Association of renal functional impairment and the severity of coronary artery disease

Renal fonksiyon bozukluğu ve koroner arter hastalığının ciddiyeti arasındaki ilişki

Serkan Çay, Fatma Metin, Şule Korkmaz

Department of Cardiology, Yüksek İhtisas Heart-Education and Research Hospital, Ankara, Turkey

ABSTRACT

Objective: Cardiovascular diseases are the most common cause of death in patients with renal failure. Glomerular filtration rate (GFR) is used for the assessment of the renal functional status. In this study we aimed to examine the association between severity of coronary stenosis and renal function by quantifying the coronary lesions, angiographically and calculating the renal function with the use of GFR.

Methods: Forty-three patients with decreased renal function (calculated GFR<80 ml/min) with a mean age of 67.8 ± 9.0 years and 49 patients without impaired renal function (calculated GFR≥80 ml/min) with a mean age of 52.5 ± 10.3 years were studied consecutively from March 2005 to September 2005. Glomerular filtration rate was calculated according to a given formula. All patients underwent selective coronary artery angiography and Gensini scoring system was used for the detection of severity of coronary atherosclerosis.

Results: In linear regression analysis, a negative correlation was found between renal function and the severity of coronary atherosclerosis (r=0.326, p=0.002). All patients were classified into quartiles of Gensini score level. In multivariate analysis, the multiple-adjusted odds ratio (OR) of the risk of decreased renal function was 0.99 (95% CI 0.24-4.15) for quartile 2, 4.38 (95% CI 1.11-17.20, p=0.03) for quartile 3, and 7.01 (95% CI 1.72-28.61, p=0.007) for quartile 4 of Gensini score level compared with the quartile 1.

Conclusion: Coronary atherosclerosis quantified by Gensini score is significantly associated with the severity of decreased renal function and this association is independent of age and other cardiovascular risk factors. *(Anadolu Kardiyol Derg 2007; 7: 44-8)*

Key words: Coronary artery disease, renal insufficiency, coronary angiography

ÖZET

Amaç: Kardiyovasküler hastalıklar böbrek yetmezliği bulunan hastalardaki ölümün en sık nedenidir. Glomerüler filtrasyon hızı (GFH), renal fonksiyonun durumunu değerlendirmek için kullanılır. Bu çalışmada anjiyografik olarak koroner lezyonların ve GFH nin kullanılarak renal fonksiyonların tespiti ile koroner stenozun ciddiyeti ve renal fonksiyonlar arasındaki ilişkiyi çalışmayı amaçladık.

Yöntemler: Ortalama yaşı 67.8 ± 9.0 olan azalmış renal fonksiyonlu (GFH<80 ml/dak) 43 hasta ile ortalama yaşı 52.5 ± 10.3 olan renal fonksiyon bozukluğu bulunmayan (GFH≥80 ml/dak) 49 hasta Mart-Eylül 2005 tarihleri arasında ardışık olarak çalışıldı. Glomerüler filtrasyon hızı verilen formüle göre hesaplandı. Tüm hastalara selektif koroner anjiyografi uygulandı ve koroner aterosklerozun ciddiyetinin tespiti için Gensini skorlama sistemi kullanıldı.

Bulgular: Lineer regresyon analizinde, renal fonksiyon ve koroner aterosklerozun ciddiyeti arasında negatif korelasyon bulundu (r=0.326, p=0.002). Gensini skor düzeyine göre tüm hastalar dörtlü gruplara ayrıldı. Çoklu değişken analizinde, azalmış renal fonksiyon riskinin çoklu değişkenlere göre ayarlanmış OR si, Gensini skoru için grup 1 ile kıyaslandığında, grup 2 için 0.99 (%95 CI 0.24-4.15), grup 3 için 4.38 (%95 CI 1.11-17.20, p=0.03) ve grup 4 için 7.01 (%95 CI 1.72-28.61, p=0.007) idi.

