Impaired kidney function is associated with SYNTAX score in patients with stable coronary artery disease

Kararlı koroner arter hastalığı olan kişilerde SYNTAX skoru böbrek fonksiyon bozukluğu ile ilişkilidir

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ABSTRACT

Objectives: The strong relationship between severe renal dysfunction and coronary artery disease (CAD) is well-known. However, the association between kidney function with SYNTAX Score (SS) has not been investigated in patients with stable CAD with normal to mildly impaired renal function. We aimed to investigate the association between kidney function with SS.

Study design: In this study, 411 stable CAD patients in whom coronary angiography (CAG) was performed were prospectively included (247 male, 164 female; mean age 58.6±12.4 years). Glomerular filtration rate was estimated (eGFR) by a modification of diet in renal disease (MDRD) formula. Two different groups were determined according to median eGFR values (GFR_{low} group <90, and GRF_{high} group ≥90). CAG was performed based on clinical indications. SS was determined in all patients.

Results: Patients in GFR_{low} group were older, and have a history of hypertension (HT) and diabetes mellitus and high body mass index. SS values of GFR_{low} group were higher than GFR_{high} group (p<0.001 for all). Multivariate regression analysis showed that eGFR was independently associated with diabetes (β, –0.206, p<0.001), HT (β, –0.093, p=0.026) and SS (β, –0.445, p<0.001).

Conclusion: eGFR is independently associated with extent and complexity of CAD as well as diabetes and HT. Importantly, these results may explain, in part, the increase in cardiovascular risk in with slightly impaired renal function.

ÖZET

Amaç: Koroner arter hastalığı (KAH) ile ciddi böbrek fonksiyon bozukluğu arasındaki güçlü ilişki iyi bilinmektedir. Fakat, kararlı KAH tanısı konan ve normal veya hafif böbrek fonksiyon bozukluğu olan hastalarda böbrek fonksiyonları ile SYNTAX skoru (SS) arasındaki ilişki araştırılmamıştır. Bu çalışmada böbrek fonksiyonları ile SS arasındaki ilişkiyi göstermeyi amaçladık.

Çalışma planı: Bu çalışmaya koroner anjiyografi ile kararlı KAH tanısı konan 411 hasta (247 erkek, 164 kadın; ortalama yaş 58.6±12.4 yıl) prospektif olarak alındı. Glomerül filtrasyon hızı (GFR) her hasta için MDRD (Modification of Diet in Renal Disease) formülü ile belirlendi. GFR değerlerine göre hastalar iki gruba ayrıldı ($GFR_{düşük}$ grup <90 ve $GRF_{yüksek}$ grup ≥90). Koroner anjiyografiler klinik endikasyonlar dahilinde yapıldı. Tüm hastalarda SS değerleri hesaplandı.

Bulgular: $GFR_{düşük}$ grup daha yaşlı olup beden kütle indeksi (BKİ) değerleri daha yüksek idi ve daha fazla diyabet ve hipertansiyon öyküsüne sahipti. $GFR_{düşük}$ gruptaki hastaların SS değerleri $GRF_{yüksek}$ gruba kıyasla daha yüksekti (hepsi için, p<0.001). Çok değişkenli regresyon analizi bize GFR'nin diyabet (β, -0.206, p<0.001), hipertansiyon (β, -0.093, p=0.026) ve SS (β, -0.445, p<0.001) ile bağımsız bir şekilde ilişkili olduğunu gösterdi.

Sonuç: GFR hipertansiyon ve diyabet ile ilişkili olduğu gibi aynı zamanda bağımsız bir şekilde KAH'nin yaygınlığı ve ciddiyeti ile ilişkilidir. Bu sonuç bize hafif düzeyde bozulan böbrek fonksiyonu sonrası bile artan kardiyovasküler riski kısmen de olsa açıklayabilir.

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It is well-known that impaired renal function is associated with an increased frequency of cardiovascular disease.[1] Patients with end-stage renal disease have a high risk for cardiovascular events, including mortality, worsening of heart failure and recurrent myocardial infarction (MI).[2] Glomerular filtration rate (GFR) is a widely accepted, easily measured, and reproducible parameter used for assessment of renal functions. It has recently been recognized that a declined level of renal function is an independent risk factor for all-cause mortality as well as adverse cardiovascular disease outcomes.[3,4]

The SYNTAX Score (SS) (synergy between percutaneous coronary intervention [PCI] with TAXUS and cardiac surgery) was developed to characterize coronary vasculature with respect to the number, location, complexity and functional impact of lesions. Higher SS indicates a complex condition, a bigger therapeutic challenge, and a potentially worse prognosis in patients undergoing revascularization.[4,5]

A strong relationship between severe renal dysfunction, and extent and complexity of coronary artery disease (CAD) has been investigated in only a few previous studies.[5-7] It has been demonstrated that even a slight decrease in the GFR poses an independent risk factor for cardiovascular diseases.[8] However, this association was not investigated in patients with stable CAD and normal to mildly impaired renal function. Therefore, in our study we aimed to investigate the association between kidney function and extent and complexity of CAD, calculated by SS, in patients with stable CAD and normal to mildly impaired renal function.

