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Original Article

ORIGINAL ARTICLE

Serum osteoprotegerin and renal function in the general population: the Tromsø Study

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Abstract

Background: Serum osteoprotegerin (OPG) is elevated in patients with chronic kidney disease (CKD) and increases with decreasing renal function. However, there are limited data regarding the association between OPG and renal function in the general population. The aim of the present study was to explore the relation between serum OPG and renal function in subjects recruited from the general population.

Methods: We conducted a cross-sectional study with 6689 participants recruited from the general population in Tromsø, Norway. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equations. OPG was modelled both as a continuous and categorical variable. General linear models and linear regression with adjustment for possible confounders were used to study the association between OPG and eGFR. Analyses were stratified by the median age, as serum OPG and age displayed a significant interaction on eGFR.

Results: In participants ≤62.2 years with normal renal function (eGFR ≥90 mL/min/1.73 m^2) eGFR increased by 0.35 mL/min/1.73 m^2 (95% CI 0.13–0.56) per 1 standard deviation (SD) increase in serum OPG after multiple adjustment. In participants older than the median age with impaired renal function (eGFR <90 mL/min/1.73 m^2), eGFR decreased by 1.54 (95% CI −2.06 to −1.01) per 1 SD increase in serum OPG.

Conclusions: OPG was associated with an increased eGFR in younger subjects with normal renal function and with a decreased eGFR in older subjects with reduced renal function. Our findings imply that the association between OPG and eGFR varies with age and renal function.

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Key words: estimated glomerular filtration rate, general population, osteoprotegerin, renal function

Introduction

The glycoprotein osteoprotegerin (OPG) and its cytokine network has been proposed to represent a link between the skeletal and cardiovascular systems [1]. OPG is a member of the tumour necrosis factor receptor superfamily [2] and functions as a decoy receptor for receptor activator of nuclear factor κB ligand (RANKL) [3]. RANKL is necessary for the differentiation and activation of osteoclasts [3]. Serum OPG is a marker of cardiovascular disease [4–9] and is increased in patients with diabetes mellitus [10].

Development of osteoporosis and subintimal vascular calcification are both prominent features in OPG double knockout mice [11]. Patients with chronic kidney disease (CKD) have a high prevalence of cardiovascular mineralization and reduced bone mineral density [12]. Even at a predialytic stage, more than half of CKD patients have some form of cardiovascular calcification and reduced bone formation [13].

Progression of impaired renal function is inversely related to serum OPG in patients with CKD [14]. Plasma OPG has also been found to be associated with coronary artery calcification in patients undergoing haemodialysis [15] and a predictor of all-cause mortality and cardiovascular mortality after adjustment for cardiovascular risk factors [16]. Furthermore, serum OPG was associated with cardiovascular events, cardiac mortality and all-cause mortality in kidney transplant patients [17, 18] and predicted graft failure in one of the studies [18]. Moreover, elevated OPG at baseline was associated with a more rapid and greater magnitude of reduced glomerular filtration rate (GFR) in elderly women from the general population [19].

There is a paucity of data regarding the relation between OPG and renal function across age groups in the general population. In the present large, cross-sectional, population-based study with a wide age span, we aimed to investigate the relationship between serum OPG and renal function in subjects with normal and impaired renal function.

Materials and methods

Study population

Participants were recruited from the fourth survey of the Tromsø Study (conducted in 1994–95), a single-centre prospective, population-based study, with repeated health surveys of inhabitants in Tromsø, Norway. The fourth survey consisted of two visits, where all inhabitants 55–74 years of age and 5–10% of random samples in the other 5-year age groups (25–54 and 75–85 years) were eligible for the second visit. Seventy-eight per cent ($n = 6887$) of the eligible subjects attended. Furthermore, subjects were excluded due to a lack of consent to contribute to research ($n = 57$). Measurement of OPG and/or creatinine was lacking in 141 subjects. Thus 6689 participants were included in the present study. Informed written consent was obtained from all participants and the study was approved by the regional committee for research ethics.