Sonuç: Gensini skoru ile gösterilen koroner ateroskleroz azalmış renal fonksiyonun ciddiyeti ile anlamlı olarak ilişkilidir ve bu ilişki yaş ve diğer kardiyovasküler risk faktörlerinden bağımsızdır. *(Anadolu Kardiyol Derg 2007; 7: 44-8)*

Anahtar kelimeler: Koroner arter hastalığı, böbrek yetersizliği, koroner anjiyografi

Introduction

Survival of patients with renal functional impairment is low because of increased risk of death from cardiovascular causes. However, cardiovascular diseases are not the only cause of high mortality. There are other reasons (infection, malnutrition etc) for increased mortality in these patients. Cardiovascular disease (CVD) accounts for around 44% of overall mortality among patients on long term dialysis and the mortality rate from the cardiovascular causes in a young patient undergoing dialysis is about the same as that of a elderly patient from the general population (1). Angiographically significant coronary artery disease (CAD) has been found in 85% of patients with end-stage renal disease (ESRD) (2). The traditional risk factors for coronary artery disease including age, sex,

Address for Correspondence: Dr. Serkan Çay, Oba Sokak 11/6 Hürriyet Apt., Cebeci 06480, Ankara, Turkey
Tel: +90 312 319 65 68 Fax: +90 312 287 23 90 E-mail: cayserkan@yahoo.com

hypertension, diabetes mellitus, dyslipidemia, smoking habit and family history have been well-established. Although the prevalence of traditional Framingham risk factors is found much more in patients with ESRD, non-traditional risk factors such as inflammation and oxidative stress have been studied recently (3, 4).

Glomerular filtration rate (GFR) is a widely accepted, useful, easily calculated, and reproducible parameter used for the assessment of the renal functional status. Gradual decrease in this parameter demonstrates more decrease in renal function. Unfortunately, ESRD develops at the end of this progress. As mentioned above, decreased renal function is associated with higher incidence of atherosclerotic process and mortality from the cardiovascular disorders. Joki N, et al. have postulated in their studies that the severity of coronary atherosclerosis should be determined using numbers of effected vessels, numbers of stenotic lesions, and the degree of narrowing in patients with renal impairment (5, 6).

In the present study, we aimed to examine the association between severity of coronary stenosis and renal function by quantifying the coronary lesions, angiographically and calculating the renal function with the use of GFR. In addition, presence of any correlation between these two conditions was studied. It is a widely known fact that kidney failure, especially ESRD requiring hemodialysis, is associated with higher incidence of coronary events. However, in our study, GFR was calculated by using an indirect and easy method and we studied whether the obtained result might predict the severity of coronary artery disease. Because increased renal functional impairment is associated with more severe coronary heart disease.

Methods

Study population

Forty-three consecutive patients with the decreased renal function, GFR <80 ml/min, undergoing cardiac catheterization for proven or clinically suspected coronary artery disease were enrolled at the study between March 2005 and September 2005 (range 34-78 years). In addition, 49 patients with normal renal functional status, GFR ≥80 ml/min, undergoing cardiac catheterization for the same reason were recruited as control group (range 40-85 years). Exclusion criteria included the following: left ventricular dysfunction (left ventricular ejection fraction <50%); unstable ischemic conditions (unstable angina pectoris and myocardial infarction); valvular heart disease; hepatic dysfunction (aspartate aminotransferase and alanine aminotransferase >2 times upper limit of normal, respectively); and all forms of diabetes mellitus.

Assessment of renal function

Glomerular filtration rate was used for the detection of renal functional status. This parameter might be calculated by different methods. Although collected 24-hour urine sample is widely used for the calculation, in the present study we chose a more simple method, which does not contain 24-hour urine sampling:

GFR (ml/min) = (140-age [years]) X body weight (kg)/ plasma creatinine X 72. For female patients, obtained value was multiplied by 0.85.

Cardiac catheterization and determination of the severity of coronary atherosclerosis

All patients in the study underwent selective coronary artery angiography after appropriate patient preparation. Femoral artery cannulation was used for arterial access site and Judkins system was applied for cannulation the left and right coronary arteries. All angiograms were evaluated by two experienced physicians blinded to the study. Angiograms with stenotic lesion in all major epicardial coronary arteries including left main, left anterior descending (LAD), left circumflex (LCx), and right coronary (RCA) arteries were assessed and the severity of coronary artery disease was assessed by using the Gensini scoring system (7) which grades narrowing of the lumens of the coronary arteries as: 1 for 1-25% narrowing, 2 - 26-50% narrowing, 4 - 51-75% narrowing, 8 - 76-90% narrowing, 16 - 91- 99% narrowing, and 32 for total occlusion. This score was then multiplied by a factor that takes into account the importance of the lesion's position in the coronary arterial tree, for example, 5 for the left main coronary artery, 2.5 for the proximal LAD or proximal LCx, 1.5 for the mid-region of the LAD, and 1 for the distal LAD or mid-distal region of the LCx.

