown to positively predict the incidence of cardiovascular diseases (especially myocardial infarction and ischemic stroke) [19], but not atherosclerotic plaque burden [19,20]. However, in another population-based study [12], sRANKL concentrations have not been associated with new cardiovascular events. Recently, low sTRAIL has been shown to predict mortality in older patients with cardiovascular disease [21] and in CKD patients [22,23].

The aim of our study was to assess the relationships between plasma concentrations of OPG and serum concentrations of sRANKL and sTRAIL as well as the molar ratios of OPG to its soluble ligands, and the extend of cardiovascular dysfunction as well as long-term cardiovascular and all-cause mortality in hemodialyzed CKD patients. Cardiovascular dysfunction was assessed with the use of widely accepted, non-invasive tests, i.e. aortic pulse wave velocity (AoPWV), carotid artery intima-media thickness (CCA-IMT), coronary artery calcium score (CACS) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) serum concentrations.

2. Patients and methods

2.1. Patients and study protocol

Sixty-nine CKD patients (39 men, 30 women, aged 31–90 years, mean 60 ± 12 years) treated with maintenance hemodialysis at our Nephrology Department were recruited for the study between October and December 2004. The inclusion criteria were stable clinical course for at least 3 months. Patients with acute inflammatory states, neoplastic diseases, hepatitis or HIV infections were excluded. The patients were dialyzed three times a week for 4–5 h, with the use of reutilized polysulphone dialyzers, bicarbonate dialysate and low molecular weight heparin anticoagulation. The median period of dialysis treatment was 60 months (range 11–360 months). The causes of end-stage renal disease were: chronic glomerulonephritis (34 patients), pyelonephritis (16), polycystic kidney disease (10), diabetic nephropathy (3), unknown (6). Clinical characteristics of patients and most important comorbidities are listed in Table 1.

Thirty-five healthy volunteers (i.e. with no signs or symptoms of cardiovascular disease, kidney diseases, acute inflammation or malignancy), in age and sex comparable with CKD patients (Table 1), were recruited in order to obtain control values for key laboratory tests.

Table 1
Clinical and epidemiological characteristics of patients.

	CDK patients ($n = 69$)	Control group ($n = 35$)
Age, years	60 ± 12	57 ± 9[NS]
Men, *n* (%)	39 (57)	19 (54)[NS]
Dialysis therapy duration, months	60 (36–100), range 11–360	–
Observation period, months	56 (29–84), range 4–84	–
Median survival, months	56.6	–
All-cause mortality, *n* (%)	39 (57)	–
Cardiovascular mortality, *n* (%)	31 (45)	–
BMI, kg/m^2	23.6 (21.0–26.7)	23.3 (21.8–23.9)[NS]
Systolic blood pressure, mmHg	137 ± 15	126 ± 8*
Diastolic blood pressure, mmHg	81 ± 7	74 ± 6*
Mean arterial pressure, mmHg	100 ± 9	91 ± 6*
Pulse pressure, mmHg	56 ± 10	52 ± 7[NS]
Hypertension, *n* (%)	55 (80)	0
Diabetes, *n* (%)	8 (12)	0
Current smoking, *n* (%)	15 (22)	4 (11)[NS]
Ischemic heart disease, *n* (%)	35 (51)	0

[NS] No statistically significant difference between CKD patients and controls.
Abbreviations: BMI, body mass index; *n*, number.
* $P < 0.001$ in comparison between CKD patients and controls.

The study was a priori approved by the local Bioethical Committee (approval number KBET/127/B/2006). All the participants gave the written informed consent for the study.

At the start of the study, CKD patients were subjected to clinical examination, followed by venous blood collection for laboratory tests. The measurements of AoPWV, CACS and CCA-IMT were performed within two months from recruitment. AoPWV was measured between carotid and femoral arteries with the use of Complior device (Colson, France), after 10 min rest in supine position, and was arithmetic mean of 10 measurements. CACS was measured with multislice spiral computed tomography using Somatom Sensation 64 Cardiac equipped with calcium scoring software, as previously described [24]. CCA-IMT was measured by one examinator during diastolic phase of heart cycle with the use of an Aloka 5500 SV ultrasonograph with a 7.5 MHz head for vascular examination. Two-three measurements were taken at the level of the bulb, 1 cm from a bifurcation and at half length of right and left common carotid artery. The final result was an arithmetic mean of the measurements.

The mortality data of CKD patients were recorded over a 7-year (84-month) period. The causes of death were verified based on the disease histories of patients who died in hospital and medical records from general practitioners for outside-hospital deaths. Cardiovascular mortality was defined as death from acute myocardial infarction, left-ventricular failure, or cerebral stroke. A follow-up interviewer was not aware of laboratory or imaging tests' results.

2.2. Laboratory tests

Fasted blood samples were collected before middle-week dialysis session. The routine laboratory tests: complete blood count, serum albumin, glucose, calcium (Ca), inorganic phosphate (Pi), intact parathormone (iPTH), total cholesterol and cholesterol fractions, NT-proBNP and C-reactive protein (CRP) were performed on the day of collection. Biochemical tests were performed with Modular P analyzer (Roche Diagnostics), NT-proBNP was measured by electrochemiluminescence immunoassay with Modular P Analyzer (Roche, Germany) and CRP with BN II Nephelometer (Siemens, Germany). K_2-EDTA plasma samples (for OPG determination) and sera (for sRANKL and sTRAIL determination) from CKD patients and healthy volunteers were aliquoted and stored in

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