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Glomerular Filtration Rate and Coronary Artery Disease Burden in Patients with Acute Coronary Syndrome

José Pedro L. Nunes,* Maria do Sameiro Faria,† J. M. Mota Garcia,‡ Francisco Rocha Gonçalves*

*Faculty of Medicine, University of Porto; †Department of Nephrology, Hospital Maria Pia, Porto; ‡Department of Cardiology, Hospital São João, Porto, Portugal

Summary

Background: Mild renal dysfunction may be associated with increased cardiovascular morbidity and mortality.

Methods: The relation between estimated glomerular filtration rate (eGFR), as calculated from plasma creatinine at admission, and coronary artery disease burden (CADB), was studied in a cohort of 110 patients with acute coronary syndrome and coronary atherosclerosis.

Results: A relatively weak but significant negative correlation was found between eGFR and CADB as measured by angiography (coefficient correlation of −0.26, probability value of 0.006); a similar association was seen in multiple regression analysis, taking CADB as dependent variable, and eGFR, age, plasma calcium and plasma phosphorus as independent variables. After dividing the 110 patients into eGFR tertiles (with mean values of 102.9 ± 22.8, $n = 37$, $75.7 +$ or $-$ 5.6, $n = 36$, and 53.1 ± 13.4, $n = 37$, all in mL/min per 1.73 m^2), mean CADB values of the lower and higher eGFR tertiles were found to be significantly different (270.6 ± 176.4 and 192.9 ± 78.5, respectively). Similar mean values for CADB and for eGFR were noted when patients with elevated ST segment/new left bundle branch block and patients with nonelevated ST segment acute coronary syndrome were compared.

Conclusions: We conclude that renal function of patients with acute coronary syndromes and coronary atherosclerosis, as estimated at admission, is negatively correlated with coronary artery disease burden. It is unknown whether renal dysfunction acts as a cause for accelerated coronary artery disease or if it merely acts as a surrogate marker for the overall systemic vascular system status.

Key words: glomerular filtration rate, acute coronary syndrome, coronary artery disease

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Introduction

One of the main consequences of end-stage chronic renal failure is the increase in the incidence of cardiovascular disease, particularly of atherosclerotic disease.[1] Milder degrees of renal impairment, however, have also been shown to lead to adverse cardiovascular consequences. Renal function has been noted to be inversely associated with all-cause and with cardiovascular mortality in a population-based cohort.[2] A similar phenomenon was seen in patients with coronary heart disease.[3,4] Impaired renal function has also been found to be associated with angiographic coronary disease,[4] although one study showed such association to exist in women only.[5] Other studies, however, failed to note an association between serum creatinine and cardiovascular mortality,[6] or found an association only in the male sex and in age-adjusted and multivariable adjusted analysis.[7]

In the present investigation, the relation between renal function and coronary artery disease burden was studied in a cohort of 110 patients with acute coronary syndrome and coronary atherosclerosis that were prospectively studied and that were the subject of a previous report.[8] As previously reported,[8] coronary artery disease burden (CADB) was estimated by adding the degree of stenosis measured in every lesion that was found. A relatively weak but significant correlation was previously noted between CADB and plasma calcium. In the present

Address for reprints:
José Pedro L. Nunes
Faculty of Medicine
4200 Porto, Portugal
e-mail: jplnunes@med.up.pt

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investigation, a similar conclusion is reached regarding estimated glomerular filtration rate (eGFR).

