Vascular health, systemic inflammation and progressive reduction in kidney function; clinical determinants and impact on cardiovascular outcomes

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Summary of key findings of the article

Introduction. Systemic inflammation, endothelial dysfunction and arterial thickening contribute to the elevated cardiovascular risk of dialysis patients. However, the course of these derangements and their relative contribution to the cardiovascular risk of nondialysed chronic kidney disease (CKD) are scarcely investigated.

Methods. Flow-mediated dilatation (FMD) and intima-media thickness (IMT) were assessed in 304 nondialysed CKD patients Stages 1–5 (mean age 46 ± 12 years, 158 men), together with routine biochemical measurements, C-reactive protein (CRP) and insulin resistance. Patients were then followed for time-to-event analysis of cardiovascular outcomes (fatal and nonfatal).

Results. CRP and IMT increased, while FMD decreased in parallel with estimated glomerular filtration rate (eGFR) decline (P < 0.001 for all). CRP and intact parathormone, as well as eGFR, appeared as strong determinants of FMD and IMT in multivariate analyses. After a median follow-up of 41 (range 6–46) months, 30 fatal and 59 nonfatal cardiovascular events occurred. In univariate analysis, FMD, IMT and CRP were significant predictors of outcome. In a multivariate Cox model excluding IMT, both FMD [hazard ratios 0.52 (95% confidence intervals 0.37–0.73) per %] and CRP [1.07 (1.03–1.11) per mg/L] predicted cardiovascular outcomes independently of confounders. In a model excluding FMD, only CRP (and not IMT) was a significant predictor.

Conclusions. Endothelial dysfunction, arterial thickening and inflammation occur in parallel with the decline in eGFR, contributing to the increased cardiovascular risk of nondialysed CKD. Our results support the use of FMD over IMT measurements to monitor nondialysed CKD patients at risk.

Keywords: cardiovascular; C-reactive protein; flow-mediated dilatation; intima-media thickness

Introduction

Chronic kidney disease (CKD) is an escalating worldwide public health problem [1]. Progression towards end-stage renal disease (ESRD) exposes patients to increased risk of developing premature vascular disease and cardiovascular morbidity, thus contributing to exceedingly high mortality rates [2]. In fact, cardiovascular disease (CVD) and death are a more likely outcome in subjects with CKD than progression to ESRD and subsequent initiation of renal replacement therapy [3].

The mechanisms for the elevated CVD risk in early CKD are complex and may, in addition to classical Framingham risk factors, include systemic inflammation, oxidative stress and endothelial dysfunction [4]. While the relevance of inflammation and vascular health in the morbidity and mortality of dialysis patients has been largely investigated [5–10], less attention has been given to their respective roles in early-moderate CKD. Endothelial dysfunction increases in prevalence as renal function declines and is considered an obligatory prodromal phase in the atherosclerosis that precedes cardiovascular complications [11]. Endothelial dysfunction, as assessed by flow-mediated dilatation (FMD), has been associated to progressive kidney failure, CVD, anaemia, inflammation and oxidative stress [12–17]. Studies on vascular health using carotid artery intima-media thickness (IMT) in early-moderate CKD have shown associations with declining kidney function and future CVD [18–22]. However, existing evidence is limited by community-based studies or studies with
reduced sample size, selected individuals or restricted to moderate CKD stages only.

The prevalence of systemic inflammation also rises across progressive CKD and is believed to promote atherogenesis [23, 24]. Relatively few studies have addressed the clinical associates and the prognostic use of C-reactive protein (CRP) measurements in earlier CKD stages [25–27]. Importantly, no studies have addressed the relative contribution of inflammation and vascular derangements in patients with mild-moderate CKD. Such study seems pertinent since these putative risk factors to CVD are believed interconnected and causally related through the atherosclerotic–cardiovascular process [28]. Hence, the aim of this study was to assess in nondialysed CKD the clinical determinants of systemic inflammation, endothelial function and vascular health, on one hand, and to study the implications of such alterations on cardiovascular outcomes (both fatal and nonfatal) on the other. We did so in a large cohort of CKD patients uniformly distributed and balanced across the different disease stages.