Abbreviations:

ARIC	*Atherosclerosis Risk in Communities*
BMI	*Body mass index*
CAD	*Coronary artery disease*
CAG	*Coronary angiography*
DBP	*Diastolic blood pressure*
DM	*Diabetes mellitus*
eGFR	*Estimated GFR*
GFR	*Glomerular filtration rate*
HT	*Hypertension*
MI	*Myocardial infarction*
PCI	*Percutaneous coronary intervention*
SBP	*Systolic blood pressure*
SS	*SYNTAX Score*

PATIENTS AND METHODS

Study population

We prospectively included 411 stable CAD patients in the present study (247 male, 164 female; mean age 58.6±12.4 years). The study population was selected from among patients who underwent coronary angiography (CAG) with various indications. Kidney disease: improving global outcomes clinical practice guidelines have been used to define renal dysfunction.[9] The criteria for normal renal function are defined as having an eGFR ≥90 ml/min/1.73 m^2. Mild dysfunction is defined as a eGFR between 60 and 89 ml/min/1.73 m^2 and moderate to severe renal function is defined as a eGFR <60 ml/min/1.73m^2. Then, the patients were divided into two groups according to median eGFR values (GFRlow group <90 and GFRhigh group ≥ 90). CAG was performed for the investigation of ischemic heart disease based on clinical indications (typical chest discomfort and/or abnormal stress test results such as positive treadmill test, dobutamine stress echo, and myocardial perfusion scintigraphy). Patients with coronary lesions of a diameter stenosis ≥50%, in vessel ≥1.5 mm were included in the study. All patients were clinically stable. Exclusion criteria were the presence of neoplastic disease, heart failure, recent major surgical procedure, or chronic liver or kidney disease and hemodialysis-dependency. Patients with previous MI and angina episodes 48 h before hospitalization, who had undergone coronary angioplasty or bypass surgery and those with valvular, myocardial, or pericardial disease, were also excluded. The study was conducted according to the recommendations set forth by the Helsinki Declaration on Biomedical Research Involving Human Subjects. The institutional ethics committee approved the study protocol, and each participant provided written informed consent.

Baseline characteristics of patients with CAD were recorded;age, gender, body mass index (BMI), history of hyperlipidemia, smoker at admission, history of hypertension (HT), history of diabetes mellitus (DM), family history, previous medications, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (beats/min), and medication. HT was defined as mean SBP ≥140 and/or mean DBP ≥90 mmHg or current use of any antihypertensive drug.[10] Hyperlipidemia was defined as a total cholesterol >200 mg/dL or current use of cholesterol-lowering therapy.[11]

Blood samples

Samples of peripheral venous blood were drawn from the antecubital vein at admission. Blood counts were measured by a Sysmex K-1000 (Block Scientific, Bohemia, New York, USA) autoanalyzer within 5 min

of sampling. Plasma triglyceride, low-density lipoprotein, high density lipoprotein, glucose, uric acid, and creatinine concentrations were measured with an automated chemistry analyzer (Abbott, Aeroset) using commercial kits (Abbott, USA).

Calculation of eGFR

The most recent creatinine measurement prior to CAG was used. Estimated GFR (eGFR) was calculated by the simplified MDRD equation: eGFR (mL/min/1.73 m^2) = 186.3 × (serum creatinine)−1.154 (mg/dL) × (age)−0.203 × 0.742 (if female) × 1.212 (if black).[12]

SS and angiographic analysis

All patients underwent selective CAG using the Judkins technique. Coronary lesions leading to ≥50% diameter stenosis in vessels ≥1.5 mm were scored separately and added together to provide the cumulative SS, which was prospectively calculated using the SS algorithm on the baseline diagnostic angiogram.[13,14] Two experienced interventional cardiologists analyzed the SS; the opinion of a third analyst was obtained and the final judgment was made by consensus in cases of disagreement. The final score was calculat-