Patients and Methods

The patients and methods studied in the present investigation have already been reported,[8] and a general description is hereby presented. We prospectively studied 110 Caucasian patients with a first episode of acute coronary syndrome (ACS). Eighty patients (63%) were male and thirty (27%) were female. Their mean age was 59.0 ± 11.8 years. Thirty-one patients had a diagnosis of diabetes mellitus, 59 patients had a history of cigarette smoking, 51 patients had a history of arterial hypertension, and 60 patients had a history of hypercholesterolemia.[8] The study had an observational character and required no intervention whatsoever to be performed on patients due to the study. The patients were diagnosed as suffering from unstable angina (7 patients) or acute myocardial infarction (AMI–103 patients) according to established criteria.[9] The 99th percentile for the distribution of plasma biomarkers was studied at our institution in 305 normal persons.[10] The patients underwent coronary angiography in one of these contexts: AMI with ST-segment elevation or new left bundle branch block, either aiming at primary percutaneous coronary intervention (PCI), or because of persistent or recurrent ischemia, or due to the presence of ischemia in noninvasive testing; AMI without ST segment elevation or new left bundle branch block, because of persistent or recurrent ischemia, or due to the presence of ischemia in noninvasive testing. PCI was performed in 80 patients (63%), and in every case was accompanied by stenting (sirolimus-eluting stents were used in 3 patients). In the case of total occlusion of a coronary artery undergoing PCI, the angiographic data concerning the distal part of the vessel, obtained after blood reflow, was considered in the estimation of the severity of coronary artery disease (CAD). Quantitative evaluation of coronary arteriography was performed in all patients in two orthogonal views. The percent stenosis were calculated as the mean of the values obtained in the two views. CADB was estimated as the sum of the percentage of the luminal stenosis encountered in all the lesions of the coronary arterial trees, as previously reported.[8] Patients with a prior ACS, patients with a normal coronary angiogram, and patients with major mechanical complications of AMI were excluded from the study. All patients under study were discharged alive, indicating that patients who died shortly after the ACS were also not included. Indications for coronary artery bypass surgery followed published guidelines.[11] Only 7 patients in this series were considered to have an indication for surgery, reflecting the fact that patients transferred to the cardiac surgical department in the first few days after the ACS were also not included in the study. Details on drug use in this cohort were previously reported.[8]

Glomerular Filtration Rate Calculation

The study protocol aimed at selecting patients excluding significant renal insufficiency, with the exclusion of patients with a discharge plasma creatinine equal to or greater than 2 mg/dL (176.8 μmol/L). For the purpose of the present investigation, however, the creatinine value taken for further study was the value at admission (thus excluding the possible influence of contrast-induced nephropathy[12]). eGFR mL/min per 1.73 m^2 was calculated according to the abbreviated Modification of Diet in Renal Disease (MDRD) study equation: $GFR = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ (in women), as described in the corresponding K/DOQI Clinical Practice Guidelines.[13–15]

Statistical Analysis

Data are presented as arithmetic mean and standard deviation, except for Figs 1 and 2 (mean and standard error of the mean). Correlations between the various parameters under study were calculated by using the Pearson correlation coefficient. Patients were divided into tertiles of eGFR values, and one-way analysis of variance was performed with post hoc Scheffe test. Multiple linear regression, taking as dependent variable the estimation of CADB and as independent variables eGFR, plasma calcium, plasma phosphorus and age was performed, with the calculation of the overall probability and subsequent calculation of the individual probabilities for each independent variable. Pair of means was compared by using the Mann–Whitney test. Probability values <0.05 were considered significant.

Results

A significant negative correlation was found between the estimated glomerular filtration rate and the coronary artery disease burden, with a correlation coefficient (r) value of -0.26 corresponding to a probability value of 0.006. Plasma creatinine at admission was also significantly correlated to CADB, with a correlation coefficient value of 0.19 and a probability value of 0.045.

The division of the 110 patients into eGFR tertiles led to a mean value of 102.9 ± 22.8 mL/min per 1.73 m^2 for the tertile with the higher eGFR values ($n = 37$), 75.7 ± 5.6 mL/min per 1.73 m^2 for the intermediate tertile ($n = 36$) and 53.1 ± 13.4 mL/min per 1.73 m^2 for the tertile with the lower eGFR values ($n = 37$). The corresponding values for CADB were 192.9 ± 78.5, 251.1 ± 113.6 and 270.6 ± 176.4, respectively (Fig. 1); one-way analysis of variance showed an overall significant difference to exist (p-value of 0.031).