Methods

Patients and study design

The ethical committee of Gulhane School of Medicine (Haydarpasa, Ankara, Turkey) approved the study, and informed consent was obtained from each subject. Between January 2005 and July 2009, 908 patients <70 years of age were referred to the Renal Unit of the Gulhane School of Medicine Center, Ankara, Turkey, for the first time because of CKD according to their estimated glomerular filtration rate (eGFR) and the suspected or manifest renal failure. All patients were diagnosed as having CKD the clinical determinants of systemic inflammation, endothelial function and vascular health, on one hand, and to study the implications of such alterations on cardiovascular outcomes (both fatal and nonfatal) on the other. We did so in a large cohort of CKD patients uniformly distributed and balanced across the different disease stages.

Laboratory measurements

All samples were obtained from patients and controls in the morning after 12 h of fasting for measurement of serum albumin, total serum cholesterol, triglyceride (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol. Total plasma cholesterol, HDL and LDL cholesterol were measured by enzymatic colorimetric method with Olympus AU 600 auto analyser using reagents from Olympus Diagnostics GmbH (Hamburg, Germany). LDL cholesterol was calculated by the Friedewald’s formula. Serum total calcium was measured by the crosolphate complexone method using Menagent Calcium 60sec kits (Menarini Diagnostics, Florence, Italy). Serum phosphorus was measured by the ammonia molybdate complex method using Menagent Phosphofix kits (Menarini Diagnostics). Intact parathyroid hormone (iPTH) was measured by immunoradiometric assay using kits (Immune Intact PTH) from Diagnostic Product Corporation (Los Angeles, CA) with a sensitivity of 1 pg/mL. For the measurement of high-sensitivity C-reactive protein (hsCRP), serum samples were diluted with a ratio of 1/101 with the diluents solution. Calibrators, kit controls and serum samples were all added on each microwell with an incubation period of 30 min. After three washing intervals, 100 μL enzyme conjugate (peroxidase-labeled anti-CRP) was added on each microwell for additional 15 min incubation in room temperature in the dark. The reaction was stopped with a stop solution and photometric measurement was performed at the 450 nm wavelength. The amount of serum samples was calculated as mg/L with a graphic that was made by noting the absorbance levels of the calibrators. The intraassay Coefficient of variation (CVs), at hsCRP concentrations of 0.47, 10.5 and 54.9 mg/L, were 6.4, 3.7 and 2.9%, respectively. The intraassay CVs at 1.24, 3.28 and 8.36 mg/L were 0.82, 1.20 and 0.84% for the hsCRP assay. Lower limits of detection and quantification were 0.02 and 0.15 mg/L for the hsCRP assay, respectively. The maximum measurable concentration was 110 mg/L.

Vascular assessment

Arterial blood pressure was measured by a physician in the morning three consecutive times after a 15-min resting period and mean values were calculated for systolic and diastolic pressure in all patients.

Endothelium-dependent vasodilatation (FMD) and endothelium-independent vasodilatation [nitroglycerine-mediated dilatation (NMD)] of the brachial artery were assessed noninvasively, using high-resolution ultrasound. Measurements were made by a single observer using an ATL 5000 ultrasound system (Advanced Technology Laboratories Inc., Bothell, WA) with a 12-MHz probe. The subjects remained at rest in the supine position for at least 15 min before the examination started. The subject’s arm was comfortably immobilized in the extended position to allow consistent recording of the brachial artery 2–4 cm above the antecubital fossa. Three adjacent measurements of end-diastolic brachial artery diameter were made from single 2-D frames. All ultrasound images were recorded on a VHS videotape for subsequent blinded analysis. A pneumatic tourniquet was inflated to 200 mmHg with obliteration of the radial pulse. After 5 min, the cuff was deflated. Flow measurements were made 60 s post-deflation. After a further 15-min, measurements were repeated and again 3 min after administration of sublingual glyceryl trinitrate 400 μg po. The maximum FMD and NMD dilatation diameters were calculated as the average of the three consecutive maximum diameter measurements. The FMD and NMD were then calculated as the percent change in diameter compared with baseline resting diameters.