Medical history, blood collection and measurements

Information about the study participants was obtained from self-administrated questionnaires, anthropometric measurements, and measurements of non-fasting blood samples. In brief, blood samples were collected from an antecubital vein and serum prepared by centrifugation after 1 h respite at room temperature. OPG concentrations were analysed in freshly thawed serum aliquots stored at −70°C for 12 years by an enzyme-linked immunosorbent assay (R&D Systems, Abingdon, UK) with mouse anti-human OPG as capture antibody. Biotinylated goat anti-human OPG and streptavidin horseradish peroxidase were used for detection. The OPG assay was performed according to the manufacturer's instructions. The intra- and interassay coefficients of variation (CVs) in our laboratory were 6.5 and 9.3%, respectively. Between-assay variations in OPG were adjusted for by use of an internal standard. All samples were analysed in duplicate and the mean value was used in this report. Serum lipids [total and high-density lipoprotein (HDL) cholesterol and triglycerides], haemoglobin A1c (HbA1c), high-sensitivity C-reactive protein (hs-CRP) and creatinine were assessed as previously described [20].

Assessment of renal function

Plasma creatinine was analysed by a modified Jaffe reaction, but a subsample was reanalysed with an enzymatic method and recalculated creatinine values were used for the estimation of GFR (eGFRcrea) [21]. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations [22]. CKD was categorized based on the National Kidney Foundation guidelines using eGFRcrea: eGFR ≥90 mL/min/1.73 m^2 for normal kidney function, eGFR between 60 and 89 mL/min/1.73 m^2 for mildly impaired kidney function and eGFR between 15 and 59 mL/min/1.73 m^2 for Stage 3–4 CKD [23].

Statistical methods

The frequency distribution for all variables was checked by inspection of the distribution curves. Continuous variables are presented as means with 95% confidence intervals (CIs) or standard deviation (SD). Categorical data are presented as numbers or percentages. A general linear model (GLM) or logistic regression models were used for sex and age adjustment for continuous and binary dependant variables. The χ^2 test for linear trend was applied for categorical variables. OPG was modelled both as a continuous and categorical variable (tertiles in the analyses). GLM was used to test for linear trends across categories of OPG and linear regression was used to analyse OPG as a continuous variable. Crude analyses, adjustment for age and gender and further adjustments were carried out for variables shown to be associated with OPG (cardiovascular disease, smoking, body mass index, calcium, hypertension, HDL cholesterol, hs-CRP, self-reported diabetes mellitus, non-fasting glucose level ≥11.1 mmol/L or HbA1c >6.1%). Model assumptions were carefully checked and assessed by residual analysis. Tests of interaction between gender and OPG and between age and OPG were performed by including cross-product terms between the variables. There were significant interactions between age and OPG on eGFR. Therefore, we stratified the participants in two groups according to age (above and below median age). Subjects with incomplete data for the assessed covariates were excluded from the multivariable models (<1%). The statistical analyses were performed using SPSS for Windows, version 23.0 (IBM, Armonk, NY, USA). Two-sided P-values <0.05 were considered statistically significant. Figures were made in GraphPad Prism 7.00 (GraphPad Software, La Jolla, CA, USA).

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Results

The characteristics of the study participants are summarized in Table 1. The mean age was 61.0 years. eGFR was ≥90 mL/min/1.73 m^2 in 63.1%, between 60 and 89.9 in 34.8% and <60 in 2.1% of the participants (n = 6689). The serum concentration of OPG increased significantly across categories of eGFR. Serum OPG increased linearly across categories of renal function from 3.11 ± 0.94 ng/mL in subjects with normal renal function (eGFR ≥90 mL/min/1.73 m^2) to 3.71 ± 1.30 in subjects with mildly impaired renal function (eGFR 60–89) and to 4.50 ± 1.54 in subjects with Stage 3–4 CKD (eGFR 15–59). Subjects with normal renal function were, on average, about 10 years younger than subjects with impaired renal function. The Pearson correlation coefficient between OPG and age was 0.49.