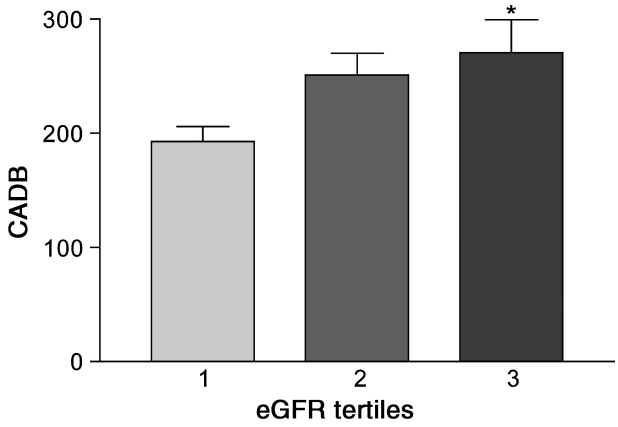

FIG. 1 Coronary artery disease burden (CADB) of 110 patients with acute coronary syndrome as divided into estimated glomerular filtration rate (eGFR) tertiles, with mean values of 102.9 ± 22.8, $n = 37$ (1), 75.7 ± 5.6, $n = 36$ (2), and 53.1 ± 13.4, $n = 37$ (3), all in mL/min per 1.73 m^2. *significantly different from the first tertile, one way analysis of variance.

Regression analysis taking CADB as the dependent variable and eGFR, age, plasma calcium and plasma phosphorus as independent variables showed an overall probability of 0.006 and individual probabilities of 0.04 for eGFR, 0.019 for plasma calcium, 0.79 for plasma phosphorus and 0.20 for age.

When patients with acute coronary syndrome and elevated ST-segment, or new left bundle branch block in the electrocardiogram were compared to patients without ST-segment elevation, similar levels of CADB were seen–235.3 ± 128.2, $n = 68$, vs. 242.6 ± 140.8, $n = 42$ (nonsignificant difference, Mann–Whitney test; Fig. 2), the same happening to eGFR -77.5 ± 28.8z mL/min per 1.73 m^2 vs. 76.9 ± 20.1 mL per min per 1.73 m^2–respectively (nonsignificant difference, Mann–Whitney test; Fig. 2). Maximum plasma levels of troponin I, however, were significantly higher in patients with elevated ST-segment or new left bundle branch block, when compared to the other group of patients (Fig. 2).

Discussion

In the present study, coronary artery disease burden, calculated by adding the various arterial lesions found in the coronary angiogram, was found to be negatively correlated to the estimated glomerular filtration rate. The analysis of the eGFR, as divided into tertiles, led to a significant difference in mean CADB value, when the two extreme tertiles were compared.

These findings are in good agreement with the concept that depressed renal function may act as a risk factor for coronary artery disease. They do not imply, however, that a causal relation exists. In the present study, all patients had angiographic evidence of coronary atherosclerosis. However, disease of different degrees was present in different patients. Thus, calculated GFR was correlated to the angiographic severity of the disease and not to the mere presence of the disease, which was universal in the population under study.

Some previous studies using plasma creatinine either failed to show an association between creatinine and cardiovascular mortality,[6] or showed an association only in the male sex and in age-adjusted and multivariable adjusted analysis.[7] Other studies, however, found a significant relation between renal function and mortality. As has already been noted,[15] the use of a formula to estimate GFR may have led to greater analytical power. In the Cholesterol and Recurrent Events trial, impaired kidney function and proteinuria were independently associated with all-cause mortality.[3] In the Atherosclerosis risk in Communities study, the level of glomerular filtration rate acted as an independent risk factor for atherosclerotic cardiovascular disease.[16] In the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack trial, a low glomerular filtration rate independently predicted increased risk for coronary heart disease.[17] In the Alberta provincial project for outcomes assessment in coronary heart disease, the all-cause mortality increased in relation to decreased glomerular filtration rate.[4]