IMT was assessed in all subjects. Briefly, a high-resolution B-mode ultrasound of the common carotid arteries with scanning of the longitudinal axis until the bifurcation and of the transversal axis was performed using an instrument generating a wide band ultrasonic pulse with a middle frequency of 12 MHz (ATL 5000; Advanced Technology Laboratories Inc.). For each carotid artery, two longitudinal measurements were obtained by rotating the vessels at 180° increments along their axis. All patients and controls were blindly examined by one experienced operator (the intra-operator variability was 4%). IMT was measured at 1 cm proximal to the bifurcation on each side. IMT and FMD measurements were performed ideally in the same day or within 7 days from blood extraction and biochemical assessment.

Statistical analysis

All the statistical analyses were performed by using SPSS 11.0 (SPSS Inc., Chicago, IL) statistical package. Nonnormally distributed
variables were expressed as median (range) and normally distributed variables were as mean ± SD, as appropriate. A P-value <0.05 was considered to be statistically significant. Between group comparisons were assessed for nominal variables with the chi-square test and by Kruskal–Wallis test (analysis of variance) for the rest of variables. Spearman’s rank correlation was used to determine correlations between paired variables. Stepwise multivariate regression analysis was used to assess the predictors for FMD and IMT levels. Survival and time-to-event analysis of cardiovascular outcomes (using a composite of fatal and nonfatal events) was done using Cox proportional hazards model, including adjustment for potential confounding factors. Data are presented in the form of hazard ratios (HR) and 95% confidence intervals (CI).

**Results**

The demographic and clinical characteristics of the patients are given in Table 1. No differences were observed across the CKD stages with regard to age, gender, body mass index, smoking status, history of CVD and the etiology of CKD. The biochemical and vascular assessments are given in Table 2. Blood pressure and lipid profiles did not differ across stages, but albumin and calcium levels were detrimentally reduced, while the iPTH and hsCRP gradually rose. The IMT increased and the FMD decreased in parallel with CKD stages (Figure 1).

The univariate and multivariate associates of FMD and IMT are shown in Table 3. FMD values were independently predicted by hsCRP, NMD, SBP, comorbid diabetes, iPTH and eGFR. IMT was independently predicted by the presence diabetes mellitus, iPTH levels and eGFR. Because diabetes may be considered an important confounder in association studies of endothelial function we repeated, as a sensitivity analysis, both uni- and multivariate associates of FMD and IMT after exclusion of 73 diabetics. Results were the same: the multivariate independent predictors of FMD were hsCRP, NMD, SBP, iPTH and eGFR (adjusted \( r^2 = 0.70 \)) and the multivariate independent predictors of IMT were iPTH levels and eGFR (adjusted \( r^2 = 0.54 \)).

Cardiovascular outcomes were determined from the day of examination onwards, with a mean follow-up period of 41 (range 6–46) months. Thirty-three patients died, 30 of which due to cardiovascular causes, 2 due to malignancies and 1 due to infection. Cardiovascular mortality (\( n = 30 \)) was defined as death due to coronary heart disease (\( n = 14 \)), sudden death (\( n = 7 \)), stroke (\( n = 6 \)) or complicated peripheral vascular disease (\( n = 3 \)).

In univariate Cox analysis, each unit increase of FMD \([HR 0.44 (95\% CI 0.32–0.60)]\), IMT \([1.88 (1.39–2.54)]\) and hsCRP \([1.08 (1.05–1.12)]\) significantly predicted future deaths. However, since only 33 fatal events were registered, we do not report multivariate Cox adjustment due to likelihood of model overfitting.