Age- and gender-adjusted characteristics of participants stratified by tertiles of OPG are shown in Table 2. No significant trend in eGFR was found across categories of OPG (P = 0.497). Age, blood pressure, total cholesterol, HDL cholesterol, HbA1c, CRP, creatinine, fibrinogen, calcium, percentage of smokers and persons with self-reported cardiovascular disease, hypertension or diabetes mellitus increased significantly across tertiles of OPG, whereas the percentage of men, BMI and triglycerides decreased. Differences in eGFR across tertiles of OPG in the total study population in the crude analysis and after adjustment for age, sex, smoking, systolic blood pressure, BMI, plasma calcium, CRP, HDL cholesterol, hypertension, CVD (ischaemic stroke and/or myocardial infarction before baseline) and diabetes mellitus are shown in Figure 1. A significant interaction between OPG and age was found in the multivariable model (P = 0.0003) but not between OPG and gender.

Table 3 shows the relation between OPG and eGFR stratified by age. In participants ≤62.2 years of age (median), no significant association was found after multivariable adjustment. In contrast, in participants older than the median age, eGFR decreased across tertiles of OPG (P < 0.0001) and per 1 SD higher level of OPG (P < 0.0001) (Table 3).

The relation between tertiles of OPG and eGFR stratified by renal function is shown in Figure 2. In subjects with normal renal function (eGFR ≥90 mL/min/1.73 m^2), eGFR increased significantly (P-value trend <0.0001) across tertiles of OPG (panel A). The increase in eGFR per 1 SD increase in OPG was 0.43 mL/min/1.73 m^2 (95% CI 0.26–0.60; P < 0.0001). In participants with impaired renal function (eGFR <90 mL/min/1.73 m^2), eGFR decreased significantly (P-value trend <0.0001) across tertiles of OPG (panel B) and decreased by −1.07 mL/min/1.73 m^2 (95% CI −1.53 to −0.60; P < 0.0001) per 1 SD increase in OPG. Tables 4 and 5 show the relation between OPG and eGFR in participants ≤62.2 years of age (median) and >62.2 years, respectively. Significant positive associations between OPG and eGFR in subjects with normal renal function who were younger than the median age were found (Table 4). However, no significant association was present in younger subjects with impaired renal function (Table 4). No significant association was found between OPG and eGFR in participants older than the median age with normal renal function (Table 5). However, significant negative associations were present in subjects with impaired renal function in the oldest age group.

Discussion

In the present large population-based cross-sectional study including participants 25–85 years of age, a positive association between OPG and eGFR was found in participants with normal renal function (eGFR ≥90.0 mL/min/1.73 m^2) and an inverse association was found in participants with reduced renal function