In a study involving only women with chest pain, Reis *et al*. found that plasma creatinine correlated with coronary artery disease score and with maximum coronary artery stenosis.[18] Chen *et al*., on the other hand, found that decreased renal function was associated with angiographic coronary artery disease in women but not in men.[5] In what concerns non-ST-elevation acute coronary syndrome, Gibson *et al*.[19] and Fácila *et al*.[20] have shown that mortality is associated with eGFR[19] and both with eGFR and creatinine as measured at admission.[20]

In the present study and in what concerns the comparison between patients with and without ST-segment elevation, no significant differences were found either in eGFR or in CADB. These results point in the direction that renal function may not be a determinant of the type of acute coronary syndrome that any given patient develops.

The present results therefore corroborate previous findings of a relation between coronary artery disease severity and decreased renal function, in a specific setting–acute coronary syndrome–taking the creatinine value measured at admission. It is important to note that this association may establish renal dysfunction as a risk factor for coronary artery disease, but no clear indication for causality exists at the present stage. Glomeruli acting, to a certain extent, as modified blood vessels, renal dysfunction could stand as a surrogate marker for the overall systemic vascular system status. Plasma lipids, calcium and phosphorus have an altered physiology in the setting of renal failure, and lipid-lowering drugs seem to

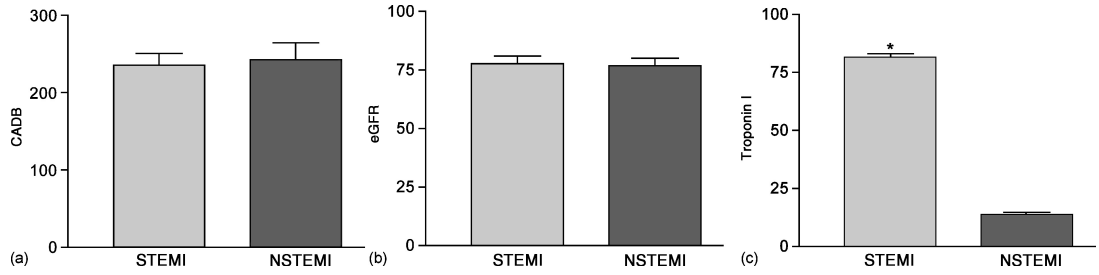

FIG. 2 Coronary artery disease burden (CADB), estimated glomerular filtration rate (eGFR; mL/min per 1.73 m^2) and maximum plasma troponin I (ng/mL) of 110 patients with acute coronary syndrome, as divided into patients with elevated ST segment/new left bundle branch block (STEMI; n = 68) or nonelevated ST segment (NSTEMI; n = 42), *significantly different from NSTEMI, Mann–Whitney test.

have an atypical behaviour in renal failure patients.[21,22] The interplay between calcium, phosphorus and lipids may take place in patients with different degrees of renal function.[23]

Study Limitations

Angiography is a technique that detects major coronary arterial lesions, leaving important segments of diseased vessels unrecognized as such.[24] This fact represents a significant limitation of the present study. The population under study is clearly not representative of the entire spectrum of patients with coronary atherosclerosis or, indeed, of the entire spectrum of patients with acute coronary syndromes. This constitutes a further limitation of the present study. Patients with marked renal impairment were also excluded from the study and thus the population under study does not represent the whole spectrum of renal function in patients with ACS. Last but not the least, renal function was not the subject of the original study protocol.[8]

Conclusion

We conclude that renal function of patients with acute coronary syndromes and coronary atherosclerosis, as estimated at admission, is negatively correlated with coronary artery disease burden. The correlation found was relatively weak but highly significant. It is unknown whether renal dysfunction acts as a cause for more significant coronary artery disease or if it merely acts as a surrogate marker for the overall systemic vascular system status. Renal function may not be a determinant of the type of acute coronary syndrome that any given patient develops.

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