Table 1. The comparison of baseline characteristics of the patient groups

Variables	GFR_{low} group (n=239)			GFR_{high} group (n=172)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			65.2±9.3			56.3±8.02	**<0.001**
Body mass index (kg/m^2)			26.5±3.6			28.05±3.7	**<0.001**
Gender (male)	143	61.9		97	56.3		0.143
Ejection fraction (%)			63.6±4.5			63.9±4.5	0.481
Systolic blood pressure (mmHg)			127.4±16.8			123.9±16.4	0.038
Diastolic blood pressure (mmHg)			77.6±10.0			76.2±9.6	0.146
Heart rate (beats/min)			76.03±10.2			76.1±8.9	0.906
Diabetes mellitus	140	58.6		14	8.1		**<0.001***
Hypertension	127	53.1		68	39.5		0.007
Smoking	84	35.1		51	29.7		0.243
Hyperlipidemia	126	52.7		119	69.2		0.751
Family history	75	32.2		46	28.1		0.102
Total cholesterol (mg/dl)			180±45			194±42	0.003
Triglyceride (mg/dl)			160±84			177±116	0.104
LDL-C (mg/dl)			118±52			128±34	0.019
HDL-C (mg/dl)			40±10			43±19	0.032
Glucose (mg/dl)			141±73			116±55	**<0.001**
Hemoglobin (mg/dL)			13.7±7.5			14.9±8.5	0.154
White blood cell (×1000/μl)			10.4±4.1			9.7±3.9	0.278
Creatinine (mg/dl)			1.001±0.24			0.73±0.156	**<0.001**
Uric acid (mg/dl)			5.6±1.5			4.7±1.2	**<0.001**
SYNTAX Score			18.52±8.4			5.5±2.1	**<0.001**
ACE-I use	48	20.1		33	19.2		0.82*
Angiotensin receptor blocker use	74	31		31	18		**0.003***
Statin use	85	41.4		88	42.7		0.842*
Oral antidiabetic use	126	52.7		33	19.2		**<0.001***
Acetyl salicylic acid use	74	31		46	28.1		0.078*

*Chi-square. LDL-C: Low density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol; ACE-I: Angiotensin converting enzyme inhibitor; eGFR: Estimated glomerular filtration rate.

ed from the individual lesion scores by analysts who were blinded to procedural data and clinical outcome.

Statistical analysis

All analyses were conducted using SPSS 17.0 for Windows statistical software (SPSS, Inc.). Continuous variables were expressed as mean±standard deviation and categorical variables were expressed as percentages. Distribution of parametric values was evaluated with a one-sample Kolmogorov-Smirnov test. Comparison of categorical variables between the groups was performed using the Chi-square (χ^2) test. The Independent- samples t-test was used in the analysis of continuous variables. The correlation between GFR with SS, clinical and laboratory parameters were assessed by the Pearson correlation test. Multiple linear regression analysis was performed to identify the independent predictors of SS by including the parameters, which were correlated with GFR in bivariate analysis. Standardized β-regression coefficients and their significance from multiple linear regression analysis were reported. A two-tailed $p<0.001$ was considered as significant.

RESULTS

Patients were divided into two groups according to median GFR level. Patients with GFR <90 ml/min/1.73 m^2 were referred to as GFR_{low} group and patients with GFR ≥90 ml/min/1.73 m^2 were referred to as GFR_{high} group.

Baseline characteristics

Comparison of baseline laboratory, angiographic and clinical characteristics between the two groups is shown in Table 1. Smoking, hyperlipidemia, and family history of CAD were similar between the groups ($p>0.001$ for all). Age, frequencies of DM and HT, differ between the groups ($p<0.001$ for all). BMI, UA and creatinine levels differ between the groups ($p<0.001$ for all). Oral antidiabetic (OAD) and angiotensin receptor blocker (ARB) use was higher in GFR_{low} group as compared to GFR_{high} group ($p<0.001$ for all). SS was higher in GFR_{low} group as compared to GFR_{high} group ($p<0.001$).

Bivariate and multivariate relationships of GFR

Bivariate and multivariate relationships of eGFR are demonstrated in Table 2. eGFR was associated with age ($r=-0.529$, $p<0.001$), presence of DM ($r=-0.480$, $p<0.001$), presence of HT ($r=-0.209$, $p<0.001$), OAD use ($r=-0.297$, $p<0.001$), ARB use ($r=0.137$, $p=0.005$), creatinine level ($r=-0.794$, $p<0.001$), BMI (-0.411, $p<0.001$) and SS ($r=-0.566$, $p<0.001$) in bivariate analysis.