Table 1. Characteristics of participants overall and across categories of eGFR

		eGFRcrea (mL/min/1.73 m^2)			
	Overall	≥90	60–89	15–59	P-value (trend)
Participants, *n* (%)	6689	4219 (63.1)	2328 (34.8)	142 (2.1)	
Age (years)	61.0 (10.1)	57.7 (10.2)	66.6 (6.9)	68.3 (5.7)	<0.0001
Male sex, *n* (%)	3298 (49.3)	2161 (51.2)	1070 (46.0)	67 (47.2)	0.0001
Osteoprotegerin (ng/mL)	3.34 (1.15)	3.11 (0.94)	3.71 (1.30)	4.50 (1.54)	<0.0001
eGFR (mL/min/1.73 m^2)	92.3 (13.4)	100.0 (7.8)	80.8 (7.4)	50.7 (9.5)	<0.0001
Creatinine (μmol/L)	67.6 (16.1)	61.6 (10.0)	75.3 (11.4)	117.8 (50.5)	<0.0001
BMI (kg/m^2)	26.0 (4.0)	25.8 (3.9)	26.3 (3.9)	27.2 (4.1)	<0.0001
Systolic BP (mmHg)	145 (23)	142 (21)	150 (23)	156 (26)	<0.0001
Diastolic BP (mmHg)	83 (13)	82 (13)	85 (13)	88 (15)	<0.0001
Total cholesterol (mmol/L)	6.72 (1.25)	6.64 (1.27)	6.84 (1.20)	7.05 (1.32)	<0.0001
HDL cholesterol (mmol/L)	1.52 (0.42)	1.53 (0.42)	1.52 (0.42)	1.43 (0.40)	0.013
Triglycerides (mmol/L)	1.63 (0.93)	1.59 (0.96)	1.69 (0.85)	1.98 (0.95)	<0.0001
Fibrinogen (g/L)	3.39 (0.85)	3.34 (0.85)	3.46 (0.83)	3.88 (0.96)	<0.0001
CRP (mg/L)	2.70 (6.51)	2.56 (6.33)	2.85 (6.73)	4.35 (7.44)	0.040
Plasma calcium (mmol/L)	2.38 (0.11)	2.37 (0.11)	2.39 (0.11)	2.40 (0.13)	<0.0001
PTH (pmol/L)	4.68 (2.13)	4.49 (1.90)	4.91 (2.27)	6.54 (3.95)	<0.0001
HbA1c (%)	5.48 (0.68)	5.45 (0.70)	5.50 (0.60)	5.73 (0.93)	<0.0001
Current smoking, *n* (%)	2117 (31.7)	1539 (36.5)	549 (23.6)	29 (20.4)	<0.0001
CVD, *n* (%)[a]	477 (7.1)	213 (5.0)	234 (10.1)	30 (21.1)	<0.0001
Hypertension, *n* (%)[b]	3972 (59.4)	2256 (53.6)	1603 (68.9)	113 (79.6)	<0.0001
Diabetes mellitus, *n* (%)[c]	386 (5.8)	222 (5.3)	146 (6.3)	18 (12.7)	0.02

Continuous variables are reported as mean (SD).

BMI, body mass index; BP, blood pressure; PTH, parathyroid hormone; CVD, cardiovascular disease.

[a]Self-reported ischaemic stroke and/or myocardial infarction before baseline.

[b]Antihypertensive medication and/or systolic blood pressure ≥140 mmHg and/or diastolic BP ≥90 mmHg.

[c]Self-reported use of glucose-lowering drugs, non-fasting glucose level ≥11.1 mmol/L or HbA1c ≥6.5%.

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Table 2. Characteristics of participants across tertiles of OPG, adjusted for age and sex ($n = 6689$)

	T1, 0.46–2.80 ng/mL	T2, 2.80–3.59 ng/mL	T3, 3.59–25.81 ng/mL	P-value (trend)
Number	2229	2230	2230	
eGFR (mL/min/1.73 m^2)	92.1 (91.6, 92.5)	92.9 (92.4, 93.3)	91.9 (91.4, 92.3)	0.497
Age (years)[a]	54.0 (53.7, 54.4)	61.9 (61.5, 62.2)	67.1 (66.7, 67.5)	<0.0001
Male (%)[b]	58.2	48.1	41.9	<0.0001
Current smoker (%)	26.7	32.4	35.4	<0.0001
Body mass index (kg/m^2)	26.4 (26.2, 26.6)	26.0 (25.9, 26.2)	25.6 (25.5, 25.8)	<0.0001
Systolic BP (mmHg)	142 (141, 143)	144 (143, 145)	149 (148, 150)	<0.0001
Diastolic BP (mmHg)	82 (82, 83)	83 (83, 84)	84 (84, 85)	<0.0001
Total cholesterol (mmol/L)	6.64 (6.59, 6.70)	6.80 (6.75, 6.85)	6.72 (6.67, 6.77)	0.088
HDL cholesterol (mmol/L)	1.48 (1.46, 1.50)	1.54 (1.52, 1.55)	1.56 (1.54, 1.57)	<0.0001
Triglycerides (mmol/L)	1.68 (1.64, 1.72)	1.62 (1.58, 1.66)	1.60 (1.55, 1.64)	0.012
HbA1c (%)	5.41 (5.38, 5.44)	5.45 (5.42, 5.48)	5.57 (5.54, 5.60)	<0.0001
C-reactive protein (mg/L)	2.24 (1.94, 2.54)	2.54 (2.27, 2.81)	3.34 (3.04, 3.63)	<0.0001
Fibrinogen (g/L)	3.24 (3.21, 3.28)	3.38 (3.35, 3.42)	3.55 (3.51, 3.59)	<0.0001
Creatinine (μmol/L)	67.5 (66.9, 68.2)	66.7 (66.1, 67.3)	68.5 (67.9, 69.2)	0.027
Plasma calcium (mmol/L)	2.38 (2.37, 2.38)	2.38 (2.38, 2.38)	2.38 (2.38, 2.39)	0.021
PTH (pmol/L)	4.69 (4.59, 4.78)	4.60 (4.52, 4.69)	4.76 (4.66, 4.85)	0.323
CVD (%)[c]	4.9	4.6	6.2	0.041
Hypertension (%)[d]	55.3	57.2	65.9	<0.0001
Diabetes mellitus (%)[e]	4.1	4.6	7.4	<0.0001