In addition to the 30 cardiovascular deaths, 59 nonfatal cardiovascular events were registered during the follow-up as follows: stroke (\( n = 15 \)); myocardial infarction (\( n = 32 \)); peripheral vascular disease (\( n = 7 \)) and aortic aneurysm (\( n = 5 \)). The predictors for time-to-cardiovascular event (\( n = 89 \), including a composite of fatal and nonfatal) were studied by univariate and multivariate COX analysis (Table 4, Panel A). In univariate Cox, FMD, IMT and hsCRP were significant predictors of cardiovascular outcomes. Multivariate Cox was used to study the impact of these variables in pairs or together, considering the adjustment for age, sex, eGFR, diabetes and cardiovascular comorbidity. In a model excluding IMT measurements, both FMD and hsCRP significantly contributed to predicting outcome, independent of each other and confounders. In a model excluding FMD, only hsCRP was able to predict outcome. In a model containing the three measurements, FMD and hsCRP, but not IMT, contributed to predicting outcome. As a sensitivity analysis, multivariate Cox models were repeated after exclusion of diabetic patients, finding similar results (Table 4, Panel B).
This observational cohort study provides a comprehensive overview of the evolution of vascular health and inflammatory status in patients with progressive kidney failure. We show that increased inflammation, arterial thickening and impaired dilatation occur in parallel with the decline of eGFR. Inflammation (as assessed by CRP) and iPTH appeared as strong determinants for FMD in multivariate analyses. Both FMD and CRP values, but not IMT, emerged as independent predictors of future cardiovascular outcomes. Although these findings may seem, a priori, expected, this is the first study demonstrating this in etiologically diagnosed CKD patients across the different stages.

A progressive reduction in kidney function is accompanied by retention of uraemic solutes and purportedly are linked with the elevated mortality risk of this patient population. Low-grade inflammation is an early and frequently characterized feature of CKD, likely a consequence of both retention and increased production [24, 29]. Higher CRP levels are associated with a faster rate of kidney function loss [30, 31] and it has been proposed as an intermediate link between renal insufficiency and the appearance of endothelial dysfunction and thickening [32]. It is well established that the endothelium synthesizes a variety of inflammatory molecules [23, 24]. Our study supports previous studies showing that inflammation occurs hand in hand with the decline in GFR and that in multivariate analyses, CRP levels stood as an independent contributor to the variance of FMD. These results expand previous observations in community-based studies [33], nondiabetic CKD patients [12, 13] and studies confined to moderate CKD stages [17]. Nonetheless, ours is probably the largest study population of this kind including uniformly distributed etiologically diagnosed CKD patients across the different disease stages. This, together with the exclusion of drugs that

**Table 2. Biochemical and vascular assessment according to CKD stages**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Biochemical and Vascular Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>eGFR (mL/min)</td>
</tr>
<tr>
<td>1 (≥90)</td>
<td>96 (91–107)</td>
</tr>
<tr>
<td>2 (60–89)</td>
<td>68 (61–89)</td>
</tr>
<tr>
<td>3 (30–59)</td>
<td>45 (31–58)</td>
</tr>
<tr>
<td>4 (15–29)</td>
<td>20 (15–29)</td>
</tr>
<tr>
<td>5 (&lt;15)</td>
<td>9 (4–14)</td>
</tr>
</tbody>
</table>

**Notes:**

- NMD: nitroglycerine-mediated dilatation; hsCRP: high-sensitivity C-reactive protein.
- Differences assessed by chi-square test for categorical variables, and by Kruskal–Wallis test. Statistically significant if *P* < 0.05. To convert total cholesterol in mg/dL to mmol/L, multiply by 0.02586; TG in mg/dL to mmol/L, multiply by 0.01129.

**Fig. 1.** Box plots showing the decrease in FMD levels (Panel A) and the increases in IMT (Panel B) and CRP (Panel C) in parallel with eGFR reduction.

**Discussion**

This observational cohort study provides a comprehensive overview of the evolution of vascular health and inflammatory status in patients with progressive kidney failure. We show that increased inflammation, arterial thickening and impaired dilatation occur in parallel with the decline of eGFR. Inflammation (as assessed by CRP) and iPTH appeared as strong determinants for FMD in multivariate analyses. Both FMD and CRP values, but not IMT, emerged as independent predictors of future cardiovascular outcomes. Although these findings may seem, a priori, expected, this is the first study demonstrating this in etiologically diagnosed CKD patients across the different stages.