Multivariate regression analysis showed that eGFR was independently related with HT ($\beta=-0.093$, $p=0.026$), presence of DM (β; -0.206, $p<0.001$), and SS ($\beta=-0.445$, $p<0.001$). Regression analysis did not include age, BMI and creatinine level because these parameters were used to calculate GFR. Relationships

Table 2. Bivariate and multivariate relationships of GFR

Variables	Pearson correlation coefficients	*p*	Standardized ß regression coefficients	*p*
Diabetes	–0.480	**<0.001**	–0.206	**<0.001**
Hypertension	–0.209	**<0.001**	–0.093	0.026
Creatinine	–0.794	**<0.001**		
SYNTAX Score	–0.566	**<0.001**	–0.445	**<0.001**
Uric acid	–0.135	**<0.001**	–0.037	0.286
Age	–0.529	**<0.001**		
Body mass index	–0.411	**<0.001**		
Angiotensin receptor blocker use	–0.137	**0.005**	0.073	0.106
Oral antidiabetic use	–0.297	**<0.001**	0.083	0.078
Glucose (mg/dl)	–0.115	0.020		
Systolic blood pressure (mmHg)	–0.067	0.172		

eGFR: Estimated glomerular filtration rate.

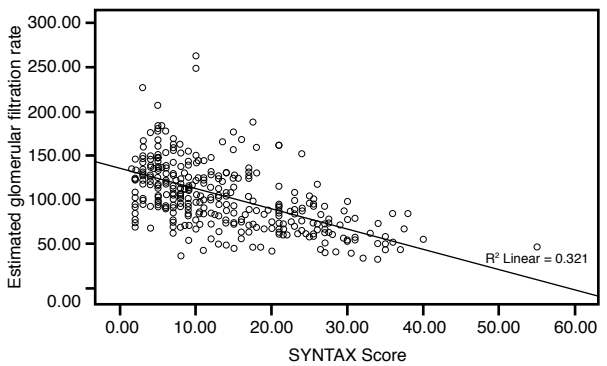

Figure 1. The relation between glomerular filtration rate and SYNTAX score.

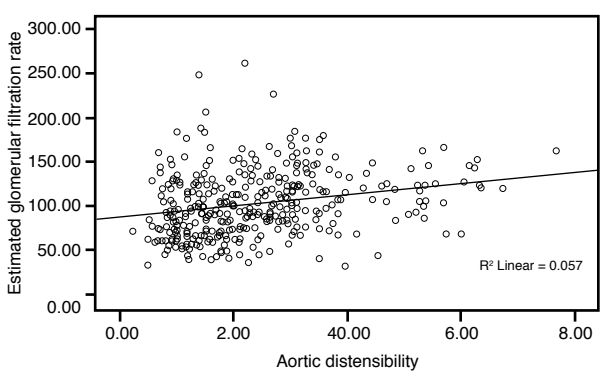

Figure 2. The relation between glomerular filtration rate and aortic distensibility.

between eGFR with SS are shown in Figures 1 and 2.

DISCUSSION

The main finding of the present study was that in patients with stable CAD, a lower eGFR, estimated by the MDRD formula, was independently associated with higher SS. In the present study, we also demonstrated that renal function has an inverse relation with SS as eGFR value increases.

Low GFR is highly prevalent and represents an important high-risk subset of patients undergoing revascularization.[12] Renal dysfunction is associated with poor prognosis after coronary artery bypass graft, perhaps because of the longer post-operative mechanical ventilation time, higher postoperative bleeding rates, and increased length of hospital stay.[15] Several studies showed the presence of low GFR to be associated with increased mortality and adverse cardiovascular events after PCI.[14,16,17] This increased risk was shown to occur despite the use of stent technology and optimal adjunctive medical therapy.[16] The increased risk in this population may be associated with high SS that have complex coronary anatomy and the resulting inability to perform PCI effectively. These findings are indicative of more complex and heavily calcified anatomy.[18]

Some studies showed an association between renal failure and CAD. Goodman et al.[19] reported that CAD is common in young adult patients with end-stage renal disease. Kılıckesmez et al.[6,7] examined 216 coronary angiographies of patients with normal renal function and different stages of renal dysfunction and identified coronary lesion complexity according to the ACC/AHA lesion classification.[20] The frequency of complex lesions was higher in the renal failure group. Abaci et al.[21] concluded that the eGFR was an independent predictor of extension and severity of CAD among diabetic patients. They used vessel and Gensini scores to identify the extent and severity of CAD. Kiyosue et al.[22] showed the severity of CAD in Japanese patients and revealed that the number of stenotic coronary arteries were higher in the renal failure group. However, in above-mentioned studies, SS was not used to assess the severity of CAD. SS shows not only the prevalence of CAD, but also its complexity. Furthermore, this scoring system was developed to help patient's selection and risk stratification for the SYNTAX trial and provides the first evidence-based approach in using optimal revascularization strategies for patients with multivessel and/or left main CAD. Only one study evaluated the extent and complexity of CAD in patients with low GFR using the SS.[7] Compared with patients with chronic renal failure and seriously low GFR, included in this study, patients in our study had mild to moderate low GFR.