Continuous variables are reported as means (95% CI) and categorical data as percentages.
BP, blood pressure; PTH, parathyroid hormone; CVD, cardiovascular disease.
[a]Adjusted for sex.
[b]Adjusted for age.
[c]Self-reported ischaemic stroke and/or myocardial infarction before baseline.
[d]Antihypertensive medication and/or systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg.
[e]Self-reported, use of glucose-lowering drugs, non-fasting glucose level ≥11.1 mmol/L or greater, or HbA1C ≥6.5%.

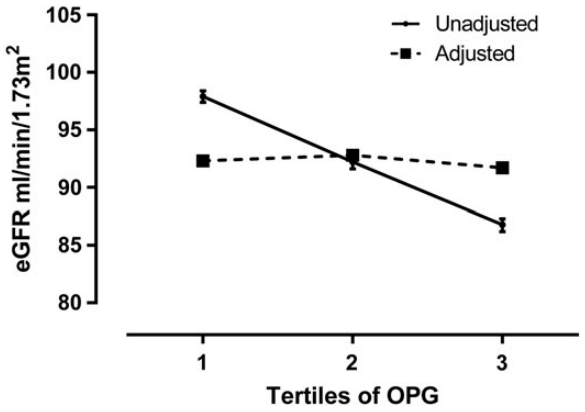

Fig. 1. Estimated GFR with 95% CI across tertiles of OPG in the total population ($n = 6689$). Unadjusted P-value for trend <0.0001. Multivariable adjusted P-value for trend 0.084.

(eGFR <90.0 mL/min/1.73 m^2). In age-stratified analyses, a positive association between OPG and eGFR was found in younger subjects (≤62.2 years) with normal renal function, whereas an inverse association was present in older subjects (>62.2 years) with reduced renal function. The modest changes in eGFR across tertiles of OPG are probably of questionable clinical relevance. However, our study shows that the relation between OPG and eGFR varies between age groups and stages of renal function.

An inverse relation between serum OPG and eGFR has previously been reported in elderly women. Subjects with serum OPG greater than the median serum concentration had 5% lower eGFR compared with those with lower serum OPG [19]. Furthermore, elevated OPG at baseline predicted a more rapid and greater decline in eGFR during follow-up [19]. Correspondingly, we found an inverse association between OPG and eGFR in participants older than the median age. In contrast, we found a positive association between OPG and eGFR in subjects with normal renal function, accounting for the majority of the study population.