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may confound the interpretation of the eGFR vascular health axis, are clear strengths of the study. At the same time, however, due to these medical exclusions, our data are not necessarily representative of the normal CKD population and should be interpreted with caution. In this sense, we bring attention to the fact that CRP or iPTH levels in our study seem higher than in previous reports, and patients included were overall relatively young. Because eGFR is subjected to inaccuracies in CKD classification, we included only etiologically diagnosed patients, and eGFR was treated as a continuous variable in all our analyses. Finally, we should also emphasize that the cross-sectional nature of this analysis does not allow us to infer whether the impairment of eGFR causes increased inflammation and vascular abnormalities or vice versa and/or if they operate in a common system involving also other factors. These associations may well indeed be bidirectional, in light of the recent observation that endothelial dysfunction was a strong predictor of subsequent eGFR decline in never treated uncomplicated hypertensive patients [34].

Another observation of the present study pertains to the multivariate association of iPTH in prediction of both FMD and IMT levels. The endothelium is a recognized target organ of PTH and may contribute to its effects on vascular tone and blood pressure regulation [35]. Indeed, in nonrenal patients with primary hyperparathyroidism, measures of both FMD [36] and IMT [35] have been associated with the extent of PTH elevation. Parathyroidectomy is able to restore these arterial derangements [37]. In CKD patients,

### Table 3. Univariate and multivariate associates of FMD and IMT in nondialysis CKD patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>FMD (%)</th>
<th>IMT (mm)</th>
<th>HsCRP (mg/L)</th>
<th>NMD (%)</th>
<th>Age (year)</th>
<th>Gender (M/F)</th>
<th>Body mass index (kg/m²)</th>
<th>Smoking</th>
<th>SBP (mmHg)</th>
<th>Diabetes mellitus</th>
<th>Previous CVD</th>
<th>S-albumin (g/dL)</th>
<th>24 h proteinuria (mg/day)</th>
<th>S-calcium (mg/dL)</th>
<th>S-phosphate (mg/dL)</th>
<th>iPTH (pg/mL)</th>
<th>eGFR (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate a ρ</td>
<td>−0.66</td>
<td>−0.65</td>
<td>0.44</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>−0.17</td>
<td>−0.26</td>
<td>NS</td>
<td>0.14</td>
<td>0.18</td>
<td>0.48</td>
<td>−0.60</td>
<td>0.71</td>
<td>0.79</td>
</tr>
<tr>
<td>Multivariate b, c β (P)</td>
<td>−0.10 (0.03)</td>
<td>0.16 (&lt;0.001)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>−0.09 (0.006)</td>
<td>−0.14 (&lt;0.001)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Crude analysis</td>
<td>−0.66</td>
<td>0.61</td>
<td>−0.30</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.17</td>
<td>0.11 (0.005)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>−0.75</td>
</tr>
</tbody>
</table>

*a* Denoted are statistically significant (P < 0.05) β values as assessed by Spearman Rank’s test, as well as P-values from multivariate regression models.

*b* Variables known to influence FMD levels (age, gender, diabetes, history of CVD, smoking, IMT, hsCRP, NMD, SBP, albumin, 24 h proteinuria, Ca, P, iPTH, eGFR) and IMT levels (age, gender, diabetes, history of CVD, smoking, FMD, hsCRP, NMD, 24 h proteinuria, Ca, P, iPTH, eGFR) were initially included in the multivariate analyses.

The r² of the multivariate models was 0.72.

The r² of the multivariate models was 0.57.

### Table 4. Univariate and multivariate Cox analysis predicting for cardiovascular outcomes (a composite of 89 fatal and nonfatal events)*

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Panel A: in all patients (n = 304)</th>
<th>Panel B: in nondiabetic patients only (n = 231)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMD (%)</td>
<td>0.59 (0.49–0.70) (&lt;0.001)</td>
<td>0.50 (0.39–0.65) (&lt;0.001)</td>
</tr>
<tr>
<td>IMT (mm)</td>
<td>1.37 (1.16–1.61) (&lt;0.001)</td>
<td>1.06 (1.04–1.08) (&lt;0.001)</td>
</tr>
<tr>
<td>HsCRP (mg/L)</td>
<td>1.06 (1.04–1.08) (&lt;0.001)</td>
<td>1.08 (1.05–1.11) (&lt;0.001)</td>
</tr>
<tr>
<td>Panel B: in nondiabetic patients only (n = 231)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMD (%)</td>
<td>0.50 (0.39–0.65) (&lt;0.001)</td>
<td>0.67 (0.48–0.93) (0.02)</td>
</tr>
<tr>
<td>IMT (mm)</td>
<td>1.56 (1.21–2.01) (0.001)</td>
<td>0.96 (0.65–1.40) (0.8)</td>
</tr>
<tr>
<td>HsCRP (mg/L)</td>
<td>1.08 (1.05–1.11) (&lt;0.001)</td>
<td>1.07 (1.04–1.10) (&lt;0.001)</td>
</tr>
</tbody>
</table>