Laboratory data

Fasting peripheral venous blood samples were obtained from all patients in the study for the measurement of fasting plasma glucose, total cholesterol, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, and triglyceride levels. Blood samples were centrifuged and plasma was obtained. Fasting blood glucose, total cholesterol, HDL-cholesterol, and triglyceride levels were measured by different laboratory techniques. Measurement of LDL-cholesterol level was done through application of a formula as described by Friedewald et al (8). In addition, renal functional parameters (urea and creatinine) and fibrinogen levels were measured.

Anthropometric measurement

Height and weight of patients were measured and body mass index (BMI) was calculated through dividing weight in kilograms by height in meters squared and described as kg/m2.

Statistical analysis

Data were analyzed with the SPSS software version 10.0 for Windows (SPSS Inc., Chicago, Illinois). Continuous variables were presented as mean ± SD and categorical variables as frequency and percentage. The Kolmogorov–Smirnov test was applied to assess the distribution of continuous variables. Student's t-test was used to compare normally distributed continuous variables and the Mann–Whitney U test for variables without normal distribution. A two-tailed p-value of <0.05 was considered to be statistically significant. Multiple logistic regression analysis was used to evaluate the independent associates of decreased renal function group. Parameters with a p-value <0.1 in univariate analysis were included in the model. The odds ratios (OR) and 95% confidence intervals (CI) were calculated.

Results

Baseline characteristics

Baseline demographic, laboratory, and hemodynamic characteristics of patients in both groups are outlined in Table 1. Patients with renal functional impairment were older than those without impairment (p<0.001). The prevalence of hypertension was significantly higher in decreased renal function group compared to control group (p=0.02). There were no significant differences between two groups concerning sex and BMI. Urea and creatinine, and fibrinogen levels were significantly higher in decreased

renal function group compared to control group. No statistical significance was present between both groups for the measurement of fasting plasma glucose, total-, HDL-, LDL-cholesterols, and triglyceride levels. Hemodynamic parameters including systolic and diastolic blood pressures were not different between two groups (Table 1). More patients in decreased renal function group had history of hypertension yet the blood pressure measurements were same in both groups. This may be the result of medical treatment. Same can be true for the lipid values. Presumably, untreated patients with renal functional impairment for the traditional risk factors will have more severe atherosclerotic lesions. Nine patients (21%) in decreased renal function group were undergoing regular hemodialysis. Glomerular filtration rate values in decreased renal function group were significantly lower compared to control group. Similarly, Gensini scores were significantly higher in decreased renal function group compared to control group. This significant difference between groups might be essentially caused by the patients who were on dialysis.

Severity of the stenotic lesion

According to severity of the stenotic lesion, (Fig. 1) patients with ≥ 50% of narrowing of any epicardial coronary arterial segment had more decreased GFR compared to those with < 50% of narrowing.

Linear regression analysis of relationship between renal function and the severity of coronary atherosclerosis

The significant linear relationship between Gensini score and glomerular filtration rate is reported in Figure 2 (r=0.326, p=0.002). With the decrease of GFR and so renal function, Gensini score increases demonstrating more severe coronary atherosclerosis.

Logistic regression analysis of the severity of renal functional impairment

All patients were classified into quartiles of Gensini score level to evaluate whether Gensini score was associated with the severity of decreased renal function in the study. We found that Gensini score was positively and significantly associated with the severity of renal functional impairment (Table 2). Twenty-seven percent of patients in the lowest quartile, 26% in the second quartile, 58% in the third quartile, and 74% in the highest quartile were found to have decreased renal function. The crude OR of the risk of decreased renal functional status was 0.94 (95% CI 0.25-3.53) for quartile 2, 3.73 (95% CI 1.08-12.91) for quartile 3, and 7.56 (95% CI 2.02-28.33) for quartile 4 of Gensini score level compared to quartile 1. The multiple-adjusted OR of the risk of decreased renal function was 0.99 (95% CI 0.24-4.15) for the second quartile, 4.38 (95% CI 1.11-17.20) for the third quartile, and 7.01 (95% CI 1.72-28.61) for the fourth quartile of Gensini score level compared with the lowest quartile after adjustment for age, the presence of hypertension, serum levels of fibrinogen, urea, and creatinine.