Vascular calcification is a prominent feature in renal disease and the term 'chronic kidney disease–mineral bone disorder' reflects the interplay between various organ systems [12]. More than half of patients with predialytic renal failure have vascular calcification and reduced bone formation [13]. An association between serum OPG and rapid progression of vascular calcification has been reported in dialysis patients [24]. In contrast, animal studies indicate that OPG acts as an inhibitor of both atherosclerotic plaque growth and vascular calcification. Both osteoporosis and subintimal vascular calcification occurred in OPG$^{-/-}$ mice [11] and increased vascular calcification and plaque size appeared in double knockout mice (Apo E$^{-/-}$ and OPG$^{-/-}$) compared with Apo E$^{-/-}$ OPG$^{+/+}$ mice [25]. Serum OPG increased within a few weeks in ldlr$^{-/-}$ mice fed a diet promoting atherosclerosis [26]. Administration of recombinant OPG did not influence atherosclerotic plaque size, but reduced vascular calcification [26]. Consistent with findings in animal studies, we have reported lower serum OPG in subjects with echogenic carotid plaques compared with subjects with echolucent plaques and controls [27]. Moreover, an inverse association between OPG and increasing plaque echogenicity has also been reported in subjects with prior cardiovascular disease [28].

It has been hypothesized that the positive association between serum OPG and future risk of cardiovascular diseases, cardiovascular mortality and all-cause mortality might be a

Table 3. Estimated GFR (mL/min/1.73 m^2) across tertiles of OPG

	Unadjusted	Adjusted for age and sex	Multivariable adjusted
Age ≤62.2 years	*n* = 3345	*n* = 3345	*n* = 3301
OPG *n*			
T1: 1115	101.6 (100.9–102.3)	98.1 (97.5–98.7)	98.2 (97.6–98.7)
T2: 1115	97.7 (97.0–98.3)	98.6 (98.0–99.1)	98.7 (98.1–99.2)
T3: 1115	96.6 (95.9–97.3)	99.2 (98.6–99.8)	99.0 (98.4–99.6)
P-value (trend)	<0.0001	0.009	0.056
SD OPG 0.90	−1.89 (−2.29 to −1.49)	−0.01 (−0.34–0.33)	−0.07 (−0.42–0.28)
P-value	<0.0001	0.972	0.708
Age >62.2 years	*n* = 3344	*n* = 3344	*n* = 3284
OPG *n*			
T1: 1114	88.0 (87.3–88.7)	86.6 (86.0–87.3)	86.8 (86.2–87.5)
T2: 1115	86.7 (86.0–87.4)	86.6 (85.9–87.2)	86.5 (85.8–87.1)
T3: 1115	83.0 (82.3–83.7)	84.5 (83.8–85.2)	84.3 (83.6–84.9)
P-value (trend)	<0.0001	<0.0001	<0.0001
SD OPG 1.15	−2.40 (−2.79 to −2.01)	−1.31 (−1.72 to −0.91)	−1.43 (−1.84 to −1.02)
P-value	<0.0001	<0.0001	<0.0001

Values are mean (95% CI).
Multivariable model adjusted for age, sex, smoking, systolic blood pressure, BMI, plasma calcium, CRP, HDL cholesterol, hypertension, self-reported CVD (ischaemic stroke and/or myocardial infarction before baseline) and diabetes mellitus (self-reported use of glucose-lowering drugs, non-fasting glucose level ≥11.1 mmol/l or HbA1c ≥6.5%).