*a* Represented are HR (and 95%CI) in univariate (crude) Cox model and after different adjustments. Models 1–3 show different combinations of the variables of interest after adjustment for age (per year), sex (women as reference), SBP (per mmHg), total cholesterol (per mg/dL), eGFR (per mL/min), diabetes (absence as reference) and medical history of cardiovascular disease (absence as reference) at baseline. In Panel B, the same analysis is contemplated excluding diabetic patients, and therefore multivariate adjustment does not include diabetes mellitus. HsCRP, high-sensitivity c-reactive protein.
disorders in parathyroid function are believed to play an important role in the high prevalence of CVD and mortality [38]. In dialysis patients, vascular calcification and compromised reactivity and elasticity are frequently observed in connection with CKD and hyperparathyroidism and associated with increased risk of cardiovascular complications [39]. Two small studies in haemodialysis patients have reported associations between FMD [40] and IMT [41] with iPTH levels. To the best of our knowledge, ours is the first report confirming this important link in nondialysis CKD stages. Although we are unable to confirm this hypothesis in our study, the association of iPTH and endothelial function may be the consequence of progressive increased prevalence of vitamin D deficiency with progressive loss of kidney function, as low 25-hydroxy vitamin D levels importantly disturb the biological control of PTH synthesis [42]. In support of this, Drechsler et al. [43] recently showed that the impact of 25-hydroxy vitamin D levels on clinical events in the NECOSAD cohort was modified by PTH status, with low vitamin D levels meaningfully affecting outcomes only in patients with PTH levels above the median.

Finally, an important and novel input of this study is the analysis of the relative contribution of these interrelated factors on prediction of cardiovascular outcomes. To the best of our knowledge, there are no previous studies linking FMD derangements and future cardiovascular outcomes in nondialysis CKD patients. In our study, CRP levels, endothelial function (FMD) and arterial stiffness (IMT) were all significant predictors of cardiovascular outcomes in univariate analysis. However, the predictive effect of IMT was dependent on inflammation and basic confounders such as age, sex, eGFR and comorbidities. Szeto et al. [18] showed that increasing quartiles of IMT increased the hazards of future cardiovascular events in 203 patients with CKD Stages 3 and 4 independently of CRP levels. Our analysis, using IMT as a continuous variable, cannot confirm this finding in an enlarged population with CKD Stages 1–5. Desbien et al. [44] observed a significant interaction between creatinine clearance and IMT progression in prediction of 36 cardiovascular events in a community study of 3364 individuals. However, results were not adjusted for important confounders in this association like age or CRP. Although the use of continuous variables reduces residual confounding in our analysis, we cannot exclude the possibility of other unknown confounders. Nevertheless, despite a thorough phenotypical characterization and a relatively large sample size, we should not rule out the odds that larger sample sizes would modify this observation.

Taken together, our study provides solid evidence which, from a mechanistic point of view, illustrates that endothelial dysfunction and systemic inflammation may contribute in parallel to the increased cardiovascular risk of nondialysis CKD. This observation agrees with the multiple detrimental effects of systemic inflammation in CKD, including development of protein-energy wasting, muscle catabolism or hormonal derangements [10]. From a prognostic point of view, our results support the use of FMD over IMT measurements to monitor nondialysis CKD patients at risk.

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Conflict of interest statement. None declared.

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Rosiglitazone does not improve vascular function in subjects with chronic kidney disease

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Abstract

**Background.** Thiazolidinediones such as rosiglitazone (RSG) are insulin-sensitizing agents, which may improve inflammation and vascular function, and thus potentially lower cardiovascular risk in patients with chronic kidney disease (CKD). However, there is growing concern about

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