Discussion

In our study, we found that patients with decreased renal function had significantly increased severity of coronary atherosclerosis compared to control subjects. In addition, this significant and positive correlation was independent of risk factors for coronary artery disease although smoking and diabetes mellitus were not included in the study.

Table 1. Baseline demographic, laboratory, and hemodynamic characteristics

Variables	Normal renal function group (n=49)	Decreased renal function group (n=43)	P
Age, years	52.5 ± 10.3	67.8 ± 9.0	<0.001
Male sex, n (%)	43 (88)	35 (81)	NS
Hypertension, n (%)	4 (8)	11 (26)	0.02
Body mass index, kg/m2	27.3 ± 5.2	25.3 ± 4.5	NS
Fasting plasma glucose, mg/dl	92 ± 14	97 ± 14	NS
Cholesterol, mg/dl			
Total	172 ± 25	164 ± 28	NS
LDL	104 ± 20	99 ± 23	NS
HDL	41 ± 10	42 ± 10	NS
Triglycerides, mg/dl	134 ± 65	118 ± 50	NS
Fibrinogen, mg/dl	3.49 ± 1.45	4.30 ± 1.74	0.02
Urea, mg/dl	36 ± 10	61 ± 35	<0.001
Creatinine, mg/dl	0.87 ± 0.17	1.47 ± 0.91	<0.001
Systemic pressures, mmHg			
Systolic	118 ± 13	123 ± 15	NS
Diastolic	73 ± 9	75 ± 9	NS
GFR, ml/min	108 ± 24	55 ± 17	<0.001
Gensini score	13 ± 16	35 ± 33	<0.001

Values are mean ± SD or number and percentages of patients
GFR- glomerular filtration rate, HDL- high-density lipoprotein, LDL- low-density lipoprotein, NS- not significant

Patients with renal functional impairment (renovascular or renal parenchymal) have increased risk of cardiovascular diseases and increased mortality. This association is stronger in ESRD patients. Actually, the risk for CVD in a 30-year-old ESRD patient is similar to the calculated risk of a 70 to 80-year-old subject from the nonrenal population (9). Though the prevalence of traditional Framingham risk factors is very high in patients with renal impairment, non-traditional risk factors such as inflammation and oxidative stress, which are observed largely in renal failure causing atherosclerosis, have also been investigated (3, 4). Subjects with high risk have an active inflammatory process causing atherosclerosis. In addition, calcification in vascular wall is another important underlying inflammatory mechanism in the pathogenesis of atherosclerosis (10). Coronary artery calcification correlates with the extent of coronary artery atherosclerosis occurring more frequent in uremic patients than in the general population. Goodman et al. (11) used electron-beam computed tomography to demonstrate that coronary artery calcification is common and progressive, even in young adults undergoing dialysis. The highly possible etiology of uremic vasculopathy is derangement of the calcium-phosphate-parathyroid hormone axis resulted in secondary hyperparathyroidism. Recently, strong relationships among increased serum phosphate, calcium-phosphate product, parathyroid hormone, and mortality from cardiovascular causes have been demonstrated (12). Oh et al. (13) showed that coronary artery calcification in young adults was associated not only with a calcium-phosphate overload and hyperparathyroidism, but also with inflammation. Activated monocytes and macrophages infiltrate the vascular wall and enhance vascular calcification via cell-cell interaction and production of inflammatory mediators, such as tumor necrosis factor-α (14). Therefore, patients with decreased renal function have increased risk of coronary artery calcification resulted in enhanced coronary atherosclerosis.