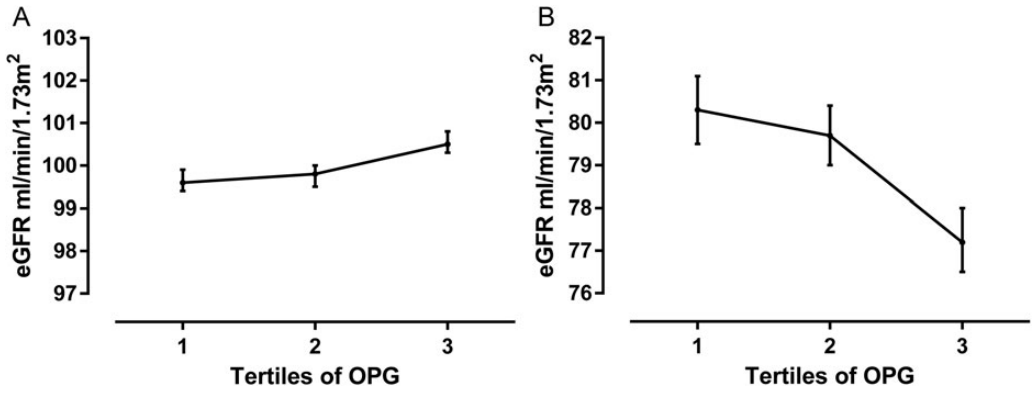

Fig. 2. Estimated GFR with 95% CI after multivariable adjustment across tertiles of OPG. (A) Participants with eGFR ≥90 mL/min/1.73 m^2 (*n* = 4147), P-value for trend <0.0001. (B) Participants with eGFR <90 mL/min/1.73 m^2 (*n* = 2438), P-value for trend <0.0001.

Table 4. Estimated GFR in participants ≤62.2 years of age stratified by renal function across tertiles of OPG and per 1 SD increase in serum OPG

	Unadjusted	Adjusted for age and sex	Multivariable adjusted
eGFR ≥90 mL/min/1.73 m^2	*n* = 2728	*n* = 2728	*n* = 2688
T1: 909	105.4 (104.9–105.9)	102.3 (101.9–102.6)	102.3 (102.0–102.7)
T2: 910	101.9 (101.4–102.4)	102.7 (102.4–103.1)	102.7 (102.4–103.1)
T3: 909	100.8 (100.3–101.4)	103.1 (102.8–103.5)	103.0 (102.6–103.4)
P-value (trend)	<0.0001	0.002	0.013
SD OPG 0.79	−1.60 (−1.89 to −1.30)	0.45 (0.23–0.65)	0.35 (0.13–0.56)
P-value	<0.0001	<0.0001	0.002
eGFR <90 mL/min/1.73 m^2	*n* = 617	*n* = 617	*n* = 613
T1: 205	82.1 (80.9–83.2)	81.6 (80.4–82.8)	81.4 (80.1–82.6)
T2: 206	80.4 (79.2–81.6)	80.4 (79.3–81.6)	80.4 (79.3–81.6)
T3: 206	79.5 (78.3–80.7)	79.9 (78.7–81.1)	80.1 (78.8–81.3)
P-value (trend)	0.003	0.062	0.158
SD OPG 1.26	−0.80 (−1.48 to −0.11)	−0.79 (−1.47 to −0.11)	−0.27 (−1.20–0.66)
P-value	0.024	0.022	0.569

Values are mean (95% CI).
Multivariable model adjusted for age, sex, smoking, systolic blood pressure, BMI, plasma calcium, CRP, HDL cholesterol, hypertension, self-reported CVD (ischaemic stroke and/or myocardial infarction before baseline) and diabetes mellitus (self-reported non-fasting glucose level ≥11.1 mmol/L or HbA1c ≥6.5%).

Table 5. Estimated GFR in participants >62.2 years of age stratified by renal function across tertiles of OPG and per 1 SD increase in serum OPG