The relation between renal failure and CAD is well-known, but the precise mechanisms of this interaction are not clearly understood. Explanations of this interaction include the greater frequency of risk factors, such as DM, HT and age, in patients with renal insufficiency, as well as the effects of renal failure on lipids, oxidative stress, homocysteine and fibrinogen.[23,24] DM and HT were associated with progressive renal dysfunction and also with the extent and severity of CAD. Renal dysfunction worsens more rapidly in diabetic and hypertensive patients.[25] In addition, in

the present study, patients with low GFR were older, which may affect the severity of CAD. Renal dysfunction activates the renin-angiotensin system and sympathetic nervous system, elevates blood pressure, causes anemia and vascular stiffness and calcification, and so on.[26,27] The potential pathophysiological mechanisms by which renal dysfunction increases aortic stiffness and coronary calcification include the detrimental effect of oxidative stress and inflammation,[28,29] as well as elevated plasma levels of asymmetric dimethylarginine[30] and homocysteine,[31] seen even in mild to moderate renal dysfunction, on endothelial function.[32] These metabolic changes may also facilitate the coronary atherosclerotic process.

Another possible explanation for the worsening of renal dysfunction in patients with severe CAD is that, they may be exposed to more contrast medium, because of the complex PCI process.

On the other hand, several studies proved that atherosclerosis caused renal dysfunction and common mechanisms promoted CAD and CKD. O'Hare et al.[33] showed that the frequency of increased Cr was significantly higher in those with a reduced ankle-brachial blood pressure index among subjects who participated in the Atherosclerosis Risk in Communities (ARIC) Study. Elsayed et al.[34] monitored renal function for 9.3 years on average in subjects from the ARIC Study and the Cardiovascular Health Study. In patients with cardiovascular disease, the odds ratio for worsening of renal failure was significantly high. Furthermore, in the Framingham Heart Study, the new onset of renal disease was closely related to the coexistence of coronary risk factors.[2] These findings imply that the presence of atherosclerosis is a risk factor for worsening of renal dysfunction.

Our study showed that even patients with stable CAD with normal to mildly impaired renal function had higher SS. Therefore, clinicians should pay more attention to this group of patients with low GFR. Early stages of renal dysfunction may be the only marker of CAD severity. Alternatively, even mild or moderate renal dysfunction may be a pathogenic contributor to the progression of coronary atherosclerosis.

Clinical implication

Early stages of renal dysfunction may be a marker of the severity of CAD. Therefore, patients with mildly low GFR should be evaluated more carefully to prevent cardiovascular diseases and should receive optimal treatment for risk factors.

Study limitation

First, we classified level of renal function based on an eGFR derived from a single serum creatinine determination prior to coronary angiogram, rather than a direct measurement of kidney function like iothalamate clearance. Second, the creatinine levels used to calculate eGFR might have been influenced by medications or clinical status. Thirdly, since this is a cross-sectional study, it is difficult to make causal inference. In addition, due to the observational nature of this study, it is not possible to determine the duration or cause of renal dysfunction. Furthermore, this is a single-center experience with a lack of long-term follow-up.

eGFR is independently associated with extent and complexity of CAD as well as frequencies of diabetes and HT. Importantly, these results may explain, in part, the increase in cardiovascular risk in patients with slightly impaired renal function. So, even Patients with mildly low GFR should be considered as a high-risk population for CAD and more effort should be spent on aggressive control of vascular risk factors. Moreover, also GFR may be used as an indicator of coronary lesion morphology because of its negative effect on SS. Future research should explain the pathophysiological mechanisms responsible for these findings.

Conflict-of-interest issues regarding the authorship or article: None declared

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Key words: Coronary artery disease; glomerular filtration rate; kidney function; SYNTAX score.

Anahtar sözcükler: Koroner arter hastalığı; glomerül filtrasyon hızı; böbrek fonksiyonu; SYNTAX skoru.