Gradaus et al. (15) have demonstrated that a more rapid progression of coronary stenosis in patients with ESRD is present compared to patients with normal renal function. Increased prevalence of traditional cardiovascular risk factors including hypertension, diabetes mellitus and associated nephropathy, and dyslipidemia in these patients might be some mechanisms associated with the rapid progression (16). In addition, inflammatory substances like C-reactive protein have also been found in high concentrations. Prothrombotic factors (increased fibrinogen, decreased plasminogen activator inhibitor, and tissue plasminogen activator), increased oxidant stress, and hyperhomocysteinemia are the other causes and the mechanisms of why coronary lesions are more complex and severe in patients with impaired renal function (17, 18).

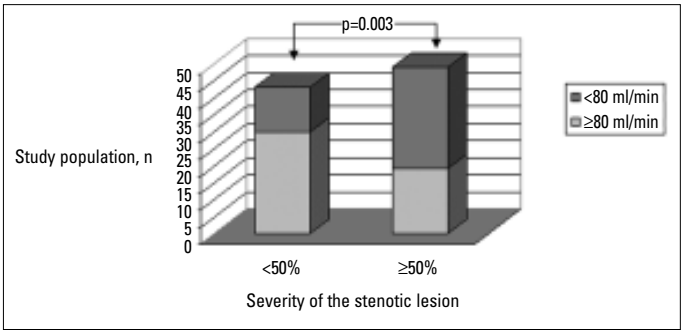

Figure 1. Association between the severity of stenotic lesion and renal function according to cut-off percentage of 50% of narrowing

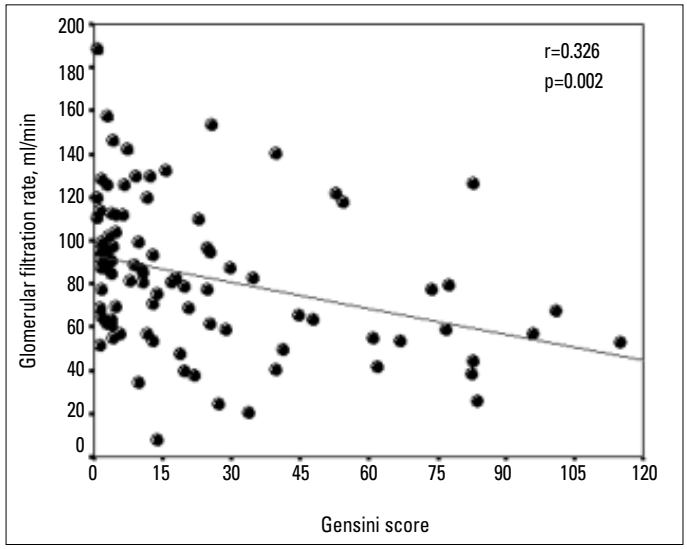

Figure 2. Linear regression analysis between Gensini score and glomerular filtration rate observed in 92 patients

Table 2. Logistic regression analysis odds ratios of decreased renal function according to Gensini score

	n	OR (95% CI)		
		Decreased renal function. n (%)	Crude	Multiple-adjusted*
Gensini score				
Quartile 1 (1.0-3.5)	22	6 (27)	1.00	1.00
Quartile 2 (4.0–11.0)	23	6 (26)	0.94 (0.25-3.53) p=0.93	0.99 (0.24-4.15) p=0.99
Quartile 3 (11.5–29.0)	24	14 (58)	3.73 (1.08-12.91) p=0.04	4.38 (1.11-17.20) p=0.03
Quartile 4 (29.5–115.0)	23	17 (74)	7.56 (2.02-28.33) p=0.003	7.01 (1.72-28.61) p=0.007

*Adjusted for age, the presence of hypertension, serum levels of fibrinogen, urea, and creatinine
CI- confidence interval, OR- odds ratio

Study limitations

Although the relatively large number of study population was used in our study, we believe that it is still limited in number to generalize the results because of invasive nature of the study. The patients in the study group are heterogenous. That is; 9 patients having end-stage renal disease and undergoing maintenance hemodialysis while the rest have impaired renal function defined by a GFR of <80 ml/min. Patients having ESRD are very different from those who have a mild renal functional impairment. The mean age of the patients with impaired renal function is older than that of the control group. This is a major factor affecting the severity of coronary artery lesions. Lastly, the prerenal azotemia could not be ruled out in our study.

Conclusion

We have demonstrated that Gensini score, indicator of the risk of severity for coronary artery disease, in patients with decreased renal functional status was significantly and independently elevated compared to control subjects.

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