	Unadjusted	Adjusted for age and sex	Multivariable adjusted
eGFR ≥90 mL/min/1.73 m^2	*n* = 1491	*n* = 1491	*n* = 1459
T1: 497	95.0 (94.6–95.3)	94.6 (94.3–95.0)	94.8 (94.4–95.1)
T2: 497	95.1 (94.8–95.5)	95.1 (94.7–95.4)	95.1 (94.7–95.4)
T3: 497	94.9 (94.6–95.2)	95.3 (95.0–95.6)	95.1 (94.8–95.5)
P-value (trend)	0.758	0.006	0.124
SD OPG 0.98	−0.02 (−0.22–0.17)	0.25 (0.05–0.44)	0.11 (−0.08–0.31)
P-value	0.810	0.014	0.264
eGFR <90 mL/min/1.73 m^2	*n* = 1853	*n* = 1853	*n* = 1825
T1: 617	79.9 (79.1–80.8)	80.1 (79.3–81.0)	80.2 (79.3–81.1)
T2: 618	79.5 (78.7–80.3)	79.5 (78.7–80.3)	79.3 (78.5–80.2)
T3: 618	76.4 (75.5–77.2)	76.1 (75.3–77.0)	76.1 (75.3–77.0)
P-value (trend)	<0.0001	<0.0001	<0.0001
SD OPG 1.24	−1.77 (−2.25 to −1.29)	−1.97 (−2.49 to −1.46)	−1.95 (−2.48 to −1.43)
P-value	<0.0001	<0.0001	<0.0001

Values are mean (95% CI).
Multivariable model adjusted for age, sex, smoking, systolic blood pressure, BMI, plasma calcium, CRP, HDL cholesterol, hypertension, self-reported CVD (ischaemic stroke and/or myocardial infarction before baseline) and diabetes mellitus (self-reported non-fasting glucose level ≥11.1 mmol/L or HbA1c ≥6.5%).

response to rather than a cause of atherosclerosis or vascular calcification in an attempt to regulate those processes [1, 10, 27]. Recently we found an age-dependent association between serum OPG and carotid intima media thickness, where subjects <45 years of age had a 50% lower risk of being in the uppermost quartile of carotid intima media thickness per 1 SD increase in serum OPG [29]. Our findings, of varying strength and direction of the relation between serum OPG across age groups and categories of renal function, are intriguing and difficult to explain, but may nurture the hypothesis that increased serum OPG observed in renal failure is secondary to ageing and disease. However, the results of a cross-sectional epidemiological study cannot be used to distinguish between these or other potential explanations, such as a counterregulatory mechanism.

Although epidemiological studies may provide valuable information, targeted interventional studies are needed. Denosumab, a monoclonal antibody to RANKL (decoy receptor for OPG), is used for the treatment of osteoporosis. It remains elusive whether long-term treatment with denosumab has effects on the renal and cardiovascular system.

Possible explanations for increased serum concentration of OPG with ageing, and in subjects with atherosclerosis and renal failure, may include decreased clearance of OPG or increased inflammatory activity. Clearance studies in rats showed that ^{125}I-labelled OPG was rapidly and predominantly distributed to the sinusoids of the liver after intravenous injection [30]. Thus, if this result is transferable to humans, impaired renal function seems a less probable explanation for the increase in serum OPG. Inflammatory mediators are known to promote the production of OPG [31]. As ageing, renal failure and cardiovascular disease are conditions associated with increased inflammatory activity, it is likely that inflammatory responses may partly explain increased serum OPG in these conditions.

The main strengths of our study are the large number of participants from a general population, with a wide age span and both genders represented. Possible confounding factors have been judiciously recorded and included in the multivariable statistical model, however, confounding by unmeasured factors cannot be ruled out. Limitations also include potential sources of misclassification. Renal function estimated by the CKD-EPI equation is not as accurate as direct measurement from iothalamate or creatinine clearance using a 24-h urine collection. However, direct measurement of GFR is not feasible in a large epidemiological study. Furthermore, estimation of renal function was based on only one measurement of serum creatinine and may be subject to intra-individual variation. Serum samples were kept frozen for 12 years at −70°C without any freezing–thawing cycles before measurement of OPG. However, others have reported long-term stability of OPG measurements in serum samples stored at −70°C [9].

Conclusions

Results from our large population-based cross-sectional study showed that the relation between OPG and eGFR varies with age and renal function. An inverse association was found in subjects older than the median age with impaired renal function, whereas a positive association was found in younger subjects with normal renal function. The clinical significance of these findings remains to be determined in future studies.

Conflict of interest statement

None declared.

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